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Protective Effects of Baobab Plant Extract on Doxorubicin-induced Histological and Biological Changes on Liver and Kidney of Albino Rats

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ABSTRACT

Background: Doxorubicin (DOX), a chemotherapeutic drug, is effective against various cancers but can cause liver and kidney damage due to oxidative stress and inflammation.
Objectives: To determine whether managing albino rats with an aqueous extract of the baobab plant can reduce the potential histological effects of DOX on the renal and hepatic tissues.
Materials and methods: Forty rats were acclimatized under controlled conditions and divided into four groups: Control group receiving saline, DOX group receiving one intraperitoneal injection of 15 mg/kg DOX, DOX + baobab group co-administered with DOX at 15 mg/kg intraperitoneally plus baobab extract (500 mg/kg/day) orally, and the baobab-only group administered with 500 mg/kg/day baobab extract. Then, the baobab effects on liver and kidney function after the use of DOX were evaluated.
Results: Rats treated with DOX had higher serum urea and creatinine levels. While baobab extract, when co-administered with DOX, reduced urea and creatinine levels, thus bringing them closer to the control group and pointing towards the protective potential of baobab against DOX-induced nephrotoxicity. The effect of DOX treatment was an increase in the levels of the liver markers (alanine aminotransferase and aspartate aminotransferase), whereas baobab resulted in significant decreases in these liver markers. After receiving DOX, the baobab extract exists in advanced hepatic and renal function in association with the control group. Baobab had significant possessions on kidney function and may be experienced incompatible tissue damage spread by DOX.
Conclusion: Co-administration of baobab extract with DOX improved kidney and liver function.
Keywords: *Adansonia digitata*; Doxorubicin; Urea; Creatinine; Alanine aminotransferase.

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INTRODUCTION

Doxorubicin (DOX), an anthracycline antibiotic, has major side effects, like cardiotoxicity, myeloid toxicity, hepatotoxicity, and nephrotoxicity. It is effective against various types of cancers, including bladder, kidney, liver, acute lymphocytic leukaemia, breast cancer, and acute myeloblastic leukemia [1].

DOX, designed to target cancer cells, has numerous side effects including hepatorenal dysfunction, liver and kidney toxicity, and poor quality of life. Its ability to fight cancer depends on topoisomerase II activity, which stops DNA replication and the death of cancer cells [2]. Dox also has effects against cancer, but because it doesn't target specific cells, it builds up in healthy tissues and does a lot of damage [3].

Several molecular pathways affect DOX-induced toxicity. Oxidative stress is a major cause of organ damage and produces reactive oxygen species. Studies on undeniable plants that may assist in protecting the liver and kidney from drug-induced harm emphasize the potential of medicinal plants as adjunctive therapies to shield adjacent medication-induced damage to the liver and kidney. *Adansonia digitata* (Baobab) is a steamy tree that originaated in Madagascar, Africa, and Australia. The baobab tree belongs to the family Malvaceae-and the genus Adansonia, which consists of eight species. The most widely distributed species throughout mainland Africa

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is *Adansonia digitata*. People have greatly increased its population, and it frequently appears in the thorny forests of the African savannah. This durable tree is well-recognized for its many uses, greatly improving African people's quality of life and confirming their approach to food. Baobab exhibits recurrent biological properties, involving antimicrobial, anti-malarial, anti-diarrheal, anti-anemic, anti-asthmatic, antiviral, antioxidant, and anti-inflammatory activities [4–6].

Phytochemical inquiries have discovered the presence of various bioactive compounds such as flavonoids, phytosterols, amino acids, fatty acids, vitamins, minerals, glycosides, saponins, and steroids. These seeds are very abundant in significant amino acids, proteins, lipids, and fatty acids, such as palmitic, oleic, and linoleic acids, as well as Omega 3, 6, and 9 [7]. The baobab tree, rich in phytochemicals and bioactive substances, is widely used for its medical benefits. Fruit pulp, seeds, and leaves, particularly the fruit pulp, are known for their anti-inflammatory, antibacterial, and antioxidant properties [4].

