Journal of Pharmaceutical Research International

33(37B): 158-167, 2021; Article no.JPRI.70980
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Protective Role of *Phoenix dactylifera* Date Palm Pollen against Doxorubicin-Induced Toxicity in the Liver, Kidney, Testis and Biochemical Parameters in Male Rats

Sara Faez Hassan[1], Muneef Saab Ahmed[1*] and Aziz Khalid Hameed[2]

[1]Department of Biology, College of Education for Pure Sciences, Tikrit University, Iraq.
[2]Department of Biology, College of Science, Tikrit University, Iraq.

Authors' contributions

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

Article Information

DOI: 10.9734/JPRI/2021/v33i37B32035
Editor(s):
(1) Dr. Dharmesh Chandra Sharma, G. R. Medical College & J. A. Hospital, India.
Reviewers:
(1) Abdulhakim Bawadekji, Northern Border University, Saudi Arabia.
(2) Abdul Rauf Shakoori, University of the Punjab, Pakistan.
Complete Peer review History: https://www.sdiarticle4.com/review-history/70980

Original Research Article

Received 07 May 2021
Accepted 12 July 2021
Published 20 July 2021

ABSTRACT

Date palm pollen (DPP) has a prophylactic role, known for its antioxidant effects. For this, the present study was designed to study the protective role of DPP against histological toxicity in hepatic, renal, and testicular tissues, as well as the level of (Total cholesterol, Triglyceride, Total proteins, Albumin, and testosterone hormone) in male white rats. The Iraqi date palm trees (*Phoenix dactylifera L.*) were selected from Salah Aldeen farms located at Salah Aldeen governorate. Pollen was collected from 20th March to 25th April 2019. This study used 20 male white rats that were distributed to four groups and weights close. All groups were given food and water continuously throughout the experiment, the second group (DPP) was given an orally administered suspension of date palm pollen (60 mg/kg) every day for four weeks, the third group intraperitoneal injections were given (10 mg/kg), and the fourth group (10 mg/kg) were given intraperitoneal injections one time per week and four weeks, in addition to that, orally-administered suspension of DPP (60 mg/kg) was given as well every day for four weeks. The results of the study showed a significant increase (P≤0.05) in the level of total cholesterol (TC), triglycerides (TG), and

**Corresponding author: E-mail: muneef.s962@tu.edu.iq;*

a significant decrease (P≤0.05) in the level of Total Protein, Albumin, and testosterone hormones, Current results suggest that the protective effect of (DPP) may by its antioxidant properties, and thus reduce the positive effects.

Keywords: Toxicity; date palm pollen; biochemical parameters; testosterone hormone.

1. INTRODUCTION

Plant-derived crude medicines and nutraceuticals are commonly thought to have beneficial benefits in the treatment of liver and kidney disorders in herbal folk medicine. The fruits of the date palm *Phoenix dactylifera L.* (Arecaceae) are widely utilized in a variety of daily food across the world. Dates are high in dietary fiber, vitamins such vitamin C, B1, B2, and A, and minerals. To prove their usage in traditional medicine, several in vitro and in vivo investigations have been undertaken [1]. Antioxidant [2], anti-inflammatory [3], hepatoprotective, anticancer [4], nephroprotective [5], antimicrobial, antiallergic [6], immunostimulatory, antifungal [7], and gastrointestinal transition stimulatory activities have all been demonstrated in date extracts [8]. In an Alzheimer's disease transgenic mouse model, date supplementation proved to be beneficial [9]. The bioactive components of dates with strong antioxidant properties, such as tannins [10] and polyphenols (which comprise phenolic acids, hydroxybenzoic and hydroxycinnamic acids, flavonoid glycosides, and proanthocyanidins), are thought to be responsible for their pharmacological actions [11]. Date pit extract was additionally demonstrated to hinder DNA damage and mediate antigenotoxic effects [12]. Earlier research have revealed that date palm pollen (DPP) possesses allergic and antigenic components [13]. Despite this, mounting research suggests that DPP has a wide range of medicinally beneficial benefits. DPP has been demonstrated in clinical trials to decrease oral mucositis in people [14] and to have anti-inflammatory and antiproliferative properties in rats [15]. Surprisingly, recent investigations in rats have found that DPP extracts reduce testicular dysfunction and thyroid dysfunction caused by cadmium poisoning [16]. DPP, on the other hand, has been found to affect reproductive characteristics in adult male rats [17].

Doxorubicin (DOX), also known as hydroxydaunorubicin, is a potent anticancer drug that has gained widespread acclaim in recent years for its use in the treatment of a variety of hematological and solid malignancies. However, its harmful perspective, cardiotoxicity, hepatic damage, nephrotoxicity, and testis toxicities' have reticent in its clinical practice [18]. Doxorubicinol toxicity is linked to the creation of reactive oxygen species (ROS), which chelates with iron and affects bio-macromolecules as well as the production of free radicals [19]. Furthermore, ROS produces oxidative stress, lipid peroxidation, DNA breakage, and protein oxidation, all of which harm membranes and macromolecules [20]. It has also been linked to genotoxicity, as evidenced by enhanced cellular death and a strong affinity for chromosomal DNA and nucleosome eviction and replacement [21]. The toxicity of the DOX is represented by several factors that lead to liver damage, which are the disturbance of vital intracellular activities as a result of the metabolism of doxorubicin to the hepatotoxic doxorubicinol [22]. Dox-induced renal toxicity might be part of a multi-organ dysfunction assisted by the buildup of free radicals, which eventually leads to membrane lipid peroxidation [23]. DOX can cause nephrotoxicity by having a negative impact on renal tissue, since it accumulates mostly in the kidney; increasing the permeability of glomerular capillaries; and causing tubular degradation [24]. DOX has been shown to impair testicular tissue, causing testicular damage, apoptosis, and a reduction in DNA synthesis, according to research [25].

