

Hepatoprotective Effects of Ethanol Extract of *Parkia biglobosa* Leaves Against Acetaminophen-Induced Liver Damage in Rats

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ABSTRACT

Background and Objective: Liver diseases are a significant global health issue. *Parkia biglobosa* is one of the most extensively used medicinal plants in many African countries. This study evaluated the hepatoprotective effect of ethanol extract of *P. biglobosa* leaves on acetaminophen-induced liver damage in rats. **Materials and Methods:** Adult rats (Wistar strain, n = 35) were randomly assigned into five groups (7 rats/group): Group I (control: given distilled water); Group II (negative control were administered 500 mg/kg b.wt of acetaminophen only); Group III (positive control were administered 500 mg/kg b.wt of acetaminophen and 140 mg/kg of silymarin); Group IV (administered 500 mg/kg b.wt of acetaminophen and 200 mg/kg of *P. biglobosa* extract); and Group V (administered 500 mg/kg b.wt of acetaminophen and 300 mg/kg of *P. biglobosa* extract). The treatment lasted 21 days, and animals were sacrificed and blood was collected for the assay of liver function. Data were analyzed using ANOVA and Duncan's test in SPSS v20, with results expressed as Mean \pm SD (n = 5) at p<0.05. **Results:** The acetaminophen caused liver damage, which was evident in a significant increase in the serum activities of Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), Aspartate Transaminase (AST), and γ -glutamyl transferase (GGT) (p<0.05). Also, acetaminophen caused a marked decrease in total protein (TP) and albumin (ALB) levels when compared with the normal control group. **Conclusion:** However, administration of *P. biglobosa* extract improved the liver function, as evident in a marked decrease in serum liver enzymes and a significant increase in ALB levels comparable to the standard drug, silymarin (p<0.05). The hepatoprotective potential of *P. biglobosa* could be related to its previously reported antioxidant compounds.

KEYWORDS

Acetaminophen, silymarin, hepatotoxicity, *Parkia biglobosa*, liver enzymes

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INTRODUCTION

Pharmaceutical companies, drug regulatory bodies, and healthcare practitioners all face significant hurdles as a result of drug-induced liver impairment. Although herbal medicines have gained popularity recently as a complementary therapy for treating or preventing life-threatening illnesses, very little is known about how they work. The liver, an organ involved in metabolism and excretion, is vital for the detoxification of



xenobiotics, chemotherapeutic agents, and environmental pollutants. Consequently, this organ is highly susceptible to various diseases. Synthetic drugs most often cause adverse effects on the human body. An example is Acetaminophen, a well-known antipyretic drug that can induce hepatotoxicity as a major side effect. The toxicity of Acetaminophen ($C_8H_9NO_2$) causes significant acute liver damage by triggering an excessive amount of oxidative stress, inflammatory response, and the death of liver cells (hepatocyte apoptosis)¹. As a result, certain individuals have resorted to herbal therapy due to their belief that plant-based treatments are devoid of unpleasant side effects².

Medicinal plants have been examined for their potential to treat liver disorders³. A medicinal plant refers to any plant that has bioactive compounds in one or more of its organs, which can be utilized for therapeutic reasons or as precursors for the production of beneficial pharmaceuticals. The above definition enables the differentiation between medical plants that have been scientifically proven to possess therapeutic characteristics and ingredients, and plants that are considered medicinal but have not yet undergone a comprehensive scientific investigation⁴. Medicinal plants are very rich in bioactive compounds which they produce usually for defense against invaders. These bioactive compounds are secondary metabolites called phytochemicals⁵. Medicinal plants contain various phytochemicals, including anthraquinones, alkaloids, saponins, cardiac glycosides, phenols, and flavonoids. Anthraquinones are used as laxatives and dyes, alkaloids are nitrogen-rich compounds that act as stimulants, saponins can reduce cholesterol levels, cardiac glycosides are effective cardiovascular drugs, and phenols and flavonoids are abundant in antioxidants⁶.

