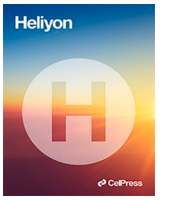
Heliyon 9 (2023) e13689

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

The methanol extract of *Ceiba pentandra* reverses monosodium glutamate-induced cardiometabolic syndrome in rats via the regulation of dyslipidemia, inflammation, oxidative stress, and insulin sensitization

Adeline K. Wuyt, Elvine P. Nguelefack-Mbuyo, Christian K. Fofié, Télesphore B. Nguelefack *

Research Unit of Animal Physiology and Phytopharmacology, Faculty of Sciences, University of Dschang, Dschang, Cameroon

ARTICLE INFO

Keywords:
Cardiometabolic syndrome
Ceiba pentandra
Cytokines
Insulin sensitivity
Obesity
Oxidative stress

ABSTRACT

The antidiabetic effects of the methanol extract of the stem bark of *Ceiba pentandra* (Cp) have been demonstrated in various experimental models. Besides, this extract is rich in 8-formyl-7-hydroxy-5-isopropyl-2-methoxy-3-methyl-1,4-naphthaquinone, 2,4,6-Trimethoxyphenol and vavain. However, it remains unknown whether Cp can mitigate cardiometabolic syndrome (CMS). The present study assessed the curative properties of Cp against Monosodium Glutamate (MSG)-induced CMS in rats. Male neonate Wistar rats were intraperitoneally administered with MSG (4 mg/g/day) during the first 5 days of life (postnatal days 2–6). They were kept under standard breeding conditions up to 5 months of age for the development of CMS. Diseased animals were then orally treated with atorvastatin (80 mg/kg/d) or Cp (75 and 150 mg/kg/day) for 28 days during which food intake, body mass, blood pressure, heart rate, glucose, and insulin tolerance were monitored. Plasma and tissues were collected on day 29th to assess the lipid profile, oxidative stress, and inflammatory parameters. The histomorphology of the adipose tissue was also evaluated. Cp significantly ($p < 0.001$) reduced the obesogenic and lipid profiles, adipocyte size, blood pressure, and oxidative and inflammatory status in MSG-treated rats. Cp also ameliorated glucose ($p < 0.05$) and insulin sensitivities ($p < 0.001$) hence, reducing animals' cardiometabolic risk score ($p < 0.001$). The curative effect of Cp on cardiometabolic syndrome is related to its capacity to reduce oxidative stress, inflammation, dyslipidemia, and increase insulin sensitivity. These results demonstrate the potential of Cp as a good candidate for alternative treatment of CMS.

1. Introduction

Cardiometabolic syndrome (CMS) is a worldwide health issue combining several interrelated risk factors that upsurge the

Abbreviations: Cp, Ceiba pentandra; CMS, Cardiometabolic syndrome; MSG, Monosodium glutamate; OGTT, Oral glucose tolerance test; ITT, Insulin tolerance test.

* Corresponding author.
E-mail addresses: adeline.wuyt@yahoo.fr (A.K. Wuyt), mbuyopamielvine@gmail.com (E.P. Nguelefack-Mbuyo), christian.fofie@gmail.com (C.K. Fofié), telesphore.nguelefack@univ-dschang.org, nguelefack@yahoo.fr (T.B. Nguelefack).

https://doi.org/10.1016/j.heliyon.2023.e13689
Received 29 August 2022; Received in revised form 28 January 2023; Accepted 7 February 2023
Available online 11 February 2023

development of chronic non-communicable diseases [1–3]. The most recognized clinical risk factors that characterized the CMS include abdominal obesity, insulin resistance, hypertriglyceridemia, low HDL-cholesterol levels, high blood pressure, and impaired fasting glucose [4–6]. CMS is diagnosed in an individual having at least three of the five above-stated clinical risk factors [6]. Among these risk factors, obesity is the main driver and its ever-increasing prevalence escalates the number of patients with CMS worldwide [6,7]. Obesity-related non-communicable diseases account for over 5 million deaths globally each year, with over half occurring under the age of 70 [8].

Recent cumulative evidence has demonstrated that visceral obesity induces CMS through mechanisms including insulin resistance, low-grade inflammation, and oxidative stress [9,10]. Excess visceral adipose tissue contributes to free fatty acid accumulation in plasma [11,12], that impairs insulin-regulated glucose metabolism. Besides, excess lipid storage in adipocytes leads to a pro-inflammatory state with subsequent release of pro-inflammatory cytokines and enhanced production of reactive oxygen species (ROS) [9,12,13]. Concordantly, oxidative stress reflected by an increased level of oxidative markers such as malondialdehyde (MDA), isoprostane, and a reduced amount of antioxidant defense mechanisms namely catalase, superoxide dismutase (SOD), and reduced glutathione (GSH) has been observed in obese patients [13].

Therefore, it is obvious that CMS is a complex health condition that gathers an incredible number of intricate pathways. This requests the usage of several drugs to effectively target all associated dysfunctions. Multitherapy medicine however, exposes patients to a large number of adverse effects [14–16]. Thus, it is essential to develop more effective and less expensive alternative therapies for better management of the CMS. One way to achieve this goal would be the use of plants, as they contain many bioactive principles that are likely to target concomitantly, several risk factors that characterize CMS.

Ceiba pentandra is a well-known Cameroonian medicinal plant that belongs to the Bombacaceae family. The stem bark extract of this plant is widely used traditionally by Cameroonian populations as a diuretic and to treat many health conditions, including diabetes, hypertension, dizziness, headaches, constipation, and fever [17]. Our previous results on the phytochemical analysis of the methanol extract of *Ceiba pentandra* revealed the presence of polyphenol and flavonoids including 8-(Formyloxy)-8a-hydroxy-4a-methyldecahydro-2-naphthalenecarboxylic acid, 2,4,6-Trimethoxyphenol, and vavain [18].

Several experimental studies have evidenced the pharmacological effects of *Ceiba pentandra* on different diabetes models. Indeed, the aqueous and methanol stem bark extracts of this plant exhibited interesting in vitro and in vivo antioxidant activities, improved glucose tolerance, insulin sensitivity, and lipid profile, with the methanol extract being the most active [18–22]. These promising results prompted us to hypothesize that the methanol extract of *Ceiba pentandra* (Cp) could be effective in the management of CMS. The present study was, therefore, undertaken to assess the curative activity of Cp on MSG-obesity induced CMS in Wistar rats.

2. Materials and methods

2.1. Chemical reagents and drugs

D-glucose, Dimethylsulfoxide (DMSO), hydrochloric acid, Sodium hydroxide, bovine serum albumin, and sodium chloride were purchased from Carl-Roth (Kalshur, Germany). Epinephrine, L-Glutamic acid Monosodium salt hydrate, hexadecyltrimethylammonium bromide, sodium azide, *O*-dianisidin Thiobarbituric acid, Trichloro-acetic acid, and paraformaldehyde were purchased from Sigma-Aldrich Chemical Co (Taufkirchen, Germany). Interleukin-1 (IL-1β) and tumor necrosis factor-alpha (TNF-α) kits were purchased for R&D Systems while sodium thiopental, atorvastatin tablet, and Insulin (Actrapid, Novo Nordisk) were purchased from a local pharmacy (Dschang, Cameroon). All chemical reagents used in this study were of analytical grade.

2.2. Plant collection and extraction

The trunk bark of *Ceiba pentandra* (CP) was collected in November 2019, in Yaoundé, Central Region, Cameroon. The plant was authenticated by Mr. Nana Victor at the National Herbarium by comparison with an existing voucher specimen number HNC 43623. The shade dried stem bark was ground and 200 g of the obtained fine powder was macerated in 1 L methanol for 48 h. The macerate was filtered using successively cotton and Whatman paper number 4. The obtained filtrate was concentrated using a rotary evaporator at 60 °C. At the end of this procedure, the residual methanol content of the extract was evaporated for 3 days at room temperature and 3.68 g of crude extract was collected and stored at 2 °C until use. This extract was dissolved in 4% DMSO before being orally administered to animals.

2.3. Experimental animals

Two-day male neonate Wistar rats weighing 4–7 g, were used in this study. They were from our animal facility (animal house of the Research Unit of Animal Physiology and Phytopharmacology of the University of Dschang). They were kept under standard conditions with a normal day/night light cycle and free access to tap water and standard laboratory chow. Bromatological analysis of the chow performed according to the AOAC (Association of Official Agricultural Chemists) method, and expressed as a percentage of the dry matter showed: 4.54 fat, 11.06 total protein, 7.56 crude fiber, 87.58 organic matter, and 12.42 ash; corresponding to a total energy composition of 4051.04 kcal/kg dry food. Animal handling and the protocol were approved by the Departmental Review Committee following the international standard ethical guidelines for laboratory animal use and care as described by the law N° 10/609/EEC.

2.4. Experimental protocol

The general diagram of the experimental design is presented in Fig. 1. The cardiometabolic syndrome was induced by intraperitoneal administration of monosodium glutamate (MSG, 4 mg/g/day) for the diseased group, from postnatal day 2 to day 6 [23], while the naive group received through the same way, NaCl 9‰. After weaning on postnatal day 21, the rats were housed in individual polypropylene cages until 5 months of age. They were further assigned into five groups of 7 animals each and treated as follows: naive group (receiving distilled water), control (diseased) group (receiving 4% DMSO, 10 mL/kg), reference group (receiving atorvastatin 80 mg/kg [24]), and 2 extract-treated groups receiving *Ceiba pentandra* stem bark methanol extract at respective doses of 75 and 150 mg/kg.

Animals in each group received their treatment as a single oral bolus once a day, for 28 consecutive days during which body mass and food consumption were recorded. Blood pressure and heart rate measurements, oral glucose tolerance test (OGTT), and insulin tolerance test (ITT) were performed before the beginning of the treatment administration, 2 weeks after, and at the end of the 28 days experimental period. The non-invasive tail-cuff method was used for blood pressure and heart rate recording using the IITC Life Science MRBP tail-cuff blood pressure system.