The present study was designed to examine the protective role of DPP against histological toxicity in hepatic, renal and testicular tissues, as well as the level of (Total cholesterol, Triglyceride, Total proteins, Albumin, and testosterone hormone) in male white rats.

2. MATERIALS AND METHODS

2.1 Dosage Preparation of Date Palm Pollen (DPP)

Iraqi date palm trees (*Phoenix dactylifera L.*) were selected from Salah Aldeen farms located at Salah Aldeen governorate. Pollen was collected from 20th March to 25th April 2019. Any visible impurities, as well as spathe

fragments, were eliminated. The pollens are removed from the kernels using a fine gauze filter and then kept chilled (4°C) in a well-closed container for 3 hours in an incubator at 35°C.

2.2 The Animals

[20] Sprague Dawley male white rats, Age (6 - 8) months and weigh (1500 - 1100) kilograms. Animals were placed in cages designed for this purpose and divided into [4] groups. These animals were subjected to laboratory conditions that included 12 hours of light and 12 hours of darkness. The degree of heat was established at (22 ± 2) ℃. Cages were taken into account, clean, and sterilized. The animals were left for two weeks to adapt to the new breeding conditions and to ensure that they were free of diseases, and given food and water continuously throughout the experiment.

2.3 Experiment Design

This study used [20] males from mature white rabbits distributed to [4] groups, each group included [5] animals with close weights:

1.The first group (control group):

2.The second group (The DPP group): This group was given an orally administered suspension of water and DPP date palm pollen (60 mg/kg) every day for four weeks.

3.The third group (The DOX group): This group was given intraperitoneal injections of doxorubicin were given (10 mg/kg) per week and for four weeks.

4.The fourth group (The DOX and DPP group): This group was given intraperitoneal injections of doxorubicin were given (10 mg/kg) once a week and an orally administered suspension of DPP date palm pollen (60 mg/kg) every day for four weeks.

All groups were given food and water continuously throughout the experiment.

2.4 Collection of Blood Samples

Blood samples were taken four weeks after the trial began. After that, blood samples were taken from the heart, and the blood was collected in anticoagulant-free plastic tubes and kept at room temperature for 15 minutes to allow the blood to coagulate, after which the tubes were centrifuged at 3000 r / min for 15 minutes to get serum blood. The serum was frozen by freezing at a temperature of 20- °C until the required chemical analysis, then the Liver, Kidney, and Testes were removed for histological study.

2.5 Biochemical Tests

The Cholesterol and Triglycerides concentration was estimated on [26] using the analysis kit manufactured by the French company (Biolabs SA, France). The Total proteins and albumin was estimated by using the analysis kits manufactured by (Biolabs SA, France), and the estimation of the concentration of the testosterone based on the technique of Elisa sandwich using the analysis kits manufactured by (Monobind INC, U.S.A).

2.6 Histological Preparations

After the animals were dissected, the liver, kidney, and testes were removed and washed with a physiological solution. Samples were prepared using microscopic tissue sections [27]. Using hematoxylin and eosin. After completing the preparation of the microscopic tissue sections, they were examined by optical microscopy.

2.7 Statistical Analysis

Statistical analysis was conducted by ANOVA Analysis of Variance. The significant differences were determined according to Duncan's multiple ranges and at a significant level (P≤0.05)[28].

3. RESULTS

The result in Table 1 showed a significant increase (P≤0.05) in the level of (TC and TG) in the(DOX) animal group compared to the healthy control group. It is noted that the group of animals that gavage with (DOX+DPP), (DPP) showed a significant decrease (P≤0.05) in the level of (TC and TG) compared to the group of (DOX) animal.

Table 1 also showed a significant decrease (P≤0.05) in the levels of (Total proteins and albumin) in the (DOX) animals group compared to the healthy control group. It is noted that the group of animals that gavage with (DOX+DPP), (DPP) showed a significant increase (P≤0.05) in total protein and albumin levels compared to the group of (DOX) animals. It also showed a significant decrease (P≤0.05) in total proteins

and albumin levels in the (DOX) animals group compared to the healthy control group. It is noted that the group of animals that gavage with (DOX+DPP), (DPP) showed a significant increase (P≤0.05) in the level of (Total protein and albumin) compared to the group of (DOX) animals.