Nevertheless, it is important to note that natural products are not drugs, but are instead a crude mixture of phytochemicals for drug development⁷. Since time immemorial, medicinal plants have been used around the world for the treatment of a wide range of diseases, wounds, and ailments, such as inflammation, hepatotoxicity, malaria, and diabetes. They are part of the socio-cultural legacy of different countries⁷. Irrespective of the current preoccupation with synthetic chemistry as the way for drug discovery and design. Medicinal plants have played an important role in the prevention and treatment of diseases⁸. Drug development using modern medicinal plants has produced active metabolites that are targeted against a wide range of illnesses and ailments, including diabetes, cancer, hepatotoxicity, inflammation, and infections⁹.

Parkia biglobosa, commonly known as African locust bean, is a perennial deciduous tree in the family of Fabaceae and sub-family Mimosaceae of the order Leguminosae. Nigeria and most African countries have utilized it to manage inflammatory disorders, liver injury, diabetes, chronic cough, and bronchitis. *Parkia biglobosa* leaves, stem bark, and seeds have a stellar reputation for their usefulness in managing disease conditions¹⁰. *Parkia biglobosa* bark extracts have been identified to have significant anti-inflammatory, analgesic, antibacterial, and anti-helminthic activities¹¹. In Nigeria, *Parkia biglobosa*' common names include; Origili in Igbo, Dorowa in Hausa, and Iru in Yoruba¹². *Parkia biglobosa* has gained popularity due to the consumption and economic value of its seed in Nigeria. African locust bean is used for making a seasoning commonly called Dawadawa. It can be formed into a variety of shapes, such as flat patties or spheres made from fermented African locust bean seed. It is small to medium in size, around the size of a gulf ball. Because of its high protein content, dawadawa is frequently utilized as a dietary protein source as well as a seasoning in regional soups. *Parkia biglobosa* contains a variety of phytochemicals in its stem barks, seeds, leaves, and pods. *Parkia biglobosa* has been shown to contain phenols, flavonoids, sugars, tannins, terpenoids, steroids, saponins, alkaloids, and glycosides in its stem bark^{13,14}, as well as trace amounts of glycosides, tannins, and alkaloids in its leaves¹⁵, flavonoids, and phenols in them. This study assesses *Parkia biglobosa*'s hepatoprotective benefits in acetaminophen-treated Wistar rats.

MATERIALS AND METHODS

Study location: The study was carried out at the Department of Biochemistry, Federal University Wukari, Taraba State, Nigeria, from September, 2022 to February, 2023.

Collection of plant material: Fresh leaves of *Parkia biglobosa* were obtained opposite Federal University Wukari, Taraba State, on 25th October, 2022. The leaves were rinsed with clean water to remove dust and dirt, shade-dried for 2 weeks, and pulverized using a milling machine.

Preparation of plant extract: A 2000 g of the pulverized leaves were dissolved in a jar containing 2 L of absolute ethanol. The mixture underwent maceration with regular stirring for a duration of 72 hrs. Subsequently, the solvent was strained through muslin cloths and then filtered using Whatman number 1 filter paper. The ethanol was extracted from the filtrate using a rotary vacuum evaporator RE52; the residues were collected and utilized for the experiment.

Experimental animals and ethical approval: A total of twenty-five albino rats, consisting of both male and female, with an average body weight of 170 g, were acquired from Yola, Adamawa State, Nigeria. These rats were then cared for in the animal house of the Biochemistry Department at Federal University Wukari. They were housed in clean cages with litter to keep them warm. They were allowed to acclimatize for 2 weeks, while being fed pellet-based food, and were handled according to the standard guidelines of the Committee on Care and Use of Experimental Animal Resources of the Faculty of Pure and Applied Sciences, Federal University Wukari, Nigeria, with the approval number, FUW/FPAS/23/019.

