Journal of Research in Applied and Basic Medical Sciences 2024; 10(3): 256-265

Original Article

RABMS Journal of Research in Applied and Basic Medical Sciences

Jatropha *Tanjorensis* attenuates doxorubicin-induced liver and spleen damages in rats

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Abstract

***Background & Aims*:** Doxorubicin is a widely used antineoplastic agent for the treatment of solid tumors but its use is limited by its several severe tissue and organ toxicities. This study investigated changes in liver and spleen as a result of toxicity produced by Doxorubicin and the protective role of aqueous leaf extract of *J. Tanjorensis*.

***Materials & Methods*:** In this experimental study, rats were divided into 5 groups as follows: Group 1 served as control and orally received normal saline once daily. Doxorubicin (15 mg/kg) was administered to Group 2 from day 10. Group 3 received *J. Tanjorensis* (300 mg/kg, orally) once daily for 12 days. Group 4 received *J. Tanjorensis* (300 mg/kg, orally) once daily for 12 days and Doxorubicin (15 mg/kg) from day 10. Group 5 received Vitamin C (100 mg/kg, orally) once daily for 12 days, and Doxorubicin (15 mg/kg) from day 10. Doxorubicin administration was done intraperitoneally for three consecutive days. Sera samples were collected and used to assess liver function enzymes and synthetic molecules. Liver and spleen tissues were used to examine histopathological analysis. Data were analyzed by SPSS v.20 at a significance level of $P<0.05$.

***Results*:** Administration of Doxorubicin caused significant increase in Alanine Transaminase (ALT), Aspartate Transaminase (AST), Acid Phosphatase (ACP), and total bilirubin (P values below 0.05), and a significant decrease in total protein and albumin compared to the control and *J. Tanjorensis* administered rats (P values below 0.05). The histopathological evaluation of liver tissue in the Doxorubicin injected rats revealed congestion, hemorrhagic necrosis, sinusoidal dilation, and mononuclear cell infiltration. Similarly, histology of spleen tissue in Doxorubicin administered rats showed degeneration and congestion, disintegrated peri-arteriolar lymphoid sheath, granuloma formation, and necrosis of lymphoid follicles. However, liver and spleen of rats given Doxorubicin and *J. Tanjorensis* showed reversal of liver function enzymes and synthetic ability towards normalcy, reduced signs of damage as well as recovering peri-arteriolar lymphoid sheath.

***Conclusion*:** Our study found that *J. Tanjorensis* is effective in preventing liver and spleen damage caused by Doxorubicin.

***Keywords*:** Doxorubicin, *Jatropha Tanjorensis*, Liver, Rat, Spleen, Toxicity

Received 15 February 2024; accepted for publication 24 July 2024

[DOI: 10.61186/rabms.10.3.256]

Introduction

Cancer incidence has increased due to population growth and aging as well as the increasing prevalence of risk factors such as smoking, obesity, and adoption of a Western lifestyle (1). Doxorubicin (DOX), an anthracycline antibiotic, is commonly used in the treatment of solid tumors in adult and pediatric patients, including breast, stomach, thyroid, liver, and ovarian cancers, as well as human hematological malignancies (2). The anticancer activity of DOX is mainly based on its intercalation into the DNA structure and the inhibition of topoisomerase II enzyme in rapidly proliferating cancer cells (3). However, most anticancer drugs, including DOX, act nonspecifically and damage both malignant and healthy tissues (4). The toxicity of DOX is attributed to mitochondrial dysfunction, reactive oxygen species (ROS) production, stimulation of apoptosis, lipid peroxidation, DNA damage, impaired calcium handling, and induction of p53 (5). Typical adverse effects of doxorubicin include myelosuppression, mouth ulcers, alopecia, fatigue, nausea, and vomiting. Additionally, DOX can cause disruption in lipid profile due to free radical-mediated processes, leading to dyslipidemia and an increased risk of cardiovascular disease (6). As the liver is the primary organ involved in detoxification and biotransformation of drugs, any damage to liver function is particularly significant (7). Such damage to the liver may occur due to oxidative stress and apoptosis (8).

Despite the development of new cancer drugs that have improved the life expectancy of cancer patients, the acute and long-term side effects of cancer chemotherapy remain an unsolved problem in the management of oncological diseases (9, 10). In this context, herbal medicine has gained attention as a potential complementary approach, owing to its perceived safety, efficacy, cost-effectiveness, and better compatibility with conventional treatments.

