



Assessment of *Parkia biglobosa* on Hepatic and Renal Biomarkers of Dexamethasone-Exposed Pregnant Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study sought to investigate its effect on hepatic and renal biomarkers of female pregnant rats.

Place and Duration: This work was carried out in the Department of Medical Biochemistry and Department of Science Laboratory Technology, Ekiti State University, Ado Ekiti between January and June 2021.

Methodology: Locust bean seeds were purchased from an open market in Ado Ekiti, Nigeria and were processed using standard method. Fifteen female pregnant rats were divided into 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 animal feed mixed with locust beans + 0.3 mg/kg body weight of dexamethasone, while those in group C were exposed to animal feed mixed with locust beans only. At the end of the eight days treatment, animals were sacrificed and blood sample, liver and kidney were collected.

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

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when compared with those in animals in the control as well as those treated with *P. biglobosa* only. The results further showed that administration of *P. biglobosa* only had no significant effect on plasma hepatic and renal biomarkers except urea which was significantly lower than those in the control group as well as those treated with dexamethasone. The results obtained from liver and kidney homogenate respectively are similar to those observed in the plasma.

Conclusion: Exposure of animals to dexamethasone adversely uninged 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; Pregnancy; *Parkia biglobosa*; Liver; Kidney.

1. INTRODUCTION

Liver is the major organ which plays key roles in processing critical biochemical and physiological phenomena including metabolism and detoxification of endogenous and exogenous compounds, such as drugs and xenobiotics, homeostasis, growth, energy and nutrient supply [1]. Hepatic injury could occur by hepatotoxic agents such as drugs, alcohol, hydrocarbon and viral infections [2]. Liver diseases like jaundice, cirrhosis and fatty liver have been public health concern across the world [3]. Prevalence of chronic liver disease worldwide is 18.5% and cirrhosis is 4.5 to 9.5% while 2 million people die each year. In terms of medication, conventional or synthetic drugs are limited. Moreover they can have serious side effects [4,5]. Due to this fact, a huge number of medicinal plants have been used to figure out hepato-protective activities [6]. Approximately 160 phytochemical constituents originated from 101 plants have been reported to be potentially hepato-protective [7]. At present, medicinal plants have been a vital source of treatment of liver [8].

Nephrotoxicity can be defined as the adverse effect of substances on renal function [9]. These substances can include molds and fungi, cancer therapeutics such as cisplatin, antibiotics such as aminoglycosides, metals such as mercury, arsenic and lead, and drugs of abuse such as cocaine. One indication of nephrotoxicity is a change in renal function as assessed by the glomerular filtration rate (GFR), blood urea nitrogen (BUN), serum creatinine (sCr), or bilirubin concentrations; however, nephrotoxicants can induce kidney damage without changing any established clinical marker of renal function. For example, studies have shown that proximal tubule necrosis in male Sprague Dawley rats exposed to gentamicin can be as high as 75% prior to any increases in BUN or sCr [10].

Parkia biglobosa (locust bean) has long been widely recognized as an important indigenous multipurpose fruit tree whose uses include food, medicine, manure, tannin, shade, wind breaks, bee food, stabilization of degraded environment, livestock feed, fuel, fibre, fish poison and several other domestic uses [11]. *Parkia biglobosa* has many medicinal uses in Africa [12]. It provides an ingredient that is used in treating leprosy and hypertension [13]. It has been identified as one of the candidates with promising therapeutic potential in the prevention, treatment, and management of a number of metabolic diseases including diabetes mellitus [14]. According to Tokoudagba et al. [15], *P. biglobosa* leaf extracts induce redox-sensitive endothelium-dependent relaxations in porcine coronary artery rings thereby acting as an antihypertensive agent. The leaves are used in lotions for sore eyes, burns, haemorrhoids and toothache [12]. A decoction of the leaves, bark and roots are used in treating leprosy, eye sores, toothache, fever, hypertension, wounds and ulcers [16]. Airaodion et al. [17], has reported that *P. biglobosa* seed possesses hepatoprotective ability. In another study, Airaodion and Ogbuagu [18] observed that *P. biglobosa* seed ameliorated hypertension. This study sought to investigate its effect on hepatic and renal biomarkers of female pregnant rats.