Experimental design: The randomized block design was used to assign the 25 Wistar rats into five groups (n = 5). Group I, the normal control, received only feed and distilled water without any treatment. Group II, the negative control, was administered a daily dose of 500 mg/kg body weight of acetaminophen, along with feed and distilled water without any treatment. Group III, the positive control, received a daily dose of 500 mg/kg of acetaminophen and was treated with the standard drug, silymarin (140 mg/kg). Group IV and V received a daily dose of 500 mg/kg of acetaminophen and were treated with *Parkia biglobosa* ethanol extract at doses of 200 mg/kg and 300 mg/kg, respectively. The treatment was orally delivered via oral gavage for 21 days. After the final delivery of the extract, all animals were euthanized 24 hrs later under chloroform anesthesia. The organs were promptly collected, washed with ice-cold normal saline, and refrigerated at -20°C for liver parameter analysis.

Determination of liver enzyme activities: The activities of AST and ALT were assayed for by the methods of Reitman and Frankel¹⁶. ALP was determined according to Osigwe *et al.*¹⁷.

Determination of serum total protein and albumin: Total protein by Henry *et al.*¹⁸ the Biuret method, and Serum albumin (ALB) were assayed as described by Dumas *et al.*¹⁹.

Data analysis: All data were subjected to One-way Analysis of Variance (ANOVA) for variation of means of treatments and Duncan's multiple comparisons test using Statistical Package for Social Sciences (SPSS), version 20. The results means were compared for significance at $p < 0.05$, and the group results were presented as Mean \pm Standard Deviation (n = 5).

RESULTS

The effect of the ethanolic extract of *Parkia biglobosa* leaves on hepatic marker enzymes is presented in Table 1. Rats in the negative control group (Group II) exhibited significantly elevated levels of alkaline phosphatase, aspartate transaminase, alanine transaminase, and gamma-glutamyl transferase ($p < 0.05$) compared to the normal control group (Group I), indicating hepatic injury. Treatment with the plant extract (Groups III-V) resulted in a significant reduction in enzyme levels compared to Group II ($p < 0.05$), suggesting a protective effect on liver function. Among the treated groups, Group V showed enzyme values closest to the normal range. Table 2 presents the effect of the extract on serum protein levels. Group II displayed a significant decrease in total protein and albumin concentrations relative to Group I

Table 1: Effect of ethanolic extract of *Parkia biglobosa* leaves on hepatic marker enzymes

Groups	Alkaline phosphatase (U/L)	Aspartate transaminase (U/L)	Alanine transaminase (U/L)	Gamma-GT ((U/L)
I	101.74±1.19 ⁺	59.37±7.51 ⁺	82.06±4.241 ⁺	86.62±7.73 ⁺
II	189.96±1.19*	131.83±11.56*	229.42±12.55*	102.14±5.01*
III	122.19±3.16**	90.27±6.40**	179.84±4.21**	74.81±9.80 ⁺
IV	126.67±3.34**	108.21±13.63**	179.14±2.57**	81.06±3.82 ⁺
V	108.43±12.37 ⁺	99.22±3.76**	163.43±8.74**	77.59±2.67 ⁺

Values are presented as Mean±S.E.M. for five rats in each group, *indicates a significant ($p<0.05$) difference when compared with the normal (control group I) and ⁺indicates a significant ($p<0.05$) difference when compared with the negative control (group II)

Table 2: Effect of ethanolic extract of *Parkia biglobosa* leaves on hepatic marker serum proteins

Groups	Total protein (g/dL)	Albumin (g/dL)
I	6.60±0.51 ⁺	4.24±0.28 ⁺
II	4.40±0.91*	2.67±.27*
III	7.43±0.70 ⁺	3.33±.12 ⁺
IV	6.05±0.93 ⁺	3.63±.11 ⁺
V	7.15±1.40 ⁺	3.87±.13 ⁺

Values are presented as Mean±S.E.M. for five rats in each group, *indicates a significant ($p<0.05$) difference when compared with the normal (control group I) and ⁺indicates a significant ($p<0.05$) difference when compared with the negative control (group II)

Table 3: Effect of ethanolic extract of *Parkia biglobosa* leaves on body weight

Groups	Week 1 (g)	Week 2 (g)	Week 3 (g)
I	146.40±5.59	173.80±5.86	188.60±5.75
II	169.00±11.73	145.40±10.11	121.00±8.46
III	168.20±9.29	176.80±8.41	196.80±3.93
IV	155.40±10.22	162.20±10.63	177.00±10.18
V	153.60±8.87	181.60±9.56	204.80±7.29

Values are presented as Mean±S.E.M. for five rats in each group

($p<0.05$), while Group III-V demonstrated significant improvement compared to Group II ($p<0.05$), with Group III showing the highest restoration of total protein. Table 3 shows the body weight progression over three weeks. While, Group I rats gained weight steadily, those in Group II exhibited marked weight loss over the study period. In contrast, rats treated with the extract (Group III-V) showed significant weight gain, with Group V achieving the highest mean body weight by week three, indicating a possible dose-dependent improvement in general health status.