Jatropha tanjorensis, commonly called "hospital too far," is a member of the Euphorbiaceae family. It originated in Central America and has spread to many tropical and sub-tropical regions, including Africa, India, and North America (11). In several parts of Nigeria, the leaves of *J. tanjorensis* are locally consumed as a vegetable and added to daily meals, as well as used in treating diabetes mellitus due to their anti-hyperglycemic properties (12). Traditionally, a decoction of the leaves is used to treat anemia, diabetes, skin diseases, malaria, and cardiovascular diseases (13, 14). Antimicrobial studies of *J. tanjorensis* have showed that the aqueous extract of the leaves inhibits the gram-positive bacterium *Staphylococcus aureus* and the gram-negative bacterium *Escherichia coli* (15). *J. tanjorensis* possesses antioxidant properties and contains vitamins and ions, including phosphorus, selenium, and zinc (16, 17). Phytochemical analysis of *J. tanjorensis* leaves has shown that the plant is rich in cardiac glycosides, flavonoids, tannins, terpenoids, and saponins (16, 18).

Given the potential of *J. tanjorensis* as a natural therapeutic agent, this study aimed to evaluate the protective effects of *J. tanjorensis* against Doxorubicin-induced toxicity in the liver and spleen of rats.

Materials & Methods

Study Type and population:

This study employed an experimental design using 35 rats, which were randomly divided into 5 groups with 7 rats per group.

Chemicals and Reagents: Doxorubicin was obtained from Neon Laboratories Limited (India) as a solution for injection. All reagents and chemicals used were of analytical grade **and** highest purity.

Collection and Extraction of *Jatropha tanjorensis* Leaves: *J. tanjorensis* leaves were collected from a garden in Benin City, Edo State, Nigeria and botanically identified at the Department of Plant Biology and Biotechnology, Edo State University Uzairue, Nigeria. The collected leaves were thoroughly rinsed, air-dried at room temperature for four weeks, and pulverized into a fine powder using an electric blender. For aqueous extract preparation, 1 kg of the powdered plant material was soaked in 5 liters of double-distilled water for 48 hours at room temperature with daily stirring to ensure thorough extraction. After 48 hours, the mixture was filtered first through Whatman filter paper No. 42 (125 mm) followed by cotton wool. The resulting filtrate was

[DOI: 10.61186/rabms.10.3.256]

concentrated to one-tenth of its original volume using a rotary evaporator at 40°C and then reduced to solid form using a water bath. The solid extract was weighed and dissolved in normal saline for daily administration to the rats.

Experimental Design/Procedure: Adult male Wistar albino rats (150-200g) were obtained and housed in cages under controlled temperature (22±2°C) with a 12-hour light-dark cycle. They were fed a standard laboratory diet and given free access to water. After a seven-day acclimatization period, the animals were randomly divided into five groups (7 rats per group):

- Group 1 (Control): Received normal saline orally once daily for 12 days.
- Group 2 (DOX): Received Doxorubicin injection (15 mg/kg) intraperitoneally on days 10, 11, and 12.
- Group 3 (JT): Administered aqueous extract of *J. tanjorensis* (300 mg/kg) orally once daily for 12 days.
- Group 4 (JT+DOX): Administered aqueous extract of *J. tanjorensis* (300 mg/kg) orally once daily for 12 days, followed by Doxorubicin (15 mg/kg) intraperitoneally on days 10, 11, and 12.
- Group 5 (Vit C+DOX): Administered Vitamin C (100 mg/kg) orally once daily for 12 days, followed by Doxorubicin (15 mg/kg) intraperitoneally on days 10, 11, and 12.

The Doxorubicin dosage and administration protocol were based on the study by [Author et al., Year] (19). The *J. tanjorensis* dose (300 mg/kg) was selected based on the study by El-Moselhy et al. (2014) (20). Vitamin C was chosen as a positive control for its known hepatoprotective properties. All experimental animals received humane care according to the criteria outlined in the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Science and published by the National Institutes of Health (21).

Twenty-four hours after the final administration, the rats were euthanized and blood samples were collected in plain tubes. Samples were allowed to clot for 45 minutes before being centrifuged at 4000 rpm for 25 min to obtain sera for analysis. Serum samples were used to determine Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Acid Phosphatase (ACP), Albumin (ALB), Total Bilirubin (TB), and Total Protein (TP) levels.

Biochemical Analyses:

- ACP activity was determined using a BIOSYSTEMS ACP assay kit following the manufacturer's protocol.
- AST and ALT activities were determined using RANDOX kits according to the manufacturer's instructions based on the method described by Reitman and Frankel (1957) (22).
- Albumin was determined using a RANDOX kit based on the Bromocresol green (BCG) method as described by Doumas et al. (1971) (23).
- Total protein was determined using a RANDOX kit following the method described by Tietz (1995) (24).
- Total bilirubin was determined using a RANDOX kit based on the method of Jendrassik and Grof (1938) (25).

Histopathological Analysis: Following euthanasia, liver and spleen tissues from all groups were excised, rinsed in normal saline, and fixed in 10% buffered formalin. Samples were then processed for histopathological examination at the Chemical Pathology Laboratory, University of Benin Teaching Hospital, Nigeria.

