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Hepato- and Nephro-Effect of *Sphenostylis stenocarpa*– Formulated Diet on Dexamethasone-Treated Pregnant Rats

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Abstract

This study sought to investigate the effect of *Sphenostylis stenocarpa*-formulated diet on hepatic and renal parameters of dexamethasone-treated pregnant rats. *Sphenostylis stenocarpa* were locally sourced from a market in Ado Ekiti. They were milled into powder and used in formulating feed for experimental animals. Fifteen female pregnant rats were divided in three groups of five each. Animals in group A were exposed to standard animal feed only. This served as the control group. Those in group B were exposed to *Sphenostylis stenocarpa*-formulated diet + 0.3 mg/kg body weight of dexamethasone, while those in group C were exposed to *Sphenostylis stenocarpa*-formulated diet. At the end of the eight days treatment, animals were sacrificed and blood sample, liver and kidney were collected. Exposure of pregnant rats to dexamethasone was observed to significantly ($p<0.05$) increased the activities of plasma aspartate amino transaminase (AST) and alanine amino transferase (ALT) as well as the concentrations of plasma total protein, bilirubin, creatinine and urea when compared with those in animals in the control as well as those fed with S. stenocarpa-formulated diet only. The results further showed that pregnant rats fed with S. stenocarpa-formulated diet only had no significant difference on plasma hepatic and renal biomarkers when compared with those in the control group. The results of liver and kidney homogenates are similar to those observed in the plasma. Exposure of animals to dexamethasone adversely unhinged hepatic and renal biomarkers investigated in the study. The study also revealed that *P. biglobosa* seed is beneficial to the health of the liver and kidney of pregnant female rats.

Keywords: Dexamethasone, Liver, Renal, *Sphenostylis stenocarpa.*

1. Introduction

The liver is an accessory digestive organ that produces bile, an alkaline fluid containing cholesterol and bile acids, which helps the breakdown of fat. The gallbladder, a small pouch that sits just under the liver, stores bile produced by the liver which is afterwards moved to the small intestine to complete digestion [1]. Changes in value of certain serum liver function tests occur during normal pregnancy and an understanding of these physiological changes is necessary for the management of liver diseases. Because of the phenomenon of hemodilution, the albumin level decreases as early as the first trimester. Serum alanine and aspartate aminotransferase activity levels remain within the normal limits established for nonpregnant women. Measurement of serum aminotransferase levels thus remains the most useful test for the routine diagnosis of liver diseases during pregnancy [2].

Serum total and free bilirubin concentrations are lower in pregnant women than in nonpregnant controls during all three trimesters, as are concentrations of conjugated bilirubin during the second and third trimesters. Serum alkaline phosphatase activity increases in late pregnancy, due both to the production of the placental isoenzyme and to the increase in bone isoenzyme. Consequently, measurement of serum alkaline phosphatase levels is not a suitable test for the diagnosis of cholestasis during pregnancy. Serum gamma-glutamyl transferase activity levels decrease during the second and third trimesters, and serum 5'nucleotidase activity increases slightly in the second and third trimesters. Serum total bile acid concentrations during pregnancy are not different compared to levels in nonpregnant women. Measurement of serum bile acids may be useful for the diagnosis of cholestasis, especially when serum aminotransferase levels are within normal limits. In summary, according to the clinical setting, an increase in values of serum aminotransferase activity, serum GGT activity, serum bilirubin or fasting total bile acid concentrations during pregnancy should be considered pathologic [2].

Measurement of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity levels is the most useful test for the routine diagnosis of liver diseases [3]. The effects of pregnancy in serum ALT and AST activity levels are somewhat controversial. A slight increase in ALT and/or AST activity has been found during the third trimester. However, in the majority of published studies, serum ALT and AST activity levels do not change during pregnancy or remain within the normal limits established in nonpregnant women. An increase in ALT or AST levels during labor might be due to contractions of the uterine muscle. Thus, it should be emphasized that serum AST or ALT activity values above the upper normal limit before labor should be considered pathologic and should lead to further investigations [2].