2.5. Oral glucose and insulin tolerance tests

For the oral glucose tolerance test (OGTT), animals were fasted for 14 h and baseline blood glucose was measured. Each animal was then orally administered with 3 g/kg of glucose, and blood glucose was again measured 30, 60, 90, and 120 min after glucose administration. The next day, the insulin tolerance test was performed. After 6 h of fasting, the animals' baseline blood glucose levels were measured, followed by subcutaneous injection of insulin (1 IU/kg). Their blood glucose levels were determined at 30, 60, 90, and 120 min after injection. Blood glucose measurement was performed using a glucometer (PRODIGY Diabetes Care, USA). The following indexes were used to assess insulin sensitivity:

$$TyG = Ln[\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)}/2]$$ [25,26].

$$KITT = (0.693/\ t1/2) \times 100$$ with t1/2 representing the half-life of plasma glucose decrease [27–29]

2.6. Evaluation of the lipid and obesogenic profiles

The day following the ITT test, animals were weighed, and their naso-anal length was measured under thiopental sodium anesthesia (50 mg/kg, i. p). Blood was collected by abdominal artery catheterization in heparinized tubes. Samples were centrifuged at 3500 rpm for 10 min and the plasma obtained was used to assess lipid parameters: triglycerides (TG), total cholesterol (TC), and HDL-cholesterol (HDL-C). These parameters were determined using commercial kits (from Dutch Diagnostics, Netherlands) and the tests were performed according to the manufacturer's instructions. Additionally, LDL-cholesterol (LDL-C) level was obtained by calculation using the formula described by Friedewald et al. (1972) [30]:

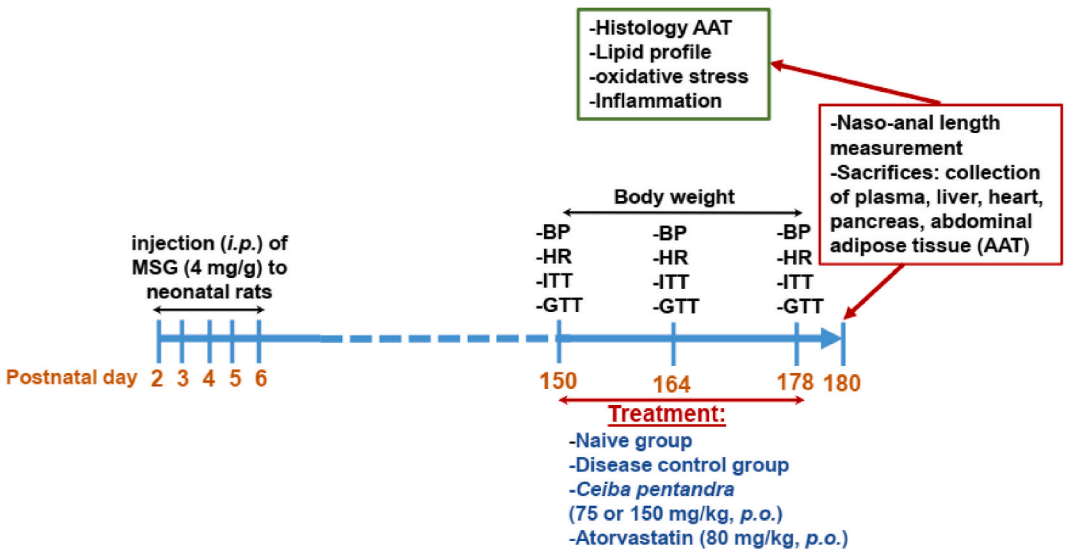


Fig. 1. Flow chart of the study. Vertical bars indicate the intervention points and the parameters measured at each point. MSG: monosodium glutamate, BW: Body weight, BP: blood pressure, HR: heart rate, ITT: insulin tolerance test, GTT: oral glucose tolerance test.

LDL-C = TC – HDL-C – (TG/5)

The pancreas, abdominal adipose tissue, heart, liver, and gastrocnemius muscle were collected, weighed, and homogenized in 0.1 M ice-cold Tris-HCl buffer, pH 7.4. Homogenates were aliquoted and stored at −20°C for subsequent evaluation of oxidative stress and inflammatory parameters. The retroperitoneal portion of the abdominal adipose tissue was fixed in 4% buffered paraformaldehyde (pH = 7.4) for histological sections. The Lee [31] and adiposity indexes [32] were calculated using the following formulas:

Lee Index (LI) = [(Cube root of weight (g)/Nasal length (mm)] × 1000

Adiposity index (AI) = [(visceral adipose tissue (g))/body weight (g)] ×100

2.7. Assessment of oxidative parameters

Malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD) were determined as previously described [18].

2.8. Evaluation of inflammatory parameters

In adipose tissue and pancreas homogenates, TNF-α and IL-1β levels were assessed by ELISA, using commercial kits (from R&D Systems, USA) and performed according to the manufacturer's instructions. Additionally, tissue NO level was quantified by the reaction of Griess whose principle is based on the diazotization of NO^{2-} ions with sulfanilamide couple to naphthyethylene diamine (NED) in acid milieu as described by Ref. [18]. Briefly, to 250 μl of the tissue sample was added 250 μl of 1% sulfaniladide prepared in 5% orthophosphoric acid. The mixture was incubated for 5 min in the dark, then 250 μl of 0.1% naphthyl ethylenediamine was added, and then all incubated in the dark for additional 5 min. The optical density was read at 530 nm. The quantity of nitric oxide was calculated from the following sodium nitrite's ($NaNO_{2)}$ standard curve.

2.9. Estimation of cardiometabolic risk

The cardiometabolic risk score was estimated using a formula adapted from the estimate proposed by D'Agostino et al. (2008) [33] and Soldatovic et al. (2016) [34] in which the adiposity index [32] and 1/KIIT [27–29] were introduced as a method of assessing abdominal obesity and as an assessment of insulin resistance respectively:

CMRS = (TG × SBP × DBP × FPG × AI × IR × Age) /1000xHDL-C

Where CMRS: Cardiometabolic Risk Score (arbitrary unit), TG: Triglycerides (g/l), SBP: systolic blood pressure (cmHg), DBP: diastolic blood pressure (cmHg), FPG: fasting plasma glucose (g/l), AI: Adiposity index (arbitrary unit), IR: insulin resistance (estimated by ITT: insulin tolerance test, expressed as 1/KITT value calculated as follows: KITT = (0.693/t1/2) × 100; (t1/2 = half-life of plasma glucose decrease), HDL-C: high-density lipoprotein cholesterol (g/l), age (months).

2.10. Histological analysis of the adipose tissue

Paraformaldehyde-fixed adipose tissue was embedded in paraffin and sectioned into 5 μm-thick slices. The slices were then stained with hematoxylin-eosin (HE), examined under a light microscope (from Swift), and photographed. Each microphotography (×100 magnification) was divided into four quadrants. Ten cells were randomly selected from each quadrant and their surface areas were calculated using ImageJ software. The average surface of adipocytes from each animal was calculated and used as one subject.

2.11. Statistical analysis

Data obtained from this methodology were expressed as mean ± SEM. One-way followed by Dunnet's post-test was used for Adiposity index, Lee index, adipocytes surface, lipid profile, Areas under the curves (AUC), 1/K ITT value, TyG index, cardiometabolic risk score, and redox and inflammatory status analyses. Two-way ANOVA followed by Bonferroni post-test was used to analyze body weight variation, food intake, OGTT, ITT, and hemodynamic parameters. Analyses were performed using GraphPad Prism 8.2 software. P value less than 0.05 was considered statistically significant.

3. Results

3.1. Effects of Ceiba pentandra administration on the obesogenic profile

Fig. 2 shows the activity of *Ceiba pentandra* methanol extract (Cp) on some obesogenic parameters of MSG-treated animals. The results in Fig. 2a show that MSG did not induce a significant variation in body weight compared to the Naïve group. However, atorvastatin and Cp (75 mg/kg and 150 mg/kg) significantly ($p < 0.05$, $p < 0.01$, and $p < 0.001$) reduced by 17.78–34.28 g the MSG-

treated animals' body weight from the 16th day till the end of the treatment period. The dose of 75 mg/kg showed better activity than 150 mg/kg. The results in Fig. 2b show that there was no significant variation in food intake in all groups. Fig. 2c shows that MSG significantly ($p < 0.05$) increased the Lee index of the animals compared to the naive group, and Cp administration did not significantly affect this parameter. However, MSG treatment significantly reduced the naso-anal length (Fig. 2d). MSG administration also induced a significant ($p < 0.001$) visceral fat accumulation marked by a 176.21% increase in adiposity index. Atorvastatin and both doses of Cp showed similar efficiency, reducing this visceral adiposity index by 29% ($p < 0.001$) (Fig. 2e).

3.2. *Effects of Ceiba pentandra administration on adipocyte morphology*

The effect of CP on adipocyte size is illustrated in Fig. 3. The analysis of adipocyte sections shows that MSG induced a significant (p

