









Research Article

Rutin and Hesperidin Alleviate Paclitaxel-Induced Nephrocardiotoxicity in Wistar Rats *via* Suppressing the Oxidative Stress and Enhancing the Antioxidant Defense Mechanisms

Yasmine A. Ali ¹, Osama M. Ahmed ², Hanan A. Soliman ¹,
Mohamed Abdel-Gabbar ¹, M. Al-Dossari ³, N. S. Abd El-Gawaad ⁴,
El-Shaymaa El-Nahass ⁵ and Noha A. Ahmed ²

¹Biochemistry Department, Faculty of Science, Beni-Suef University, P.O. Box 62521, Beni-Suef, Egypt

²Physiology Division, Zoology Department, Faculty of Science, Beni-Suef University, P.O. Box 62521, Beni-Suef, Egypt

³Research Center for Advanced Materials Science (RCAMS), King Khalid University, P.O. Box 9004, Abha 61413, Saudi Arabia

⁴Department of Physics, Faculty of Science, King Khalid University, P.O. Box 9004, Abha 62529, Saudi Arabia

⁵Department of Pathology, Faculty of Veterinary Medicine, Beni-Suef University, P.O. Box 62521, Beni-Suef, Egypt

Correspondence should be addressed to Noha A. Ahmed; drnohascience@science.bsu.edu.eg

Received 28 August 2022; Revised 5 October 2022; Accepted 27 January 2023; Published 22 February 2023

Academic Editor: Salah M. El Sayed

Copyright © 2023 Yasmine A. Ali et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Paclitaxel is a primary chemotherapy agent that displays antitumor activity against a variety of solid tumors. However, the clinical effectiveness of the drug is hampered by its nephrotoxic and cardiotoxic side effects. Thus, this investigation aimed at assessing the protective effects of rutin, hesperidin, and their combination to alleviate nephrotoxicity caused by paclitaxel (Taxol), cardiotoxicity in male Wistar rats, as well as oxidative stress. Rutin (10 mg/kg body weight), hesperidin (10 mg/kg body weight), and their mixture were given orally every other day for six weeks. Rats received intraperitoneal injections of paclitaxel twice weekly, on the second and fifth days of the week, at a dose of 2 mg/kg body weight. In paclitaxel-treated rats, the treatment of rutin and hesperidin decreased the elevated serum levels of creatinine, urea, and uric acid, indicating a recovery of kidney functions. The cardiac dysfunction in paclitaxel-treated rats that got rutin and hesperidin treatment also diminished, as shown by a substantial reduction in elevated CK-MB and LDH activity. Following paclitaxel administration, the severity of the kidney and the heart's histopathological findings and lesion scores were markedly decreased by rutin and hesperidin administration. Moreover, these treatments significantly reduced renal and cardiac lipid peroxidation while markedly increased GSH content and SOD and GPx activities. Thus, paclitaxel likely induces toxicity in the kidney and the heart by producing oxidative stress. The treatments likely countered renal and cardiac dysfunction and histopathological changes by suppressing oxidative stress and augmenting the antioxidant defenses. Rutin and hesperidin combination was most efficacious in rescuing renal and cardiac function as well as histological integrity in paclitaxel-administered rats.

1. Introduction

Taxanes are natural compounds produced by members of the genus *Taxus*. These compounds are used to treat various cancers and are preliminary therapies for earlier stages of cancer [1–4]. Paclitaxel is a key taxane and an effective antitumor agent [5]. The Food and Drug Administration (FDA) initially approved paclitaxel in 1992 to treat ovarian

cancer [6]. Subsequently, the drug was frequently tested for use in the treatment of other cancers, such as breast, prostate, bladder, cervical, and brain [7–10]. However, the clinical use of paclitaxel is considerably restricted because of its limited solubility, recrystallization after dilution, and cosolvent-induced toxicity [11]. Further, cancer cells become resistant to paclitaxel chemotherapy, and the use of the drug causes numerous adverse effects, including neuropathy,

cardiac toxicity, and hepatotoxicity [12–14]. Paclitaxel lowers levels of glutathione (GSH) and increases malondialdehyde (MDA) concentrations, suggesting oxidative stress [15], and may have caused renal injury due to induction of oxygen radicals in the reaction, which was a trigger of renal oxidative stress [16]. Furthermore, paclitaxel may cause cardiotoxic effects [17, 18]. According to several studies, different antioxidants can prevent deoxyribonucleic acid (DNA) oxidative stress damage [19–21].

