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ORIGINAL RESEARCH article

Influence of *Phoenix dactylifera* leaf extract on doxorubicin-induced nephrotoxicity and hepatotoxicity in rats

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Keywords: Doxorubicin, hepatotoxicity, palm leaf, *Phoenix dactylifera*, nephrotoxicity

Abstract: The research into plant is used to search for new agents with pharmacological activities. This study seeks to evaluate the effects of the palm leaf methanolic extract against nephrotoxicity, hepatotoxicity, and weight loss induced by chemotherapeutic drug doxorubicin in a rat's model. Five groups of rats (n= 4 in each group) were treated with or without doxorubicin (3.0 mg/kg/day, ip) and with palm leaf methanolic extract (400 mg/kg/day or 1200 mg/kg/day, po), followed by evaluation of renal and hepatic biochemical markers. The findings obtained indicated that palm leaf methanolic extract exerts protective effects against doxorubicin-induced nephrotoxicity and hepatotoxicity. Doxorubicin significantly elevated renal function markers, namely creatinine, uric acid and urea, however, these biomarkers remained within normal levels after treatment with palm leaf methanolic extract (400 mg/kg/day) as compared to the control group. Treating the rats with doxorubicin and palm leaf methanolic extract at doses 400 mg/kg/day and 1200 mg/kg/day, counteracts the doxorubicin-induced elevation of serum creatinine and uric acid compared to the doxorubicin group. Doxorubicin also significantly increased hepatic function tests namely alanine and aspartate aminotransferase, gamma-glutamyl transferase, and bilirubin as compared to the control group. In addition, treating the rats with palm leaf methanolic extract doses and doxorubicin caused a significant decrease in the serum levels of hepatic markers compared to the doxorubicin group. Doxorubicin treatment resulted in a weight loss of 34.1%, the weight loss caused by doxorubicin was prevented by treating the rats with the extract at 1200 mg/kg/day as compared to their baseline body weight. Thus, the results of the current study suggest that the active constituents present in the palm leaf methanolic extract have a protective effect against hepatotoxicity, nephrotoxicity and weight loss-induced by doxorubicin.

Introduction

Cancer is a type of neoplasia made up of abnormal cells, and is the uncontrolled enlargement of irregular cells that occurs when the body's normal control mechanism discontinues working. Elderly cells do not die but proliferate uncontrollably; giving rise to new, irregular cells [1]. Cancer is a sly disease that is generally difficult to eradicate completely [2]. To grow cancer, six key properties must be acquired, including proliferation, insensitivity to anti-proliferative signals, apoptosis evasion, infinite replicative potential,

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vascularization maintenance, and tissue invasion and metastasis. Cancer development necessitates the accumulation of genetic lesions in cells [3]. Novel and significant advances in tumor treatment involve the use of stem cells, targeted therapy, nanoparticle therapy, natural antioxidants, radionics, chemodynamic therapy, sonodynamic therapy and ferroptosis-based therapy [4]. The use of anticancer medications has been proven to be carcinogenic, teratogenic, or mutagenic in humans [5]. There are several classes of anticancer medications as alkylating chemicals that cause DNA damage; anti-metabolites that replace the usual building blocks of RNA and DNA; antibiotics that interfere with DNA replication enzymes; and topoisomerase inhibitors that inhibit either topoisomerase I or II [6].

