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Pterocarpus soyauxii Taub (*Papilionaceae*) Aqueous Stem Bark Extract Prevents Dexamethasone-induced Insulin Resistance and Oxidative Stress in Rat

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Abstract: Background: Data on safety degree and anti–type 1 diabetic effects of *Pterocarpus soyauxii* Taub are known, but not on type 2 diabetes yet. Objective: To evaluate preventive effects of *P. soyauxii* Taub aqueous stem bark extract on dexamethasone–induced insulin resistance and oxidative stress in rat. Materials and Methods: Glucose-overloaded normal Wistar rats were administered with *P. soyauxii* aqueous plant extract at various doses (38–300 mg.kg) in a single administration. Then, dexamethasone (Dex)–induced insulin-resistant rats received sub-chronic daily administration of the plant extract (38–300 mg/kg) for 21 days. Glibenclamide (10 mg/kg) and metformin (200 mg/kg) were respectively used in each test as standard treatments. Fasting blood glucose was followed for over 3 h in acute test. In sub-chronic test, body weight was followed weekly, glycemia before and at the end of treatment, and insulin sensitivity and serum and tissue biochemical parameters evaluated at the end of treatment. Results: Single administration of the plant extract significantly reduced ($p<0.05$) the serum glucose level increase of glucose-overloaded rats at lower doses, compared to hyperglycemic control. Its prolonged administration with dexamethasone in normal rats prevented insulin-resistance at all doses ($p<0.001$) similarly to metformin, without decreasing the body weight loss. The extract also prevented significantly ($p<0.001$) dexamethasone-induced increased serum creatinine, triglyceride, LDL-cholesterol, and transaminases, and decreased total proteins and HDL-cholesterol. Moreover, it improved significantly ($p<0.05$ – $p<0.001$) tissues oxidative stress parameters. Conclusion: *P. soyauxii* Taub aqueous stem bark extract can prevent the onset of type 2 diabetes.

Keywords: Dexamethasone, Insulin-resistance, Oxidative Stress, Prevention, *Pterocarpus soyauxii* Taub, Rat

1. Introduction

Diabetes mellitus is a growing health problem and was associated with 10.7% of global deaths from all causes among the 60 years people in 2017 [1]. Africa was the first continent with more deaths and undiagnosed cases (about 80%) [2]. The 463 million affected people worldwide in 2019 may increase by 51% in 2045 [3].

Type 2 diabetes, the most common form (90%) is preceded by insulin-resistance which occurs after the altered response of target tissues to the insulin action, leading to need for excess insulin (hyperinsulinism) to obtain a quantitatively normal response, and subsequently to an insulin deficiency

responsible for hyperglycemia [4]. Insulin sensitivity can be reduced under some physiological or pathological conditions, or during treatments with corticosteroids such as dexamethasone [5]. Despite its beneficial effects on pain, acute and chronic inflammation, chronic and high-dose use of dexamethasone influences insulin sensitivity and may lead to peripheral insulin-resistance, promoting hyperglycemia and therefore the development of corticoid-induced type 2 diabetes [6-8]. Studies have shown that hyperinsulinism, as well as increased free fatty acids and carbohydrates, generate oxidative stress and activate metabolic pathways that generate reactive oxygen species (ROS), which in turn aggravate both insulin-resistance, hyperinsulinism and oxidative stress, and thereby accelerate the onset of type 2 diabetes [9].

The insulin-resistance treatment is linked to type 2 diabetes one. In principle, depending on the glucocorticoid type and posology, all oral antidiabetic drugs are used to treat corticosteroid-induced diabetes; But they have well-known side effects as metformin, which mostly recommended combined with insulin [6, 8, 10], is thus sometimes contraindicated [7]. Moreover, the low purchasing power, the difficulties in supply and access to health centers, sometimes ignorance, associated with the above, constitute important barriers to successful treatment and therefore, promote in developing countries the type 2 diabetes incidence and prevalence increase. Otherwise, traditional pharmacopoeia offers inexpensive and potential natural herbal therapies. In addition, extracts from many plants as *Bombax ceiba* [11], *Moringa oleifera* [12] and others have been tested for their antidiabetic activities. *Pterocarpus soyauxii* Taub, a deciduous rainforests tree from Fabaceae family, growing in African tropical sub-regions and traditionally used to treat various diseases [13], have been recently investigated on streptozotocin-induced type 1 diabetes [14], but its effects on type 2 diabetes are not known. The present work aimed to evaluate preventive effects of *Pterocarpus soyauxii* Taub stem bark aqueous extract on dexamethasone-induced insulin-resistance, some metabolic disorders and oxidative stress, this after appreciating its effects on glucose tolerance in normal rats.

2. Material and Methods

The study was conducted in respect of All Guidelines for Care and Use of Laboratory Animals as described in the European Community Guidelines (EEC Directive 2010 / 63 / EU of the September 22, 2010) and after obtaining approval for Animal Experimentation n° 2040 CEI-UDo/06/2019/T.

2.1. Chemicals

Glibenclamide (GB) obtained from SANOFI Laboratory (SANOFI, France), dexamethasone and semi-slow Insulin from ROTEXMEDICA Gmbh Laboratory (ROTEXMEDICA Gmbh, Germany), metformin from DENK PHARMA (DENK PHARMA Gmbh & co.KG, Germany), NaCl 9‰ from S. I. P. P. Laboratory (S. I. P. P, Cameroun), Accu-chek Aviva blood glucose test strips and glucometer from Roche Diagnostics (Mannheim, Germany) and all other reagents and chemicals (Extra pure analytical grade) from common commercial suppliers were used in the study.

2.2. Plant Material

Fresh stem barks of *Pterocarpus soyauxii* were harvested in July 2017 in Nkolbibanda village (Mefou and Akono Department, Centre region, Cameroun). Botanical identification of the plant was made at the National Herbarium of Yaoundé in comparison to the voucher specimen N°247/HNC.

2.3. Preparation of P. soyauxii Aqueous Extract

Fresh stem barks of the plant were cut, dried at room temperature and ground into powder using a grinder. Dried powder (500 g) was macerated in 2.5 L of boiling distilled water for 5 min and then kept 12 h at room temperature before filtering. The procedure was repeated with the residues and the two filtrates obtained were mixed and freeze-dried concentrated by freeze-drying, yielding 40.7 g (W/W 8.14%) well-dried aqueous residue, and stored at – 20°C until use.

For administration to rats in each experiment, the dried aqueous extract was weighed and dissolved in distilled water to obtain 30 mg/ml stock solutions every 3 days. Fixation of plant dosing was based on usual doses used in previous works [14].