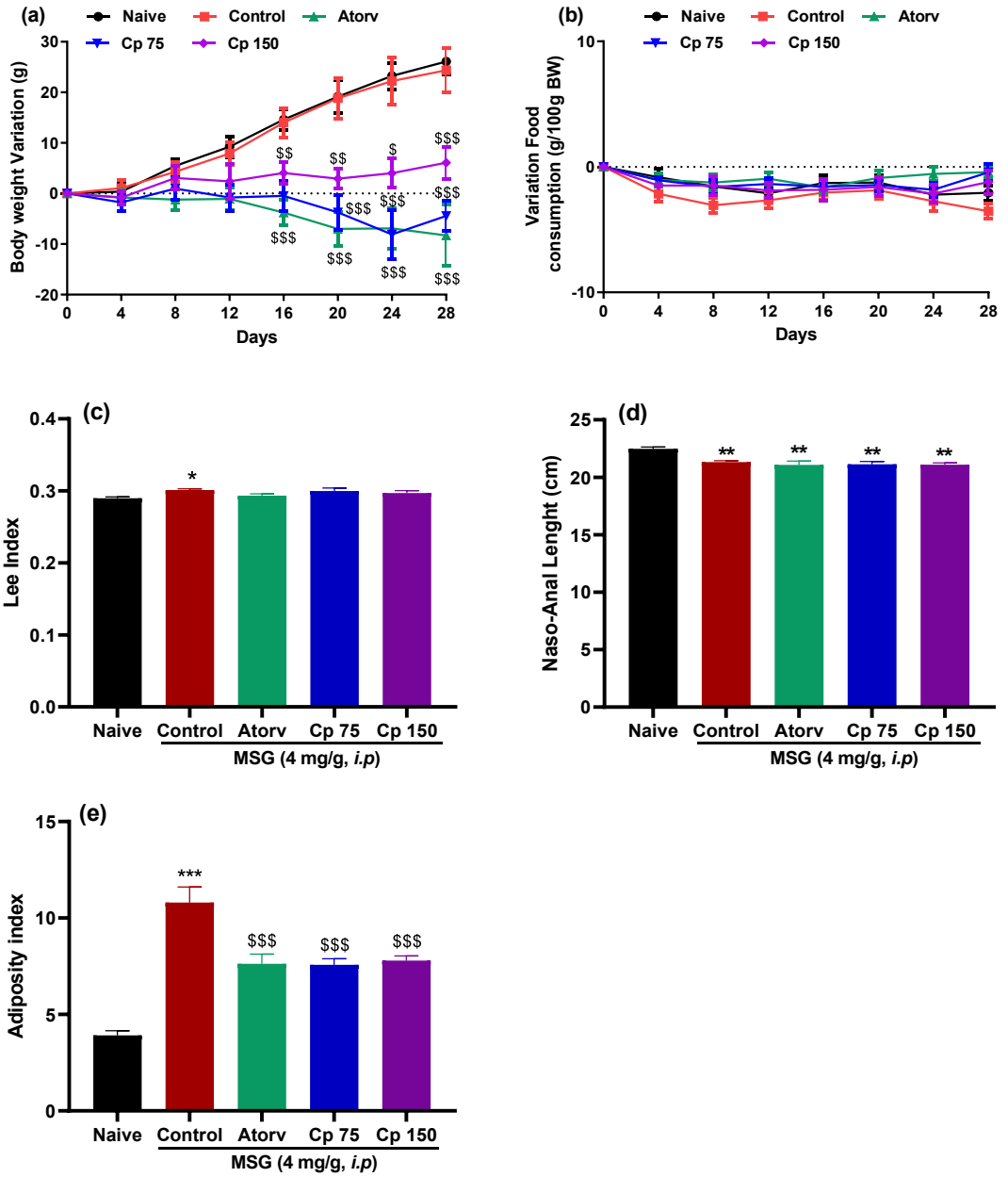


Fig. 2. Oral repeated administration of *Ceiba pentandra* methanol extract reduced body mass (a), Lee index (c), and adiposity index (e) but did not affect food intake (b), and naso-anal length (d), in MSG-treated animals. N = 7. *$p < 0.05$, and ***$p < 0.001$ significant differences as compared to naive group; $^{\$}p < 0.05$, $^{\$\$}p < 0.01$ and $^{\$\$\$}p < 0.001$ significant difference as compared to the diseased (control) group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg.

< 0.001) increase in the surface area (hypertrophy) of adipocytes compared to the naive group. Treatment with both doses of CP and atorvastatin induced significantly ($p < 0.01$) and similar reduction of this hypertrophy by about 60.24% (Fig. 3 a – f).

3.3. Effects of Ceiba pentandra administration on lipid profile

Fig. 4 shows that early administration of MSG altered the animals' lipid profile. It can be observed that total cholesterol (Fig. 4a), triglycerides (Fig. 4b), and LDL-cholesterol (Fig. 4c) levels were significantly ($p < 0.01$ and $p < 0.001$) increased while HDL-cholesterol (Fig. 4d) was significantly ($p < 0.001$) reduced in disease control rats when compared to those in the naïve group. The LDL level has almost tripled while that of HDL-C has decreased threefold. The administration of Cp at both doses improved the animals' lipid profile with up to 18.03% ($p < 0.01$) reduction in total cholesterol level, 29.03% ($p < 0.05$) in triglycerides, and 37.68% ($p < 0.001$) in LDL-cholesterol levels, respectively. The plant extract reduced total cholesterol and triglycerides levels to nearly the normal values when compared with the naïve group. Moreover, atorvastatin significantly reduced by 12.63% the total cholesterol level ($p < 0.05$) and 29.82% of triglycerides levels ($p < 0.01$). Nevertheless, Cp, similar to atorvastatin, failed to restore the normal HDL-cholesterol levels.

3.4. Effects of Ceiba pentandra on glucose tolerance in MSG-treated animals

Before the administration of atorvastatin or Cp extract, all animals except those of the naïve group were treated with MSG only. As shown in Fig. 5a–b, MSG altered glucose tolerance. Following atorvastatin or Cp administration, glucose tolerance was time-dependently improved while this parameter remained impaired in the diseased-control group (Fig. 5c, d, 5e, and 5f). In fact, after 2 weeks of treatment, only the 150 mg/kg dose of Cp significantly ($p < 0.05$) improved this glucose dysregulation (Fig. 5c–d). After 4 weeks of treatment, atorvastatin and CP at both doses significantly ($p < 0.05$) improved the glucose tolerance, reducing by 23.57%, 25.26%, and 21.79% of the OGTT's area under the curve respectively (Fig. 5e–f).

3.5. Effects of Ceiba pentandra on insulin tolerance in MSG-treated animals

Fig. 6 depicts the effect of *C. pentandra* stem bark methanol extract on insulin sensitivity in rats previously treated with MSG. Similar to the results obtained with the OGTT, animals from the diseased control were insulin intolerant throughout the observation period (Fig. 6 a, c, and e). This is evidenced by the significant ($p < 0.001$) increase in AUC (Fig. 6b). After 2 weeks of treatment with Cp or atorvastatin, an improvement in insulin sensitivity was observed. But this improvement was only significant ($p < 0.05$) in rats treated with the plant extract at the dose of 75 mg/kg (Fig. 6c–d). At the end of the experimental period, insulin sensitivity of animals treated with either atorvastatin or both doses of the plant extract was similar to that of the naive group (Fig. 6e–f).

To better characterize the insulin sensitivity of animals, we calculated the TyG index and the 1/KITT by using the fasting glucose, triglyceride levels, and ITT, respectively. At the end of the experiment (4 weeks), animals from the atorvastatin or Cp groups exhibited a significant reduction of up to 29% ($p < 0.001$) in 1/KITT value and 4.25% ($p < 0.001$) in TyG index as compared to the diseased

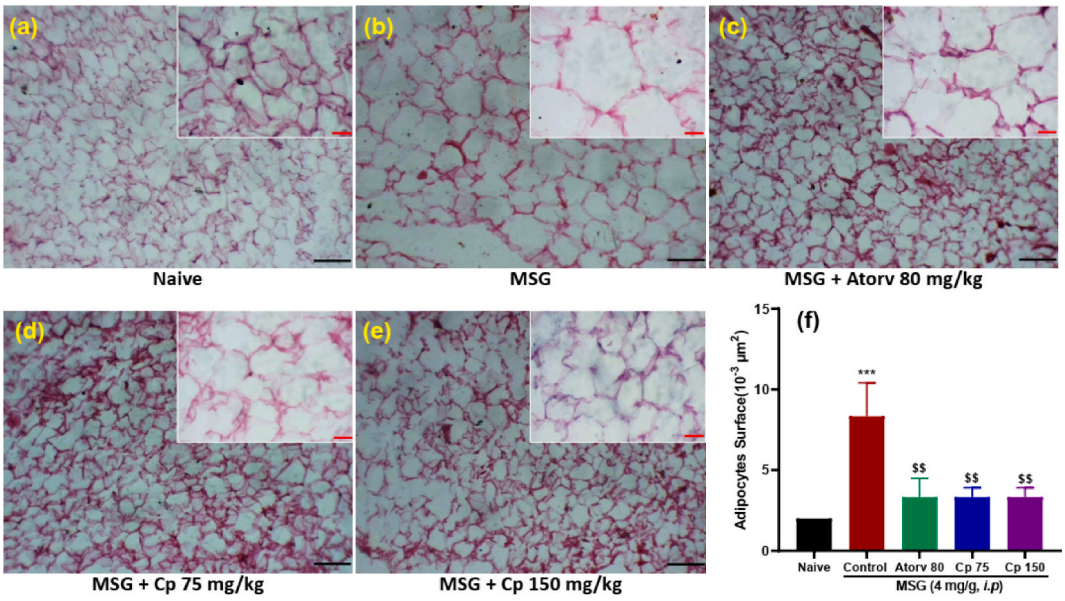


Fig. 3. *Ceiba pentandra* oral administration reduced the adipocyte hypertrophy induced by the MSG injection. N = 3. ***$p < 0.001$ significant difference as compared to naive group; $^{\$\$}p < 0.01$ significant difference as compared to diseased control group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg. Black bars = 27.2 µm, Red bars = 6.8 µm. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

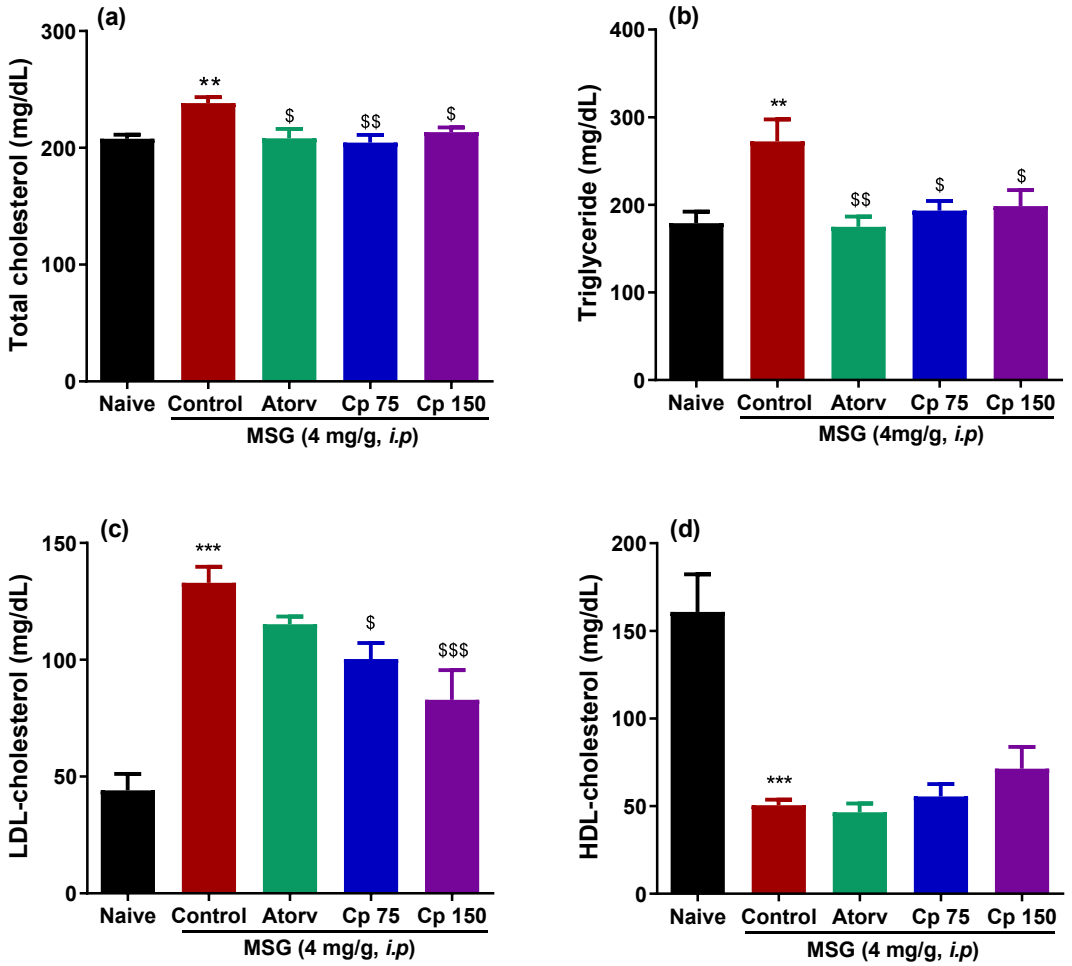


Fig. 4. Oral administration of the methanol extract of *Ceiba pentandra* reversed MSG-induced dyslipidemia in rats. N = 7. **p < 0.01, ***p < 0.001 significant difference as compared to the naive group; $p < 0.05, $$p < 0.01, $$$p < 0.001 significant difference as compared to the diseased (control) group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg given orally.

control group (Fig. 6g and 6h).