Citrus species are an important biological resource from an economic perspective; these plants produce a diversity of phytonutrients and phytochemicals with promising therapeutic properties [22]. Flavonoids exhibit varied bioavailability and biological efficacy. These chemicals may confer health benefits *via* anti-inflammatory, antioxidant, antimicrobial, antiproliferative, proapoptotic, and hormone regulatory properties [23–25]. Combining rutin with other drugs can reduce drug resistance and the side effects of chemotherapy [26]. Rutin eliminated oxidative/nitrosative stress, inflammation, and apoptosis in rat kidney [27]. Also, it significantly inhibited myocardial oxidative insults by modulating ROS levels [28–31]. Hesperidin is a strong candidate phytochemical that displays antimicrobial, anticancer, antioxidant, anti-inflammatory, antidiabetic, and cardiovascular protective properties [32]. The compound also counteracts acute nephrotoxicity *via* antioxidant activity [33]. Further, hesperidin exhibits chemopreventive and chemotherapeutic effects against various carcinomas [34].

Chemotherapeutic drugs such as paclitaxel have several deleterious side effects, including kidney and heart damage, and we intend to reduce these effects by employing plant constituents with antioxidant and anti-inflammatory properties. Thus, this study assessed the renal and cardiac protection by rutin and hesperidin against the toxicity caused by paclitaxel in male Wistar rats. The study also focused on evaluating the functions of the heart and kidneys as well as the histological integrity, architecture, and defenses against oxidative stress and antioxidants.

2. Materials and Methods

2.1. Chemicals. The formulation vehicle of Cremophor® EL* (CrEL) contains paclitaxel, often known as Taxol or paclitaxel by trade (polyoxyethylated castor oil) (batch number: 7E05628), was obtained from Bristol–Myers Squibb global biopharmaceutical company (Princeton, USA). Rutin (batch number: 501) was obtained from Oxford Laboratory Company (Mumbai, India). From the Sigma-Aldrich Company, hesperidin (lot number: # SLBT3541) was obtained (St. Louis, MO, USA). Creatinine reagent kit (catalog number: M11502c-18) and urea reagent kit (catalog number: M11536c-16) were bought from Biosystem S.A. (Spain), respectively. Uric acid, creatine kinase-MB (CKMB), and lactate dehydrogenase (LDH) reagent kits were purchased from Spin React (Spain); these kits have catalog numbers: MD41001, MD41254, and MX41214, respectively. Chemicals of oxidative stress including trichloroacetic acid (TCA) (batch number: 5O011689) was obtained from PanReac

AppliChem ITW Companies (Spain); thiobarbituric acid (TBA) (batch number: L 16A/1916/1212/13) was obtained from Sd Fine Chem Limited (SDFCL) Company (India); 1,1,3,3-tetramethoxypropane or malondialdehyde (MDA) (catalog number: T9889) was obtained from Sigma-Aldrich (MO, USA); metaphosphoric acid (batch number: M 21519) was obtained from ALPHA CHEMIKA Company (India); 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB or Ellman's reagent) (batch number: 40K3652) was obtained from Sigma-Aldrich (MO, USA); GSH (batch number: 3W010085) was obtained from PanReac AppliChem ITW Companies (Spain); pyrogallol (batch number: 1280B251114) was obtained from ResearchLab Company (India). The highest purity and analytical grade reagents were used throughout the investigations.

2.2. Physiochemical Properties of Rutin and Hesperidin. Rutin has a molecular weight of 610.5 and the empirical formula C₂₇H₃₀O₁₆. It is a light-yellow crystalline powder that tastes slightly bitter. It has low solubility in water (125 mg/L), while highly soluble in polar solvents, and melts at around 176–178°C.

Hesperidin is a light yellow crystalline powder with the empirical formula C₂₈H₃₄O₁₅ and a molecular weight of 610.6; it is odorless and tasteless. It demonstrated poor pH-independent aqueous solubility; however, it is soluble in formamide and dimethyl formamide at 60°C, slightly dissolve in other polar solvents, and melts at around 258–262°C.

2.3. Experimental Animals. Thirty mature male Wistar rats weighing 130–150 g and aging 8–9 weeks were provided as the experimental rats. Rats were taken from the animal house of the National Research Center in Dokki, Giza, Egypt. For avoiding intercompetitive infection, the animals were observed for 15 days prior to the experiment. Rats were maintained in stainless steel-covered, ventilated polypropylene cages that were kept at room temperature (25 ± 5°C) and subjected to 12-hour light/dark cycles every day. Animals received unrestricted water availability but were also nourished with a well-balanced meal *ad libitum* on a daily basis. The Faculty of Science at the University of Beni-Suf in Egypt followed all guidelines and directions issued by the Experimental Animal Ethics Committee (Ethical Approval Number: BSU/FS/2017/8). All efforts have been made to mitigate animal suffering, anxiety, and discomfort.