Doxorubicin (adriamycin, Dox) is a chemotherapy drug and is a treatment for many different types of cancer. Dox belongs to the class of anthracyclines isolated from bacteria *Streptomyces peucetius*. It is utilized in the therapy of leukemia, lymphoma, hard malignancies [7] and treat solid tissue and bone sarcomas in addition to diseases of the breast, ovary, bladder, and thyroid. It is likewise utilized in the therapy of acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and little cell cellular breakdown in the lungs [8]. Dox is believed to act by intercalating between DNA bases and uncoiling the DNA helix, which results in inhibition of DNA synthesis and the normal DNA breaking and resealing action of DNA toposiomerase II. Toposiomerase II is a nuclear enzyme that is responsible for the tertiary structure of DNA [9]. In spite of anthracyclines efficacy in malignancy management, doxorubicin was reported to cause hepatotoxicity, renotoxicity and cardiotoxicity by producing free radicals in off-target tissues. The reasons regarding toxicity are oxidative stress, inflammation, and apoptosis due to reactive oxygen species (ROS) production and mitochondrial dysfunction, which cause an imbalanced energy status in the cell and eventually lead to apoptosis [10]. It was suggested that Dox-semiquinone, a non-stable metabolite of Dox, reacts with O_2, resulting in the formation of H_2O_2 and O_2 (superoxide). Dox stimulates the activity of extra mitochondrial oxidative enzymes such as xanthine oxidase and NADPH oxidase and, interferes with mitochondrial iron export, resulting in formation of ROS. Dox hinders the protective activities of endogenous enzymatic and non-enzymatic antioxidants such as vitamin E and glutathione (GSH). The oxidative stress caused by an imbalance between ROS generation and inactivation of antioxidants is harmful to vital organs [11]. Dox-nephrotoxicity is characterized by podocyte injury followed by glomerulosclerosis, tubulointerstitial inflammation and fibrosis [12]. The Dox-nephrotoxicity is revealed by kidney function changes: increased serum creatinine and blood urea nitrogen concentrations [13].

Phoenix dactylifera L. known as Date palm is a member of the Arecaceae family [14]. Date production in Arab nations accounts for 80.0% of total global output [15]. In Arab countries, parts of the *P. dactylifera* tree are utilized in traditional medicine to alleviate digestive issues, liver problems, pharyngitis, fever and sexually transmitted diseases like gonorrhea [16]. It is high in phenolic, carbohydrates, sterols, carotenoids, anthocyanins, procyanidins, flavonoids, vitamins, and tannins, according to phytochemical studies [17, 18]. *P. dactylifera* leaves, in particular, are high in total polyphenols, flavanoids, and flavonols, all of which have antioxidant qualities [16]. The significant antioxidant, hepatoprotective [19], anti-hyperlipidemic [20] and antiviral [21] activities of these phytoconstituents characteristics of *P. dactylifera* leaves have been found to produce favorable biological and pharmacological effects. Importantly, administration of *P. dactylifera* leaves improved lipid profiles in rats with alloxan-induced diabetes [22]. Administration of the methanolic and aqueous *P. dactylifera* leaf extracts possesses central and peripheral analgesic activities against chemical and thermal-induced pain [23]. The methanolic extract of Date palm leaves protects the mice against pentylene-tetrazole-induced convulsions [24]. Thus, the goals of this study are to demonstrate the effectiveness of the palm leaf methanolic extract to protect and ameliorate the rats from the hepatotoxicity, nephrotoxicity, and weight loss induced by doxorubicin.

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Materials and methods

Preparation of palm leaf methanolic extract (PLME): The leaflets of the *Phoenix dactylifera* L. (family Arecaceae) Taboni cultivares were collected during the summer of 2023 from different farmers in Misurata, Libya. These leaflets were cleaned, cut into small pieces, and dried in the shade at room temperature. For the preparation of PLME, the small pieces of Date palm leaflets were crushed into powder. After that, 500 g of the coarse powder was macerated into 99.6% methanol (1:3w/v) with agitation for 72 hours at room temperature away from the light. To obtain a clear filtrate, the mixture was filtered three times using sterile gauze and two times using filter paper CAT No.1001-150. The filtrate was concentrated in an oven at 40 ºC until the methanol was volatilized. The extract was stored in a refrigerator until use. Distilled water was used as a solvent in order to be administered orally to rats for experimental purposes.

Animals: Adult male Spraue-Dawley rats weighing 245 g to 340 g were obtained from the animal house of the Faculty of Pharmacy, Misurata University, Misurata, Libya. All rats were divided into five groups and kept in plastic cages under controlled conditions of a 12hr/12h light/dark cycle at 6:00 am to 6:00 pm and an ambient room temperature of 25.0±2.0°C with a free access to pelleted rations and water. Animal care and experimental protocol followed the principles and guidelines proposed by the Faculty of Pharmacy at Misurata University, Misurata, Libya.