2. METHODS

2.1 Collection and Preparation of Materials

Locust bean seeds were purchased from an open market in 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-2020063. They were selected for any possible dirt and was rinsed thoroughly with

water, after which, they were soaked in a cold water for about 15 minutes and boiled in a pressure pot for 2 hours, followed by de-hulling and stepping/matching on the boiled locust beans and washing with cold water, it was re-washed and cooked for 45 minutes to make it softer and rinsed using a plastic sieve. It was fermented to produce the food condiment which is used as soup seasoning/spices (flavoring agent). This was done by spreading the boiled locust beans into a fermenting can and wrapped with cloth for 48 hours to prevent oxygen. Subsequently, the fermented *P. biglobosa* seeds were air dried for 3 days and was milled into powder using an electric blender and stored for further analysis.

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 animal feed mixed with locust beans + 0.3 mg/kg body weight of dexamethasone, while those in group C were exposed to animal feed mixed with locust beans. 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 °C 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 [19]. Total Protein concentration was carried out using Biuret method described by Henry et al. [20]. Estimation of albumin was done by bromocresol green (BCG) method described by Doumas et al. [21]. Bilirubin concentration was determined by diazo method described by Royden and Alfred [22]. Creatinine concentration was determined using Jaffe reaction described by Toora and Rejagopal [23]. Urea concentration was determined using a Randox Commercial Kit based on the methods of Fesus et al. [24]. The concentrations of total protein and albumin were determined using Biorex diagnostic kit according to the methods of Lorentz [25].

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 transferase (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 treated with *P. biglobosa* only (Table 1). The results further showed that administration of *P. biglobosa* only had no significant effect on plasma hepatic and renal biomarkers except urea which was significantly lower than those in the control group as well as those treated with dexamethasone. Tables 2 and 3 contained the results from liver and kidney homogenate respectively. The results are similar to those observed in the plasma.

4. DISCUSSION

Every organ can elicit a specific pattern of enzyme release, which has not been elucidated. Specifically, above-normal plasma enzyme

activities are considered as diagnostic features for several diseases [26]. Liver tissue damage due to toxic compounds is associated with its detoxification function [27]. The results of plasma hepatic and renal parameters determined in this study are presented in Table 1.

The activity of AST in dexamethasone-treated rats was observed to be significantly ($P < 0.05$) higher when compared with those in the control group as well as those treated with *P. biglobosa* only. This increase might be an indication of hepatotoxic effect of dexamethasone as AST is a biomarker enzyme found to be abundant in cases where the liver might be damaged [28,29].

Similarly, the activity of ALT was significantly ($p < 0.05$) increased in animals exposed to dexamethasone when compared with those in control animals as well as the group treated with *P. biglobosa* only. The distribution and relative tissue concentration of ALT is similar but importantly different. Highest activity is found in the liver, followed by kidney, myocardium, skeletal muscle, pancreas, spleen, lung, and erythrocyte [30]. ALT activity is found in the cytosol, unlike AST which is both cytosolic (20% of total activity) and mitochondrial (80% of total activity) [28,31]. Release of mitochondrial enzymes from the liver is considered to provide

strong evidence for hepatic necrosis [32]. 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 [31,33]. Release of liver mitochondrial enzymes is considered as a strong evidence for hepatic necrosis, which is associated with an increased production of Reactive Oxygen Species (ROS), often leading to greater hepatic lipid peroxidation [34]. It was also observed that treatment of animals with *P. biglobosa* only had no significant effect on liver enzymes assayed in this study. This result conformed to the findings of Airaodion et al. [17] who reported that *P. biglobosa* possessed hepatoprotective propensity.

In this study, a significant increase was observed in the concentrations of total protein and albumin in dexamethasone-treated animals when compared with those in control animals as well as those in the group exposed to *P. biglobosa* only. This might suggest that dexamethasone has affected the synthetic ability of protein by the liver. It is also an indication that dexamethasone distorted 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 [35]. Increase in total protein has

Table 1. Effect of *P. biglobosa* on plasma hepatic and renal biomarkers of dexamethasone-treated pregnant rats