2.4. Animals

Adult male albino Wistar rats (3 months old, weighing 200 – 250 g) were used. They were raised in the animal core facility of the Faculty of Science, University of Douala, housed in colony cages (5 rats per cage), at controlled room temperature (28±2°C) and humidity (80 - 85%), on a 12 h light/dark cycle and allowed free access to tap water and standard rat diet. Before testing for blood glucose level, rats were fasted overnight for 12 or 16 h according to the experiment, with free access to water.

2.5. Measurement of Fasting Blood Glucose Level

Blood drop sample was collected from overnight-fasted rats and fasting blood glucose determination (at -30, 0, 30, 60, 90, 120 and 150 minutes for acute experiment, at 0 and 21 days for sub-acute experiment, and at 0, 10, 20, 30 and 60 minutes for Insulin sensitivity test) was carried out by glucose-peroxidase method using test strips (Accu-chek Aviva) and an appropriate glucometer (Accu-chek Aviva Connect, Roche Diagnostics, Germany) as previously described [14, 15].

2.6. Assessment of Oral Glucose Tolerance Test in Normal Rats

A total of 35 overnight–fasted (16 h) normal rats were

randomly divided into seven groups (5 rats each):

Group 1: normal control rats (NC) received distilled water (10 mL/kg).

Group 2: normal rats administered with distilled water (10 mL/kg) and D-glucose solution (5 mg/kg) as Hyperglycemic control (HGC).

Group 3: normal positive control rats administered with glibenclamide (GB, 10 mg/kg) and D-glucose solution (5 mg/kg).

Groups 4-7: normal rats received the plant extract at different doses (E 38, 75, 150 and 300 mg/kg BW respectively), each with D-glucose solution (5 mg/kg).

All groups of rats first received a single oral administration of the treatments by gavage and, thirty minutes after a single oral dose of D-glucose solution (5 mg/kg) (groups 2-7) or an equal volume of solvent (group 1) by gavage. Blood glucose levels were measured before treatments (-30 minutes) and D-glucose (0 minute) administrations, and at 30, 60, 90, 120, and 150 minutes after.

2.7. Experimental Design for Evaluating Preventive and Sub-chronic Effects of P. soyauxii Aqueous Extract in Dexamethasone-treated Rats

A total of 35 normal rats used were randomly divided into 7 groups (5 rats in each):

Group 1: normal control (NC) rats received 10 mL/kg of distilled water *P.O.* + 1 mL/kg of Sodium Chloride (NaCl 9‰) in *I.P.*

Group 2: Dexamethasone Control (DexC) rats received 10 mL/kg of distilled water *P.O.* + dexamethasone (0.4 mg/kg) in *I.P.*

Group 3: Metformin-treated (Met) rats received the standard drug metformin (Met, 200 mg/kg) *P.O.* + dexamethasone (0.4 mg/kg) in *I.P.*

Goups 4-7: Extract-treated (E) rats administered with *P. soyauxii* aqueous extract at different doses (38, 75, 150 and 300 mg/kg respectively) *P.O.* + dexamethasone (0.4 mg/kg) in *I.P.*

Drugs (extract doses and metformin) or vehicle was orally administered once a day for 21 days, starting just after the different groups' formation. Dexamethasone (0.4 mg/kg) and the equal volume of solvent (NaCl 9‰, 1 mL/kg) were injected intraperitoneally (*I.P.*) to dexamethasone–treated (groups 2–7) and NC (group 1) rats respectively, 30 minutes after daily drug or distilled water administration.

Fasted (12h) blood glucose levels were measured before the first treatment administration (day 0) and at the end of experiment (day 22). Body weight was monitored daily. At day 22, insulin sensitivity test was immediately performed after blood glucose determination. Immediately afterwards, rats were anesthetized (by Isoflurane inhalation) [16, 17] and euthanized by decapitation. Blood samples were then collected from the abdominal aorta via laparotomy [14]. The serum obtained after blood centrifugation (3000 g/10 min) was stored at –20°C until analysis. Organs (aorta, heart, kidney and liver) were removed, weighed, crushed and centrifuged, and homogenates obtained were also stored at –20°C until analysis of some tissue oxidative stress markers.

NB: During dexamethasone treatment, rats died at different times (probably due to dexamethasone side effects) were replaced as and when they occurred in each time for new experiment with them from the beginning such that there were ultimately 5 rats per group. The present study was planned for 35 rats, but 42 rats were needed for completion of the project.

2.8. Insulin Sensitivity Test

At the 22nd day of experiment, the 12h–overnight–fasted rats of all groups were weighed and administered with a single dose of insulin solution (2 IU/kg) in *I.P.* Blood glucose levels were measured before the insulin administration (0 minutes) and at 10, 20, 30 and 60 minutes after. At the end of the test, a glucose solution (0.5g/kg) was administered to animals orally, in order to counteract possible cases of severe hypoglycemia following the insulin injection [18], allowing sacrificing all animals without death.

2.9. Biochemical Analysis of Serum and Tissue Homogenates

The serum was analyzed using commercial diagnostic kits (SGM ITALIA, Rome, ITALY) for total proteins (Biuret), creatinine (colorimetric), Triglyceride (GPO – PAD method), total cholesterol (CHOD – PAD Method), HDL-cholesterol (colorimetric), ALT/AST (kinetic). Serum LDL-cholesterol was indirectly estimated [19], and atherogenic risk index (ARI) was calculated [20]. Tissue homogenates were analyzed using different methods and reagents for malondialdehyde (MDA) [21], reduced glutathione (GSH) [22], superoxide dismutase (SOD) [23], catalase [24] and nitrite oxide (NO) [25].

2.10. Statistical Analysis

Data are presented as mean±standard error of mean. One-way and two-way analysis of variance with respective Turkey's or Bonferroni's multiple comparison post test were performed to assess differences between groups (GraphPad PRISM Software, Version 5.03, San Diego, California, USA). $p<0.05$ was considered statistically significant.

3. Results

3.1. Effects of Single Doses of P. soyauxii Taub Aqueous Extract on Oral Glucose Tolerance in Normal Rats

Before glucose administration (T-30 to T0), the mean blood glucose did not change in groups or between groups (Figure 1A). After glucose administration, the blood glucose increased significantly ($p<0.001$) in all glucose-fed rats' groups, peaking at the thirtieth minute (T30) following, compared with T0 and the NC. The increase was by 141%, 100%, 135%, 144%, 173% and 183% respectively for Hyperglycemic control (HGC), glibenclamide, and respective plant extract doses of 38, 75,

150 and 300 mg/kg (E38, E75, E150 and E300), compared to T0. Only glibenclamide significantly reduced the T30 recorded hyperglycemia (41%, $p<0.001$), compared to HGC (Figure 1A). Thereafter, blood glucose gradually decreased in all groups until the 150th minute, with a normalization in glibenclamide-treated rats, but significant decreases at the 90th ($p<0.01$–$p<0.001$) and 120th ($p<0.05$–$p<0.01$) minutes in plant extract-treated groups, all compared to HGC (Figure 1A). Interestingly, the mean blood glucose values recorded between T0 and T150 (Area Under each blood glucose Curve (AUC) reflecting the overall effect of each treatment on blood glucose at a time interval) decreased by 24% and 23.55% respectively at 38 and 75 mg/kg plant extract doses ($p<0.05$), and by 61.57% ($p<0.001$) with glibenclamide, compared to HGC (AUC increased by 126.16% ($p<0.001$) compared to NC).