Statistical Analysis: Data were expressed as mean ± standard deviation. Differences among groups were determined by One-way ANOVA followed by [specific post-hoc test, e.g., Tukey's HSD] using Statistical Package for Social Sciences (SPSS) version 20. A probability level of less than 5% ($P<0.05$) was considered significant.

Results

The result of the Table 1 shown below established a significant increase in AST, ALT and ACP activities in Doxorubicin-administered rats compared to control, *J. Tanjorensis* and Vitamin C groups, an indication of hepatotoxicity. However, treatments with *J. Tanjorensis* and Vitamin C reduce AST, ALT and ACP activities

[DOI: 10.61186/rabms.10.3.256]

compared to Doxorubicin-alone rats, an indication of hepatoprotection.

Table 1. Effects of aqueous leaf extract of *J. Tanjorensis* on liver function enzymes in Doxorubicin-induced toxicity Wistar rats

Treatment	ALT (U/L)	AST (U/L)	ACP (U/L)
Control group	23.20^{a}± 2.39	40.80^{a} ± 1.03	1.34^{a} ± 0.14
DOX (15mg/kg)	87.53^{b}±2.33	99.40^{b} ± 2.75	7.86^{b} ± 1.01
*J. Tanjorensis (*300 mg/kg*)*	22.30^{a}± 2.35	37.20^{a} ± 1.39	1.72^{a}± 0.19
*J. Tanjorensis (*300 mg/kg*)* + DOX (15mg/kg)	42.40^{c}±4.37	56.50^{c} ± 1.67	4.18^{c} ± 0.68
Vit C. + DOX (15mg/kg)	57.80^{d}± 2.12	66.40^{d} ± 1.20	3.57^{c} ± 0.40

Values are expressed as Mean ± Standard Error of Mean, n=5. Values with different superscripts (a, b, c, d) down the column differ significantly at ($P<0.05$). AST-Aspartate Aminotransferase; ALT-Alanine Aminotransferase; ACP-Acid Phosphatase; Vit. C- Vitamin C; DOX- Doxorubicin.

The results shown in Table 2 revealed a significant decrease in the total protein and albumin of doxorubicin-treated group compared to the control and extract treated groups ($p < 0.05$). However, for groups administered *J. Tanjorensis* and Vitamin C, the values of total protein and albumin were significantly higher compared to the group that received only Doxorubicin. The result of Table 2 also showed that total bilirubin significantly increased in the doxorubicin-treated group compared to the control and extract group ($p < 0.05$). However, the group administered *J. Tanjorensis* and Vitamin C had total bilirubin with significantly lower values compared to the group that received only doxorubicin.

Table 2. Effects of aqueous extract of *J. Tanjorensis* on liver synthetic molecules in Doxorubicin-induced Wistar rats

Treatment	Total Protein (g/dl)	Albumin (g/dl)	Total Bilirubin (mg/dl)
Control group	6.74^{a} ± 0.19	5.54a ± 0.11	2.33^{a} ± 0.91
DOX (15mg/kg)	3.31^{b} ± 0.16	2.98^{b} ± 0.12	11.10^{b} ± 1.50
*J. Tanjorensis (*300 mg/kg*)*	7.43^{a} ± 0.14	5.99^{a} ± 0.13	2.76^{a} ± 0.71
*J. Tanjorensis (*300 mg/kg*)* + Dox (15mg/kg)	4.97^{c} ± 0.13	4.10^{c} ± 0.15	6.11^{c} ± 1.07
Vit C. + DOX (15mg/kg)	4.87^{c} ± 0.85	4.39^{c} ± 0.17	7.85^{c} ± 1.57

Values are expressed as Mean ± Standard Error of Mean, n=3. Values with different superscripts (a, b, c, d) down the column differ significantly at ($P<0.05$). Vit. C- Vitamin C; DOX- Doxorubicin

The histopathological assessments of the liver were examined and showed the liver of the control and extract treated groups had visible centriole and hepatocytes with no necrosis, no congestion and no inflammation (Figure A and C). The histopathological evaluation of liver tissue in the Doxorubicin group revealed visible vascular congestion, hemorrhage, necrosis, vacuolar degeneration in hepatocytes, sinusoidal dilation, mononuclear cell infiltration in portal region and parenchyma, macro and microvascular steatosis, pyknotic and hyperchromatic nuclei in hepatocytes. However, the liver of rats given Doxorubicin and *J. Tanjorensis* or Vitamin C showed hepatocyte regeneration, reduced signs of liver damage, and mild degeneration of hepatocytes. Figures 1 and 2 represents Photomicrographs of five study groups in liver and spleen, respectively.