DOX is one of the most usable chemotherapeutic agents and is efficient against a wide range of cancers. Its clinical utility is often overtaken by serious side effects that are predominantly induced by liver and kidney damage linked to oxidative stress and inflammation. The aforementioned adverse effects have raised the demand for protective agents with the ability to mitigate DOX-induced toxicity without affecting its anticancer efficacy. The present study aimed to establish whether the natural properties of *Adansonia digitata*, popularly known for their renal and hepatic protective effect, may mitigate histological and functional damage induced by DOX in hepatic and renal tissues of albino rats.

MATERIALS AND METHODS

Experimental animals

This experimental study examined forty male albino rats at the University of Mosul's Veterinary College, maintaining a healthy environment in hygienic iron cages with a regular pellet diet for seven days before dosing [8]. The research protocol was approved by the Animal Ethics Committee of Mosul University, Mosul, Iraq (Reference number: UOM/COM/MREC/23-24/DEC2 on 24-12-2023).

Body weight measurement

The difference between the starting and end body weights was ascertained by tracking each group's changes in body weight over time. During the investigation, aberrant symptoms were seen in the experimental animals [9].

Preparation of *baobab* extract

A study on baobab fruit shells from Sudan was conducted, involving mechanical separation, cold extraction, and aqueous extract creation [10]. Rats were given a daily dose of 500 mg/kg/day via oral gavage.

Study design

The rates were divided into four groups:

1. Control Group (n = 10): Animals in this group were left untreated and were subjected to the administration of saline to serve as a placebo and to provide the baseline for comparison.
2. DOX Group (n = 10): Rats in this group received a single intraperitoneal injection of DOX at a dose of 15 mg/kg to induce the condition being studied.
3. DOX+ Baobab extract Group (n = 10): In this group, rats were administered intraperitoneally with DOX at a dose of 15 mg/kg and were co-administered with an oral dose of baobab extract at 500 mg/kg throughout the experiment to assess its possible protective or therapeutic effect.
4. Baobab extract only Group (n =10): Rats in this group were given 500 mg/kg of Baobab extract orally to assess any standalone effects of the extract without the influence of DOX.

All treatments were conducted under controlled conditions, with duration, route, and frequency of administration standardized for each group.

Evaluation of renal function

Assessment of serum urea (Reference range 15–45 mg/dL)

Method of serum urea

The enzymatic colorimetric technique measures serum urea by hydrolyzing it with urease, resulting in a green-colored molecule with hypochlorite, salicylate, and ammonium ions, allowing accurate quantification [11].

Assessment of serum creatinine (Reference range 0.4–0.8 mg/dL)

Serum creatinine is determined through the Jaffe reaction, forming an orange-colored complex with an alkaline picrate solution, and its concentration is calculated by comparing absorbance to a standard [12].

Evaluation of liver function

Evaluation of liver enzyme by measurement of alanine aminotransferase (ALT) aspartate aminotransferase (AST).

Assessment of serum ALT (Reference range (10 to 40 U/L)) [12]

The ALT assay was performed according to the International Federation of Clinical Chemistry (IFCC) recommendations and has been optimized for improved performance and stability. ALT catalyzes the following reaction: Transamination of L-alanine with 2-oxoglutarate, forming pyruvate and L-glutamate. Pyruvate produced is then reduced by NADH in a coupled reaction catalyzed by lactate dehydrogenase to form L-lactate and NAD+ as in the following:

$$\text{L-Alanine} + \text{2-oxoglutarate} \xrightarrow{ALT} \text{- pyruvate} + \text{L-glutamat}$$

$$\text{Pyruvate} + \text{NADH} + \text{H+} \xrightarrow{LDH} \text{L -lactate} + \text{NAD}^{+}$$

Measurement of AST (Reference range 50 to 150 IU/L)

The rate of oxidation of NADH is directly proportional to the catalytic activity of ALT. The decrease in absorbance serves as a measurement.

Principle of the AST test: This assay is based on the IFCC recommendations but has been optimized for enhanced performance and stability. In the sample, AST catalyzes the interconversion of an amino group between L-aspartate and

2-oxoglutarate to form oxaloacetateand L-glutamate. The oxaloacetate is then reduced, in the presence of NADH and malate dehydrogenase (MDH), to form NAD+ as seen below:

$$\text{L-Aspartate} + 2\ \text{oxoglutarate} \xrightarrow{AST} \text{oxaloacetate} + \text{L-glutamate}$$

$$\text{Oxaloacetate} + \text{NADH} + \text{H}^{+} \xrightarrow{MDH} \text{L-malate} + \text{NAD}^{+}$$

Preparation of tissues

Subsequently, euthanizing rats was performed by cervical dislocation, and immediately preserving their kidneys and livers in 10% formalin as a preservative, then histopathological examination by two pathologists can expose various pathological changes in these organs.