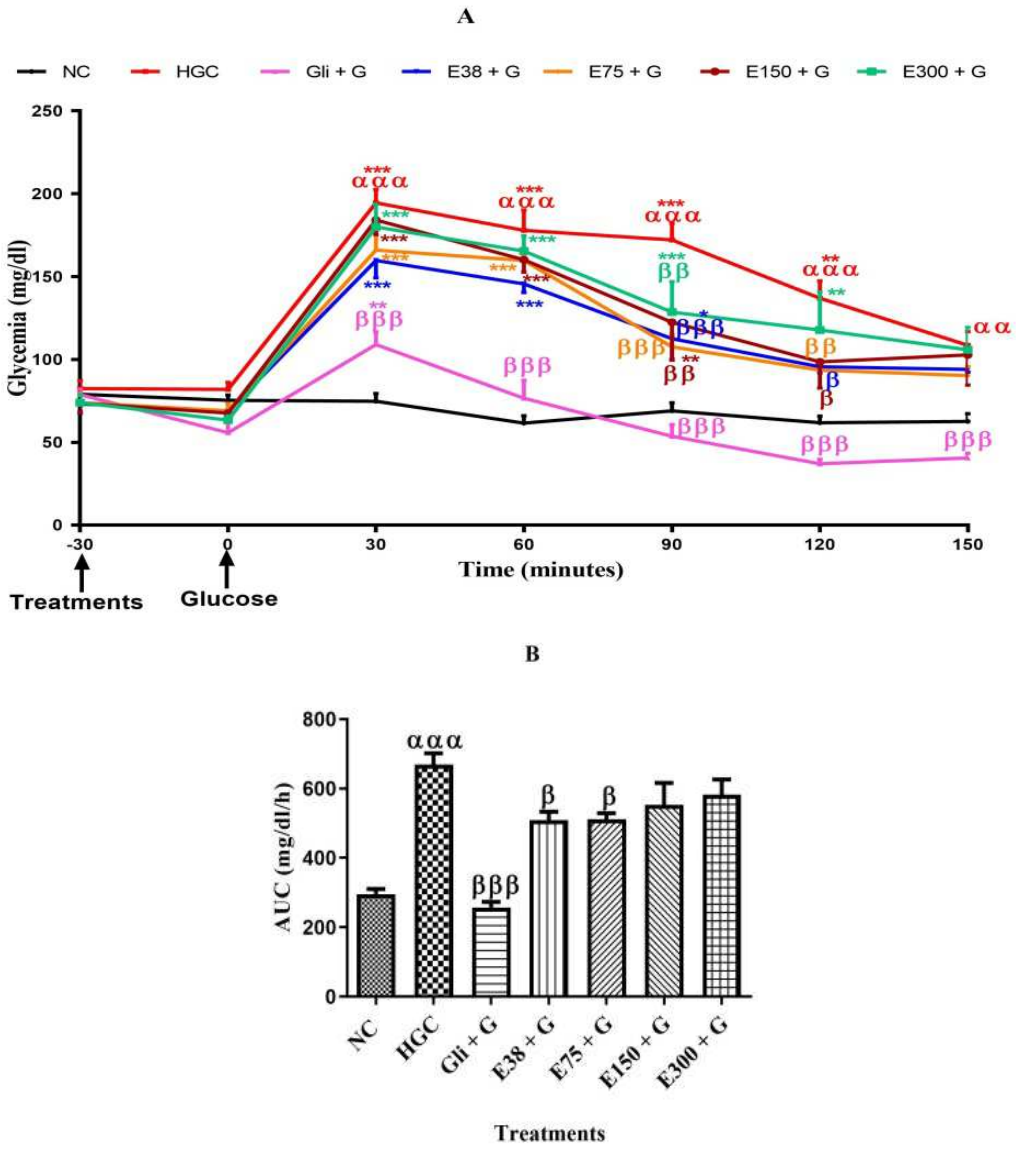


Figure 1. *Time course changes in blood glucose levels during OGTT (A) and area under the curve for glucose concentrations calculated during the OGTT test (B) in P. soyauxii Taub stem bark aqueous extract-treated normal rats.*

The values are given as the mean±MSE, (n=5). $^{\alpha\alpha}p<0.01$, $^{\alpha\alpha\alpha}p<0.001$: versus the NC group. $^{\beta}p<0.05$, $^{\beta\beta\beta}p<0.001$: versus the HGC group. *$p<0.05$, ***$p<0.001$: versus the time T0. NC=normal control. HGC=hyperglycemic control. Gli+G=glibenclamide + glucose. E38+G, E75+G, E150+G, E300+G=*P. soyauxii* aqueous extract at indicated doses (in mg/kg) + Glucose.

3.2. Prolonged Effects of P. soyauxii Taub Stem Bark Aqueous Extract on Blood Glucose and Insulin Sensitivity in Dexamethasone-treated Rats

At day 22nd, blood glucose did not change between groups, nor compared to day 0 in each group (Table 1).

The insulin sensitivity test (Figure 2) showed a significant blood glucose increase in DexC rats (32%; $p<0.001$) at the 10th minute following the insulin administration, and a very little decrease thereafter until the 60th minute, compared to T0 (Figure 2A). Interestingly, blood glucose gradually and significantly decreased after

insulin administration in NC and (plant extract or metformin)/dexamethasone co-treated rats until the 60th minute, compared to DexC rats ($p<0.001$) and T0 ($p<0.05$ – $p<0.001$) in each group (Figure 2A). The mean blood glucose values (AUC from T0 to T60) increased in DexC group (73.46%, $p<0.001$) compared to NC, and was normalized in (plant extract doses or metformin)/Dexamethasone co-treated groups (Figure 2B).