3.1 Histological Study of the Liver

Microscopic inspection of the healthy control group's liver tissue sections and (DPP) group showed the natural shapes of the Central vein (CV), Radial arrangements of hepatocytes (HC), and Sinusoids(S) as in (Fig. 1a and b). Whereas in the (DOX) group many histological changes included thickening wall (TW) of central vein, hepatocytes necrosis (N), degeneration(D), karyolysis (KL) the usual radial arrangements of the hepatocytes were segmentally lost, infiltration of lymphocytes between hepatocytes and hemolysis (HL), as shown in (Fig. 1c). As for the group (DOX+DPP), an improvement in the central vein greatly reduced chemotherapeutic-induced degeneration and necrosis, but the radial organization of the hepatocytes was mostly preserved with an increased number of individual kupffers cells, as demonstrated in (Fig. 1d).

3.2 Histological Study of Kidney

The normal forms of the glomerulus (G), Bowman's capsule (BC), proximal urinary tubules (PUT), and distal urinary tubules (DUT) were observed in the renal tissue sections of the healthy control and (DPP) groups (Fig. 2a and b). The renal micrographs of the rats treated with (DOX) only exhibited severe tissue damage in the form of the most glomerulus (DG) and there bowman's capsules (DB), degeneration (D), and necrosis(N) numerous of proximal and distal urinary tubules, separate of fibrocystic cells (FB) as shown in (Fig. 2c). Animals revealed DOX +DPP almost showed nearly normal tubular and glomerular tissue architecture (Fig. 2d).

3.3 Histological Study of Testis

Normal seminiferous tubules (SNT) with normal spermatogenesis (SPG) and interstitial Leydig cells (LD) were seen in the testicular histological sections of the healthy control and (DPP) groups (Fig. 3a and b). In the rats treated with (DOX) were affected by less spermatogenesis(SPG) and Leydig cells (LD) with necrotic materials (NM) as shown in (Fig. 3c). Except for the appearance of many intratubular vacuolations, seminiferous tubules in rats treated with (DOX+DPP) seemed virtually normal (Fig. 3d).

4. DISCUSSION

Chemotherapy for cancer has been linked to side effects in numerous organ systems, including the liver, kidneys, and testes. It was hypothesized that combining a chemotherapeutic medication with cell protecting agents might be an effective strategy to decrease the risk of side effects [29]. The current work investigates the previously unknown hepatic, renal, and testicular protective effects of date palm pollen (DPP) therapy in rats when they are exposed to doxorubicin toxicity. To this aim, DPP therapy in rats reduced DOX-induced changes in indicators of hepatic, renal, and testicular function. DPP therapy also reduced DOX-induced oxidative stress in hepatic, renal, and testicular tissue, resulting in less redox-sensitive tissue damage.

Table 1. The effect of DPP extract and DOX drug of the studied parameters in serum of rats male

Groups	Control	DPP	DOX	DOX+DPP
Total cholesterol	61±0.707 c	50.80±0.837 f	70.600±0.894b	55.200±0.837e
Triglyceride	73.20±6.67 e	61.20±0.837 f	111.0±1.0 a	87.80±0.837 c
Total protein	5.308±0.699 b	6.440±0.803 a	3.378±0.829 d	5.148±0.548bc
Albumin	4.366±0.528 b	4.954±0.292 a	2.442±0.346 d	3.582±0.354 c
Testosterone	3.100±0.880 d	8.544±0.742 a	1.030±0.599 f	3.964±0.667 c

Values are expressed in mean± standard deviation. The number of rats (5) in each group. The numbers followed by vertically different letters indicate a significant difference at the probability level (P≤0.05)