Experimental design: 20 rats were divided according to their weight into five groups, with four rats in each group. The rats were treated for four weeks as following, group I: untreated group (control), group II: received Dox 3.0 mg/kg i.p. every third day for a total of six doses, group III: received PLME 400 mg/kg p.o. daily, and group IV and group V: received PLME 400 mg/kg and 1200 mg/kg p.o. daily for four weeks, respectively. During these treatments, each group of IV and V received Dox 3.0 mg/kg/day twice per week for a total dose of 18.0 mg/kg.

Samples collection: At the end of treatment, the rats were euthanized using halothane, and blood samples were collected directly from the heart. Immediately, the samples for enzyme analysis were placed in tubes without anticoagulant. All the tests were performed at the Misurata Center laboratory, Misurata, Libya.

Statistical analysis: The significant differences between the groups were analyzed by using Student t-test test. The figures were generated using the Excel program, and data were expressed as mean±SEM. The level of significance was set at $p<0.05$.

Results

Effect of Dox and PLME on serum creatinine, uric acid and urea levels: The effects of Dox and PLME alone or in combination on the levels of serum creatinine, uric acid, and urea are illustrated in **Figures 1a**, **1b** and **1c**. The Dox-treated group (II) showed a significant increase in the levels of serum creatinine (0.653±0.125) ($p<0.04$) and uric acid (4.425±1.036) ($p<0.05$), with a high elevation in the level of serum urea (32.47±2.980) when compared with the control group (I). While no significant difference in kidney function tests was observed in the PLME-treated group (III) when compared to control rats (I).

In **Figures 1a**, **1b** and **1c**, the PLME with Dox-treated groups IV and V significantly decreased the levels of serum creatinine (0.275±0.025) ($p<0.01$) and uric acid (2.025±0.461) ($p<0.04$), respectively, when compared with the Dox group (II). No significant difference was observed in these two parameters when compared to group (I). On the other hand, PLME-treated group IV (Dox with PLME 400 mg/kg) and group V (Dox with 1200 mg/kg) showed significant increases ($p<0.009$) and ($p<0.02$) in the serum urea (50.75±7.560) and (56.75±6.28), respectively, when compared to the control group (I) and the Dox group (II).

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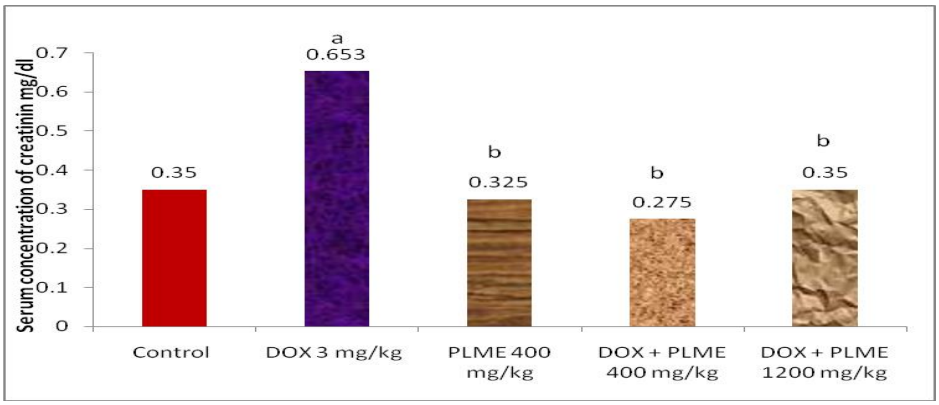
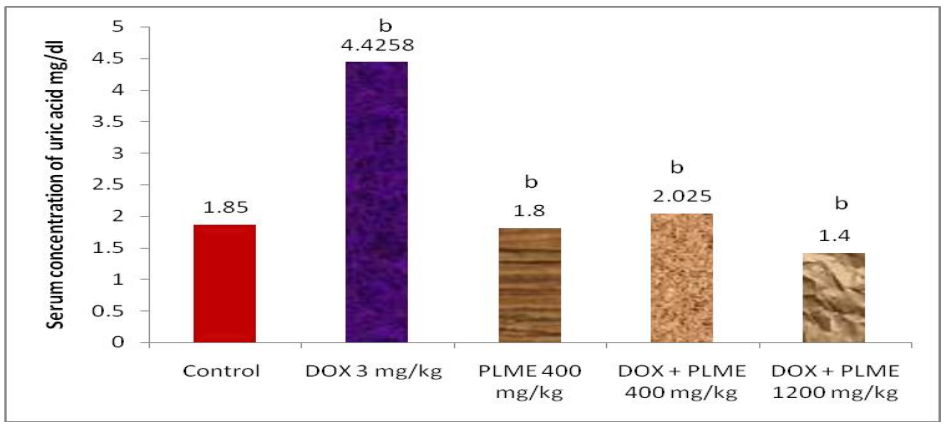
Figure 1a: Effects of Dox, PLME, Dox & PLME on serum creatinine level in the rat