Table 1. *Changes in blood glucose levels during sub-chronic administration of P. soyauxii stem bark aqueous extract in dexamethasone-treated rats.*

Groups (n=5)	Treatments	Glycemia (mg/dl)		
		Day 0	Day 21	Variation (%)
CN	(Distilled H_2O; 10 ml/kg)	88,84±7,14	74,6±4,18	-
DexC	Dexamethasone (0.4 mg/kg)	94±9,66	105,75±4,82	12
E38 + D	Extract (38 mg/kg) + Dex	89,5±7,77	100,25±3,47	9,12
E75 + D	Extract (75 mg/kg) + Dex	76±5,89	97,2±7,42	27,89
E150 + D	Extract (150 mg/kg) + Dex	73±9,60	82,5±3,97	13,01
E300 + D	Extract (300 mg/kg) + Dex	83,4±6,70	100,2±3,48	20,14
Met + D	Metformin (200 mg/kg) + Dex	84,5±7,93	89,75±10,39	06,21

Values are given as the mean±MSE, (n=5). Statistical differences between the groups are not significant. NC=normal control; DexC=Dexamethasone control; Met+D=Metformin + Dexamethasone (0.4 mg/kg); E38+D, E75+D, E150+D, E300+D=*P. soyauxii* aqueous extract at indicated doses (in mg/kg) + Dexamethasone (0.4 mg/kg).

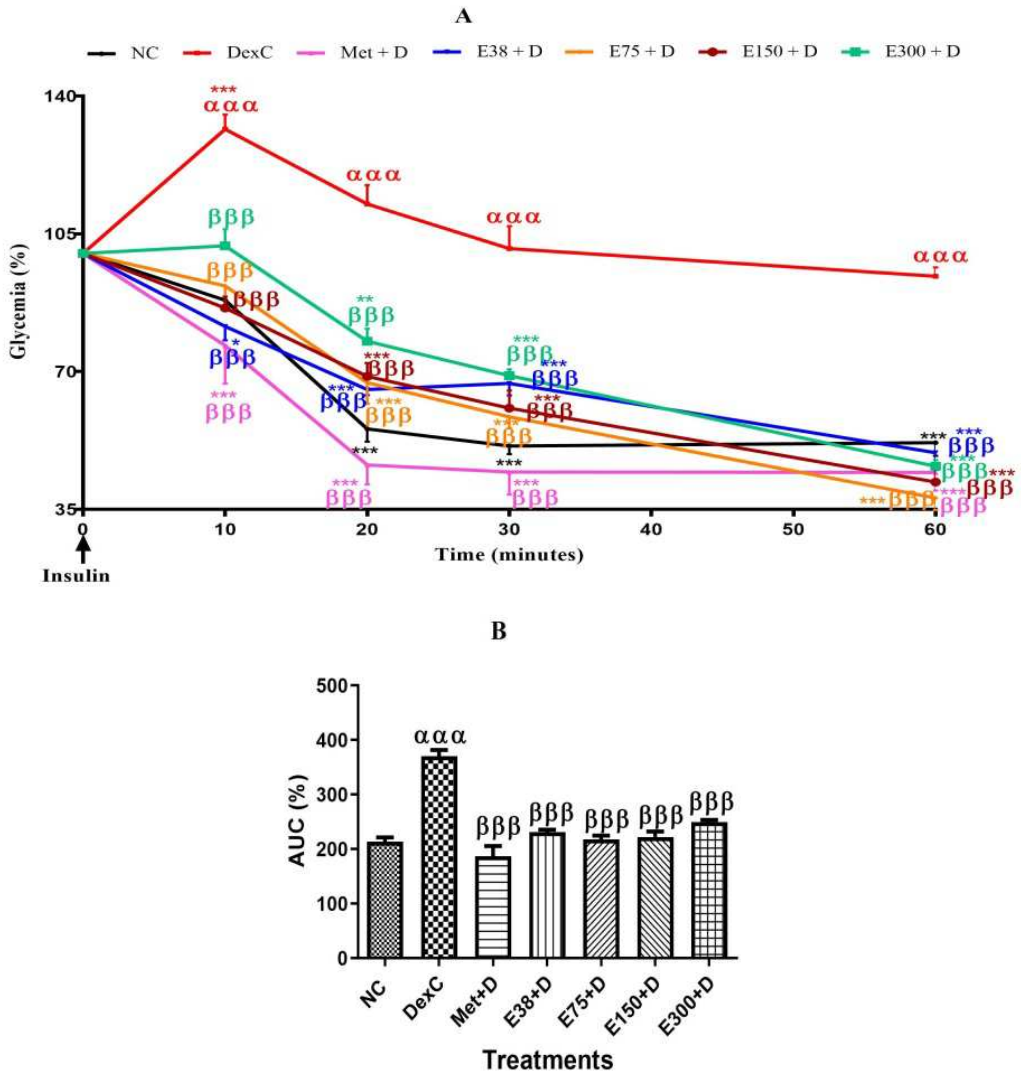


Figure 2. *Time course changes in blood glucose levels during Insulin sensitivity test (IST) (A) and area under the curve for glucose concentrations calculated during the IST test (B) in Dexamethasone–treated rats.*

Blood glucose is expressed as a percentage of variation at each time point compared to the baseline glycemia at T0. The values are given as the mean±MSE, (n=5). $^{\alpha\alpha}p<0.01$, $^{\alpha\alpha\alpha}p<0.001$: versus the NC group. $^{\beta}p<0.05$, $^{\beta\beta\beta}p<0.001$: versus the DexC group. *p<0.05, ***p<0.001: versus the time T0. NC=normal control. DexC=Dexamethasone control. Met+D=Metformin + Dexamethasone. E38+D, E75+D, E150+D, E300+D=*P. soyauxii* aqueous extract at indicated doses (in mg/kg) + Dexamethasone.

3.3. Sub-acute Effects of P. soyauxii Taub Stem Bark Aqueous Extract on Body Weight and Relative Organ Weight in Dexamethasone-treated Rats

The 22nd day body mass of NC rats increased significantly (13.53%; p<0.001) compared to day 0 (D0), while it gradually and significantly decreased in all dexamethasone-treated rats' groups, compared to NC (p<0.001) and D0 (p<0.05 – p<0.001) without any improvement after plant extract or metformin co-administration (Table 2). Relative organs masses did not vary between the groups (Table 2).