3.6. Effects of Ceiba pentandra on the hemodynamic parameters of animals treated with MSG

When administered to neonates, MSG induced a progressive rise in the systolic and diastolic blood pressure of animals as they grow. As observed in Fig. 7a–b blood pressure was significantly ($p < 0.001$) elevated in all groups as compared to the naïve group before the administration of any treatment. Oral administration of atorvastatin or Cp at both doses reversed ($p < 0.001$) the effect of MSG with a maximal effect of 7.4% on the systolic and 15.63% on diastolic blood pressure, observed in the group treated with Cp at the dose of 150 mg/kg. During the treatment period, blood pressure still increased in a time-dependent manner in the diseased control group.

The heart rate of MSG-treated animals remained significantly ($p < 0.05$) elevated throughout the experiment. Atorvastatin and Cp at the dose of 75 mg/kg significantly ($p < 0.01$) decreased the heart rate by 25.39% and 27.66% from the second week after the beginning of the treatment. Only the dose of 150 mg/kg of the extract at the 4th week elicited a significant ($p < 0.01$) decrease (28.51%) in heart rate (Fig. 7c).

3.7. Effects of Ceiba pentandra on some redox parameters and NO level in MSG-treated animals

Table 1 illustrates the effect of Cp on some oxidative stress parameters namely: GSH, SOD, and MDA. Early injection of MSG to neonate rats induced a significant decrease in GSH levels in the liver ($p < 0.05$) and adipose tissue ($p < 0.001$). When Cp was administered to these 5-month-old rats, the 75 mg/kg dose induced a significant increase of 33.07% in GSH in the heart ($p < 0.05$) and 27.99% in muscle ($p < 0.01$). The 150 mg/kg dose significantly elevated the GSH level in the liver (38.56%) adipose tissue (61.26%),

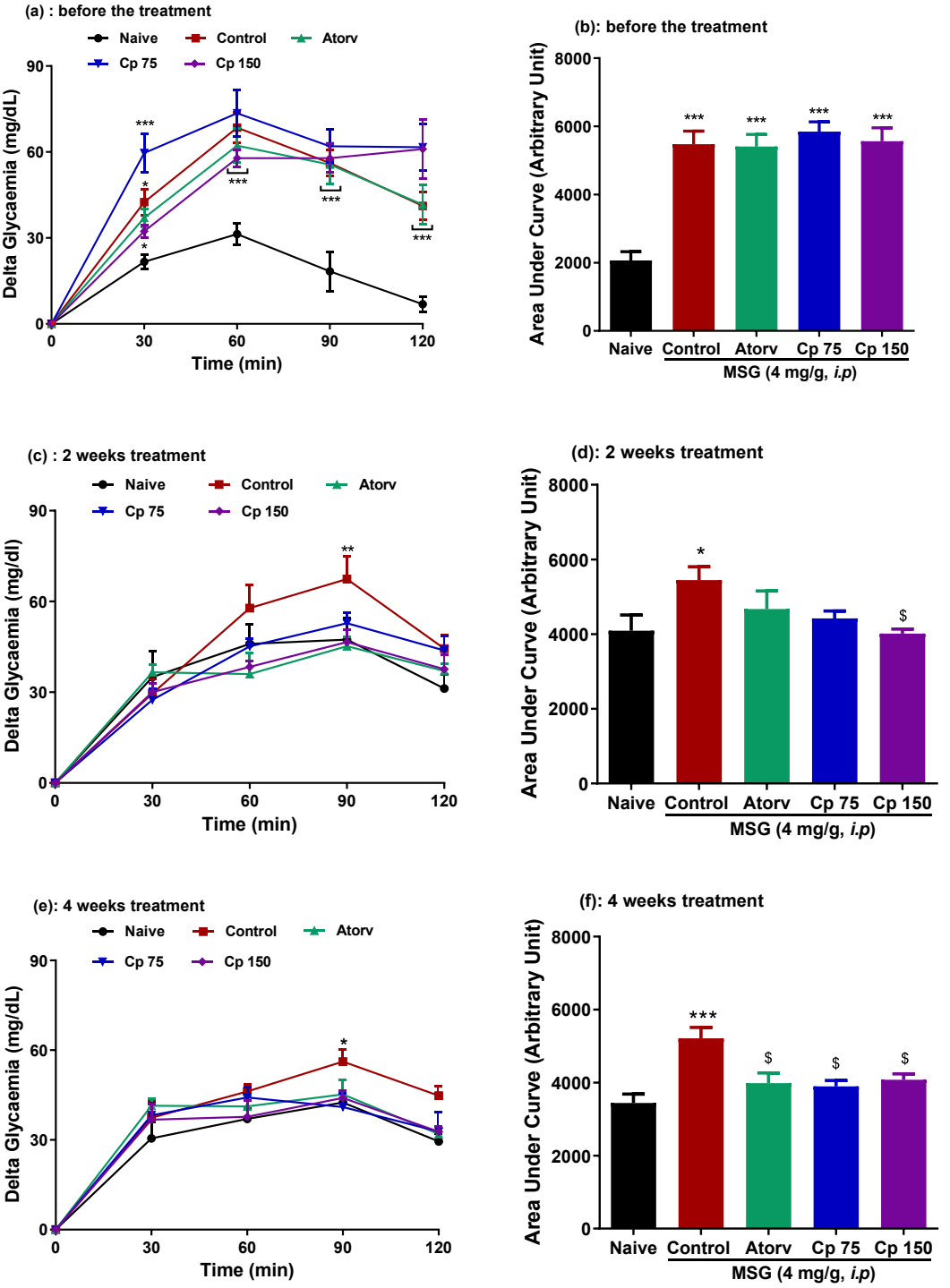
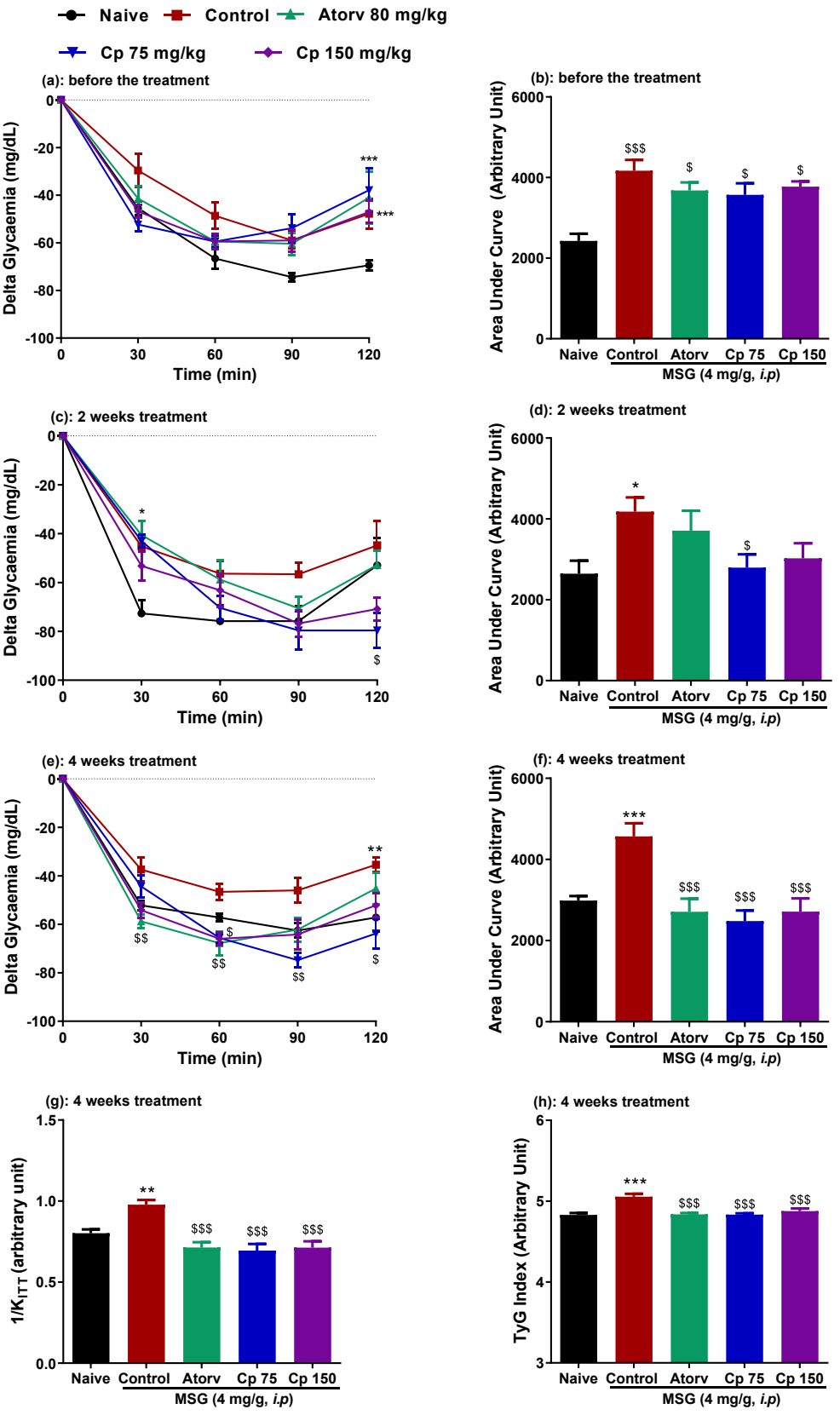


Fig. 5. Repeated administration of *Ceiba pentandra* extract given orally improved glucose tolerance (OGTT) in MSG-treated animals. N = 7. **p < 0.001, ***p < 0.001 significant difference as compared to the Naive group; $p < 0.05 significant difference as compared to the diseased group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg given orally.

and heart (37.9%). Atorvastatin significantly increased GSH levels in the liver and heart by 36.45% and 29.9%, respectively.