African yam bean (AYB) *Sphenostylis stenocarpa*, Horst ex. Rich, belongs to the Fabaceae family characterized by its fruit (legume) and stipulated leaves. It originated in Ethiopia, but both wild and cultivated types now occur in tropical Africa as far north as Egypt and also throughout West Africa from Guinea to southern Africa [4]. African Yam Bean or *Sphenostylis stenocarpa* is locally known as Otili among the Yorubas. The under-exploited specie is of important food source in Africa, seeds are usually added to soups, made into sauces, or milled into flour [5,6].

It grows as a vine to heights of about 3m and produces brightly colored flowers in 100 - 150 days. The yam bean is a useful source of nutrients for many African communities with a nutritional value comparable to that of the soybean, although the cooking time for the yam bean is much longer.

Figure 1: African yam bean [7].

The chemical composition of these grain legumes was shown to contain high quantities of proteins, amino acids, fiber, and minerals [8,9]. Different foods and chemicals consumed by man have put the liver and kidney at great risk of toxicity. Some foods have the propensity to ameliorate the adverse effects of these toxic substances in the liver and kidney. Thus, this study examined the effect of African yam bean (*Sphenostylis stenocarpa*) on hepatic and renal parameters of dexamethasone-treated pregnant rats.

2. Methods

2.1. Collection and Preparation of Materials

Dried *Sphenostylis stenocarpa* seeds were locally sourced from open bushes within Ado Ekiti, Nigeria. They were authenticated by the Chief botanist of the Department of Plant Science, Ekiti State University, Ado-Ekiti and deposited in the University's Herbarium with Voucher number UHAE-1010065. They were carefully selected to remove the perceived bad seeds.

The seeds were sun-dried and milled into powder using and electric blender.

2.2. Experimental Design

The use of animals for this study was approved by the Experimental Animal Research Ethics Committee of Ekiti State University, Ado-Ekiti with ethical approval number ORD/ETHICS/AD/043. Twenty one Albino rats (6 males and 15 females) were obtained from the Animal House, Faculty of Basic Medical Sciences, College of Medicine, Ekiti State University, Ado-Ekiti. They were grouped into three of 2 males and 5 females in each group using plastic cages with steel wire lids to copulate, since the experiment requires the female Albino rats to be pregnant. They were kept at room temperature with adequate access to rat chow and water throughout the experimental period. After a week of copulation, all the female Albino rats were confirmed pregnant by the animal house technician. The males rats were removed from their cages and the female pregnant rats were treated as follows:

animals in group A were exposed to standard animals feed only. This served as the control group. Those in group B were exposed to S. stenocarpa-formulated diet + 0.3 mg/kg body weight of dexamethasone, while those in group C were exposed to S. stenocarpa-formulated diet only. At the end of the eight days treatment, animals were sacrificed and blood sample was collected into EDTA bottles and centrifuged. Plasma was separated and preserved at 4 ℃ for further analysis. Liver and kidney were also harvested from the rats and were homogenized in phosphate water using a mechanical homogenizer and the homogenates were centrifuged for 5 minutes. The supernatant were collected and were used to carry out the biochemical assays.

2.3. Determination of Biochemical Parameters

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) activities were determined using Randox commercial Enzyme kits according to the method of Reitman and Frankel [10]. Total Protein concentration was carried out using Biuret method described by Henry et al. [11]. Estimation of albumin was done by bromocresol green (BCG) method described by Doumas et al. [12]. Bilirubin concentration was determined by diazo method described by Royden and Alfred [13]. Creatinine concentration was determined using Jaffe reaction described by Toora and Rejagopal [14]. Urea concentration was determined using a Randox Commercial Kit based on the methods of Fesus et al. [15]. The concentrations of total protein and albumin were determined using Biorex diagnostic kit according to the methods of Lorentz [16].

2.4. Statistical Analysis

Data were subjected to analysis of variance using Graph Pad Prism. Results were presented as Mean ± Standard deviation.

One way analysis of variance (ANOVA) was used for comparison of the means followed by Tukey's post hoc test. Differences between means were considered to be significant at $p<0.05$.