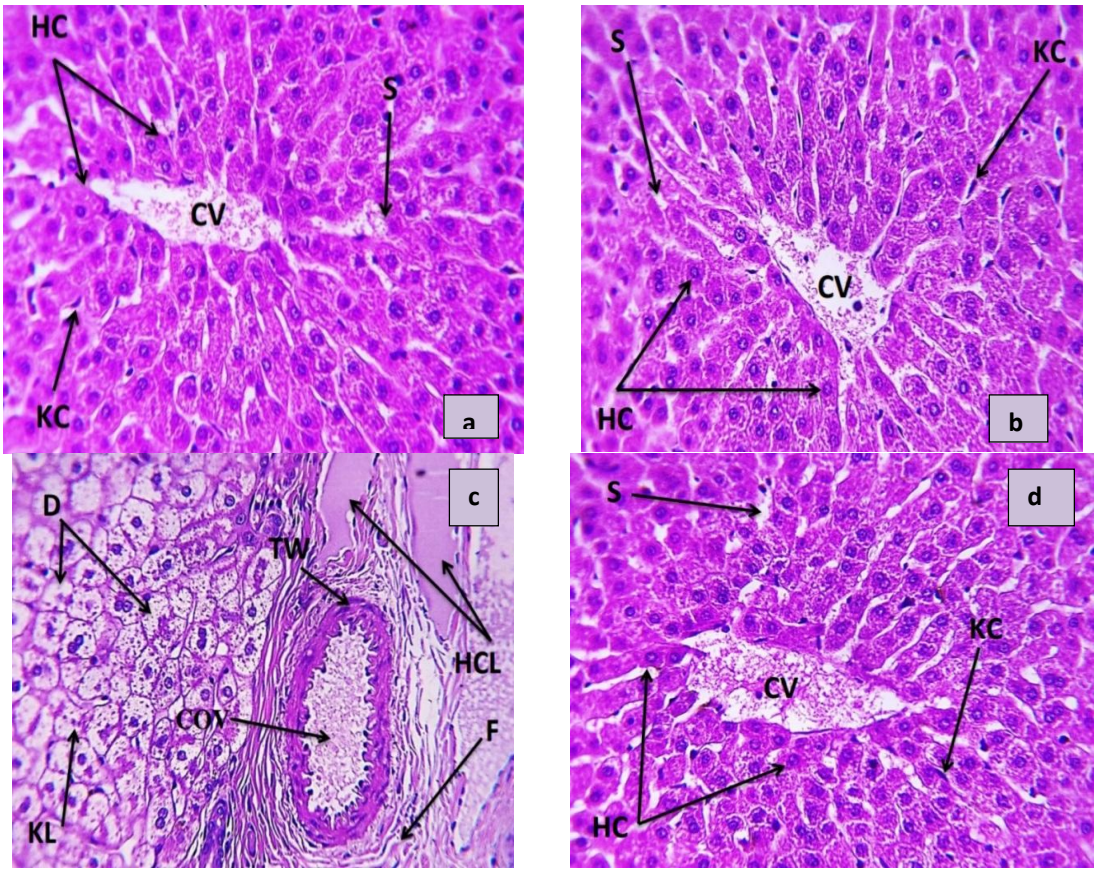

Fig. 1. All sections of liver stained with (H&E) 400x, the control group (A) and the group treated with DPP (B) show the normal stretcher central vein (CV), Hepatocytes (HC), Sinusoids (S), Kupffer cells (KC). Figure(C): section of the liver of the group treated with DOX only shows Thickens of central vein wall (TW), Degeneration (D), Karyolysis (KL), Fibrosis (F), Congestion (COV). Figure (D): section of the liver of the group treated with DOX and DPP showing the normal stretcher of central vein (CV), Kupffer cells (KC), Hepatocytes (HC), and sinusoids (S)

Doxorubicin-based chemotherapy is used to treat a wide spectrum of solid tumors and hematological cancers. It's also linked to organ toxicity, including the heart, liver, kidneys, and testicles [30]. It has also been linked to genotoxicity, as evidenced by enhanced cellular death and a strong affinity for chromosomal DNA and nucleosome eviction and replacement. DOX is converted in the liver to doxorubicinol, which is poisonous [31]. DOX targets CYP 450-mediated hepatic glutathione depletion; downregulation of hepatic glutathione causes mitochondrial dysfunction, reactive oxygen species production, and tissue necrosis [32]. In this study, the cholesterol and triglyceride levels in the doxorubicin-treated group (G3) were significantly higher than in the healthy control group. As a result of these alterations, the doxorubicin therapy may cause an increase in oxidative stress and lipid peroxidation [33], It might also be related to the harmful impact of DOX on the liver [34]. DOX-induced acute nephrotoxicity is mostly regulated by proximal tubule cell damage, which is still being studied [35]. Chemotherapy-induced severe renal tubular deficiencies result in acute renal failure [36]. The underlying reasons of DOX-induced renal damage might be inflammation, which increases the formation of reactive oxygen species (ROS), oxidative stress, apoptosis, and a reduction in antioxidant enzymes in the kidney [37]. Total protein and albumin levels in the afflicted animal group (G3) are significantly lower than in the healthy control group. The reason for this is due to doxorubicin-induced nephrotoxicity, which resulted in renal failure. The iron-anthracyclin complex causes an increase in the formation of free radicals, which causes severe damage to vital molecules,

resulting in a defect in nephron function and protein loss in the urine [38]. DOX's anticancer and toxic actions are caused by the production of intracellular ROS and free radicals, which intercalated with DNA and inhibited topoisomerase [39]. Due to the high polyunsaturated fatty acid content of mammalian spermatozoa and the intrinsic lack of the superoxide dismutase (SOD) family in the testis, spermatozoa may be more susceptible to free radical damage [40]. ROS and their metabolites can damage DNA, proteins, and lipids, as well as disrupt enzymatic systems, induce cell death, and eventually lead to a drop in sperm parameters, which is associated with male infertility [41]. In the afflicted animal group (G3), testosterone levels are much lower than in the healthy control group. Furthermore, El-Maddawy et al [42] treatment with DOX caused a decrease in the testosterone concentration. DPP generated a substantial decrease in high lipid profiles and a significant rise in total protein, albumin, growth, and testosterone hormone levels, according to our findings. DPP therapy, on the other hand, has a strong antioxidant impact on DOX-induced changes in hepatic, renal, and testicular malondialdehyde, as well as non-protein sulfhydryl concentrations, according to our findings.