[DOI: 10.61186/rabms.10.3.256]

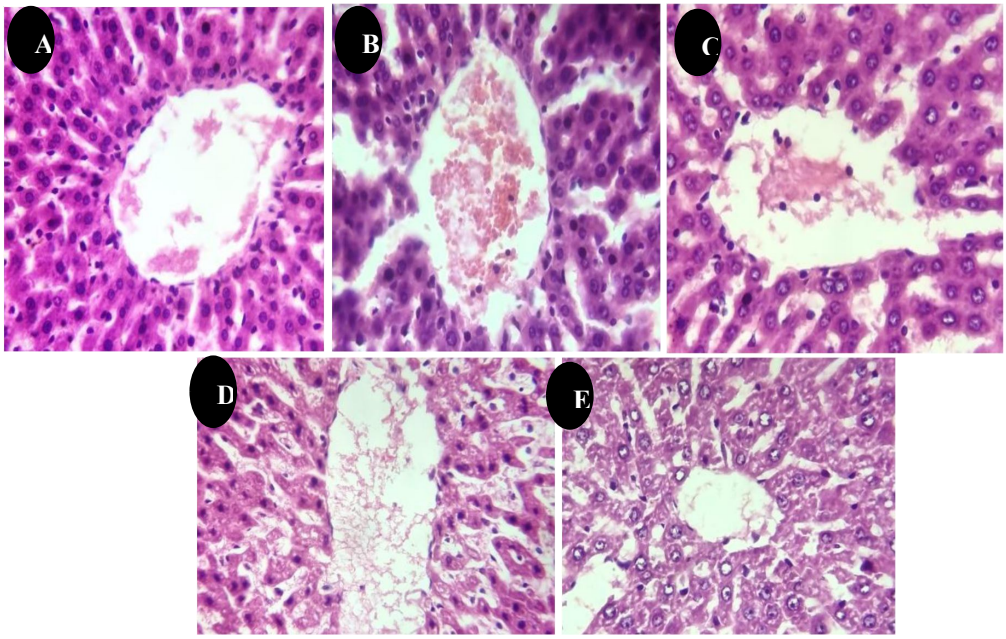

Fig. 1. A: Photomicrograph of the liver of control rats which received only normal saline showing normal hepatic architecture, with hepatocytes having a normal lobular appearance with central veins surrounded by radiating hepatic cords (X400 magnification). **B:** Photomicrograph of liver of rats which received doxorubicin (15 mg/kg) from day 10 for three consecutive days showing vascular congestion, hemorrhage, necrosis, vacuolar degeneration in hepatocytes, sinusoidal dilation, mononuclear cell infiltration in portal region and parenchyma, macro and microvesicular steatosis, pyknotic and hyperchromatic nuclei in hepatocytes (X400 magnification). **C:** Photomicrograph of liver of rats which received *J. Tanjorensis* (300 mg/kg) with normal hepatocytes, with visible nuclei. (X400 magnification). **D:** Photomicrograph of liver of rats which received *J. Tanjorensis* (300 mg/kg) and then doxorubicin (15mg/kg) showing reduced signs of liver damage; mild degeneration of hepatocytes (X400 magnification). **E:** Photomicrograph of liver of rats which received *Vitamin C* (100 mg/kg) and then doxorubicin (15mg/kg) (X400 magnification)

Histological analysis of the spleen of the control rats given saline alone showed a precise splenic organization with distinct identifiable regions of red and white pulp with prominent central artery as splenic cords, venous sinuses, and veins in the spleen (Figure 1). The group administered Doxorubicin alone at a dose of 15mg/kg from day 10 for three consecutive days showed white and red pulp with congestion and thickened dilatation, disintegrated peri-arteriolar lymphoid sheath, depletion of lymphoid follicle, and tangible macrophages that appears granulated, lymphoid depletion of the white pulp as well as severe necrosis of lymphoid follicles (Figure 2). The spleen of rats administered *J. Tanjorensis* alone at a dose of 300mg/kg showed normal splenic tissues with normal red and white pulp & peri-arteriolar lymphoid sheath (Figure 3), while the spleen of rats administered *J. Tanjorensis* at a dose of 300mg/kg or Vitamin C at a dose of 100mg/kg and thereafter given Doxorubicin from day 10 for three consecutive days showed recovering peri-arteriolar lymphoid sheath and restoration of splenic architecture (Figure 4 and 5).