3. Results

Exposure of pregnant rats to dexamethasone was observed to significantly ($p<0.05$) increased the activities of plasma aspartate amino transaminase (AST) and alanine amino transferase (ALT) as well as the concentrations of plasma total protein, bilirubin, creatinine and urea when compared with those in animals in the control as well as those fed with S. stenocarpa-formulated diet only **(table 1).** The results further showed that pregnant rats fed with S. stenocarpa-formulated diet only had no significant difference on plasma hepatic and renal biomarkers when compared with those in the control group. Tables 2 and 3 contained the results from liver and kidney homogenate respectively. These results are similar to those observed in the plasma.

4. Discussion

Biological Enzymes such as Aspartate transaminases (AST), alanine transaminases (ALT) and alkaline are useful biomarkers of liver injury [17]. These enzymes can be found mainly in the liver, red blood cells, heart, pancreas, kidneys and biliary ducts of the liver. The results of this study showed that dexamethasone exposure significantly increased the activities of liver enzymes (AST and ALT) in the plasma and liver of treated rats when compared with those in the control group. This could be suggestive that dexamethasone is toxic to the liver and might have induced hepatotoxicity in the pregnant rats used in this study. A similar study by Oladele et al. [18] reported the hepatotoxic potential of dexamethasone in pregnant rats. Release of mitochondrial enzymes from the liver is considered to provide strong evidence for hepatic necrosis [19].

Parameters	Control	Dexamethasone + S. stenocarpa	S. stenocarpa only
AST (U/L)	46.75 ± 1.16^{b}	59.33±1.06^{a}	49.750±3.67^{b}
ALT (U/L)	38.21 ± 3.07 ^{b}	48.86±1.98^{a}	36.76±1.77^{b}
Total Protein (mmol/L)	49.95 ± 1.92^{b}	61.81±3.73^{a}	43.67±1.57^{b}
Albumin (mmol/L)	28.38 ± 0.89^{b}	36.23±1.58^{a}	26.70± 2.00^{b}
Bilirubin (mmol/L)	83.73± 1.56^{b}	118.08 ±2.92^{a}	85.92±6.71^{b}
Creatinine (mmol/L)	44.26 ± 1.74^{b}	63.673±1.43^{a}	42.21±2.19^{b}
Urea (mg/dL)	6.22±0.92^{b}	9.04±1.15 ^{a}	6.53±1.01^{b}

#Results are presented as mean±standard deviation with n = 5.

#Values with different superscripts along the same row are significantly different at P<0.05.

Legend: AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase.

Table 1: Effect of S. stenocarpa on Plasma Hepatic and Renal Biomarkers of Dexamethasone-Treated Pregnant Rats**.**

Treatment Group	AST (U/L)	ALT (U/L)	Total Protein (mmol/L)	Albumin (mmol/L)
Control	44.20±1.47 ^{b}	39.29± 0.87 ^{b}	86.58±1.92 ^{b}	22.67± 2.23 ^{b}
Dexamethasone + S. stenocarpa	57.55 ± 0.63 ^{a}	45.90± 1.57 ^{a}	97.78±2.64 ^{a}	25.10± 1.95 ^{a}
S. stenocarpa only	42.44 ± 3.13 ^{b}	36.93 ±1.23 ^{b}	84.63±0.83 ^{b}	21.92±1.05 ^{b}

#Results are presented as mean±standard deviation with n = 5.

#Values with different superscripts along the same column are significantly different at P<0.05.

Legend: AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase.

Table 2: Effect of S. stenocarpa on the Hepatic Biomarkers of Liver-Homogenate of Dexamethasone-Treated Pregnant Rats.

Treatment Group	Urea (mmol/dL)	Creatinine (mmol/L)
Control	51.87 ± 1.42 [b]	54.23 ± 1.74 [b]
Dexamethasone + S. stenocarpa	64.09 ± 2.720 [a]	65.32 ± 1.77 [a]
S. stenocarpa only	53.28±4.32 [b]	55.17±3.28 [b]

#Results are presented as mean±standard deviation with n = 5.

#Values with different superscripts along the same column are significantly different at P<0.05.

Table 3: Effect of S. stenocarpa on the Renal Biomarkers of Kidney-Homogenate of Dexamethasone-Treated Pregnant Rats.