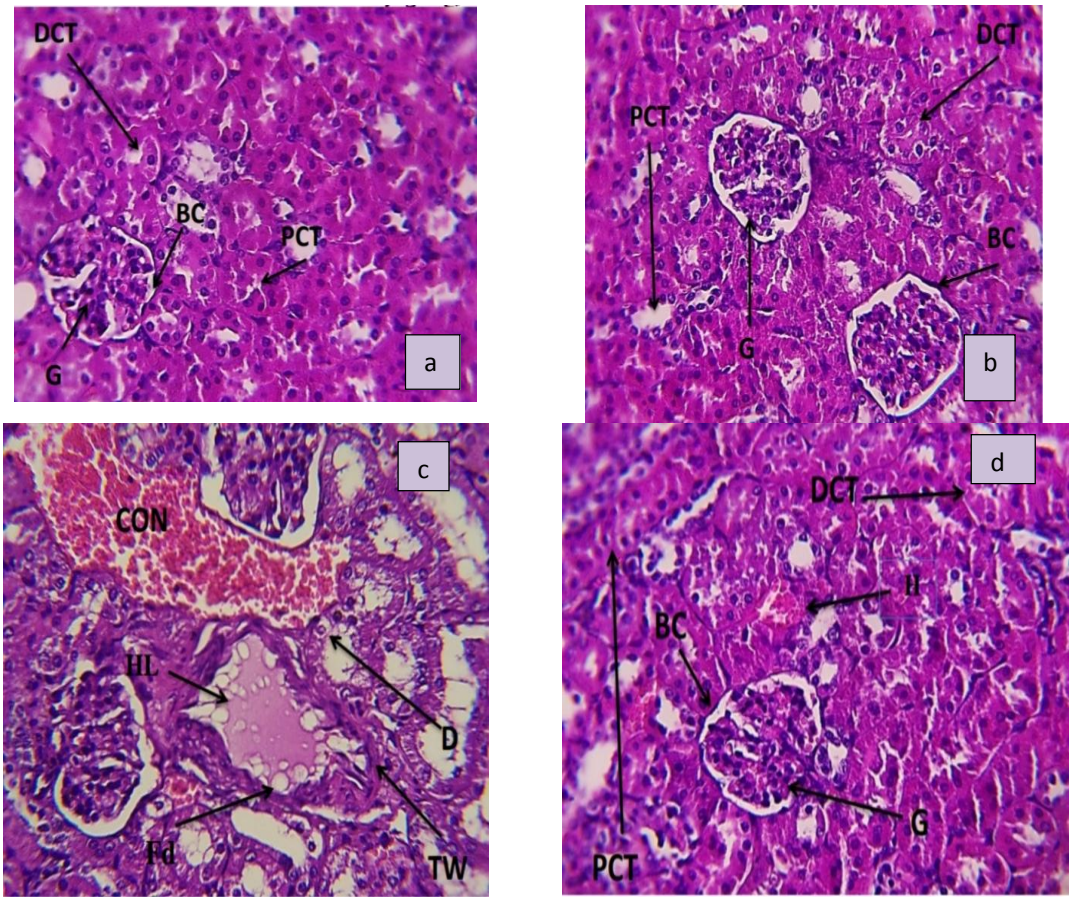

Fig. 2. All sections of kidney stained with (H&E) 400x, the control group (A) and the group treated with DPP (B) show the normal stretcher of Glomerulus(G), Bowman's capsule (BC), Proximal urinary tubules (PCT), and Distal urinary tubules (DCT). Figure (C) section of the kidney of the group treated with DOX only shows Congestion (CON), Glomerulus shrinkage, Degeneration (D), Hemolysis (HL), Fate drops (FD), and Thickness (TW) of the blood vessel. Figure (D): section of the kidney of the group treated with DOX and DPP showing the normal stretcher Glomerulus (G), Bowman's capsule (BC), Proximal urinary tubules (PCT), Distal urinary tubules (DCT), with Hemorrhage (H) and Hemolysis (HL)