[DOI: 10.61186/rabms.10.3.256]

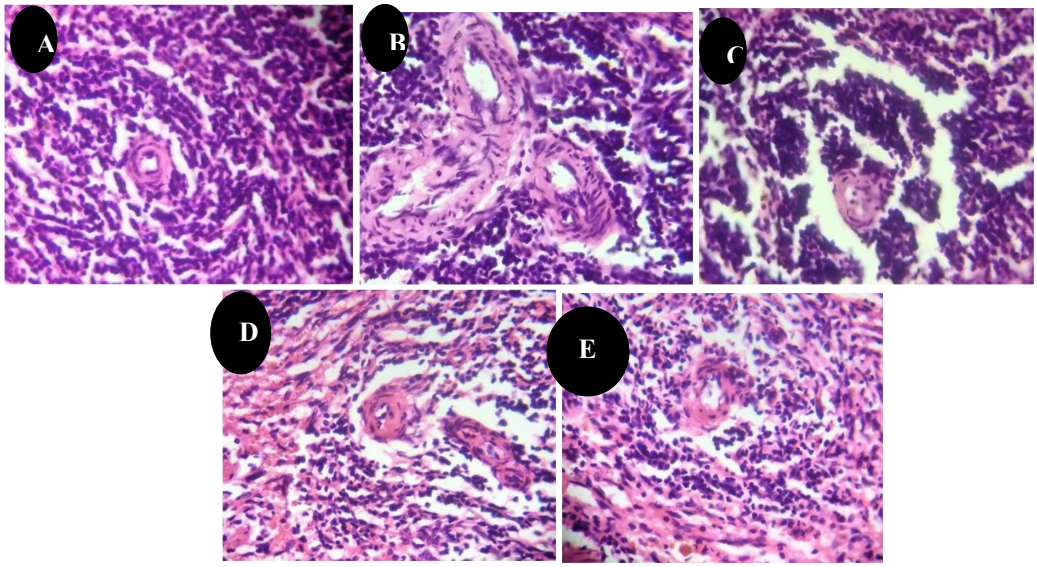

Fig. 2. A: Photomicrograph of the spleen of control rats which received only normal saline showing white and red pulp with prominent central artery (X400 magnification)

B: Photomicrograph of spleen of rats which received doxorubicin (15 mg/kg) from day 10 for three consecutive days showing degeneration of white pulp, disintegrated peri-arteriolar lymphoid sheath, granuloma formation, severe necrosis of lymphoid follicles, thickened dilated and congested central arteries, development of vacuoles and progressing degeneration of splenic tissues (X400 magnification). **C:** Photomicrograph of spleen of rats which received *J. Tanjorensis* (300 mg/kg) showing normal Red Pulp, White Pulp and peri-arteriolar lymphoid sheath (X400 magnification)**. D:** Photomicrograph of spleen of rats which received *J. Tanjorensis* (300 mg/kg) and then Doxorubicin (15mg/kg) showing recovering peri-arteriolar lymphoid sheath and restoration of splenic architecture (X400 magnification)**. E:** Photomicrograph of spleen of rats which received *Vitamin C* (100 mg/kg) and then Doxorubicin showing restoration of splenic architecture (15mg/kg) (X400 magnification)

Discussion

The liver is a crucial metabolic organ that plays a key role in glycogen storage, detoxification, and protein synthesis (26). Doxorubicin (DOX) treatment is known to increase reactive oxygen species (ROS) production and oxidative damage, leading to hepatocellular injury (27). These factors contribute to the liver's susceptibility to drug-induced toxicity (28). Mounting evidence suggests that even low doses of DOX in rats can cause irreversible liver damage and elevate apoptotic processes in hepatic tissue (29).

Our results demonstrated that DOX administration (15 mg/kg) caused significant liver toxicity, as evidenced by elevated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), confirming previous findings (30). However, co-administration of *J. tanjorensis* or Vitamin C with DOX improved liver function, as indicated by reduced AST and ALT levels compared to the DOX-only group. These findings are consistent with previous studies (31-33). The reduction in ALT and AST levels following treatment with *J. tanjorensis* leaf extract suggests hepatoprotection, possibly mediated by its constituent phytochemicals, particularly flavonoids, as previously reported (16).

Acid phosphatase (ACP), primarily located in cell lysosomes, serves as an indicator of cellular toxicity. Enhanced lysosomal membrane peroxidation can lead to membrane lysis and increased ACP release and activity (34). In our study, DOX administration (15 mg/kg for

[DOI: 10.61186/rabms.10.3.256]

three consecutive days) significantly increased ACP activity compared to control and *J. tanjorensis* groups, indicating cell damage and lysosomal membrane instability. Notably, administration of *J. tanjorensis* or Vitamin C effectively decreased ACP activity compared to the DOX-only group, consistent with other studies (36, 37).