Histopathological assessment

Samples from the gastrointestinal tract, kidney, and liver were preserved in formalin. Histological analysis of kidney and liver tissues was performed using Suvarna et al.'s 2018 protocol [13].

Statically analysis

Data collection was organized using Microsoft Excel sheets. GraphPad Prism, version 8.4.3, build 686, was utilized for statistical analysis. Data are presented as means ± standard error of the mean (SEM). For comparisons involving more than two groups, one-way ANOVA and Tukey's post hoc test were both used in the data analysis. A paired t-test was used for pairwise comparisons of two groups. Normality was calculated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. A P-value of less than 0.05 was considered statistically significant and < 0.001 was highly significant [14].

RESULTS

The study revealed that DOX treatment significantly reduced body weight in rats, contrasting with control, DOX with baobab, and baobab groups (Table 1).

Table 2 shows DOX treatment may harm kidney function, raising blood urea levels. Combining baobab with DOX counteracted this, dropping urea levels closer to the control group's healthy range.

Table 1. Impact of baobab on body weight (gm)[†].

Body weight of rats (gm) Mean ± S.E				
Groups \ Period	Before	After	Difference	P-value
Control group	233.2 ± 5.3[a]	251.4±14.8[a]	18.20	0.109 ns
Doxorubicin (DOX) group	231.2±10.6[a]	156.0±49.8[a]	-75.20	0.001**
DOX with Baobab group	217.4±11.7[a]	224.2±18.5[a]	14.79	0.151ns
Baobab group	253.8± 16.3[a]	266.4±13.8[a]	12.60	0.059 ns

[†] In paired *t*-test, different letter means a significant difference, same letter means a non-significant, and ns mean no significant, *Significant,** Highly significant.

Table 2. Evaluation of the impact of baobab on urea levels(mg/dl) in rats challenged with doxorubicin (DOX)[†].

Urea levels (mg/dl) Mean ± S.E				
Parameters \ Groups	Control group	DOX group	DOXwith Baobab group	Baobab group
Blood Urea (mg/dl)	44.14±0.82 a	107.9±4.5 b	52.0±1.55 a	45.0±1.52 a
P-value	0.001**			
Control group *vs.* DOX with Baobab group	0.12ns			
Control group *vs.* Baobab group	0.99ns			
DOX group *vs.* DOX with Baobab group			0.001**	
DOX group *vs.* Baobab group				0.001**
DOX with Baobab group *vs.* Baobab group				0.22ns

[†] Data was normalized and analyzed using ANOVA, Kolmogorov-Smirnov, Shapiro-Wilk, and Tukey's multiple comparisons test. Different letter means a significant difference, the same letter means a non-significant, and ns mean no significant, *Significant,** Highly significant.

The study showed that DOX supplementation led to higher creatinine levels, while baobab supplementation significantly decreased these levels (Table 3).

The study found a significant (P-value < 0.05) increase in serum ALT levels in the DOX group compared to the control group (Table 4).

The data includes serum AST levels in different groups, along with P-values indicating the statistical significance of differences between these groups (Table 5).

Rat kidneys show normal renal tissue architecture, with signs of damage in the DOX group. Baobab treatment may shield against damage, with less drastic changes in glomerular architecture (Figure 1).

DOX treatment caused severe liver tissue impairment, but baobab treatment improved liver morphology, suggesting potential protection from baobab, while baobab alone did not significantly influence healthy liver tissue (Figure 2).

DISCUSSION

The current study discovered that *Adansonia digitata* had a strong ability to protect against the harmful effects of DOX on the liver and kidneys. It was found that baobab, rich in flavonoids, polyphenols, and vitamin C, effectively mitigates oxidative stress, inflammation, and structural damage caused by DOX. Key outcomes included the preservation of hepatic and renal tissue integrity, reduction in inflammatory cell in-

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Table 3. Impact of baobab on creatinine levels in rats challenged with doxorubicin (DOX) evaluation of the impact of Baobab on creatinine levels[†].