DISCUSSION

Drug-induced hepatic injury is the most common reason cited for withdrawal of an approved drug, and one-third of all drugs withdrawn from the market are withdrawn for liver injury²⁰. Acetaminophen is a commonly used analgesic. It is commonly used in the laboratory to induce hepatotoxicity using high doses. The process via which it causes hepatotoxic consequences has long been documented. Because the liver has a large concentration of cytochrome P450 enzymes, it is the main organ to target for acetaminophen toxicity²¹. When administered orally in high doses, hepatic glutathione, which acts as a natural antioxidant, becomes depleted, and N-acetyl-para-benzoquinone imine (NAPQI), an active metabolite of acetaminophen, can cause acute necrosis due to cell damage. The cellular enzymes may leak out of the membrane as a result of the constituent lipids' tendency to peroxidize and lose their integrity. Because of this, acetaminophen hepatotoxicity is frequently evaluated by measuring the number of cytosolic enzymes that leak into plasma²². Table 1 showed that the ALT level in the negative control group increased significantly ($p\leq 0.05$) after acetaminophen was administered, with a serum level of (229.42±12.55*) compared to the normal control group (82.06±4.241⁺). There was also a significant decrease in the treatment groups that received the standard drug and ethanol extract when compared with the serum level of the negative control group. This establishes two facts: that there was a liver injury, and that the extract reduced the injury to the liver, resulting in a decrease in liver enzymes. According to the results described in Table 1 above, group II (229.42±12.55*), which received only acetaminophen,

showed a significant ($p \leq 0.05$) increase in ALT level when compared with group I ($82.06 \pm 4.241^*$), which received only distilled water and served as the normal control. Given that the liver primarily expresses ALT, this suggests a potential liver injury due to acetaminophen biotransformation. Group III ($179.84 \pm 4.21^{**}$), which received the standard drug Silymarin, showed a significant decrease in ALT, which is a sign that there is some level of repair in the liver cells. Group IV ($179.14 \pm 2.57^{**}$) and group V ($163.43 \pm 8.74^{**}$) which received 200 and 300 mg/kg body weight of extract, respectively, also showed a remarkable decrease in ALT when compared with the negative control group II ($229.42 \pm 12.55^*$). The group that received the standard drug exhibited a significantly lower ALT level than the group that received the extract. Table 1 showed that the ALP level went up significantly ($p \leq 0.05$) in group II ($189.96 \pm 1.19^*$) that was administered acetaminophen compared to the normal control group I ($101.74 \pm 1.19^*$). This supports the idea that the rise in ALP level indicates liver damage. The treatment groups III ($122.19 \pm 3.16^{**}$), IV ($126.67 \pm 3.34^{**}$) and V ($108.43 \pm 12.37^*$) showed a significant decrease in serum concentration of ALP. The result on gamma GT, as shown in Table 1, showed a significant ($p \leq 0.05$) increase in GGT level for the group that received acetaminophen. However, the group that received the standard drug showed a significant decrease in GGT levels when compared to the negative control group. There was also a significant decrease in protein levels due to liver injury, but the treatment group showed an increase in both total protein and albumin levels as shown in Table 2.