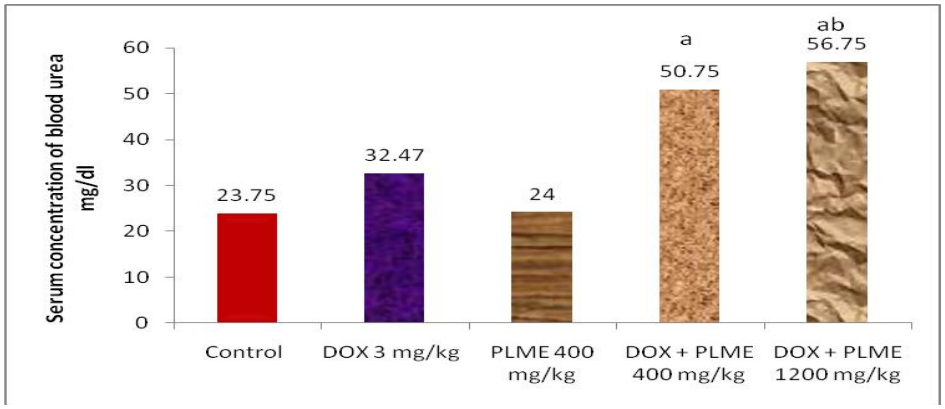
Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

Figure 1b: Effects of Dox, PLME, Dox & PLME on serum uric acid level in the rat



Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

Figure 1c: Effects of Dox, PLME, Dox & PLME on serum urea level in the rat



Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

Serum hepatic biochemical markers: **Figures 2a** to **2e** show that Dox at a dose of 3.0 mg/kg/day resulted in a significant increase in the activities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) and total bilirubin (T. bil.) level when compared to the control group (I). The percentage of elevation were found to be 50.27%, 80.99 %, 06.29%, 53.19%, and 84.21%, respectively. The data also demonstrate that simultaneous treatment of Dox with PLME