Regarding the SOD level, MSG treatment only significantly decreased its activity in the liver ($p < 0.05$) and the adipose tissue ($p < 0.001$). None of the drugs administered reversed this dysregulation. However, Cp at the dose of 150 mg/kg induced a significant ($p <$



(caption on next page)

Fig. 6. Repeated administration of *Ceiba pentandra* methanol extract improved insulin sensitivity in MSG-treated animals. N = 7. *p < 0.05, **p < 0.01, ***p < 0.001 significant differences as compared to the Naive group; $p < 0.05, $$p < 0.01, $$$p < 0.001 significant differences as compared to the diseased group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg given orally.

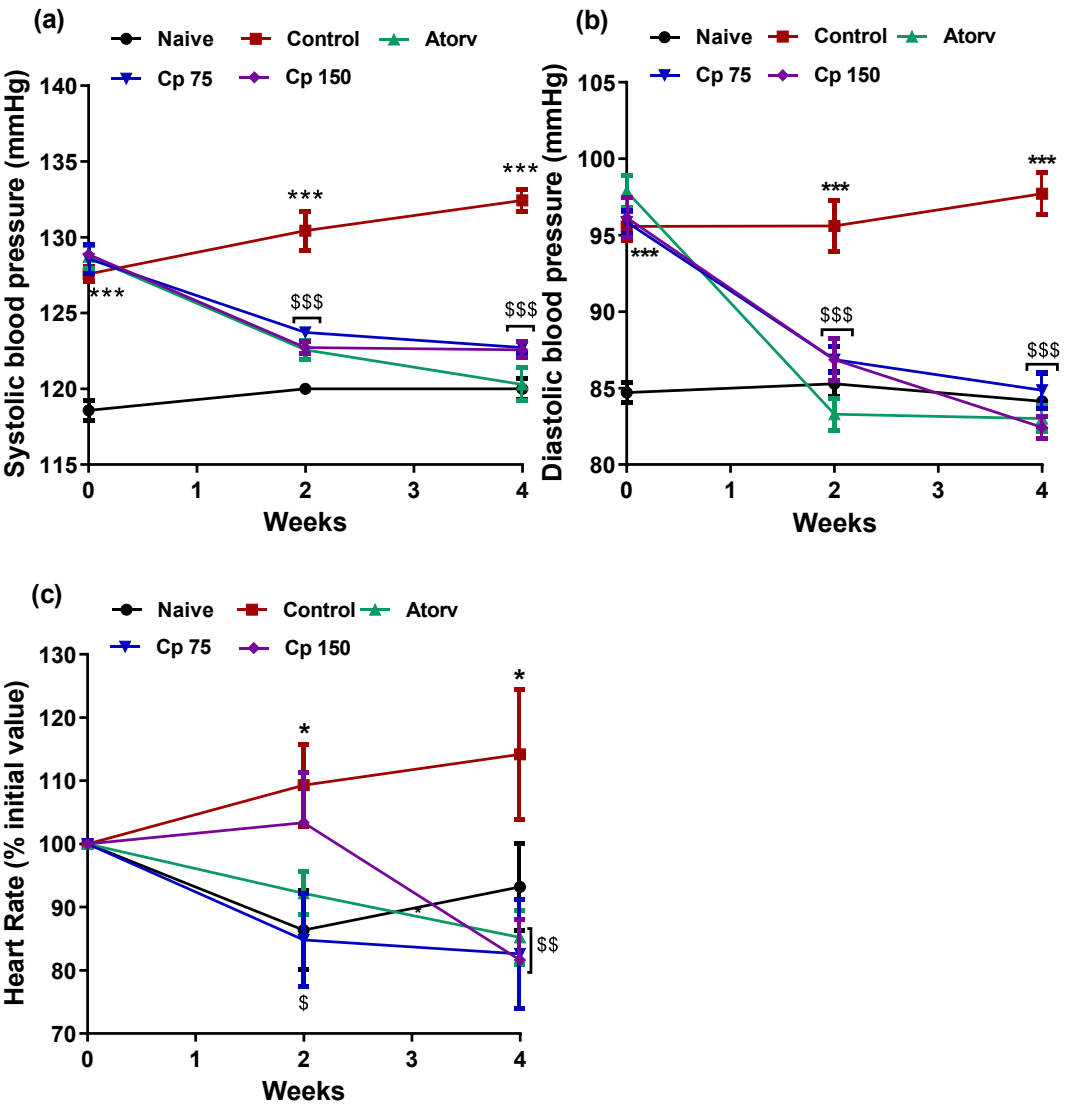


Fig. 7. *Ceiba pentandra* methanol extract reversed the elevated systolic (a) and diastolic (b) blood pressure and heart rate (HR, c) in MSG-treated rats. N = 7. *p < 0.05, ***p < 0.001 significant difference compared to the naive group; $p < 0.05, $$p < 0.01, $$$p < 0.001 significant differences compared to the diseased control group. Naïve = NaCl + distilled water, Control = diseased group, MSG + DMSO 4%, Atorv 80 = reference group - MSG + Atorvastatin 80 mg/kg, CP 75 = treated group 1, MSG+75 mg/kg CP and CP 150 = treated group 2, MSG+150 mg/kg CP.

0.01) increase (68.28%) in SOD activity in the pancreas.

Concerning MDA, MSG administration increased the level of lipid peroxidation in the liver ($p < 0.01$) and the adipose tissue ($p < 0.001$). The extracts were not able to correct the dysregulation in the liver but in adipocytes, both doses of Cp significantly ($p < 0.05$) inhibited the lipid peroxidation by about 40%. Furthermore, Cp significantly ($p < 0.05$) reduced the MDA formation in the heart (47.01%) and pancreas (58.82%). In adipose tissue, atorvastatin also significantly ($p < 0.01$) reduced MDA levels by 53.88% compared to the diseased control group.

Table 1
Ceiba pentandra mitigate oxidative stress and nitric oxide in tissues from MSG-treated animals.

Organ	Treatment	GSH (mmol/g protein)	SOD (mmol/g protein)	MDA (μmol/g tissue)	NO (μmol/g tissue)
Pancreas	Naïve	0.0451 ± 0.004	0.0018 ± 0.000	0.0353 ± 0.003	0.334 ± 0.074
	Control	0.0445 ± 0.006	0.0013 ± 0.000	0.0525 ± 0.002	0.930 ± 0.060***
	Atorv	0.0619 ± 0.004	0.0009 ± 0.000	0.0347 ± 0.005	0.480 ± 0.100$$$
	Cp 75	0.0702 ± 0.014	0.0014 ± 0.000	0.0349 ± 0.005	0.325 ± 0.051$$$
	Cp 150	0.0545 ± 0.069	0.0043 ± 0.000$$	0.0216 ± 0.005$	0.103 ± 0.027$$$
Liver	Naïve	0.276 ± 0.023	0.0049 ± 0.000	0.0138 ± 0.004	0.281 ± 0.041
	Control	0.178 ± 0.003*	0.0025 ± 0.000**	0.0475 ± 0.006*	0.339 ± 0.034
	Atorv	0.281 ± 0.025$	0.0042 ± 0.000$	0.0544 ± 0.005	0.313 ± 0.039
	Cp 75	0.256 ± 0.017	0.0033 ± 0.000	0.0546 ± 0.005	0.290 ± 0.027
	Cp 150	0.290 ± 0.023$	0.0035 ± 0.000	0.0331 ± 0.011	0.298 ± 0.028
Adipose Tissue	Naïve	0.0246 ± 0.001	0.0262 ± 0.003	0.0039 ± 0.000	0.0203 ± 0.002
	Control	0.0066 ± 0.000***	0.0011 ± 0.002***	0.0062 ± 0.000*	0.0482 ± 0.01
	Atorv	0.0114 ± 0.003	0.0008 ± 0.001	0.0028 ± 0.000$$	0.0401 ± 0.020
	Cp 75	0.0129 ± 0.001	0.0017 ± 0.000	0.0037 ± 0.000$	0.0717 ± 0.002
	Cp 150	0.0171 ± 0.004$	0.0019 ± 0.000	0.0037 ± 0.000$	0.0989 ± 0.122
Heart	Naïve	0.111 ± 0.011	0.0044 ± 0.002	0.0241 ± 0.002	0.0139 ± 0.007
	Control	0.0886 ± 0.002	0.0012 ± 0.000	0.0242 ± 0.002	0.0104 ± 0.010
	Atorv	0.1265 ± 0.002$	0.0087 ± 0.002	0.0137 ± 0.002	0.0098 ± 0.007
	Cp 75	0.1325 ± 0.014$	0.0065 ± 0.001	0.0128 ± 0.001$	0.0257 ± 0.019
	Cp 150	0.1428 ± 0.011$$	0.0075 ± 0.003	0.0192 ± 0.002	0.1161 ± 0.019$$$
Muscle	Naïve	0.0866 ± 0.005	0.0167 ± 0.007	0.0159 ± 0.003	0.0853 ± 0.004
	Control	0.0969 ± 0.005	0.0012 ± 0.002	0.0265 ± 0.007	0.0330 ± 0.009
	Atorv	0.1335 ± 0.008$$	0.0018 ± 0.001	0.0243 ± 0.005	0.0741 ± 0.007
	Cp 75	0.1346 ± 0.004$$	0.0110 ± 0.002	0.0301 ± 0.002	0.1035 ± 0.022
	Cp 150	0.0779 ± 0.006	0.0111 ± 0.002	0.0150 ± 0.002	0.1062 ± 0.040

N = 7. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ significant differences as compared to the naive group; $^{\$}p < 0.05$, $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$ significant differences as compared to the diseased control group. Naïve = NaCl + distilled water, Control = diseased group, MSG + DMSO 4%, Atorv = reference group-MSG + Atorvastatin 80 mg/kg, CP 75 = treated group1, MSG+75 mg/kg CP and CP 150 = treated group2, MSG+150 mg/kg CP.