2.4. Experimental Approach. Male adult Wistar rats had been subdivided into 5 groups in this study (6 rats per group) (Figure 1)

- (1) Negative control group: this group of rats received 5 mL of 1% carboxymethylcellulose orally (CMC) (vehicle used to dissolve rutin and hesperidin)/kg body weight (b. wt) on an alternate day and 2 mL of isotonic saline (0.9% NaCl) (vehicle in which paclitaxel is dissolved)/kg b. wt twice per week *via* the intraperitoneal (i.p.) route for 6 weeks.

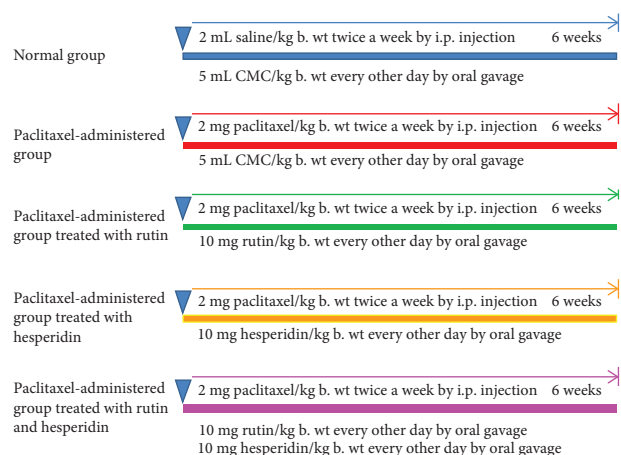


FIGURE 1: Animal grouping and experimental design.

- (2) **Paclitaxel-administered control group:** paclitaxel was given to this group of rats at a dose of 2 mg/kg body weight (in 2 mL 0.9% NaCl) by i.p. injection [35] twice a week at the 2nd and 5th days of each week for 6 weeks; every other day an oral equivalent dose from 1% CMC (5 mL/kg body weight) was also administered.
- (3) **Paclitaxel-administered group treated with rutin:** this group of rats received paclitaxel as in the paclitaxel-administered control group, as well as rutin at a dose of 10 mg/kg b. wt [36] (dissolved in 5 mL of 1% CMC) taken orally on an alternate day for six weeks.
- (4) **Paclitaxel-administered group treated with hesperidin:** Paclitaxel was administered to this group of rats in the same manner as it was to the paclitaxel-treated control group, along with hesperidin, orally twice weekly in a dose of 10 mg/kg body weight [37] (dissolved in 5 mL of 1% CMC).
- (5) **Paclitaxel-administered group treated with rutin as well as hesperidin combination:** paclitaxel was delivered to this group of rats in the same manner as it was in the paclitaxel control group, along with rutin and hesperidin at a dose of 10 mg/kg b. wt. (dissolved in 5 mL of 1% CMC) on an alternate day for six weeks.

2.5. Blood and Tissue Sampling. Rats were slaughtered under diethyl ether anesthesia [38] after receiving the prescribed dosages for six weeks. Jugular vein blood samples were drawn into gel and clot activating tubes, which were then centrifuged for 15 minutes at 3000 rounds per minute after allowing the clots to form at room temperature (rpm). For biochemical analysis, the sera were rapidly collected, divided into four sections, and kept at 30°C. Following decapitation and dissection, the kidneys and heart were rapidly resected and weighed. Tissue samples from the kidney and heart were removed for biochemical analysis and histopathology analysis. A piece of tissue was excised and transferred to 70%

alcohol after being fixed in phosphate buffered formalin (10%) for 24 hours for histology. Using a Teflon homogenizer, 0.5 g of tissue was homogenised in 5 ml of saline (0.9% NaCl) (made by Glas-Col, Terre Haute, USA). The homogenates were then centrifuged for 15 minutes at 3000 rpm, and the supernatants were collected and stored in the refrigerator at -20°C until employed to measure biochemical parameters of antioxidant defenses and oxidative stress markers.

2.6. Determination of Serum Kidney Function Parameters. Urea and creatinine levels were detected as previously described, respectively, by Fabiny and Ertingshausen [39] and Tabacco et al. [40]. Uric acid had been measured using a method previously reported by Fossati et al. [41].

2.7. Evaluation of Serum Heart Function Parameters. So according to the respective methods belonging to Young [42] and Pesce [43], the CK-MB and LDH activities were assessed.