Creatinine levels (mg/dl) Mean ± S.E				
Groups / Parameters	Control group	DOX group	DOXwith Baobab group	Baobab group
Blood creatinine (mg/dl)	0.47±0.02 a	1.42±0.09 b	0.57±0.07 a	0.43±0.01 a
P-value	0.001**			
Control group *vs.* DOX group	0.001***			
Control group *vs.* DOX with Baobab group	0.87			
Control group *vs.* Baobab group	0.99			
DOX group *vs.* DOX with Baobab group			0.001***	
DOX group *vs.* Baobab group				0.001***
DOX with Baobab group *vs.* Baobab group				0.59

[†] Data was normalized and analyzed using ANOVA, Kolmogorov-Smirnov, Shapiro-Wilk, and Tukey's multiple comparisons test. Significant differences were noted at *P-value < 0.05 or Highly significant ** P-value < 0.01. The same letter means nonsignificant and a different letter means significant.

Table 4. Impact of baobab on (ALT) alanine aminotransferase in rats challenged with doxorubicin (DOX) evaluation of ALT[†].

ALT levels (IU/L) Mean ± S.E				
Groups / Parameters	Control group	DOX group	DOXwith Baobab group	Baobab group
Serum ALT level	29.88±0.06 a	66.03±6.4 b	41.63±4.5 a	30.97±1.55 a
P-value	0.001**			
Control group *vs.* DOX group	0.001***			
Control group *vs.* DOX with Baobab group	0.24			
Control group *vs.* Baobab group	0.99			
DOX group vs. DOX with Baobab group			0.001***	
DOX group vs. Baobab group				0.001***
DOX with Baobab group vs. Baobab group				0.31

[†] Data was normalized and analyzed using ANOVA, Kolmogorov-Smirnov, Shapiro-Wilk, and Tukey's multiple comparisons test. Significant differences were noted at * P-value < 0.05 or Highly significant ** P-value < 0.01. The same letter means nonsignificant and a different letter means significant.

filtration, and promotion of tissue repair and regeneration. These results demonstrate that baobab, as a natural adjuvant to therapy, may reduce the toxic side effects of DOX, preserving its therapeutic efficacy; hence, it may represent a promising strategy to enhance chemotherapy safety [15].

The rats share high genetic similarities with humans, allowing for disease induction and medication administration. They reproduce quickly, are inexpensive, and are easy to grow in scientific environments [16]. Rats, despite being larger than mice, are manageable in handling and housing, and their complex behavior makes them useful in research on memory, learning, and cognitive processes [17].

consistent with known hepatotoxic effects. This aligns with recent studies, which also demonstrated that DOX can cause degeneration, necrosis, and hyperplasia of Kupffer cells, as well as dilation of the central vein and sinusoidal congestion [18, 19]. The infiltration of inflammatory cells is a common response to DOX-induced liver injury, further exacerbating tissue damage and contributing to the overall pathology [20, 21].

Our finding was consistent with a recent study, which reported that DOX therapy in rats leads to significant renal tubule and glomerular necrosis, interstitial cell infiltration, and reduced glomerular diameter [22]. Furthermore, studies show DOX causes significant histological changes, including vacuolar degeneration and necrosis of renal tubule epithelial cells, expansion of tubular cells, loss of brush boundary, and unclear DOX treatment causes significant hepatic tissue damage, including hydropic degeneration, oncotic necrosis, sinusoidal dilation, and blood vessel congestion, degeneration [23]. Moreover, Baloch et al. (2020) demonstrated that kidneys treated with DOX exhibit structural damage, including enlarged Bowman's space and increased collagen content, indicating chronic kidney injury in models of DOX-induced nephrotoxicity [24].

Baobab, with its rich sources of flavonoids, vitamin C, and polyphenols, diminishes oxidative damage by neutralizing reactive oxygen species (ROS) and suppressing the generation of pro-inflammatory cytokines. Its bioactive content maintains the structural integrity of renal tubules and glomeruli, preventing abnormal enlargement, and supporting vascular and cellular repair. In this manner, baobab protects the kidneys from these pathological changes, maintaining kidney function and allowing for tissue regeneration; thus, it can be

Table 5. Impact of baobab on aspartate aminotransferase (AST) in rats challenged with doxorubicin (DOX) evaluation of AST[†].