AST is also found in other organs such as the heart and skeletal muscle, while ALT has low concentrations in the skeletal muscle and kidney, and is chiefly produced in the hepatocytes [20,21]. Release of liver mitochondrial enzymes is considered as strong evidence for hepatic necrosis, which is associated with an increased production of Reactive Oxygen Species (ROS), often leading to greater hepatic lipid peroxidation [22]. Interestingly, Oladele et al. [23] have reported that dexamethasone induced oxidative stress by increasing the generation of ROS. Thus, the hepatotoxic effect of dexamethasone observed in this study might be due to its increased generation of free radicals.

It was also observed that the activities of AST and ALT in the plasma of animals fed with S. stenocarpa-formulated diet only were not significantly different when compared with those in the control group. This result is similar to the nonsignificant difference observed in the activities of liver enzymes by Okoye and Esiobise [24] when they treated animals with S. stenocarpa aqueous extracts for 3, 7, and 10 days respectively. In fact, Okonkwo et al. [25] reported that S. stenocarpa possessed hepatoprotective ability against CCl_4-induced liver damage.

Similarly, a significant increase was observed in the concentrations of bilirubin, total protein and albumin in dexamethasone-treated animals when compared with those in control animals. This might suggest that dexamethasone has affected the synthetic ability of protein by the liver. It might also be suggestive that dexamethasone perturbed the functional activity of the liver by interfering with the equilibrium in the rate of synthesis and destruction, removal or clearance of total protein and albumin from the system of the animals [26]. Increase in total protein has been reported to lead to dehydration which is detrimental to cellular homeostasis [27] which negatively affects the metabolic activities of the liver and consequently the health of the animals. Albumin binds and transports metal ions, bilirubin, and drugs [28]. Its level is used to assess the synthetic function of the liver. Plasma protein levels are regulated via synthesis in the liver and its levels thus reflect the synthetic ability of the liver. Increase in concentration of bilirubin in blood causes hyperbilirubinaemia, which is toxic under certain conditions inducing jaundice, hyperbilirubinemia-induced auditory dysfunction and neurotoxicity resulting in brain damage [29]. Therefore, the result of this study is an indication that dexamethasone compromised the integrity of the liver. The nonsignificant difference observed in the concentrations of hepatic biomarkers in animals fed with S. stenocarpa–formulated diet only when compared with those in the control group in this study predicts that the S. stenocarpa did not cause liver damage. This observation affirms the hepatoprotective ability of S. stenocarpa reported earlier reported by Okonkwo et al. [25].

Dexamethasone used in this study significantly ($p<0.05$) increased the concentrations of creatinine and urea in both plasma and kidney homogenate when compared with those of animals in the control group. This is consistent with the findings of Oladele et al. [18] who observed that dexamethasone increased the concentrations of urea and creatinine in both plasma and kidney homogenate. Urea is a major nitrogenous end product of protein and amino acid catabolism, and creatinine is a breakdown product of creatinine phosphate in the muscle [30]. They are eliminated from the body by the kidney. The significant rise in the concentrations of creatinine and urea in plasma and kidney homogenate observed in this study most probably represents increased production of both creatinine and urea to meet the energy demand following severe oxidative stress caused by dexamethasone.

Urea and creatinine have been reported to be good markers of a normal functioning nephron and elevation in the plasma could also be a pointer to kidney dysfunction as they are widely accepted and commonest parameters to assess renal functions [31]. These results showed that renal functions were adversely unhinged by dexamethasone exposure. This could elevate the incidence of chronic kidney disease arising from nephrotoxicity of dexamethasone and its ability to damage the kidney. The effect of *S. stenocarpa* in animals fed with *S. stenocarpa*–formulated diet only when compared with those in the control group suggests that the *S. stenocarpa* did not cause damage, and thus could be nephron-protective. This corresponds to the findings of Okoye and Esiobise [24] who treated animals with *S. stenocarpa* aqueous extracts for 3, 7, and 10 days respectively. Ojiako et al. [32] reported a similar finding when they investigated the functional assessments and histopathology of hepatorenal tissues of rats treated with raw and processed herbs.

5. Conclusion

Dexamethasone was observed to adversely perturbed liver and kidney biomarkers assayed in the study while S. stenocarpa –formulated diet is beneficial to hepatic and renal health of pregnant female rats.

6. Consent

It is not applicable.

7. Conflict Of Interests

Authors have declared that no conflict of interests exist in this study and publication.

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