2.8. Assessing the Parameters of the Antioxidant Defense System and Oxidative Stress. Utilizing chemical reagents made in the lab, the heart and kidney oxidative stress and antioxidant defense parameters were evaluated. Lipid peroxidation (LPO) was determined as stated earlier by Preuss et al. [44]. In brief, protein was precipitated by mixing 1 mL of homogenate with 0.15 mL of 76% TCA. Next, 0.35 mL of TBA, a color-enhancing substance, was added to the separated supernatants. After 30 minutes of incubation in a water bath at 80°C, the produced light pink colour was observable at 532 nm. The benchmark was MDA. Based on Beutler et al. [45], the GSH content was evaluated by adding 0.5 mL of DTNB or Ellman's reagent to the homogenate supernatant after protein precipitation (as a color-developing agent). The yellow colour of the samples and GSH standards had been contrasted with a blank at 412 nm. Matkovics et al. [46] procedure was used to determine GPx activity with some modifications. The method works by identifying any remaining GSH and deducting it from the total amount of GSH converted by the enzyme to oxidized glutathione (GSSG). In a Wasserman tube, 350 µl of Tris buffer (pH 7.6), 50 µl of GSH solution (2 mM), and 50 µl of hydrogen peroxide (H₂O₂) (3.38 mM) were combined with 50 µl of homogenate supernatant (3.38 mM). The remaining GSH content was then evaluated using the aforementioned procedure for GSH measurement at 430 nm following a 10-minute incubation period. Standard tests were prepared by substituting 50 µl of distilled water for 50 µl of the sample, and a blank test tube was prepared by substituting 100 µl of distilled water for 50 µl each of the sample and GSH solution. The sample's residual GSH concentration may then be detected, and GSH can then be transformed to GSSG to measure the activity of the enzyme. Using the Marklund and Marklund [47] method, SOD activity was evaluated. The suppression of pyrogallol autooxidation by SOD is the basis of the mechanism. Superoxide ions are necessary for the

process to take place. The amount of enzyme that results in 50% suppression in extinction changes in comparison to the control after one minute is referred to as one unit of enzyme activity.

2.9. Histological Investigations. All animals were immediately decapitated by cervical dislocation and dissection, and their kidneys and hearts were removed. They were subsequently transferred to the pathology department of the faculty of veterinary medicine at Beni-Suef University in Egypt for additional processing, wax blocking, sectioning, and staining with hematoxylin and eosin after being stored in 10% neutral buffered formalin for 24 hours (H&E) [48]. Five random fields were estimated for each section. The number of sections in each group is six. Sections of tissues were examined under light microscopy. The methodology outlined by El-Far et al. [49] was used to determine the histopathological lesion scores. Score scale 0 = normal, 1 = 25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%. The lesions were graded in a blinded manner.

2.10. Statistical Analysis. The mean and standard error of the mean were used to reveal all the data $SEM \pm Mean$. The statistical analyses were carried out using the IBM software, USA, Statistical Package for the Social Sciences (SPSS) computer software (version 22). To determine the significance of group means, a one-way analysis of variance (ANOVA) test was conducted. Tukey's posthoc test was then used to compare pair averaged results. Differences were deemed significant at $p < 0.05$ [50]:

$$\% \text{ change} = \frac{\text{Final value} - \text{Initial value}}{\text{initial value}} \times 100. \quad (1)$$

3. Results

3.1. Effects of Toxicity Studies on the Kidney Function-Related Serum Parameters. Rats receiving paclitaxel intraperitoneally for six weeks revealed a significant rise ($p < 0.05$) in their serum levels of urea, uric acid, and creatinine with respective percentage changes +111.90, +68.94, and +361.67%, compared with corresponding normal controls. Rutin and its combination with hesperidin significantly restored increased creatinine, urea, and uric acid levels to normal in paclitaxel-induced rat models. Treatment with hesperidin indicated a nonsignificant decrease ($p \geq 0.05$) in serum creatinine and urea levels but significant improvement in serum uric acid levels. The combination of rutin and hesperidin treatment of paclitaxel-administered rats was the most efficacious in lowering high creatinine, urea, and uric acid levels, with respective percentage decreases −43.82, −38.03, and −60.65% (Figure 2).