Liver synthetic function parameters, such as albumin and total protein, are reliable indicators of hepatic damage. Albumin, the most abundant serum protein, is primarily synthesized in the liver and serves various physiological functions, including osmotic pressure regulation, redox balance, and transport of fatty acids, bilirubin, drugs, hormones, and vitamins (38). Our results showed significantly reduced concentrations of total protein and albumin in DOX-administered rats compared to control and plant-treated groups, indicating impaired hepatic function. This reduction may be due to compromised hepatic synthesis, increased intestinal protein loss, or protein-losing nephropathy (39). These findings align with previous reports (31-33, 40). Importantly, treatment with *J. tanjorensis* or Vitamin C in DOX-administered rats resulted in significantly higher total protein and albumin levels compared to the DOX-only group, suggesting protective and antioxidant effects.

The elevated total bilirubin levels observed in the DOX-administered group compared to control and plant-treated groups further indicate liver dysfunction, specifically impaired bilirubin clearance. This finding is consistent with previous studies (41, 42). Treatment with *J. tanjorensis* or Vitamin C significantly decreased total bilirubin levels in DOX-administered rats, likely due to their protective effects against DOX-induced oxidative damage in the liver.

Our histological findings corroborated the biochemical results. The livers and spleens of DOX-administered rats exhibited histopathological features consistent with previous reports (32, 43). Notably, treatment with *J. tanjorensis* following DOX administration attenuated hepatic injury and degenerative changes in both the liver and spleen.

Conclusion

In conclusion, our study demonstrates that *J. tanjorensis* effectively mitigates DOX-induced biochemical and histological liver injury in rats. These findings suggest that *J. tanjorensis* has promising potential in ameliorating DOX-induced hepatotoxicity and spleen damage. To further validate these results and establish their clinical relevance, we recommend additional in vivo and in vitro studies with larger sample sizes in both animal models and human subjects. Moreover, investigations into the molecular mechanisms underlying the protective effects of *J. tanjorensis* against DOX-induced toxicity would provide valuable insights for potential therapeutic applications.

Acknowledgments

The authors humbly thank the staff in animal house unit of the Department of Biochemistry, Edo State University Uzairue where the *in vivo* study was carried out.

Financial support

None

Ethical Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and according to the *Guide for the Care and Use of Laboratory Animals* prepared by the National Academy of Science and published by the National Institutes of Health. The study protocol was approved by the Department of Biochemistry, Faculty of Basic Medical Sciences, Edo State University Uzairue with Mat. No.: PGS/BCH/21003018.

Data availability

Data will be available as per request.

Conflict of interest

The authors have no conflict of interest in this study.

[DOI: 10.61186/rabms.10.3.256]

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics 2012. CA: Cancer J Clinicians 2015;65:87-108. https://doi.org/10.3322/caac.21262
2. van Dalen EC, van der Pal HJH, Kok WEM, Caron HN, Kremer LCM. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. Eur J Cancer 2006;42(18):3191-8. https://doi.org/10.1016/j.ejca.2006.08.005
3. Rawat PS, Jaiswal A, Khurana A, Bhatti, JS, Navik U. Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomed Pharmacother 2021;139:111708. https://doi.org/10.1016/j.biopha.2021.111708
4. Rochette L, Guenancia C, Gudjoncik A, Hachet O, Zeller M, Cottin Y, Vergely C. (2015). Anthracyclines/trastuzumab: new aspects of cardiotoxicity and molecular mechanisms. Trends Pharmacol Sci 2015;36:326–48. https://doi.org/10.1016/j.tips.2015.03.005.
5. Hashish FER, Abdel-Wahedb MM, El-Odemia MH, El-Naidanyc SS, ElBatsh MM. (2021). Possible protective effects of quercetin on doxorubicin-induced cardiotoxicity in rats. Menoufia Med J 2021;34:333–9. https://doi.org/10.4103/mmj.mmj_5_20
6. Subashini R, Ragavendran B, Gnanapragasam AK, Yogeeta S, Devaki T. Biochemical study on the protective potential of *Nardostachys jatamansi* extract on lipid profile and lipid metabolizing enzymes in doxorubicin intoxicated rats. Pharmazie 2007;62(5):382-7.https://doi.org/10.1691/ph.2007.5.6678
7. Li S, Tan HY, Wang N, Zhang ZJ, Lao L, Wong CW, Feng Y. The role of oxidative stress and antioxidants in liver diseases. Int J Mol Sci 2015;16:26087–124. https://doi.org/10.3390/ijms161125942.
8. Jung HA, Kim JI, Choung SY, Choi J. Protective effect of the edible brown alga *Ecklonia stolonifera* on doxorubicin-induced hepatotoxicity in primary rat hepatocytes. J Pharm Pharmacol 2014;66(8):1180-8. https://doi.org/10.1111/jphp.12241
9. Nurgali K, Jagoe RT, Abalo R. Editorial: Adverse Effects of Cancer Chemotherapy: Anything New to Improve Tolerance and Reduce Sequelae? Front Pharmacol 2018;9:245. https://doi.org/10.3389/fphar.2018.00245
10. Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review). Int J Oncol 2019;54(2):407–19. https://doi.org/10.3892/ijo.2018.4661
11. Prabakaran AJ, Sujatha M. *Jatropha Tanjorensis* Ellis and saroja, a natural interspecific hybrid occurring in Tamil Nadu, India. Genet Resour Crop Evol 1999;46:213-8. http://dx.doi.org/10.1023/A:1008635821757
12. Olayiwola G, Iwalewa EO, Omobuwajo OR, Adeniyi AA, Verspohi EJ. The antidiabetic potential of *Jatropha Tanjorensis* leaves. Niger J Nat Prod Med 2004;8(1):55-8. https://doi.org/10.4314/njnpm.v8i1.11817
13. Iwalewa EO, Adewumi CO, Omisore NO, Adebanji OA, Azike CK. Pro-antioxidant effects and cytoprotective potentials of nine edible vegetables in SouthWest, Niger J Med Food 2005;8:539-44. https://doi.org/10.1089/jmf.2005.8.539
14. Oduola T, Avwioro OG, Ayanniyi TB. Suitability of the leaf extract of *Jatropha gossipifolia*as an anticoagulant for biochemical and haematological analysis. Afr J Biotech 2005;4:679-81. https://doi.org/10.5897/AJB2005.000-3125
15. Oboh FOJ, Masodje HI. Nutritional and antimicrobial properties of *Jatropha Tanjorensis* leaves. Am-Euras J Sci Res 2009;4(1):7-10.
16. Usunobun U, Osa-Osadolor SE. Elemental Concentration, Phytochemical Analysis and *in vitro* Antioxidant activity of *Jatropha Tanjorensis* Leaves. Proceedings of the 3rd International Conference and Exhibition of Organization for Women in Science for the Developing World (OWSD–BIU), held at Benson Idahosa University from 31st July – 4th August, 2017; Pp 846 – 856.
17. Atansuyi K, Ibukun EO, Ogunmoyole T. Antioxidant properties of free and bound phenolic extract of the leaves of *Jatropha Tanjorensis in vitro*. J Med Plants Res 2012;6(31):4667-4. https://doi.org/10.5897/JMPR12.294.