Table 2. *Body weight gain and relative organs masses of normal and 21-days Dexamethasone-treated rats.*

Groups	Body weight gain (%)		
	W1	W2	W3
NC	+ 3.38±1.44	+ 6.14±2.14	+ 13.53±2.79***
DexC	-0.69±0.89	-9.96±1.44$^{**\alpha\alpha\alpha}$	-14.22±1.84$^{***\alpha\alpha\alpha}$
Met. + D	-2.29±1.66	-11.96±2.35$^{***\alpha\alpha\alpha}$	-14.62±1.91$^{***\alpha\alpha\alpha}$
E 38 + D	-1.51±0.86	-9.91±2.26$^{**\alpha\alpha\alpha}$	-13.31±4.23$^{***\alpha\alpha\alpha}$
E 75 + D	-4.29±1.32$^{\alpha}$	-11.16±2.67$^{**\alpha\alpha\alpha}$	-13.45±4.09$^{***\alpha\alpha\alpha}$
E 150 + D	-4.80±0.85$^{\alpha}$	-12.20±2.05$^{***\alpha\alpha\alpha}$	-13.90±2.77$^{***\alpha\alpha\alpha}$
E 300 + D	-3.99±0.93$^{\alpha}$	-11.64±0.95$^{***\alpha\alpha\alpha}$	-16.22±1.80$^{***\alpha\alpha\alpha}$

Table 2. *Continued.*

Groups	Relative organs masses (g/100 g of body weight)				
	Heart	Kidneys	Liver	Lungs	Pancreas
NC	0,32±0,02	0,29±0,05	3,10±0,16	0,78±0,12	0,23±0,09
DexC	0,34±0,02	0,36±0,08	3,01±0,59	0,87±0,08	0,20±0,05
Met. + D	0,39±0,07	0,38±0,08	3,28±0,50	1,05±0,21	0,29±0,02
E 38 + D	0,36±0,07	0,44±0,24	3,55±0,57	1,05±0,18	0,25±0,07
E 75 + D	0,34±0,04	0,33±0,04	2,97±0,22	0,79±0,13	0,16±0,11
E 150 + D	0,33±0,04	0,33±0,04	3,35±0,42	0,96±0,21	0,13±0,10
E 300 + D	0,35±0,06	0,37±0,08	3,41±0,26	1,12±0,37	0,20±0,10

The values are given as the mean±MSE, (n=5). Letters above numbers indicate statistical differences at p<0.05 in the Analysis of Variance (ANOVA) with the Bonferroni post-test. $^{\alpha}$p<0.05, $^{\alpha\alpha}$p<0.01, $^{\alpha\alpha\alpha}$p<0.001: versus the NC group. *p<0.05, ***p<0.001: versus the Week 1. NC=normal control. DexC=Dexamethasone control. Met+D=Metformin + Dexamethasone (0.4 mg/kg). E38+D, E75+D, E150+D, E300+D=*P. soyauxii* aqueous extract at indicated doses (in mg/kg) + Dexamethasone (0.4 mg/kg).

3.4. Prolonged Effects of P. soyauxii Taub Stem Bark Aqueous Extract on Serum Biochemical Parameters in Dexamethasone-treated Rats

The Table 3 shows significant total proteinemia decrease (53.47%; p<0.01) and creatinemia increase (94%; p<0.001) in DexC rats, compared with NC rats. All plant extract doses and metformin significantly increased the proteinemia (p<0.05 – p<0.001) and decreased the creatinemia (p<0.001), compared to DexC. Likewise, serum ASAT (256%, p<0.001) and ALAT (19.13%, non-significant) activities increase observed in DexC rats compared to NC was significantly decreased (p<0.05 – p<0.001) in (plant extract doses or metformin)/dexamethasone-treated rats. Furthermore, significant serum triglyceride (74.83%; p<0.001), LDL-cholesterol (176.30%; p<0.01) with non-significant serum total cholesterol (20.30%; p>0.05) increases, and HDL-cholesterol (72.25%; p<0.001) decrease, associated to the Atherogenic Risk Index (ARI) increase (314.74%; p<0.001) were recorded in DexC rats, compared to NC rats. The plant extract and metformin significantly decreased the serum triglyceride (p<0.001) and LDL-cholesterol (p<0.01), increased the serum HDL-cholesterol (p<0.01 – p<0.001) and normalized the serum total cholesterol, thus reducing (p<0.001) the ARI in all groups, compared to DexC rats (Table 3).

Table 3. *Serum total protein, creatinine, ALAT/ASAT levels or activities and lipid profile of normal and dexamethasone–treated rats.*

Groups	NC	DexC	Met. + D	E 38 + D
Total Protein	3.31±0.31	1.54±0.09$^{\alpha\alpha}$	4.21±0.20$^{\beta\beta\beta}$	3.22±0.49$^{\beta}$
Creatinine (mg/dl)	4.23±0.41	8.82±0.74$^{\alpha\alpha\alpha}$	4.28±0.63$^{\beta\beta\beta}$	3.12±0.49$^{\beta\beta\beta}$
ALAT (IU)	34.86±3.14	53.38±4.79$^{\alpha}$	32.67±5.10$^{\beta}$	28.37±6.62$^{\beta}$
ASAT (IU)	21.28±2.72	70.15±10.93$^{\alpha\alpha\alpha}$	43.02±4.08$^{\beta}$	25.67±3.23$^{\beta\beta\beta}$
Triglycerides (mg/dl)	158.06±12.03	276.34±5.97$^{\alpha\alpha\alpha}$	186.04±4.51$^{\beta\beta\beta}$	182.28±5.92$^{\beta\beta\beta}$
Total Cholesterol (mg/dl)	179.91±8.48	216.43±25.56	179.52±10.42	172.74±1.49
HDL-Cholesterol (mg/dl)	100.26±13.58	27.82±1.35$^{\alpha\alpha\alpha}$	108.62±11.93$^{\beta\beta\beta}$	81.39±6.21$^{\beta\beta\beta}$
LDL-Cholesterol (mg/dl)	48.45±11.87	133.85±25.04$^{\alpha\alpha}$	48.73±13.50$^{\beta\beta}$	55.35±5.63$^{\beta\beta}$
ARI	1.90±0.23	7.88±1.01$^{\alpha\alpha\alpha}$	1.76±0.26$^{\beta\beta\beta}$	2.14±0.17$^{\beta\beta\beta}$