Groups / Parameters	AST levels (IU/L) Mean ± S.E Control group	DOX group	DOXwith Baobab group	Baobab group
Serum AST level	100.2±1.2	211.0±0.56	119.9±2.1	106.5±4.2
P-value	0.001***			
Control group *vs.* DOX group	0.001***			
Control group *vs.* DOX with Baobab group	0.002**			
Control group *vs.* Baobab group	0.34			
DOX group vs. DOX with Baobab group			0.001**	
DOX group vs. Baobab group				0.001**
DOX with Baobab group vs. Baobab group				0.023*

[†] * Significant difference at P-value < 0.05 ** Highly significant P-value < 0.01.

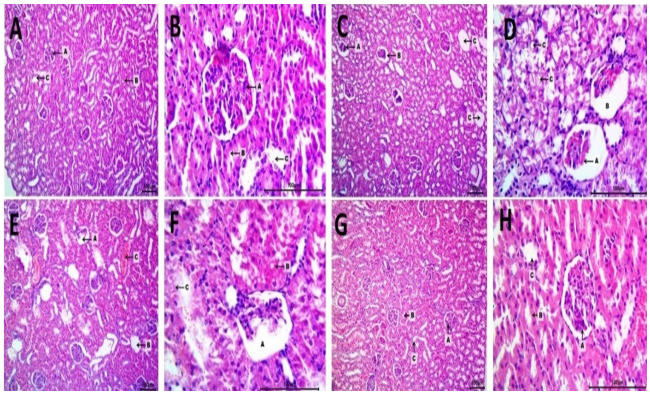

Figure 1. Comparison of kidney tissue morphology across treatment groups (H&E stain). A: Rat kidney of the control group presenting normal architecture of renal tissue characterized by glomeruli (A), proximal renal tubules (B) and distal renal tubules (C) 100 X , photomicrograph 100X. B: Rat kidney of the control group 400X. C: Rat kidney of the DOX group shows atrophy of glomeruli (A), dilation of Bowman's space (B), and renal cyst (C). H&E stain, 100X. D: Rat kidney of the DOX group400X. E: Rat kidney of the DOX with Baobab group shows mild dilation of Bowman's space (A), renal cyst (B) and hemorrhage (C). H&E stain, 100X. F: Rat kidney of the DOX with Baobab group400X. G: Histological section of rat kidney of the baobab group showing normal architecture of renal tissue characterized by glomeruli (A), proximal renal tubules (B) and distal renal tubules (C). H&E stain, 100X. H: Rat kidney of the baobab group 400X.

considered as a natural protective therapy against renal damage [25]. A recent study reported that *Adansonia digitata* fruit pulp treatment reduced liver lesion intensity, restored heart and kidney tissues, and eliminated inflammatory infiltration, demonstrating strong anti-inflammatory properties, especially at higher doses. Flavonoids present in *Adansonia digitata* strengthen cellular defense mechanisms by stabilizing cellular membranes and reducing mitochondrial dysfunction, generally induced by $HgCl_2$ exposure. This cytoprotective effect reduces liver steatosis and kidney degeneration [26]. A recent study found that rats treated with lead acetate and *Adansonia digitata* showed less liver damage and normal kidney structures with minor damage to tubules [27].

Adansonia digitata flavonoid fractions showed mild liver steatosis and fatty droplets, suggesting partial protection against $HgCl_2$-induced damage and less degeneration in kidneys compared to $HgCl_2$-treated rats [15]. The good effects of *Adansonia digitata* flavonoid fractions on the liver may be due to their high level of bioactive substances, such as flavonoids, polyphenols, and vitamin C. These compounds are well known for their considerable antioxidant and anti-inflammatory properties and cytoprotective effects, contributing to their protective action on the hepatic tissue. This is the reason they have been effective due to the cytoprotective nature that contributes to their protection of hepatic tissue [15].

The current finding disagrees with Rufa'i et al.'s study they found that at high doses (800 mg/kg), the *Adansonia digitata* leaf extract caused slight damage to the liver and kidneys, including glomerular and hepatic necrosis, and increased inflammatory cells in the spleen tissue [28].