Parameters	Control	Dexamethasone + <i>P. biglobosa</i>	<i>P. biglobosa</i> only
AST (U/L)	46.75 ± 1.16 ^b	63.88 ± 2.21 ^a	47.32 ± 2.29 ^b
ALT (U/L)	38.21 ± 3.07 ^b	48.28 ± 3.12 ^a	37.10 ± 1.83 ^b
Total Protein (mmol/L)	49.95 ± 1.92 ^b	64.85 ± 2.51 ^a	46.02 ± 3.40 ^b
Albumin (mmol/L)	28.38 ± 0.89 ^b	37.50 ± 2.43 ^a	26.11 ± 1.31 ^b
Bilirubin (mmol/L)	83.73 ± 1.56 ^b	101.12 ± 4.45 ^a	81.15 ± 5.03 ^b
Creatinine (mmol/L)	44.26 ± 1.74 ^b	67.42 ± 2.00 ^a	43.02 ± 1.04 ^b
Urea (mg/dL)	6.22 ± 0.92 ^b	8.76 ± 1.27 ^a	5.08 ± 0.63 ^c

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 2. Effect of *P. biglobosa* on the hepatic biomarkers of liver-homogenate of dexamethasone-treated pregnant rats

Treatment Group	AST (U/L)	ALT (U/L)	Total Protein (mmol/L)	Albumin (mmol/L)
Control	47.20 ± 1.47 ^b	34.29 ± 0.88 ^b	73.58 ± 1.92 ^b	15.99 ± 1.82 ^b
Dexamethasone + <i>P. biglobosa</i>	57.56 ± 0.63 ^a	46.90 ± 1.58 ^a	85.78 ± 2.64 ^a	28.03 ± 4.09 ^a
<i>P. biglobosa</i> only	42.44 ± 3.13 ^b	45.23 ± 1.28 ^b	69.63 ± 0.83 ^b	17.37 ± 1.54 ^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 3. Effect of *P. biglobosa* on the renal biomarkers of kidney-homogenate of dexamethasone-treated pregnant rats

Treatment Group	Total Protein (mmol/L)	Urea (mg/dL)	Creatinine (mmol/L)
Control	19.67 ± 2.20 ^b	51.87 ± 1.41 ^b	54.23 ± 1.73 ^b
Dexamethasone + <i>P. biglobosa</i>	25.18 ± 1.12 ^a	66.46 ± 1.93 ^a	67.62 ± 1.79 ^a
<i>P. biglobosa</i> only	17.44 ± 3.44 ^b	53.53 ± 1.13	55.04 ± 2.57 ^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

been reported to lead to dehydration which is detrimental to cellular homeostasis [36] 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. 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. Therefore, the result of this study is an indication that dexamethasone compromised the integrity of the liver.

Bilirubin is the breakdown product of heme moiety of hemeoglobin; other hemeoproteins include cytochromes, catalase, peroxidase, tryptophan pyrrolase and a small pool of free heme [37]. 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 [38]. Plasma bilirubin levels are often enhanced under a variety of clinical conditions. In the circulation of blood, bilirubin is bound to plasma albumin, which prevents its potential toxicity thought to be caused by free bilirubin [39]. Despite its high affinity of binding to albumin, bilirubin is rapidly and selectively taken up by the liver, biotransformed upon conjugation with glucuronate, and secreted into bile [40]. Thus bilirubin is converted into bilirubin glucuronic acid in the liver and excreted along with bile. The nonsignificant difference observed in the concentrations of hepatic biomarkers in animals treated with *P. biglobosa* only when compared with those in the control group in this study suggests that the *P. biglobosa* did not cause liver damage. This observation affirms the hepatoprotective ability of *P. biglobosa* reported earlier reported by Airaodion et al. [17].

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 as well as those treated with *P. biglobosa* only. 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 [41]. They are excreted 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 are good indicators of a normal functioning kidney and increase in the plasma could also be indications of kidney dysfunction as they are widely accepted and commonest parameters to assess renal functions [42]. These results suggest that kidney functions were seriously impaired by dexamethasone exposure. This may increase the incidence of chronic kidney disease arising from nephrotoxicity of dexamethasone and its ability to damage the kidney. The effect of *P. biglobosa* in animals treated with *P. biglobosa* only when compared with those in the control group suggests that the *P. biglobosa* did not cause damage, and thus could be nephron-protective.

5. CONCLUSION

Exposure of animals to dexamethasone adversely unhinged hepatic and renal biomarkers investigated in this study. The study also revealed that *P. biglobosa* seed is beneficial to the health of the liver and kidney of pregnant female rats.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for

any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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