3.8. Effects of Ceiba pentandra on the inflammatory status in tissues of MSG-treated rats

As shown in Fig. 8, the TNF-α level was significantly increased in the pancreas ($p < 0.05$) and adipose tissue ($p < 0.01$) of control rats compared to the naïve group (Fig. 8a and b). Following treatment with atorvastatin or Cp the parameter only significantly ($p < 0.05$, $p < 0.01$) reduced in adipose tissue, with a maximal effect of 43.47% obtained with the dose of 150 mg/kg of Cp.

Concerning IL-1β, MSG administration significantly ($p < 0.05$) increased the content by 29.68% in the pancreas while no change was observed in the adipose tissue (Fig. 8c and d). Atorvastatin and Cp at both doses induced a reduction of IL1-β in the pancreas but this reverse effect was significant ($p < 0.05$) only with Cp at 150 mg/kg. Treatment with extract instead tends to increase the IL-1β content in the adipose tissue as compared to both naïve and control animals (Fig. 8c and d).

Table 1 illustrates that MSG administration increased NO levels in the pancreas ($p < 0.001$) and decreased in the heart ($p < 0.01$). Cp in a dose-dependent manner and atorvastatin significantly $p < 0.001$ reversed this parameter in the pancreas. The maximal effect of 88.88% was observed with Cp at the dose of 150 mg/kg. In the heart, only Cp at 75 mg/kg significantly ($p < 0.001$) reversed the inhibitory effect of MSG on NO by 90.97%.

3.9. Effects of Ceiba pentandra on cardiometabolic risk in MSG-treated animals

Early administration of MSG to neonate rats resulted in a significant ($p < 0.001$) and drastic increase in the cardiometabolic risk score of animals as they became adults. Four weeks of treatment with Cp at both doses used and atorvastatin significantly ($p < 0.001$) reduced the score compared to the diseased control group. The maximal effect of 77.11% was obtained with CP at the dose of 150 mg/kg (Fig. 9).

4. Discussion

The present study was undertaken to assess the ability of *Ceiba pentandra* stem bark methanol extract to mitigate MSG-induced cardiometabolic syndrome (CMS). The popularity of MSG as a food additive is worldwide recognized and it is the most extensively consumed food additive [35]. It is incorporated in the composition of many processing food products and for daily house cooking dishes [35,36]. Many studies have reported the deleterious effects of MSG consumption including memory and hepatic dysfunctions, obesity, and insulin resistance [35,37]. Fouda et al. (2020) [38] recently observed the development of arterial hypertension in this model. Thus, the MSG model gathers all the characteristics of the CMS. Therefore, demonstrating its usefulness as a tool for the evaluation of different aspects of the CMS.

Concordantly, results obtained in this study showed that early administration of MSG to neonate rats induced a massive accumulation of abdominal fat, increase in adipocyte size, altered lipid profile (dyslipidemia), insulin resistance, and elevation in arterial

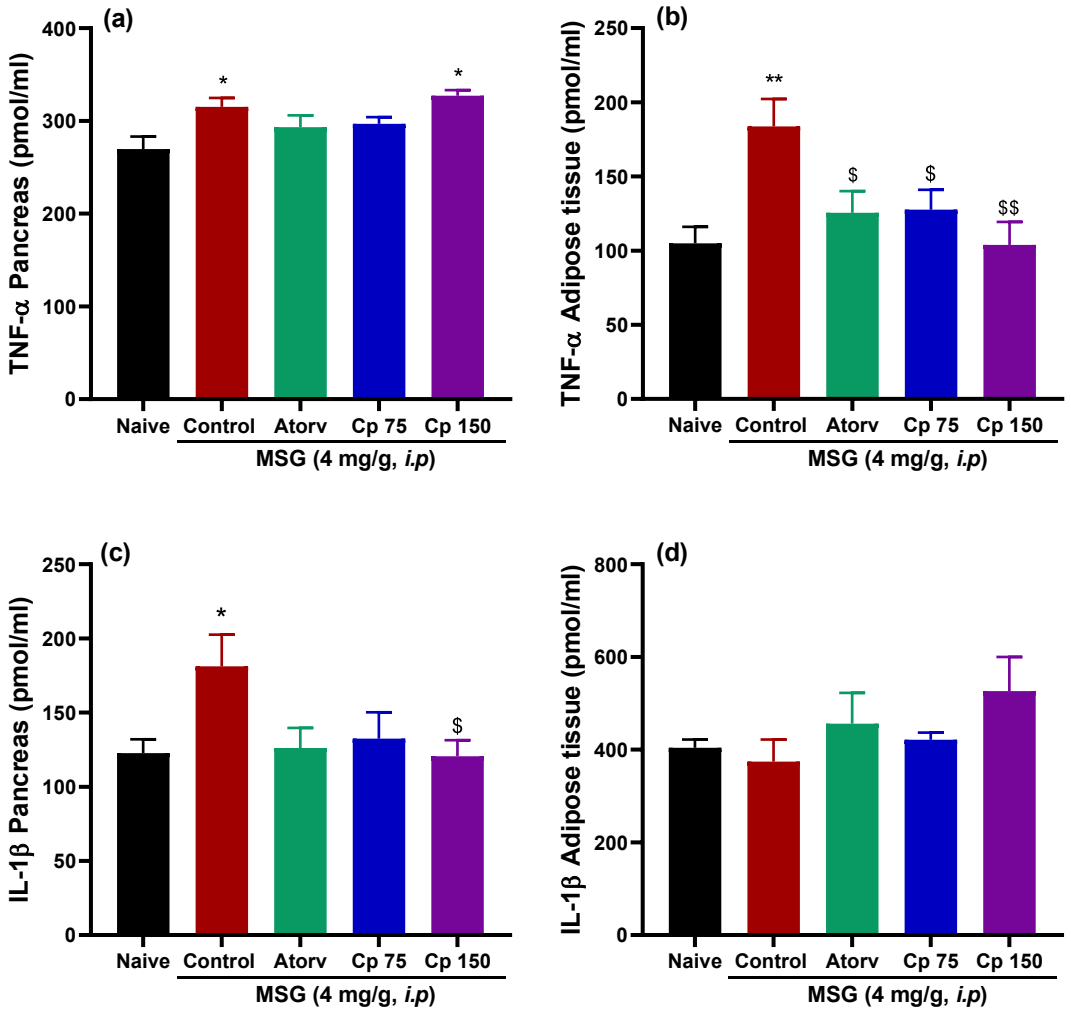


Fig. 8. Repeated oral administration of the methanol extract of *Ceiba pentandra* reduced the TNF-α level in the adipose tissue and the IL-1β content in the pancreas of MSG-treated rats. N = 7. *p < 0.05, **p < 0.01 significant differences as compared to the naive group; $p < 0.05, $$p < 0.01 significant differences as compared to the diseased control group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg.

hypertension. These observations align with many authors' findings [37–41] and reflect not only obesity but precisely a state of CMS. In fact, a drastic increase in cardiometabolic risk scores was observed in MSG-treated rats. Cp and atorvastatin as well, significantly reduced this score, suggesting their curative effects on the CMS.

To understand the mechanism underlining the pharmacological activity of the plant extract, we assessed its effect on the different parameters characterizing the CMS. Despite the drastic increase in adiposity index observed in this model, MSG did not induce a significant change in body mass and food intake but significantly increased the Lee index. In an attempt to understand this fact, we analyzed the naso-anal length. MSG significantly reduced the naso-anal distance. In fact, many reports have shown that administration of high doses of MSG to neonates causes injuries in the arcuate nuclei leading to a low growth hormone secretion that further leads to a growth delay and a reduced naso-anal length [42,43] despite a normal food intake [44]. The above results suggest that MSG-induced obesity is not related to an enhanced food intake and further advocate the non-alteration of the leptin signaling pathway in this model. Therefore, the development of obesity in this model might be rather a result of a positive energy balance.

Treatment with *C. pentandra* methanol extract (Cp) significantly reduced the animals 'body weight without altering food intake. These results suggest that the plant extract may possess slimming effects. Moreover, lipid profile was improved following Cp administration. The *anti*-lipidemic effect of Cp was demonstrated in a previous study [18]and it's similar to that exhibited by atorvastatin. The lipid-lowering effect of Cp might be at least responsible for the drop in the adiposity index, the reduction of abdominal fat accumulation, and the curtailment of adipocyte size. It is well known that dysregulation of insulin signaling can lead to hypertriglyceridemia and subsequent generalized dyslipidemia [45]. Conversely, dyslipidemia induces insulin resistance. Thus, the lipid-lowering effect of Cp can be a result or a starting point of insulin sensitization.

To verify if the insulin sensitization and lipid-lowering effect of Cp could interplay in the global biological properties of CP, we

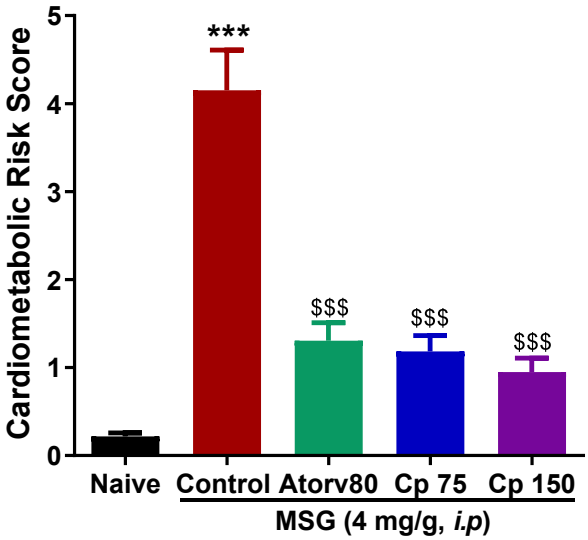


Fig. 9. Repeated oral administration of the methanol extract of *Ceiba pentandra* reduced the cardiometabolic risk score in MSG-treated animals. N = 7. ***p < 0.001 significant difference as compared to the Naive group; $$$p < 0.001 significant difference as compared to the diseased control group. Atorv = reference group - atorvastatin 80 mg/kg, Cp 75 and Cp 150 = *Ceiba pentandra* methanol extract at the doses of 75 and 150 mg/kg.

tested the insulin sensitivity using insulin tolerance, TyG index, and 1/KITT index. In this study, an impairment in glucose tolerance, and an insulin resistance state were noticed in rats that received only MSG. Insulin resistance was evidenced by a reduced insulin tolerance, an elevated TyG index, and an increased 1/KITT index. These parameters were all improved in animals orally administered with the plant extract and reflect the insulin-sensitizing activity of Cp. This finding corroborates the observations of Fofié et al. (2018) [20] on another model of insulin resistance. But whether Cp improves glucose homeostasis by acting at the central or peripheral level is still to be clarified.