Table 3. *Continued.*

Groups	E 75 + D	E 150 + D	E 300 + D
Total Protein	$4.19\pm0.24^{\beta\beta\beta}$	$4.41\pm0.29^{\beta\beta\beta}$	$3.64\pm0.62^{\beta\beta}$
Creatinin (mg/dl)	$3.07\pm0.69^{\beta\beta\beta}$	$4.46\pm0.09^{\beta\beta\beta}$	$2.69\pm0.37^{\beta\beta\beta}$
ALAT (IU)	33.07±4.13	$25.47\pm6.21^{\beta\beta}$	$24.13\pm2.94^{\beta\beta}$
ASAT (IU)	$40.08\pm9,15^{\beta}$	$38.79\pm6.44^{\beta\beta}$	$37.68\pm3.70^{\beta\beta}$
Triglycerides (mg/dl)	$191.87\pm4.11^{\beta\beta\beta}$	$192.11\pm2.74^{\beta\beta\beta}$	$182.62\pm6.72^{\beta\beta\beta}$
Total Cholesterol (mg/dl)	173.81±9.14	176.15±13.59	177.62±12.54
HDL-Cholesterol (mg/dl)	$73.10\pm4.93^{\beta\beta\beta}$	$99.76\pm6.85^{\beta\beta\beta}$	$82.25\pm9.29^{\beta\beta\beta}$
LDL-Cholesterol (mg/dl)	$62.71\pm6.80^{\beta\beta}$	$44.86\pm11.67^{\beta\beta}$	$57.39\pm18.34^{\alpha\alpha}$
ARI	$2.40\pm0.09^{\beta\beta\beta}$	$1.64\pm0.26^{\beta\beta\beta}$	$2.46\pm0.42^{\beta\beta\beta}$

Values are given as the mean±MSE, (n=5). Letters above numbers indicate statistical differences at $p<0.05$ in the Analysis of Variance (ANOVA) with the Bonferroni post-test. $^{\alpha}p<0.05$, $^{\alpha\alpha}p<0.01$, $^{\alpha\alpha\alpha}p<0.001$: versus the NC group. $^{\beta}p<0.05$, $^{\beta\beta}p<0.01$, $^{\beta\beta\beta}p<0.001$: versus the DexC. NC=normal control. DexC=Dexamethasone control. Met+D=Metformin + Dexamethasone (0.4 mg/kg). E38+D, E75+D, E150+D, E300+D=*P. soyauxii* aqueous extract at indicated doses (in mg/kg) + Dexamethasone (0.4 mg/kg).

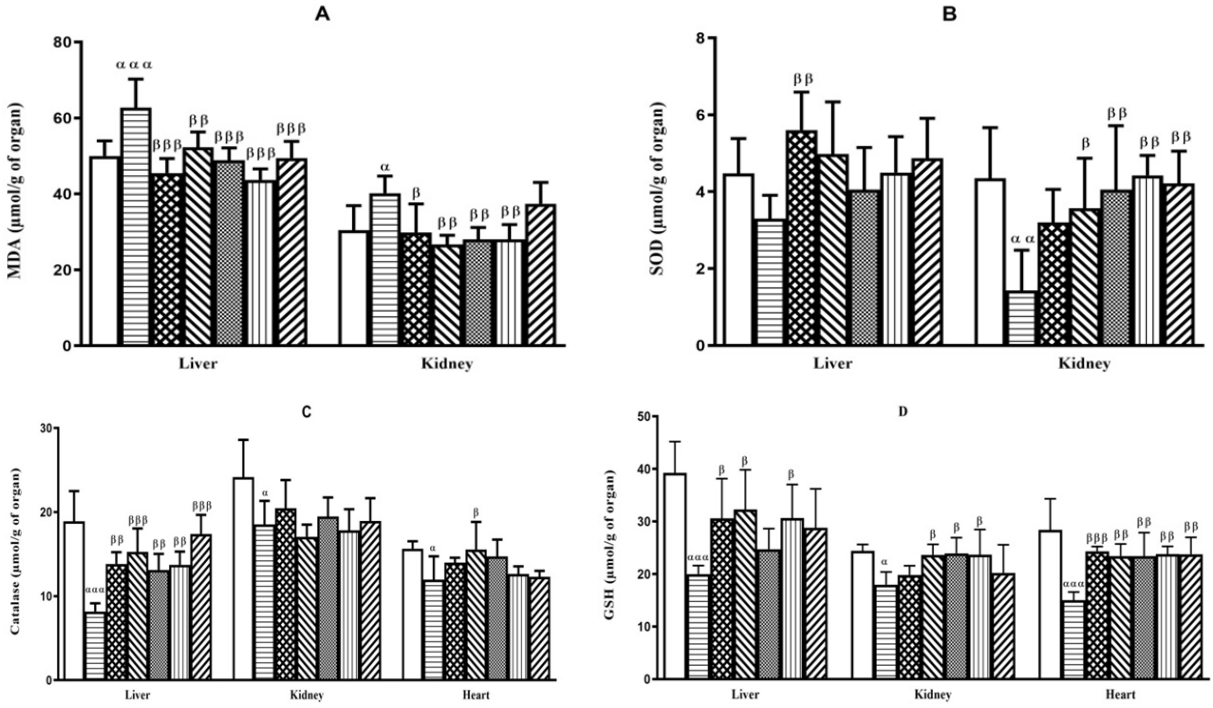
3.5. Sub-chronic Effects of P. soyauxii Taub Stem Bark Aqueous Extract on Oxidative Stress in Dexamethasone-treated Rats

At the end of the experiment, the MDA level significantly increased in the liver (25.45%; $p<0.001$) and kidney (31.89%; $p<0.05$) of DexC rats compared to NC rats, but decreased in metformin and plant extract treated groups with most effects in liver ($p<0.01$ – $p<0.001$) and kidney ($p<0.05$ – $p<0.01$), compared to DexC (Figure 3A).

Reduced glutathione (GSH) level (Figure 3B) significantly decreased in DexC rats [liver (49%, $p<0.001$); kidney (26.31%, $p<0.05$); heart (47.11%, $p<0.001$)] compared to NC, but significantly increased in plant extract/dexamethasone- [liver ($p<0.05$; E38 and E150 doses); kidney ($p<0.05$; E38, E75 and E150 doses); heart ($p<0.01$ – $p<0.001$; all doses)], and Metformin/dexamethasone- [(liver: $p<0.05$) and heart ($p<0.001$)] co-treated rats, compared to DexC rats.

The superoxide dismutase (SOD) activity (Figure 3C) also decreased in DexC rats [liver (67.19%; $p<0.01$) and kidney (26.34%; not-significant)] compared to NC. The *P. soyauxii* aqueous extract significantly enhanced this parameter at all doses in the kidney ($p<0.05$ – $p<0.01$), while metformin improved it in the liver ($p<0.01$), of dexamethasone-co-treated rats, compared to DexC rats.

In addition, there are decreased catalase (CAT) [liver (56.73%; $p<0.001$); kidney (33.20%; $p<0.01$); heart (23.64%; $p<0.05$)] (Figure 3D), and nitric oxide (NO) [cardiac (81.31%; $p<0.001$) and aortic (65.90%; $p<0.001$)] (Figure 3E) activities in DexC rats, compared to NC. All *P. soyauxii* aqueous extract doses and metformin significantly improved hepatic catalase activity ($p<0.01$ – $p<0.001$), but only the 38 mg/kg dose extract significantly improved cardiac catalase activity (30.12%; $p<0.05$), all compared to DexC (Figure 3D). Plant extract doses of 38, 75 and 150 mg/kg also improved NO activity in aorta ($p<0.001$), while Metformin almost normalized it ($p<0.01$) in heart and aorta, all compared to DexC rats (Figure 3E).