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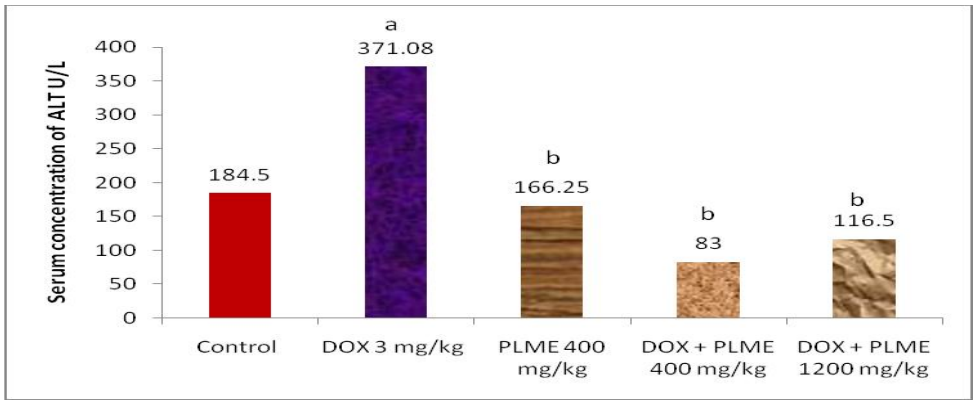
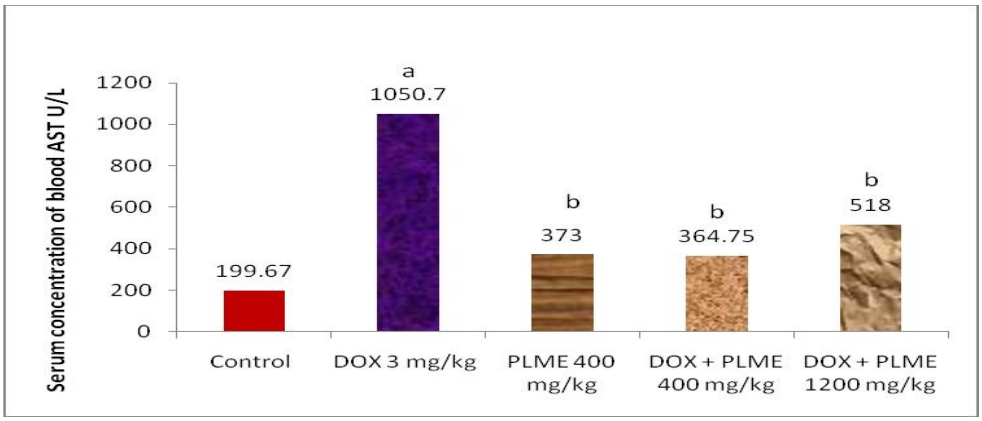
at doses of 400 mg/kg and 1200 mg/kg significantly attenuates the Dox-induced increase in the serum levels of hepatic biochemical markers as compared to the Dox-treated group (II). The decrease in elevated hepatic biochemical markers after administration of PLME 400 mg/kg with Dox were 77.63% in ALT, 65.28% in AST, 12.47 % in ALP activities, and 57.89% in the total bilirubin level as compared to the Dox group.

Figure 2a: Effects of Dox, PLME, Dox & PLME on alanine aminotransferase activity in the rat



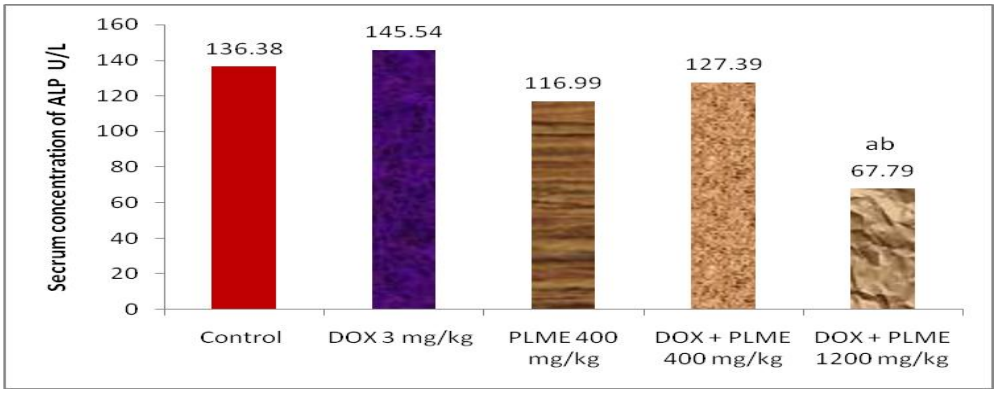
Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: as compared to the Dox group

Figure 2b: Effects of Dox, PLME, Dox & PLME on aspartate aminotransferase activity in the rat



Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

Figure 2c: Effects of Dox, PLME, Dox & PLME on alkaline phosphatase activity in the rat



Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

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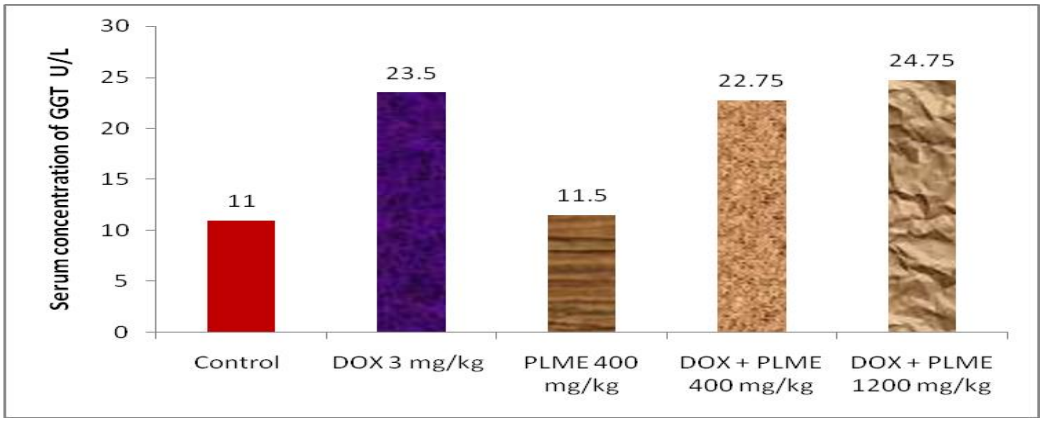
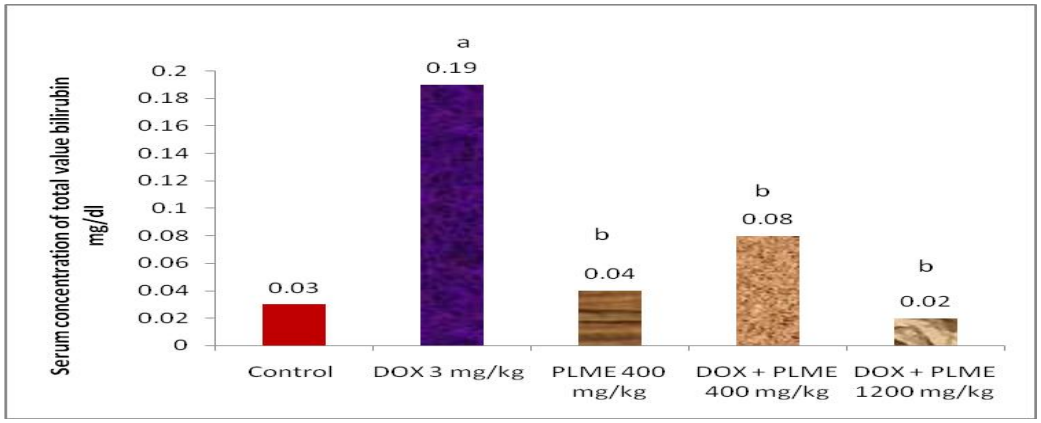
Figure 2d: Effects of Dox, PLME, Dox & PLME on gamma glutamyl transferase activity in the rat



Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

Figure 2e: Effects of Dox, PLME, Dox & PLME on total value of bilirubin in the rat



Dox is doxorubicin and PLME is palm leaf methanolic extract
a: compared to the control group & b: compared to the Dox group

Effect of PLME and Dox on survival and the weight of rats: **Table 1** shows Dox treatment resulted in a weight loss of 34.08%, while PLME administration resulted in a weight gain of 14.65. Weight loss caused by Dox was prevented by treating rats with the extract at a dose of 1200 mg/kg. Treatment with Dox alone decreased appetite, motor activity and induced physical exhaustion. Death occurred in Dox group within two weeks of treatment, while these effects did not occur in groups received PLME alone or in combination with Dox.