3.2. Effects of Toxicity Studies on the Heart Function Related to Serum Biomarkers. Rats receiving paclitaxel intraperitoneally for six weeks reported significant alleviation in their serum levels of CK-MB and LDH, with percentage changes of +433.33, +311.85, and +53.31%, respectively, in

comparison to the corresponding normal controls. Rutin, hesperidin, and their combination all significantly reduced the increased CK-MB and LDH activity in paclitaxel-induced rats. Treatment with rutin and hesperidin mixture treatment was most efficacious in reducing high levels of CK-MB and LDH, with percentage decreases of −45.83, −57.54, and −28.92% (Figure 3).

3.3. Effects of Toxicity Studies on the Kidney and Heart Oxidative Stress and Antioxidant Defense System Indicators. Following paclitaxel administration, kidney GSH content, SOD, and GPx activities all significantly decreased, while renal LPO significantly increased. Rats that received paclitaxel then treated with rutin, hesperidin, as well as their mixture showed a significant diminished kidney LPO. Hesperidin seemed to be the best in depleting elevated kidney LPO product. Additionally, compared to paclitaxel-administered controls, these treatments dramatically ameliorated decreased kidney GSH content and SOD activity. Only rutin plus hesperidin significantly increased kidney GPx activity (Figure 4).

Rats receiving paclitaxel for six weeks showed highly significant increases in the heart LPO and significant decreases in the heart GSH content, in addition to SOD and GPx activity. This was similar to what was seen in the kidney. Rats receiving paclitaxel and treated with rutin, hesperidin, and their mixture indicated significantly lower heart LPO. Hesperidin seemed to be the most effective in lowering elevated heart LPO product. Moreover, all three treatments significantly restored decreased heart SOD and GPx activities; only rutin caused a significant rise in cardiac GSH content (Figure 5).

3.4. Correlation between Kidney and Heart Function Biomarkers and Oxidative Stress Bio Indicators. The serum creatinine, urea, and uric acid levels showed positive correlation with LPO while they exhibited negative correlation with GSH content and SOD and GPx activities (Table 1).

In addition, the serum CK-MB and LDH activities showed positive correlation with LPO while they exhibited negative correlation with GSH content and SOD and GPx activities (Table 2).

3.5. Effects of the Toxicity Studies on the Kidney Histological Changes. Pathological lesions in the kidneys are summarized in Table 3 and illustrated in Figure 6. Normal histological architecture was observed in tissues from normal rats (Figure 6(a)). Paclitaxel-administered animals showed severe pathological lesions, including degenerative changes and nuclear pyknosis of the lining epithelium of the renal tubules associated with glomerulonephrosis in most glomeruli. Focal interstitial nephritis was also observed. Further, congestion was found in the glomerular tuft and interstitial blood capillaries (Figure 6(b)). Paclitaxel/rutin-treated group showed mild to moderate degenerative changes in the renal lining epithelium associated with focal leucocytic infiltration, mainly lymphocytes in the interstitial area (Figure 6(c)). Paclitaxel/hesperidin-treated group