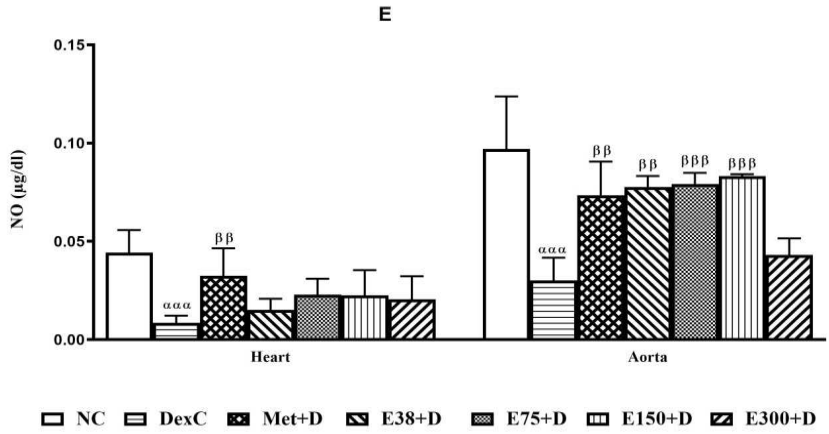


Figure 3. *Hepatic, renal and cardiac MDA (A), GSH (B), SOD (C) and CAT (D), and cardiac and aortic NO (E) levels or activities of normal and Dexamethasone-treated rats.*

The values are given as the mean±MSE, (n=5). $^{\alpha}p<0.05$, $^{\alpha\alpha}p<0.01$, $^{\alpha\alpha\alpha}p<0.001$: versus the NC group. $^{\beta}p<0.05$, $^{\beta\beta\beta}p<0.001$: versus the DexC group. NC=normal control. DexC=Dexamethasone control. Met+D=Metformin + Dexamethasone. E38+D, E75+D, E150+D, E300+D=*P. soyauxii* aqueous extract at indicated doses (in mg/kg) + Dexamethasone.

4. Discussion

Reducing the increasing type 2 diabetes incidence is a challenge, needing development of effective and low-toxic therapeutic approaches like phytomedicines that can improve insulin sensitivity or prevent insulin-resistance and oxidative stress. *Pterocarpus soyauxii* Taub stem bark aqueous extract has already been reported for its antidiabetic properties only on streptozotocin-induced type 1 diabetes [14]. The present work assessed its effects on glucose tolerance and dexamethasone–induced insulin-resistance and oxidative stress in rats, comparing to those of Glibenclamide and Metformin respectively.

The moderate, brave and late plant extract blood glucose lowering observed in oral glucose tolerance test (OGTT) suggest an anti-hyperglycemic effect of *P. soyauxii* stem bark aqueous extract (38 and 75 mg/kg doses); it would be beneficial for diabetes management than the high, prolonged and early effect of glibenclamide which causes excess insulin secretion, thus majorly limiting the best diabetes management as reported [14]. Extracts from *P. marsupium* Roxb [26] and *P. santalinoides* [27] have also been reported for their anti-hyperglycemic activities. Various *Pterocarpus* species show, with a few differences, similarities in their phytochemical composition (polyphenols, total phenols, flavonoids, glucosides, condensed tannins, sterols, terpenes, saponins and alkaloids evidenced in their various parts extracts) [13, 14, 28]. Flavonoids as pterocarpan, pterocarpin, vestitol, mucronulatol, and tannates as pterostilbene, whose biological effects are well known have even been identified in *P. soyauxii* wood extracts [29, 30]. Most compounds evidenced in *P. soyauxii* stem bark aqueous extract [14] probably involved in its anti-hyperglycemic activity would have either, inhibited or slowed intestinal glucose absorption, stimulated insulin secretion, inhibited glucagon secretion and/or pancreatic alpha-amylase as reported for the aqueous fraction of *P. osun* Craib leaves methanolic extract [31].

About 10 – 40% of patients on prolonged corticosteroid therapy develop diabetes [10]. The dose and duration of corticosteroid therapy increase the risk of impaired carbohydrate, lipid and protein metabolism, leading to hyperglycemia. Moreover, they potentiate that risk and hyperglycemia by reducing the hepatic glycogen formation (70%), stimulating the glucagon secretion, reducing the peripheral glucose use (30-50%) and oxidation, and exerting a direct toxic effect on β cells [32, 33]. In the present study, the lack of hyperglycemia of 21-days dexamethasone-treated rats (DexC rats) would be probably linked to age (2.5 to 3 months old) and a transient compensatory hyperinsulinemia as observed and suggested by Barbera *et al.* (2001), and would characterize a pre-diabetic condition. Clore and Thurby-Hay (2009) recommended that further testing being done in case of normal fasting blood glucose observed in prolonged corticosteroid-treated patient, to clarify its diabetic condition.

Thus, the insulin sensitivity test performed on day 22nd of experiment showed a significant insulin-resistance in DexC rats. Dexamethasone would have reduced the IRS-1 expression or phosphorylation in insulin target cells, thus successively deactivating the intracellular proteins (phosphatidyl inositol 3-kinase (PI3K), protein kinase B (PKB), glucose transporters (Glut)), thereby reducing oxidation and peripheral glucose use. Furthermore, the direct dexamethasone toxic effect on beta cells would have worsened insulin-resistance and carbohydrate dysregulation [32, 36, 37]. However, the co-treatment with *P. soyauxii* aqueous extract or Metformin significantly improved the insulin target cells sensitivity, and interestingly the plant extract effects were comparable to metformin's. These suggest that the plant extract thus would have inhibited or reversed the dexamethasone deleterious effects on insulin metabolic pathway [38, 39], activating thereby the peripheral glucose use and oxidation; It would also as metformin have increased the muscle glucose availability and inhibited hepatic

gluconeogenesis via the mitochondrial respiratory chain complex 1 activity inhibition, thus altering the AMP/ATP ratio in favor of AMP, successively resulting in energy deficiency, fructose-1,6-biphosphatase inhibition, AMPK activation, lipotoxicity reduction, insulin sensitivity improvement, and consequently insulin control restoration on gluconeogenesis [40]. The plant extract would also have inhibited the glycerophosphate dehydrogenase, reducing the lactate and glycerol conversion to glucose and hepatic gluconeogenesis [41]. Flavonoid and saponin phytochemical compounds, reported to inhibit the gluconeogenesis and the glycogen phosphorylase expression, and to increase the Glut expression [38, 39], could be involved in these *P. soyauxii* effects.