[DOI: 10.61186/rabms.10.3.256]

18. Oyewole OI, Akingbala PF. Phytochemical Analysis and Hypolipidemic Properties of *Jatropha Tanjorensis* Leaf Extract. European. J Med Plants 2011;1(4):180-5. https://doi.org/10.9734/EJMP/2011/497.

19. El-Moselhy MA, El-Sheikh AA. Protective mechanisms of atorvastatin against doxorubicin-induced hepato-renal toxicity. Biomed Pharmacother 2014;68(1):101–10. https://doi.org/10.1016/j.biopha.2013.09.001

20. Ebenyi LN, Yongabi KA, Ali FU, Ominyi MC, Anyanwu CB, Benjamin E, Ogbanshi ME. Effect of Aqueous Leaf Extract of *Jatropha Tanjorensis* on parasitaemia and haematological parameters in mice infected with *Plasmodium berghei.* Niger J Biotech 2021;38(1):146-53. https://dx.doi.org/10.4314/njb.v38i1.17

21. Garber JC, Barbee RW, Bielitzki JT, Clayton LA, Donovan JC. The guide for the care and use of laboratory animals, 8th ed. (Washington, DC: Institute for Laboratory Animal Research The National Academic Press), 2011.

22. Reitman S, Frankel S. A Colorimetric Method for the Determination of Serum Glutamic Oxalacetic and Glutamic Pyruvic Transaminases. Am J Clin Pathol 1957;28:56-63. http://dx.doi.org/10.1093/ajcp/28.1.56

23. Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromocresol green. Clinica Chimica Acta 1971;31:87-96. http://dx.doi.org/10.1016/0009-8981(71)90365-2

24. Tietz NW. Clinical Guide to Laboratory Tests (ELISA). 3rd Edition, W.B. Saunders, Co., Philadelphia, 1995; Pp: 22-23.

25. Jendrassik L. Grof P. Simplified Photometric Methods for the Determination of Bilirubin. Biochem J;1938;297:81-9

26. Omobowale TO, Oyagbemi AA, Ajufo UE, Adejumobi OA, Yakubu MA. Ameliorative Effect of Gallic Acid in Doxorubicin-Induced Hepatotoxicity in Wistar Rats Through Antioxidant Defense System. J Diet Suppl 2017;15(2):1-14. https://doi.org/10.1080/19390211.2017.1335822

27. Tulubas F, Gurel A, Oran M, Topcu B, Caglar V, Uygur E. The protective effects of ω-3 fatty acids on doxorubicin-induced hepatotoxicity and nephrotoxicity in rats. Toxicol Indust Health 2015;31:638–44. https://doi.org/10.1177/0748233713483203