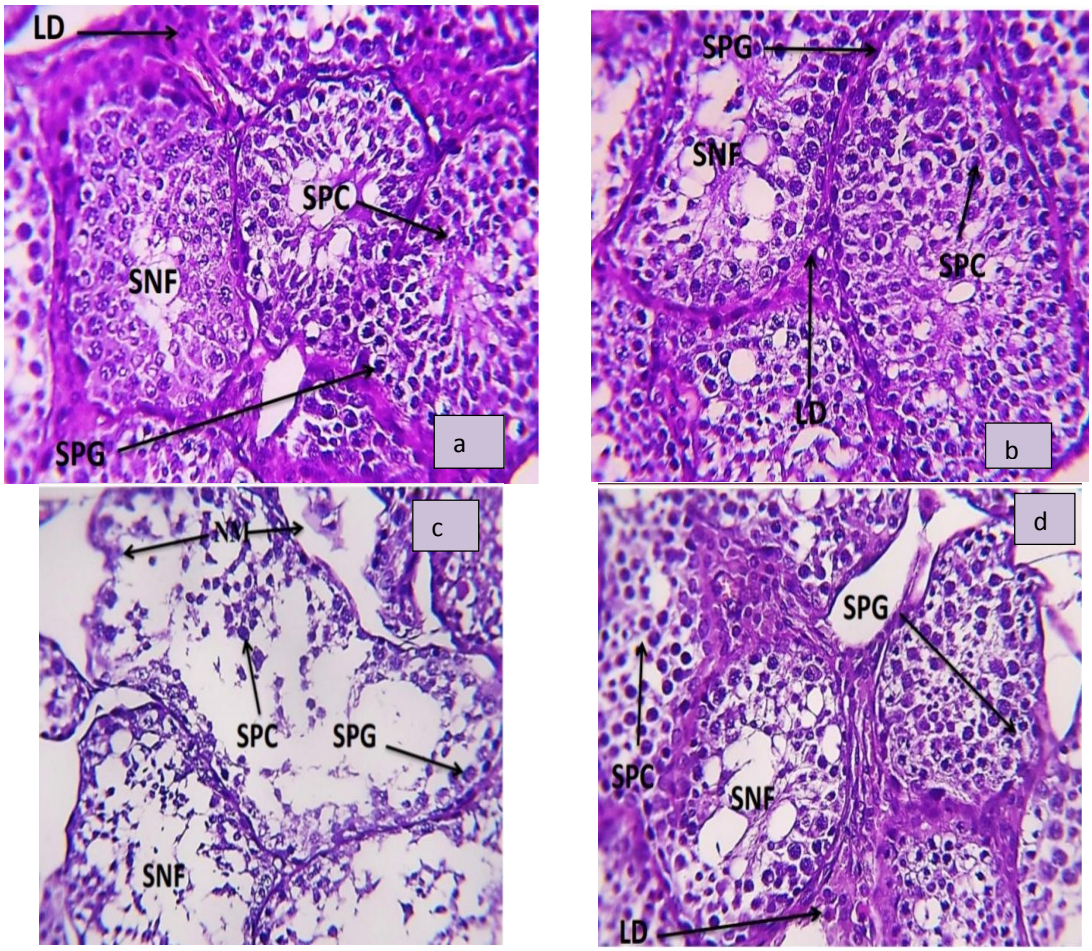

Fig. 3. All sections of Testis stained with (H&E) 400x, the control group (A), and the group treated with DPP (B) show the normal stretcher of Seminiferous tubules (SNT), Spermatogonia (SPG), Spermatocytes (SPC), Leydig cells (LD). Figure (C) section of the testis of the group treated with DOX only shows Seminiferous tubules (SNF), A little Spermatogonia (SPG), and Spermatocytes (SPC), Necrotic material (NM). Figure (D): section of the testis of the group treated with DOX and DPP showing the normal stretcher of Seminiferous tubules (SNT), Spermatogonia (SPG), Spermatocytes (SPC), Leydig cells (LD)

The redox sensitivity of DPP's protective properties may be mediated by one or more of its bioactive components. DPP was shown to be nutrient-dense, including amino acids, vitamins, and minerals. Surprisingly, DPP was discovered to contain antioxidant phytochemicals like as rutin, flavonoids, and phenolic compounds [43]. In animal models, these phytochemicals have also been demonstrated to have hepato- and nephroprotective properties. DPP therapy, it turns out, can reduce the negative consequences of cadmium-induced testicular damage by preventing increased oxidative stress [44]. DPP's protective effects on the liver, kidneys, and testes have not been documented to our knowledge. Additional putative mechanisms that may contribute to the protective effects of DPP treatment include its previously reported. DOX poisoning causes an inflammatory reaction in the hepatic tissue, therefore it has anti-inflammatory properties [45]. In animal models, compelling evidence shows that DPP bioactive components have anti-inflammatory properties. As a result, it's tempting to hypothesize about DPP's and its components' anti-inflammatory properties [46].

5. CONCLUSIONS

The administration with Date Palm Pollen prevented oxidative damage in the hepatic, renal, and testicular tissue of the experimental rabbits. DPP's protective effect can be attributed to its