Insulin-resistance inhibits the cell glucose transport leading to a muscle myofibrillary proteins catabolism increase for providing energy and therefore serum creatinine increase, promotes the amino acids capture inhibition and protein synthesis reduction, thus leading to a hypoproteinemia which would accentuate muscle wasting and body mass loss [42, 43]. All rats given dexamethasone showed a body mass loss although the relative organs masses did not change, as also observed by Severino *et al.* (2002) in 4-weeks dexamethasone-treated rats. However, the DexC rats body mass loss was associated to decreased total proteinemia and increased serum creatinine, while (plant extract or metformin)-dexamethasone-cotreated rats had total proteinemia increase and normalized creatinemia despite their body mass loss. These results show a protective role of that plant extract against dexamethasone-induced muscle wasting, probably due to the plant steroids which would have stimulated the amino acids capture and protein synthesis, and its flavonoids and saponins which would have inhibited the gluconeogenesis, improving insulin sensitivity and secretion, thereby promoting the proteolysis inhibition, and cell glucose uptake and use as energy. Furthermore, the plant extract-induced serum creatinine normalization reflects this proteolysis inhibition and suggests that *Pterocarpus soyauxii* can protect against diabetic nephropathy [14].

Dexamethasone–induced insulin-resistance also causes dyslipidemia by inhibiting the insulin anti-lipolytic action [45], leading to serum triglyceride, total cholesterol and LDL-cholesterol increase, and serum HDL-cholesterol decrease as observed in DexC rats, contributing to a very high risk of developing coronary diseases (ARI of at least 4 times the normal). The *P. soyauxii* aqueous extract (38-300 mg/kg) improving effects as metformin's on lipid profile of dexamethasone-induced diabetic rats (by preventing the serum HDL-cholesterol reduction, and triglycerides, total cholesterol, LDL-cholesterol and atherogenic risk index increase) are also due to its beneficial effect on insulin sensitivity. Okwuosa *et al.* (2011) reported that the *P. santalinoides* leaf aqueous extract–induced serum triglycerides decrease was linked to an inhibitory activity of that extract on the phosphoenolpyruvate carboxykinase and glucose-6-phosphatase expression. Furthermore, Nkono *et al.* (2014) suggested that the *Alstonia boonei* de Wild aqueous extract would improve the lipid profile probably by inhibiting the lipoprotein lipase activity, reducing the hydrolysis of triglycerides to glycerol and fatty acids. The *P. soyauxii* stem bark aqueous extract would thus have acted, probably thanks to its components which, as reported, would have inhibited the activity and/or expression of these different enzymes involved in the lipogenesis and/or gluconeogenesis (pterostilbene) [47-50], exerted an insulin-like effects (vestitol) [51], inhibited the cholesterol intestinal absorption (sterols) [52-56], activated the PPAR factor and inhibited the SRBPT receptors involved in lipid metabolism (some flavonoids as Pterostilbene, and saponins) [38, 42, 57, 58].

Serum or tissue transaminases (ALAT/ASAT) levels change provides information on hepatocyte membranes and liver function alteration, and cellular necrosis. ASAT also provides information on hearth or muscle damage. The *P. soyauxii* extract doses-induced ALAT/ASAT activities decrease suggests it protective effect against liver dysfunction, heart and muscle toxicity, probably thanks to the flavonoids, terpenes and other phenolic compounds as suggested by Sarkhail *et al.* (2007). Tchamadeu *et al.* (2017) previously reported decreasing effects of *P. soyauxii* aqueous extract on ALAT/ASAT activities in STZ-induced diabetic rats. Authors have supported the prediction of tissue damage following increased transaminases by analyzing oxidative and antioxidative parameters.

Thus, the significant kidney MDA increase and, Kidney SOD, liver, kidney and heart GSH and CAT decreases of DexC rats suggest the oxidative stress installation due to free radicals' dexamethasone-induced overproduction (reactive oxygen/nitrogen species) as reported by Koceir (2015). The combined deleterious effects of dexamethasone above observed in DexC rats (insulin-resistance – hyperglycemia – hyperlipidemia) would have led to cell glucotoxicity/lipotoxicity, contributing to free radicals increase, and later to the antioxidant components depletion (GSH, SOD, catalase) and increased cell membranes oxidation (elevated MDA). In the other hand, the NO activity decrease observed in heart and aorta of DexC rats as reported [43] was also probably due to the insulin-resistance which would have inhibited the insulin-induced NOS activation, the NO overuse as antioxidant [45, 61], and to dexamethasone altering effect on L-arginine transporters lowering the NO precursor (L-arginine) availability, thus decreasing the NO synthesis, rate and activity in tissues. However, the plant extract doses-induced MDA reduction, GSH, SOD and catalase increase level or activities, are still probably linked to its beneficial effect on insulin sensitivity. The plant extract would have increased the NO activity either by improving insulin sensitivity, stimulating the NOS synthesis, deactivating the NOS inhibitor (ADMA), ensuring the L-arginine availability and/or by reducing oxidative stress. In addition, the plant extract flavonoids, saponins and tannins, would have stimulated these antioxidants biosynthesis and trapped free radicals [38, 62-64], as reported for *P. marsupium* aqueous extract [65]. Moreover, Tannins isolated from *Guiera senegalensis* have also been reported having an anti-radical power and inhibiting lipid peroxidation [66].

5. Conclusion

The *Pterocarpus soyauxii* Taub stem bark aqueous extract has moderate (compare to glibenclamide) and inversely dose-response antihyperglycemic impact in acute administration in glucose–overloaded normal rats, and potent preventive effects (almost like metformin) against insulin-resistance with improving metabolic and antioxidant parameters in sub-chronic administration in dexamethasone-induced insulin-resistant rats. It thereby improves hepatic, renal, cardiac and vascular functions in dexamethasone-induced insulin-resistant rats. That would be due to the combined action of all or at least some of its metabolites. Therefore, following its recommendation for type 1 diabetes treatment, *P. soyauxii* aqueous extract may be useful for alternative and preventive oral treatment of type 2 diabetes and metabolic alterations, at least at the limit of the studied doses.

To better elucidate the *P. soyauxii* Taub action mechanism in the treatment of diabetes mellitus, additional studies evaluating its curative effects on type 2 diabetes, on cardiovascular, nervous and reproductive diabetic complications, on the expression of metabolism enzymes (α-amylase, lipase, G6PD…) and of proteins of insulin signaling pathways and glucose transport, are necessary.

Conflict of Interest

There are no conflicts of interest.

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