In this investigation, compared to the control animals, acetaminophen given alone at high dosages to experimental rats resulted in a significant rise in plasma ALT, AST, ALP, and GGT activities (Table 1). This implies that the rats' hepatotoxicity or liver damage was caused by acetaminophen. The peroxidation of membrane lipids caused by the free radical metabolite of acetaminophen (NAPQI) may have led to an increase in the amounts of these enzymes in plasma, causing them to leak out of their intracellular storage²³. This result is consistent with earlier research showing that rats given acetaminophen had considerably higher ($p < 0.05$) plasma activity of ALT, AST, and ALP²⁴. In comparison to the group that was given only acetaminophen, the rats treated with the ethanol extract of *Parkia biglobosa* leaves after receiving acetaminophen showed a substantial ($p < 0.05$) drop in the plasma activities of ALT, AST, ALP, and GGT. This decline is consistent with previous findings²⁴. This shows that *Parkia biglobosa* leaf ethanol extract may be able to stop liver cell damage and the ensuing leakage of intracellular enzymes. According to earlier accounts, the leaves of *Parkia biglobosa* are fairly rich in tannins^{13,14}. It has been discovered that tannin does, in fact, "tar" the mucosa's outermost layer, decreasing its permeability and boosting its resistance to irritation, chemicals, and mechanical harm²⁵. Additionally, it has been noted that tannins hasten the healing of wounds and irritated mucous membranes²⁶. This could offer some understanding of the extract's potential protective role in addition to its well-known antioxidant qualities.

Also, there was a significant ($p < 0.05$) reduction in the concentration of total protein and albumin in the acetaminophen-treated group (group II) when compared with the control and extract-treated groups (Table 2). Plasma albumin is the protein synthesized most abundantly by the liver. It therefore serves as a reflection of the extent of functioning liver cell mass. Albumin has a fairly long half-life of 20 days and is therefore not a very reliable indicator of acute liver diseases²⁷. However, values of albumin and total protein obtained in this study support the inference of hepatoprotective activity of *Parkia biglobosa* leaves, in which, after administration of the ethanol extract, there was a significant ($p < 0.05$) increase in total protein and albumin level when compared to the group that received only acetaminophen.

The rats weights were measured at the beginning and end of 21 days, with measurements taken every week, in five different groups. The variance analysis revealed a significant decrease in body weight in the group administered 500 mg/kg of acetaminophen compared to the normal group and the group treated with the standard drug and the extract. In the final body weight, a high dose of ethanol extract of *Parkia biglobosa* leaves evoked a profound increase in body weight to about 204.80 ± 7.29 when

compared to the acetaminophen group (121.00 ± 8.46) (Table 3). This was also explained as body weight gain as the acetaminophen group showed significantly lower weight gain compared to the normal group (188.60 ± 5.75). Several studies have reported the presence of high content of bioactive phytoconstituents such as phenols, flavonoids, and terpenoids in *Parkia biglobosa* leaves. Furthermore, a direct correlation has been demonstrated between the antioxidant properties and the phytochemical components of plants. For example, phenolics and flavonoids are well known for their ability to scavenge free radicals, which translates into antioxidant activity. They influence reactions to allergens, viruses, and carcinogens and have anti-inflammatory, anti-allergic, anti-microbial, and anti-cancer properties²⁸. It is therefore admissible to relate the pharmacological action of the plant to these bioactive compounds.

CONCLUSION

In conclusion, the results from this study indicate that the ethanol extract of *Parkia biglobosa* leaves has a potent hepatoprotective activity on Acetaminophen-induced liver damage in rats, as treatment with the extract resulted in inhibition of acetaminophen-induced liver damage, and improvement of liver function as determined by plasma ALT, AST, ALT, and GGT activities. The process suggested for this activity is connected to the plant extract's antioxidant capacity, which can be ascribed to the extract of *Parkia biglobosa* leaves' high flavonoid, phenolic, and terpene content.

SIGNIFICANCE STATEMENT

This study identified the hepatoprotective potential of *Parkia biglobosa* leaf extract against acetaminophen-induced liver damage in rats, which could be beneficial for the development of affordable, plant-based therapeutic agents for liver disorders, especially in resource-limited settings. This study will assist researchers in uncovering critical areas of natural hepatoprotective compounds and their mechanisms of action that have remained unexplored by many. Consequently, a new theory on the role of flavonoid- and phenolic-rich plant extracts in liver regeneration and antioxidant defense may be developed.

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