28. Melo JU, Santos JM, Kimura OS, Campos MM, Melo RB, Vasconcelos, P. R. Effects of Fatty acids on liver regeneration in rats. *Rev Co. Bras Cir* 2010;37(5):351-7. https://doi.org/10.1590/S0100-69912010000500008

29. Sprenger GA. Aromatic Amino Acids Biosynthesis, Pathways, Regulation and Metabolic Engineering; Springer pp93−127. 2006. https://doi.org/10.1007/7171_2006_067

30. Mohan M, Kamble S, Satyanarayana J, Nageshwar M. Reddy N. Protective effect of *Solanum torvum* on Doxorubicin-induced hepatotoxicity in rats. Int J Drug Dev Res 2011;3:131–8.

31. Usunobun U, Imoru NO, Ikponmwosa B, Egbo OH. Evaluation of Hepatoprotective Potential of *Chromolaena odorata* (L.) R.M. King & H.Rob. Against Methotrexate-induced Hepatic Toxicity in Rats. Plant Biotech Persa 2022;4(2):1-10. https://doi.org/10.52547/pbp.4.2.10

32. Ikponmwosa BO, Usunobun U. Aqueous leaf extract of *Chromolaena odorata* attenuates methotrexate-induced hepatotoxicity in wistar rats. J Fund Appl Pharm Sci 2022;3(1):16-29. https://doi.org/10.18196/jfaps.v3i1.15652.

33. Oladele JO, Oladele OT, Ademiluyi AO, Oyeleke OM, Awosanya OO, Oyewole OI. Chaya (*Jataropha Tanjorensis*) leafs protect against sodium benzoate mediated renal dysfunction and hepatic damage in rats. Clin Phytosci 2020;6(13):2-8. https://doi.org/10.1186/s40816020-00160-5

34. Sharma MK, Kumar M, Kumar A. Protection against mercury-induced renal damage in Swiss albino mice by *Ocimum sanctum.* Env Toxicol Pharmacol 2005;19:161–8. https://doi.org/10.1016/j.etap.2004.06.002

35. Muniyan S, Chaturvedi NK, Dwyer JG, LaGrange CA, Chaney WG, Lin MF. Human prostatic acid phosphatase: structure, function and regulation. Int J Mol Sci 2013;14(5):10438-64. https://doi.org/10.3390/ijms140510438

36. Usunobun, U, Okolie PN. Dimethylnitrosamine (DMN)-induced fibrotic rats: Effect of *Vernonia amygdalina* on extracellular matrix and hepatic/lysosomal integrity. Int

[DOI: 10.61186/rabms.10.3.256]

J Pharm Toxicol 2016;4(1):7-11. https://doi.org/10.14419/ijpt.v4i1.5785

37. Usunobun U, Okolie P.N. *Annona muricata* prevent hepatic fibrosis by enhancing lysosomal membrane stability and suppressing extracellular matrix protein accumulation. Int J Med 2016;4(1):10-3. https://doi.org/10.14419/ijm.v4i1.5784
38. Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. Int J Gen Med 2016;9:229–55. https://doi.org/10.2147/IJGM.S102819.
39. H, Jabri M-A, Souli A, Hosni K, Rtibi K, Tebourbi O, et al. Chemical composition, antioxidant properties and hepatoprotective effects of chamomile (Matricaria recutita L.) decoction extract against alcohol-induced oxidative stress in rat. Gen Physiol Biophys 2015;34(3):263–75. https://doi.org/10.4149/gpb_2014039
40. B, Bennet D, Belcher DJ, Kim H-G, Nader GA. Chemotherapy agents reduce protein synthesis and ribosomal capacity in myotubes independent of oxidative stress. Am J Physiol Cell Physiol 2021;321(6):C1000–9. https://doi.org/10.1152/ajpcell.00116.2021
41. Prša P, Karademir B, Biçim G, Mahmoud H, Dahan I, Yalçın AS, et al. The potential use of natural products to negate hepatic, renal and neuronal toxicity induced by cancer therapeutics. Biochem Pharmacol 2020;173(113551):113551. https://doi.org/10.1016/j.bcp.2019.06.007
42. C, Cui C, Wang C, Lu S, Zhang M, Chen D, et al. Systematic evaluations of doxorubicin-induced toxicity in rats based on metabolomics. ACS Omega 2021;6(1):358–66. https://doi.org/10.1021/acsomega.0c04677
43. Mansouri E, Jangaran A, Ashtari A. Protective effect of pravastatin on doxorubicin-induced hepatotoxicity. Bratisl Lek Listy 2017;118(5):273–7. https://doi.org/10.4149/BLL_2017_054.

[DOI: 10.61186/rabms.10.3.256]