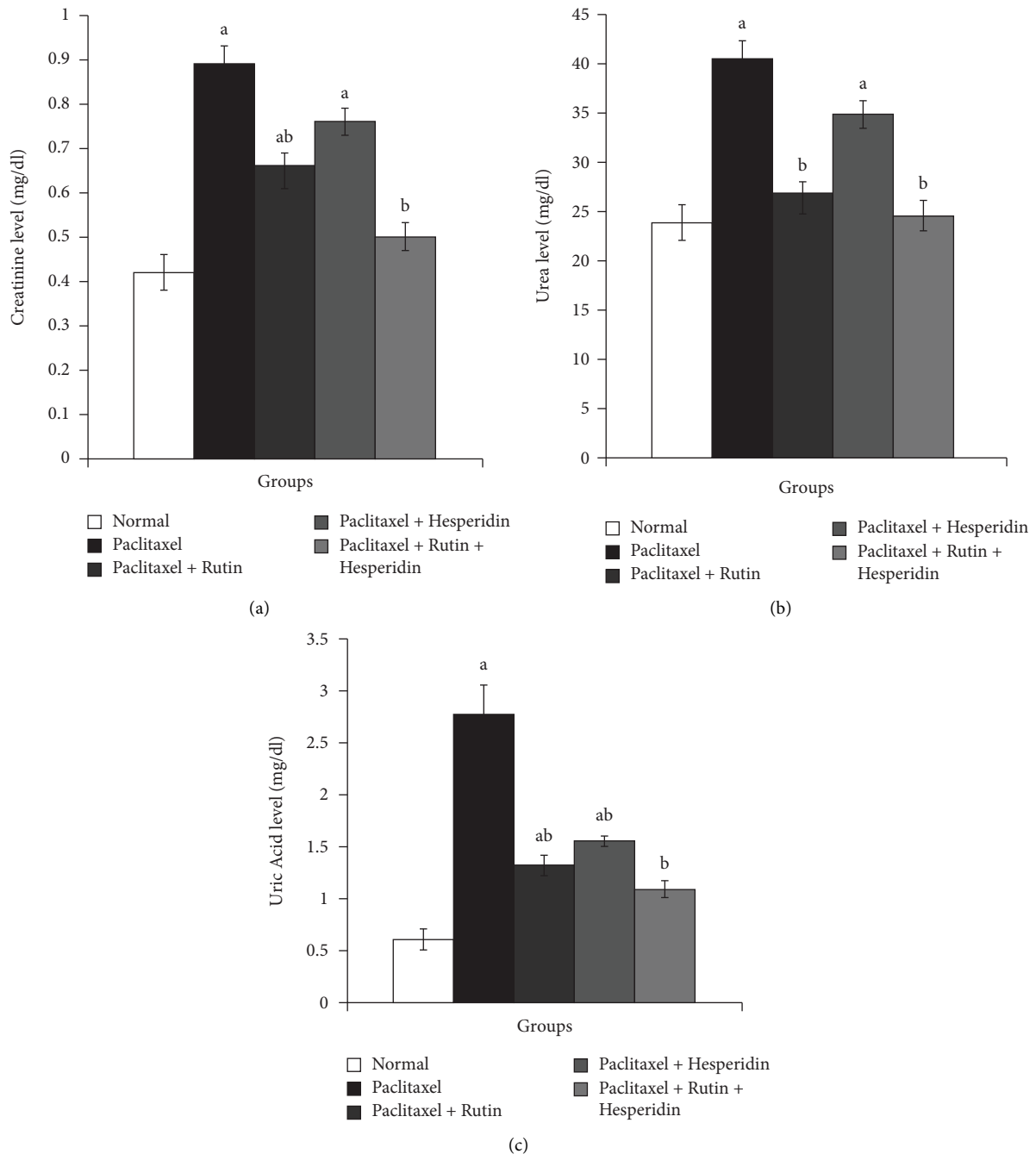


FIGURE 2: Graphs show the effects of rutin and hesperidin on, serum creatinine (a), urea (b), and uric acid (c) levels in paclitaxel-administered group. ^a $p < 0.05$: significant compared with normal group. ^b $p < 0.05$: significant compared with paclitaxel-administered group.

suffered from moderate glomerulonephrosis and mild necrosis of lining epithelium of renal tubules (Figure 6(d)). Paclitaxel/rutin/hesperidin-treated group exhibited mild degenerative changes of the glomerular tuft and lining renal epithelium (Figure 6(e)).

3.6. Effects of the Toxicity Studies on the Heart Histological Changes. Detailed pathological lesions are briefly summarized in Table 4 and illustrated in Figure 7. Primary lesions were hyalinosis and lymphocytic myocarditis. Normal histological

structure of cardiac muscles was found in normal animals (Figure 7(a)). In contrast, severe hyalinosis associated with focal leucocytic infiltration was seen in paclitaxel-administered control group (Figure 7(b)). Mild lesions were observed in paclitaxel/rutin-treated animals (Figure 7(c)). Paclitaxel/hesperidin-treated group was characterized by an absence of focal lymphocytic myocarditis; however, moderate hyalinosis was seen (Figure 7(d)). Mild degenerative changes of cardiac muscles were seen in tissues from paclitaxel/rutin/hesperidin-treated animals (Figure 7(e)).