membrane stabilizing, antioxidant, and anti-hyperlipidemic properties, which are mediated by biochemical marker regulation. The powerful and beneficial components in DPP, including as flavonoids, vitamins, amino acids, polyphenols, carotenoids, minerals, fatty acids, and organic acids, can be attributed to a wide range of pharmacological effects. Furthermore, the findings imply that DPP might be useful in identifying treatment potential for DOX-induced hepatic, renal, and testicular damage.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All animals used in this study was authorized by the ethical clearance from the local committee of Samarra University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mallhi TH, Qadir MI, Ali M, Ahmad B, Khan YH, Rehman A. Review: Ajwa date (Phoenix dactylifera) an emerging plant in pharmacological research. Pak J Pharm Sci. 2014;27:607–16.
2. El-Arem A, Saafi EB, Ghrairi F, Thouri A, Zekri M, Ayed A, et al. Aqueous date fruit extract protects against lipid peroxidation and improves antioxidant status in the liver of rats subchronically exposed to trichloroacetic acid. J Physiol Biochem. 2014a;70:451–64.
3. Borochov-Neori H, Judeinstein S, Greenberg A, Volkova N, Rosenblat M, Aviram M. Antioxidant and antiatherogenic properties of phenolic acid and flavonol fractions of fruits of 'Amari' and 'Hallawi' date (*Phoenix dactylifera* L.) varieties. J Agric Food Chem. 2015;63:3189–95.
4. El-Arem A, Zekri M, Thouri A, Saafi EB, Ghrairi F, Ayed A, et al. Oxidative damage and alterations in antioxidant enzyme activities in the kidneys of rat exposed to trichloroacetic acid: Protective role of date palm fruit. J Physiol Biochem. 2014b;70:297–309.
5. Karasawa K, Otani H. Anti-allergic properties of a matured fruit extract of the date palm tree (*Phoenix dactylifera* L.) in mite-sensitized mice. J Nutr Sci Vitaminol (Tokyo). 2012;58:272–7.
6. Boulenouar N, Marouf A, Cheriti A. Antifungal activity and phytochemical screening of extracts from Phoenix dactylifera L. cultivars. Nat Prod Res. 2011;25:1999–2002.
7. Vayalil PK. Antioxidant and antimutagenic properties of aqueous extract of date fruit (*Phoenix dactylifera* L. Arecaceae). J Agric Food Chem. 2002;50:610–7.
8. Souli A, Sebai H, Rtibi K, Chehimi L, Sakly M, Amri M, et al. Effects of dates pulp extract and palm sap (*Phoenix dactylifera* L.) on gastrointestinal transit activity in healthy rats. J Med Food. 2014;17:782–6.
9. Subash S, Essa MM, Al-Asmi A, Al-Adawi S, Vaishnav R, Guillemin GJ. Effect of dietary supplementation of dates in Alzheimer's disease APPsw/2576 transgenic mice on oxidative stress and antioxidant status. Nutr Neurosci. 2015;18:281–8.
10. Martin-Sanchez AM, Cherif S, Ben-Abda J, Barber-Valles X, Perez-Alvarez JA, Sayas-Barbera E. Phytochemicals in date co-products and their antioxidant activity. Food Chem. 2014;158:513–20.
11. Abdulrahman MA, Mustafa HA, Mustafa MA, AL-Samarraie MQ, Ahmed MT. The diagnostic value of anti-mullerian hormone in female infertility evaluation. Science. 2020;1:3.
12. Diab KA, Aboul-Ela EI. In vivo Comparative studies on antigenotoxicity of date palm (*Phoenix dactylifera* L.) pits extract against DNA damage induced by N-nitroso-N-methylurea in mice. Toxicol Int. 2012;19:279–86.
13. Kwaasi AA, Parhar RS, Harfi H, Tipirneni P, Al-Sedairy ST. Characterization of antigens and allergens of date palm (*Pheonix dactylifera*) pollen. Immunologic assessment of atopic patients by whole extract and its fractions [corrected]. Allergy. 1992;47:535–44.
14. Elkerm Y, Tawashi R. Date palm pollen as a preventative intervention in radiation- and chemotherapy-induced oral mucositis: a pilot study. Integr Cancer Ther. 2014;13:468–72.
15. AL-Samarraie MQ, Mokdadhatamabdulwahed A, Mustafa MA, Alkanaani MI, Abdulateef ID, Hameed RS, Ibrahim ZM. Vitamin D deficiency and it relation with weight, age and gender in