Table 1: Effects of Dox, PLME and their combination on the body weight of the rat

Body Weight (gram)	Control (I)	DOX 3 mg/kg (II)	PLME 400 mg/kg (III)	DOX & PLME 400 mg/kg (IV)	DOX & PLME 1200 mg/kg (V)
Baseline weight	343.00±16.63	331.25±6.25	247.50±8.29	261.25±2.39	296.25±4.27
Second-week	337.50±11.09	321.50±10.10	266.25±8.26	263.75±3.14	312.50±5.95
Third-week	360.00±2.89	240.00±36.06	276.25±8.98	255.00±3.54	320.00±11.37
Final-weight	368.33±21.86	218.33±33.46	290.00±10.80	250.00±4.56	301.25±8.98
weight gain in %	+ 25.33 (6.9%)	-	+ 42.5 (14.7%)	-	+ 05.00 (1.7%)
weight loss in %	-	- 112.92 (34.1%)	-	- 11.25 (04.3%)	-
Mortality rate	0/4	3/7	0/4	0/4	0/4

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Discussion

In the current study, the aim was to explore the potential of a methanolic extract of *Phoenix dactylifera* leaves for counteracting of Dox adverse effects such as nephrotoxicity, hepatotoxicity and weight loss. Previous studies reported that Dox's nephrotoxicity is caused by the accumulation of free radicals like quinine [21] and the release of nitric oxide (NO), which could cause an increase in apoptosis [12] and increase permeability, which leads to tubular degeneration [22]. Other studies have shown that chemotherapy causes severe renal tubular impairment, leading to renal failure [25, 26]. The drug-induced damage to kidney function can be easily studied using rat models due to their similarity to human intra-renal enzymes [27]. The present study was aimed at demonstrating the protective effects of PLME on kidney function impairment caused by Dox in order to enhance the therapeutic effect and alleviate the adverse effects of Dox as an anticancer agent. The findings of the current study showed a clear and significant increase in serum levels of creatinine and uric acid by Dox and a non-significant increase in urea level. When used alone, PLME has no effect on creatinine, uric acid, or urea levels, whereas in combination with Dox, PLME counteracts the elevation of creatinine and uric acid, and unexpectedly, the urea level was significantly increased. These observations could be explained and attributed to the high content of antioxidants in the PLME [28]. However, more studies are recommended to understand the significant increase in urea levels in the presence of PLME. Dox-induced hepatotoxicity was evidenced in the present study by an increase in the serum activities of AST, ALT and GGT, as well as in the total bilirubin level, in Dox-treated rats, indicating a serious hepatic injury. These results are consistent with Saleh's investigation into Dox-induced hepatic toxicity [29]. The mechanisms responsible for Dox-induced hepatotoxicity are complicated, but recent report suggested that oxidative stress plays an important role in hepatotoxicity [30]. Our results support these reports and hypotheses, where the sharp increase in liver enzymes was reversed by PLME and showed clear hepatoprotective effects when used with Dox in two different doses due to its antioxidant effects. Phytochemical screening of Date palm leaf extract Tabouni cultivar showed the presence of flavonoids, polyphenolic compounds, terpenoids, and steroids. Salem and others [19] reported that methanolic palm leaf extract possesses a potent antioxidant activity, as manifested by significant elevation levels of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in the rat liver homogenate. In this study, Dox led to a decrease in the motor activity of the rats, a loss of their appetite, and a significant decrease in their weight. It also led to the deaths of three animals, and this aligns with what Chen and his colleagues [31] found in their study. Thus, PLME protected rats from Dox toxicity, which is represented by hepto-renal toxicity, decreased motor activity, weight loss, and mortality. Indeed, other studies are needed to separate these constituents and determine their pharmacological benefits. Further studies are recommended to investigate the mechanism by which *Phoenix dactylifera* extracts have a protective effect against chemotherapy-induced life-threatening adverse effects and to determine the responsible constituents.

Conclusion: This study demonstrates that *Phoenix dactylifera* leaf methanol extract ameliorated nephrotoxicity, hepatotoxicity, and weight loss-induced by doxorubicin in rats. PLME alone has no effect on kidney and liver function markers.

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