Another mechanism involved in the metabolic dysregulation elicited by MSG is inflammation. Type 2 diabetes and obesity have been associated with moderate to severe inflammation in the pancreas and adipose tissue [46,47]. Early injection of MSG to neonate rats resulted in increased production of TNF-α in the pancreas and adipose tissue in adulthood. Besides, IL-1β production was increased in the pancreas but not in the adipose tissue while NO levels significantly increased in the pancreas and moderately in the adipose tissue. Taken together, these results show an inflammatory state in both pancreas and adipose tissue. It is well-known that TNF-α inhibits adipose tissue insulin sensitivity either by impairing insulin receptor signaling or by downregulating the glucose transporter type 4 (GLUT4) [48]. Treatment with Cp curbed these inflammatory states, suggesting that the anti-inflammatory effect of Cp may contribute to its insulin-sensitizing effect.

Oxidative stress appears as a cornerstone of almost all metabolic, cellular, and molecular dysfunctions. Redox imbalance was mostly observed in the liver and adipose tissue of MSG-treated rats as evidenced by a low GSH level, a diminished SOD activity, and an increased generation of MDA, the end-product of lipid peroxidation. The imbalance between prooxidant species and antioxidant defense mechanism elicited by MSG injection was reversed by the treatment with Cp. This result highlights once more that this plant extract possesses antioxidant activity, as demonstrated in previous studies. This activity may be justified by the high polyphenol and flavonoid compounds found in this plant extract [19,20,49].

It has been demonstrated that oxidative stress and insulin resistance play a pivotal role in the development of obesity-related cardiovascular diseases including arterial hypertension [49]. Moreover, tachyarrhythmia has been reported in animals challenged with MSG [35]. In this study, MSG exposure led to a significant increase in blood pressure and heart rate that was almost completely reversed by the plant extract. Effects of Cp on hemodynamic parameters can be explained by its insulin-sensitizing activity or its antioxidant activity. Indeed, cardiac GSH levels were significantly increased in animal groups that received the plant extract. In addition, it was found that Cp increased cardiac and skeletal muscle NO content that was lowered by MSG. NO is a ubiquitous signaling molecule that regulates cardiovascular homeostasis mainly through vasodilation [50,51]. The blood pressure lowering effect and the normalization of heart rate exhibited by the extract might result from its ability to increase NO bioavailability in cardiovascular tissues and suggest a possible antihypertensive effect of Cp. However, this needs to be ascertained in future studies.

It is worth noticing that results concerning NO are conflicting in this study. In the pancreas, liver, and adipose tissues, NO was increased while in the heart, and muscle a reduction was instead observed. Further studies are necessary to clarify the tissue-dependent effect of the plant extract.

5. Conclusions

The present study was undertaken to assess whether Cp can reverse a cardiometabolic syndrome condition. From the results

obtained, Cp prevented abdominal obesity, adipocyte hypertrophy, reduced hypertriglyceridemia, and hypercholesterolemia. This plant extract also reversed oxidative stress in adipose tissue and liver by increasing GSH and SOD levels, resulting in the reduction of lipid peroxidation. In addition, Cp lowered inflammation in the pancreas and adipose tissue. These various pharmacological properties of Cp, may underline the improved glucose homeostasis, insulin sensitivity, and blood pressure lowering effect, thus, the reduction of cardiometabolic risk in MSG-treated animals. These pharmacological activities could be attributed to the unique or synergistic action of chemical compounds found in this plant extract, and further support the use of the methanol extract of *C. pentandra* as a treatment against cardiometabolic syndrome.

Author contributions

Conceived and designed the experiments: T.B·N., A.K.W. and E.P·N-M.; Performed the experiments A.K·W., and C·K·F.; Analyzed and interpreted the data, A.K·W., T.B·N.; E.P·N-M., and C·K·F.; Contributed reagents, materials, analysis tools or data, T.B·N., A.K.W. and E.P·N-M.; Wrote the paper, T.B.N. A.K.W., E.P·N-M., and C·K·F.

Data availability statement

All data relevant to the study are included in the article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional review board statement

All animals procedures were done following the standard ethical guidelines for animal use and care as described by the law 2010/63/EU on the protection of animals used for scientific purposes, and approved by the institutional review board of the Department of Animal Biology – University of Dschang (025/18/304/FSa, June 22, 2018).

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Acknowledgments

The authors extend their appreciation to the University of Dschang for the facilities provided.

References

[1] R. Ash-Bernal, L.R. Peterson, The cardiometabolic syndrome and cardiovascular disease, J. Cardiometab. Syndr. 1 (2006) 25–28, https://doi.org/10.1111/j.0197-3118.2006.05452.x.
[2] A. Khosravi, M. Sadeghi, M. Barghikar, Which components of metabolic syndrome have a greater effect on mortality, CVA and myocardial infarction, hyperglycemia, high blood pressure or both? Adv. Biomed. Res. 6 (2017) 121–129, https://doi.org/10.4103/abr.abr_249_16.
[3] J.J. Frere, B.R. tenOever, Cardiometabolic syndrome — an emergent feature of Long COVID? Nat. Rev. Immunol. 22 (2022) 399–400, https://doi.org/10.1038/s41577-022-00739-8.
[4] A.T.P. NCEP III, Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, Circle 106 (2002) 3143–3421, https://doi.org/10.1161/circ.106.25.3143.
[5] G.J. Farkas, A.M. Burton, D.W. Mcmillan, A. Sneij, D.R. Gater, The diagnosis and management of cardiometabolic risk and cardiometabolic syndrome after spinal cord injury, J. Personalized Med. 12 (2022) 1–32, https://doi.org/10.3390/jpm12071088.
[6] H.L. Kim, J. Chung, K.J. Kim, H.J. Kim, W.W. Seo, K.H. Jeon, I. Cho, J.J. Park, M.H. Lee, J. Suh, K.L. Kim, K.J. Kim, H.J. Kim, M.H. Lee, S.H. Kim, Lifestyle modification in the management of metabolic syndrome: statement from Korean society of CardioMetabolic syndrome (KSCMS) lifestyle modification in metabolic syndrome, Korean Circ. J. 52 (2022) 93–109, https://doi.org/10.4070/kcj.2021.0328.
[7] E.S. Ford, Prevalence of the metabolic syndrome defined by the international diabetes, Diabetes Care 28 (2005) 2745–2749 [Online]. Available: http://care.diabetesjournals.org/cgi/content/abstract/28/11/2745.
[8] A. Okunogbe, R. Nugent, G. Spencer, J. Ralston, J. Wilding, Economic impacts of overweight and obesity: current and future estimates for eight countries, BMJ Glob. Heal. 6 (2021) 1–15, https://doi.org/10.1136/bmjgh-2021-006351.
[9] J.P. Després, From syndrome X to cardiometabolic risk: clinical and public health implications, Proc. Nutr. Soc. 79 (2020) 4–10, https://doi.org/10.1017/S0029665119001010.
[10] Y.-C. Hsiao, C.-C. Wu, Dyslipidemia and cardiometabolic syndrome, CardioMetabolic Syndr. J. 1 (2021) 18–23, https://doi.org/10.51789/cmsj.2021.1.e2.
[11] Y.T. Wondmkun, Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications, Diabetes, Metab. Syndrome Obes. Targets Ther. 13 (2020) 3611–3616, https://doi.org/10.2147/DMSO.S275898.
[12] J. Niewiadomska, A. Gajek-Marecka, J. Gajek, A. Noszczyk-Nowak, Biological potential of polyphenols in the context of metabolic syndrome: an analysis of studies on animal models, Biologe 11 (2022), https://doi.org/10.3390/biology11040559, 1–19.
[13] P.A. Nono Nankam, T.B. Nguelefack, J.H. Goedecke, M. Blüher, Contribution of adipose tissue oxidative stress to obesity-associated diabetes risk and ethnic differences: focus on women of African ancestry, Antioxidants 10 (2021) 1–19, https://doi.org/10.3390/antiox10040622.
[14] A.K. Srivastava, Challenges in the treatment of cardiometabolic syndrome, Indian J. Pharmacol. 44 (2012) 155–156, https://doi.org/10.4103/0253-7613.93579.
[15] G. Fahed, L. Aoun, M.B. Zerdan, S. Allam, M.B. Zerdan, Y. Bouferraa, H.I. Assi, Metabolic syndrome: updates on pathophysiology and management in 2021, Int. J. Mol. Sci. 23 (2022) 1–28, https://doi.org/10.3390/ijms23020786.

[16] G.S. Barragán-Zarate, A. Alexander-Aguilera, L. Lagunez-Rivera, R. Solano, I. Soto-Rodríguez, Bioactive compounds from Prosthechea karwinskii decrease obesity, insulin resistance, pro-inflammatory status, and cardiovascular risk in Wistar rats with metabolic syndrome, J. Ethnopharmacol. 279 (2021) 1–10, https://doi.org/10.1016/j.jep.2021.114376.

[17] F.N. Ngounou, A.L. Meli, D. Lontsi, B.L. Sondengam, M.I. Atta-Ur-Rahman Choudhary, Malik F. Shahid Akhtar, New isoflavones from *Ceiba pentandra*, Phytochemistry (Oxf.) 54 (2000) 107–110, https://doi.org/10.1016/S0031-9422(00)00035-2.

[18] C.K. Fofié, E.P. Nguelefack-Mbuyo, N. Tsabang, A. Kamanyi, T.B. Nguelefack, Hypoglycemic properties of the aqueous extract from the stem bark of *Ceiba pentandra* in dexamethasone-induced insulin resistant rats, Evidence-based Complement, Alternative Med. 2018 (2018) 1–11, https://doi.org/10.1155/2018/4234981.

[19] C.K. Fofie, S.L. Wansi, E.P. Nguelefack-Mbuyo, A.D. Atsamo, P. Watcho, A. Kamanyi, N. Tsabang, T.B. Nguelefack, In vitro anti-hyperglycemic and antioxidant properties of extracts from the stem bark of *Ceiba pentandra*, J. Compl. Integr. Med. 11 (2014) 185–193, https://doi.org/10.1515/jcim-2014-0031.