number of men and women in Samarra City. Annals of the Romanian Society for Cell Biology. 2021:257-63.
16. Mustafa MA, AL-Samarraie MQ. Secondary menopause and its relationship to hormonal levels among women at salah Al-Din hospital. European Journal of Molecular and Clinical Medicine. 2020;7(9):96-104.
17. Mehraban F, Jafari M, Akbartabar Toori M, Sadeghi H, Joodi B, Mostafazade M, et al. Effects of date palm pollen (*Phoenix dactylifera* L.) and Astragalus ovinus on sperm parameters and sex hormones in adult male rats. Iran J Reprod Med. 2014;12:705–12.
18. Su Z, Ye J, Qin Z, Ding X. Protective effects of madecassoside against Doxorubicin induced nephrotoxicity *In vivo* and *In vitro*. Scientific reports. 2015;5(1):1-4.
19. Khaleel ZI, Mohammed ZH, AL-Samarraie MQ. Histological Effect of the alcoholic extract of nerium oleander in the heart and brain in mice and its effect on the lymphocytes (*In vitro*). Indian Journal of Public Health Research & Development. 2019;10(8).
20. Sah SK, Khatiwada S, Chaudhary D, Jha CB, Bhattacharya S. Doxorubicin induced histomorphometric changes in testes of albino rat. Nepal Journal of Biotechnology. 2015;3(1):10-4.
21. Yang F, Kemp CJ, Henikoff S. Doxorubicin enhances nucleosome turnover around promoters. Current Biology. 2013;23(9):782-7.
22. Camaggi CM, Comparsi R, Strocchi E, Testoni F, Angelelli B, Pannuti F. Epirubicin and doxorubicin comparative metabolism and pharmacokinetics. Cancer chemotherapy and pharmacology. 1988;21(3):221-8.
23. Ghibu S, Delemasure S, Richard C, Guilland JC, Martin L, Gambert S, Rochette L, Vergely C. General oxidative stress during doxorubicin-induced cardiotoxicity in rats: Absence of cardioprotection and low antioxidant efficiency of alpha-lipoic acid. Biochimie. 2012;94(4):932-9.
24. Lee VW, Harris DC. Adriamycin nephropathy: A model of focal segmental glomerulosclerosis. Nephrology. 2011;16(1):30-8.
25. Abdulwahed AM, Alkanaani MI, Alsamarrai AH, Hamad MA, Dakheel A, AL-Samarraie MQ. Determination of some visfatin hormone level and lipid profilein some breast cancer patients in Samarra city. Annals of Tropical Medicine and Health. 2020;23:265-7.
26. El-Maddawy ZK, Abd El Naby WS. Protective effects of zinc oxide nanoparticles against doxorubicin induced testicular toxicity and DNA damage in male rats. Toxicology research. 2019;8(5):654-62.
27. Deacon AC, Dawson PJ. Enzymic assay of total cholesterol involving chemical or enzymic hydrolysis--a comparison of methods. Clinical chemistry. 1979;25(6):976-84.
28. Suvarna KS, Layton C, Bancroft JD, editors. Bancroft's theory and practice of histological techniques E-Book. Elsevier Health Sciences; 2018.
29. Dean A, Voss D, Draguljić D. Design and analysis of experiments. New York: Springer; 1999.
30. Kranti VM, Mahesh V, Srinivas P, Ganesh YV, Godwin AP, Lahkar M. Evaluation of the protective effect of silymarin on doxorubicin induced chronic testicular toxicity in rats. Int J Pharm Bio Sci. 2013;4(1):473-84.
31. Shivakumar P, Rani MU, Reddy AG, Anjaneyulu Y. A study on the toxic effects of doxorubicin on the histology of certain organs. Toxicology international. 2012;19(3):241.
32. Camaggi CM, Comparsi R, Strocchi E, Testoni F, Angelelli B, Pannuti F. Epirubicin and doxorubicin comparative metabolism and pharmacokinetics. Cancer chemotherapy and pharmacology. 1988;21(3):221-8.
33. Karapehlivan M, Uzlu E, Atakişi O, Erdoğan HM, Uzun M, Çitil M. Doksorubisin uygulanan tavşanlarda plazma sialik asit, malondialdehi t ve redükte glutatyon düzeylerine L-karnitinin etkileri. Kafkas Univ Vet Fak Derg. 2007;13(2):155-60.
34. Ambrosone CB, Ahn J, Schoenenberger V. Antioxidant supplements, genetics and chemotherapy outcomes. Current Cancer Therapy Reviews. 2005;1(3):251-8.
35. Wali AF, Rashid S, Rashid SM, Ansari MA, Khan MR, Haq N, Alhareth DY, Ahmad A, Rehman MU. Naringenin regulates doxorubicin-induced liver dysfunction: impact on oxidative stress and inflammation. Plants. 2020;9(4):550.

36. Grant MK, Seelig DM, Sharkey LC, Choi WS, Abdelgawad IY, Zordoky BN. Sexual dimorphism of acute doxorubicin-induced nephrotoxicity in C57Bl/6 mice. PloS one. 2019;14(2):e0212486.
37. Ruggiero A, Ferrara P, Attinà G, Rizzo D, Riccardi R. Renal toxicity and chemotherapy in children with cancer. British journal of clinical pharmacology. 2017;83(12):2605-14.
38. Abdelmeguid NE, Chmaisse HN, Zeinab NA. Protective effect of silymarin on cisplatin-induced nephrotoxicity in rats. Pak J Nutr. 2010;9(7):624-36.
39. Vejpongsa P, Yeh ET. Prevention of anthracycline-induced cardiotoxicity: Challenges and opportunities. Journal of the American College of Cardiology. 2014;64(9):938-45.
40. Sikka SC. Andrology lab corner*: Role of oxidative stress and antioxidants in andrology and assisted reproductive technology. Journal of andrology. 2004;25(1):5-18.
41. Agarwal A, Virk G, Ong C, Du Plessis SS. Effect of oxidative stress on male reproduction. The world journal of men's health. 2014;32(1):1.
42. El-Maddawy ZK, Abd El Naby WS. Protective effects of zinc oxide nanoparticles against doxorubicin induced testicular toxicity and DNA damage in male rats. Toxicology research. 2019;8(5):654-62.
43. Tahvilzadeh M, Hajimahmoodi M, Rahimi R. The role of date palm (*Phoenix dactylifera* L) pollen in fertility: A comprehensive review of current evidence. J Evid Based Complementary Altern Med. 2016;21:320–4.
44. Xie W, Chen C, Jiang Z, Wang J, Melzig MF, Zhang X. Apocynum venetum attenuates acetaminophen-induced liver injury in mice. Am J Chin Med. 2015;43:457–76.
45. Karuppagounder V, Arumugam S, Thandavarayan RA, Pitchaimani V, Sreedhar R, Afrin R, Harima M, Suzuki H, Suzuki K, Nakamura M, Ueno K. Naringenin ameliorates daunorubicin induced nephrotoxicity by mitigating AT1R, ERK1/2-NFκB p65 mediated inflammation. International immunopharmacology. 2015;28(1):154-9.
46. Farouk A, Metwaly A, Mohsen M. Chemical composition and antioxidant activity of date palm pollen grains (*Phoenix dactylifera* L. Palmae) essential oil for Siwe cultivar cultivated in Egypt. Middle East J Appl Sci. 2015;5:945–9.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/70980