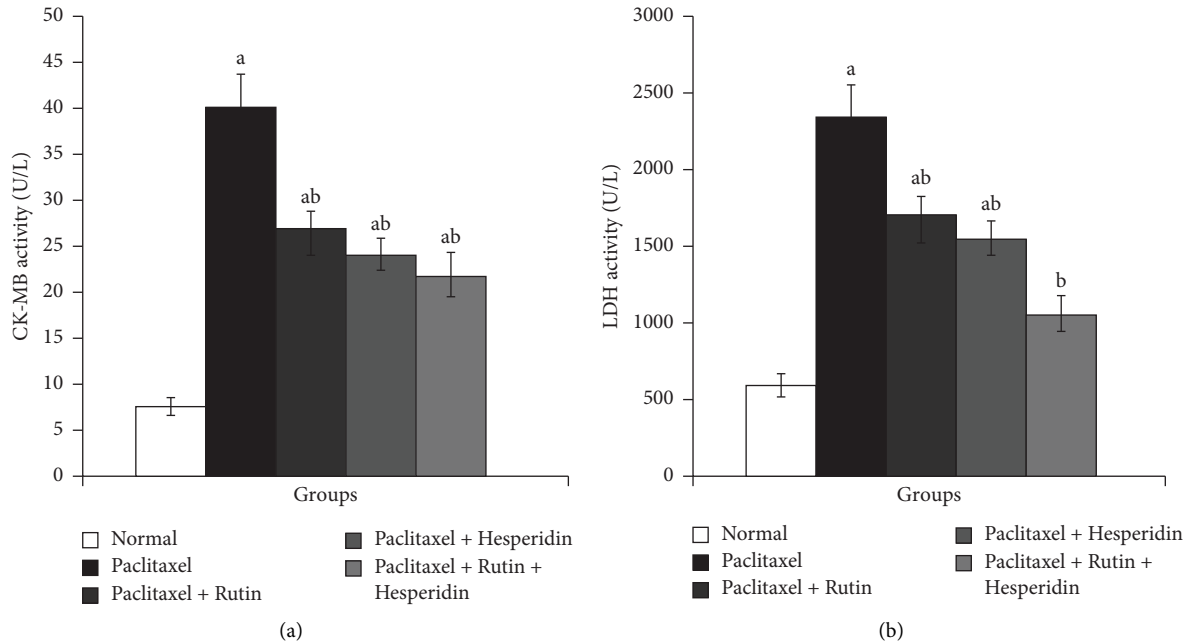


FIGURE 3: Graphs show the effects of rutin and hesperidin on serum, CK-MB (a) and LDH (b) activities in paclitaxel-administered group. ^a $p < 0.05$: significant compared with normal group. ^b $p < 0.05$: significant compared with paclitaxel-administered group.

4. Discussion

Numerous tumours are treated with paclitaxel, including aggressive and metastatic breast cancer, lung cancer, and pancreatic cancer [51]. Unfortunately, paclitaxel therapy can increase the acquired cancer resistance, resulting in chemotherapeutic failure [52]. Paclitaxel may lead to numerous adverse effects on different organs, including the liver, kidney, and heart [53–56]. It promotes oxidative stress, decreases antioxidants, increases liver enzymes, and impairs renal function, which may be due to its mechanism of action and the oxidative stress that it caused [57]. Concurrent use of potent plant antioxidants with chemotherapeutic drugs protects cells and tissues from the harmful effects of free radicals [58].

The nephrotoxicity caused by the intraperitoneal injection of paclitaxel as Taxol was biochemically demonstrated by a significant amelioration in the level of serum creatinine, urea, and uric acid. Paclitaxel inhibits the kidney function and lowers the kidney's ability to remove hazardous metabolic chemicals based on these altered blood levels. These findings are comparable to those of Adikwu et al. [16], who found that paclitaxel deteriorated renal function and caused significant alleviation in blood levels of urea, creatinine, and uric acid, as well as a distortion in normal renal histology. Paclitaxel caused significantly elevated levels of serum creatinine and urea [59, 60]. These alterations in biochemical parameters strongly correlate with several deleterious renal histological changes and lesions, including degenerative changes and nuclear pyknosis of the lining epithelium of the renal tubules, associated with glomerulonephritis, focal interstitial nephritis, and congestion. Other studies have shown similar histological alterations

[55, 61–63]. Paclitaxel-induced nephrotoxicity may reflect the alteration and degeneration of glomerular composition and decreased glomerular filtration rate in rats [60]. In our opinion, the kidney histological pathology in renal tissues is due to excessive free radical and ROS production and a reduction of antioxidant defenses. This explanation makes sense given that paclitaxel administration significantly increased renal LPO and significantly decreased renal GSH content of the kidney along with GPx and SOD activity.

In our article, delivering rutin, hesperidin, and their combination of paclitaxel-administered rats successfully reversed kidney pathology as shown by a decrease in serum levels of creatinine, urea, and uric acid as well as ameliorating the kidney histology. These results are consistent with Abou Seif [64] who reported that pretreatment with rutin and hesperidin protects the kidney against nephrotoxicity induced by doxorubicin by improving urea, creatinine, and uric acid serum levels. Rutin provides protection against nephrotoxicity after administration of carfilzomib and has also demonstrated improved histological profiles and ameliorating direct bilirubin, creatinine, and blood urea nitrogen levels [65]. Also, Emam and Madboly [66] showed hesperidin as a potent antioxidant agent that protects the kidney against acetaminophen-induced nephrotoxicity by reversing histopathological changes and reducing blood urea and serum creatinine levels. Likewise, flavonoids such as naringin and naringenin are potent anticancer agents and play a role in the management of various tumors [67].