[20] K.C. Fofie, S. Khatekaye, P.E. Nguelefack-Mbuyo, A. Kamanyi, B. Kamble, N. Chauhan, V. Singh, T.B. Nguelefack, Insulin sensitizing effect as possible mechanism of the antidiabetic properties of the methanol and the aqueous extracts from the trunk bark of *Ceiba pentandra*, Diabetes Update 5 (2018) 1–6, https://doi.org/10.15761/du.1000114.

[21] C.K. Fofie, S. Katekhaye, S. Borse, V. Sharma, M. Nivsarkar, E.P. Nguelefack-Mbuyo, A. Kamanyi, V. Singh, T.B. Nguelefack, Antidiabetic properties of aqueous and methanol extracts from the trunk bark of *Ceiba pentandra* in type 2 diabetic rat, J. Cell. Biochem. 120 (2019) 11573–11581, https://doi.org/10.1002/jcb.28437.

[22] T.B. Nguelefack, C.K. Fofie, E.P. Nguelefack-Mbuyo, A.K. Wuyt, Multimodal α-glucosidase and α-amylase inhibition and antioxidant effect of the aqueous and methanol extracts from the trunk bark of *Ceiba pentandra*, BioMed Res. Int. 2020 (2020) 1–13, https://doi.org/10.1155/2020/3063674.

[23] J.W. Olney, Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate, Science 164 (1969) 719–721, https://doi.org/10.1126/science.164.3880.719.

[24] H. Jiang, H. Zheng, Efficacy and adverse reaction to different doses of atorvastatin in the treatment of type II diabetes mellitus, Biosci. Rep. 39 (7) (2019), BSR20182371, https://doi.org/10.1042/BSR20182371, 5.

[25] L.E. Simental-Mendía, M. Rodríguez-Morán, F. Guerrero-Romero, The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects, Metab. Syndr. Relat. Disord. 6 (2008) 299–304, https://doi.org/10.1089/met.2008.0034.

[26] F. Guerrero-Romero, L.E. Simental-Mendía, M. González-Ortiz, E. Martínez-Abundis, M.G. Ramos-Zavala, S.O. Hernández-González, O. Jacques-Camarena, M. Rodríguez-Morán, The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp, J. Clin. Endocrinol. Metab. 95 (2010) 3347–3351, https://doi.org/10.1210/jc.2010-0288.

[27] R.P. Young, J.A.J.H. Critchley, P.J. Anderson, M.S.W. Lau, K.K.C. Lee, J.C.N. Chan, The short insulin tolerance test: feasibility study using venous sampling, Diabet. Med. 13 (1996) 429–433, https://doi.org/10.1002/(SICI)1096-9136(199605)13:5<429::AID-DIA98>3.0.CO;2-K.

[28] E. Bonora, P. Moghetti, C. Zancanaro, M. Cigolini, M. Querena, V. Cacciatori, A. Corgnati, M. Muggeo, Estimates of in vivo insulin action in man: comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies, J. Clin. Endocrinol. Metab. 68 (1989) 374–378, https://doi.org/10.1210/jcem-68-2-374.

[29] R.S. Patarrão, W. Wayne Lautt, M. Paula Macedo, Assessment of methods and indexes of insulin sensitivity, Rev. Port. Endocrinol. Diabetes e Metab. 9 (2014) 65–73, https://doi.org/10.1016/j.rpedm.2013.10.004.

[30] W.T. Friedewald, R.I. Levy, D.S. Fredrickson, Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge, Clin. Chem. 18 (1972) 499–502.

[31] M. Lee, Determınatıon of the surface area of the whıte rat wıth ıts applıcatıon to the expressıon of metabolıc results, Am. J. Physiol. 89 (1929) 24–33.

[32] A.S. Leopoldo, A.P. Lima-Leopoldo, A.F. Nascimento, R.A.M. Luvizotto, M.M. Sugizaki, D.H.S. Campos, D.C.T. Da Silva, C.R. Padovani, A.C. Cicogna, Classification of different degrees of adiposity in sedentary rats, Braz. J. Med. Biol. Res. 49 (2016) 1–9, https://doi.org/10.1590/1414-431X20155028.

[33] R.B. D'Agostino, R.S. Vasan, M.J. Pencina, P.A. Wolf, M. Cobain, J.M. Massaro, W.B. Kannel, General cardiovascular risk profile for use in primary care: the Framingham heart study, Circle 117 (2008) 743–753, https://doi.org/10.1161/CIRCULATIONAHA.107.699579.

[34] I. Soldatovic, R. Vukovic, D. Culafic, M. Gajic, V. Dimitrijevic-Sreckovic, SiMS score: simple method for quantifying metabolic syndrome, PLoS One 11 (2016) 1–10, https://doi.org/10.1371/journal.pone.0146143.

[35] A.I. Omogbiya, B.B. Azu, A. Taghogho, E. Aya, E. Okubo, P.O. Nwokoye, A. Mayowa, A. Solomon, Monosodium glutamate induces memory and hepatic dysfunctions in mice: ameliorative role of Jobelyn ® through the augmentation of cellular antioxidant defense machineries, Toxicol. Res. (2020) 1–13, https://doi.org/10.1007/s43188-020-00068-9.

[36] A. Zanfirescu, A. Ungurianu, A.M. Tsatsakis, G.M. Nițulescu, D. Kouretas, A. Veskoukis, D. Tsoukalas, A.B. Engin, M. Aschner, D. Margină, A review of the alleged health hazards of monosodium glutamate, Compr. Rev. Food Sci. Food Saf. 18 (2019) 1111–1134, https://doi.org/10.1111/1541-4337.12448.

[37] C. Liu, Y. Yuan, J. Zhou, R. Hu, L. Ji, Piperine ameliorates insulin resistance via inhibiting metabolic inflammation in monosodium glutamate-treated obese mice, BMC Endocr. Disord. 20 (2020) 1–15, https://doi.org/10.1186/s12902-020-00617-1.

[38] Y.B. Fouda, E. Ngo, L. Tom, A.D. Atsamo, Effects of stem bark aqueous extract of Fagara tessmannii Engl (Rutaceae) on cardiovascular risks related to monosodium glutamate-induced obesity in rat: in vivo and in vitro assessments, J. Ethnopharmacol. (2020) 1–36, https://doi.org/10.1016/j.jep.2020.112972.

[39] A.M. da Silva Mattos, C.H. Xavier, M. Karlen-Amarante, N.V. da Cunha, M.A.P. Fontes, M.C. Martins-Pinge, Renal sympathetic nerve activity is increased in monosodium glutamate induced hyperadipose rats, Neurosci. Lett. 522 (2012) 118–122, https://doi.org/10.1016/j.neulet.2012.06.021.

[40] N. Kobyliak, T. Falalyeyeva, O. Virchenko, G. Mykhalchyshyn, P. Bodnar, M. Spivak, D. Yankovsky, T. Beregova, L. Ostapchenko, Comparative experimental investigation on the efficacy of mono- and multiprobiotic strains in non-alcoholic fatty liver disease prevention, BMC Gastroenterol. 16 (2016) 1–9, https://doi.org/10.1186/s12876-016-0451-2.

[41] O.A. Rotimi, I.O. Olayiwola, O. Ademuyiwa, E.A. Balogun, Effects of fibre-enriched diets on tissue lipid profiles of MSG obese rats, Food Chem. Toxicol. 50 (2012) 4062–4067, https://doi.org/10.1016/j.fct.2012.08.001.

[42] R.A. Miranda, A.R. Agostinho, I.H. Trevenzoli, L.F. Barella, C.C.S. Franco, A.B. Trombini, A. Malta, C. Gravena, R. Torrezan, P.C.F. Mathias, J.C. De Oliveira, Insulin oversecretion in MSG-obese rats is related to alterations in cholinergic muscarinic receptor subtypes in pancreatic islets, Cell. Physiol. Biochem. 33 (2014) 1075–1086, https://doi.org/10.1159/000358677.

[43] R. Corder, P. Saudan, M. Mazlan, C. Mclean, R.C. Gaillard, Depletion of hypothalamic growth hormone-releasing hormone by neonatal monosodium glutamate treatment reveals an inhibitory effect of betamethasone on growth hormone secretion in adult rats, Neuroendocrinology 51 (1990) 85–92.

[44] R.K. Yamazaki, G.A.P. Brito, I. Coelho, D.C.T. Pequitto, A.A. Yamaguchi, G. Borghetti, D.L. Schiessel, M. Kryczyk, J. MacHado, R.E.R. Rocha, J. Aikawa, F. Iagher, K. Naliwaiko, R.A. Tanhoffer, E.A. Nunes, L.C. Fernandes, Low fish oil intake improves insulin sensitivity, lipid profile and muscle metabolism on insulin resistant MSG-obese rats, Lipids Health Dis. 10 (2011) 1–7, https://doi.org/10.1186/1476-511X-10-66.

[45] P.M. Titchenell, M.A. Lazar, J. Birnbaum, Unraveling the regulation of hepatic metabolism by insulin, Trends Endocrinol. Metabol. 1–9 (2017), https://doi.org/10.1016/j.tem.2017.03.003.

[46] J.J. Swaroop, D. Rajarajeswari, J.N. Naidu, Student IJMR Association of TNF-α with insulin resistance in type 2 diabetes mellitus, Indian J. Med. Res. 135 (2012) 127–130.

[47] M. Sajid, H. Akash, Tumor necrosis factor - alpha : role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus, Prospects 2017 (2017) 1–16, https://doi.org/10.1002/jcb.26174.

[48] E. McCracken, M. Monaghan, S. Sreenivasan, Pathophysiology of the metabolic syndrome, Clin. Dermatol. 36 (2018) 14–20, https://doi.org/10.1016/j.clindermatol.2017.09.004.

[49] Z. Fitria, Afrizal, M. Efdi, Isolation and characterization of antioxidative constituent from stem bark extract of *Ceiba pentandra* L, J. Chem. Pharmaceut. Res. 7 (2015) 257–260.
[50] F. Simko, T. Baka, K. Krajcirovicova, K. Repova, S. Aziriova, S. Zorad, M. Poglitsch, M. Adamcova, R.J. Reiter, L. Paulis, Effect of melatonin on the renin-angiotensin-aldosterone system in L -NAME-Induced hypertension, Molecules 13 (2018) 1–15, https://doi.org/10.3390/molecules23020265.
[51] G. Gallo, M. Volpe, C. Savoia, Endothelial dysfunction in hypertension: current concepts and clinical implications, Front. Med. 8 (2022) 1–8, https://doi.org/10.3389/fmed.2021.798958.