The combination of *Adansonia digitata* and DOX has vast potential to protect against DOX-induced hepatotoxicity and at the same time can maintain the chemotherapeutic effectiveness of DOX. The DOX produces ROS and, because of its oxidative stress generation, may cause hepatic injury by inflammation, lipid peroxidation, and mitochondrial dysfunction. Thus, the flavonoid-rich *Adansonia digitata* with polyphenol and vitamin C exhibited intense antioxidant and anti-inflammatory potential, thereby acting against all the above-mentioned toxic pathways. It neutralizes ROS, stabilizes cellular membranes and increases antioxidant enzyme activity to avoid oxidative damage and lipid peroxidation. Its anti-inflammatory properties inhibit the release of pro-inflammatory cytokines that reduce inflammatory cell infiltration and subsequent tissue damage. Importantly, *Adansonia digitata* prevents the liver from histopathological changes like necrosis and sinusoidal congestion and enhances the process of tissue repair and regeneration. This would be a very selected protective mechanism that, while baobab guards normal hepatic tissues, the anticancer action of DOX is not interfered with. Thus, a combination of DOX with *Adansonia digitata* could be a very promising strategy to enhance chemotherapy safety by minimizing organ toxicity without compromising the therapeutic outcome [29].

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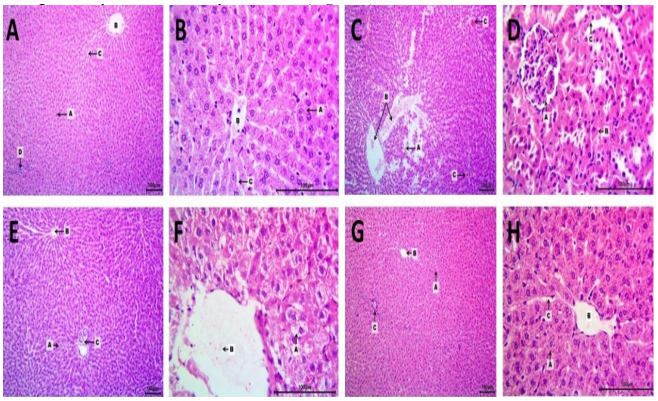

Figure 2. Comparison of liver tissue morphology across treatment groups (H&E Stain). A: Histological section of rat liver of the control group showing normal architecture of the hepatocytes (A), central vein (B), sinusoids (C) and portal area (D). H&E stain, 100X. B: Rat liver of the control group 400X. C: Rat liver of DOX with baobab group showing mild vacuolar degeneration of hepatocytes (A) with intact central vein (B) and sinusoids (C). H&E stain, 100X. D: Rat liver of DOX with baobab group 400X. E: Rat liver of DOX with baobab group showing mild vacuolar degeneration of hepatocytes (A) with intact central vein (B) and sinusoids (C). H&E stain, 100X. F: Rat liver of DOX with baobab group 400X. G: Rat liver of the baobab group showing normal architecture of the hepatocytes (A), central vein (B), and portal area (C) , 100X. H: Rat liver of the baobab group showing normal architecture of the hepatocytes (A), central vein (B), and sinusoids (C), H&E stain, 400X.

While these findings are encouraging, the current study has three limitations. First, this study was conducted on a preclinical setup, and the results do not fully comply with human clinical benefits. Second, this study did not explore the long-term effects that the combination of *Adansonia digitata* with DOX may have. Third, there was no consideration for any variability that may occur due to geographical or environmental factors, which could impact the efficacy of *Adansonia digitata*. These limitations give scope for further research to confirm these observations and allow for more wide-ranging applications of the results.

CONCLUSION

Extract of *Adansonia digitata* exhibits protective action on DOX-induced hepatorenal injuries in albino rats. The reduction of serum urea and creatinine levels showed that the plant extract treatment significantly lessened renal dysfunction, whereas the reduction of ALT and AST levels showed that the treatment improved liver function. By looking at the tissues' histopathology, it seemed that *Adansonia digitata* helps protect liver and kidney tissues from damage caused by DOX. Further studies are needed to understand the active principles and mechanisms involved to maximize its therapeutic benefits and ensure safety for use in clinical practice to ameliorate the adverse effects of chemotherapeutic agents.

ETHICAL DECLARATIONS

Acknowledgments

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Ethics Approval and Consent to Participate

The research protocol was approved by the Animal Ethics Committee of Mosul University, Mosul, Iraq (Reference number: UOM/COM/MREC/23-24/DEC2 on 24-12-2023). Informed consent was not required for such study.

Consent for Publication

Not applicable.

Availability of Data and Material

Data generated during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All stated authors contributed significantly, directly, and intellectually to the work and consented to it being published.

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