By increasing serum LDH and CK-MB activity as well as releasing these enzymes from cardiomyocytes into the plasma, the current study discovered that paclitaxel treatment caused cardiotoxicity. These results agree with those of Saad et al. [68], who observed a significant rise in serum CK-

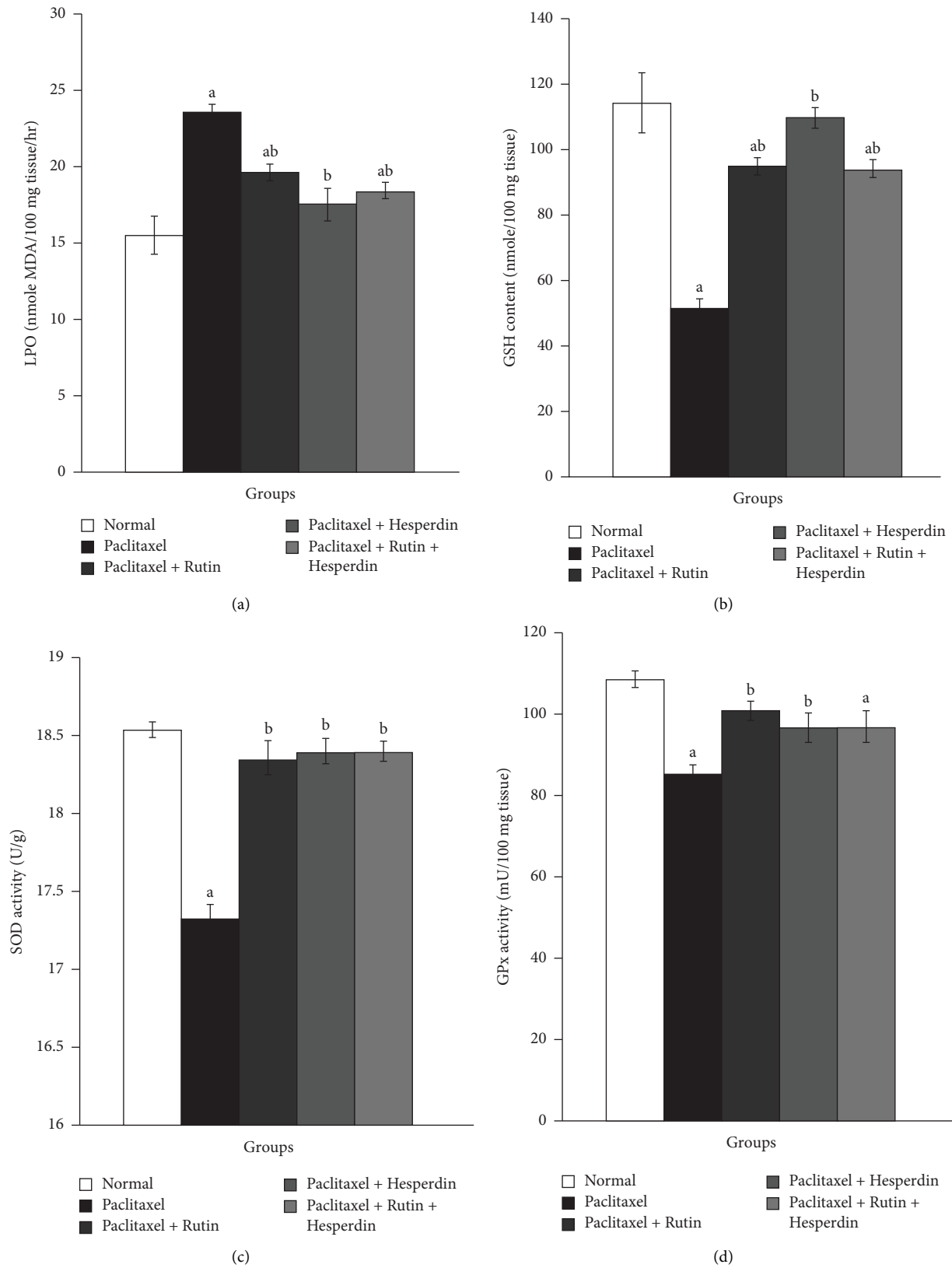


FIGURE 4: Graphs show the effects of rutin and hesperidin on the kidney LPO (a), GSH (b), SOD (c), and GPx (d) in paclitaxel-administered group. ^a $p < 0.05$: significant compared with normal group. ^b $p < 0.05$: significant compared with paclitaxel-administered group.

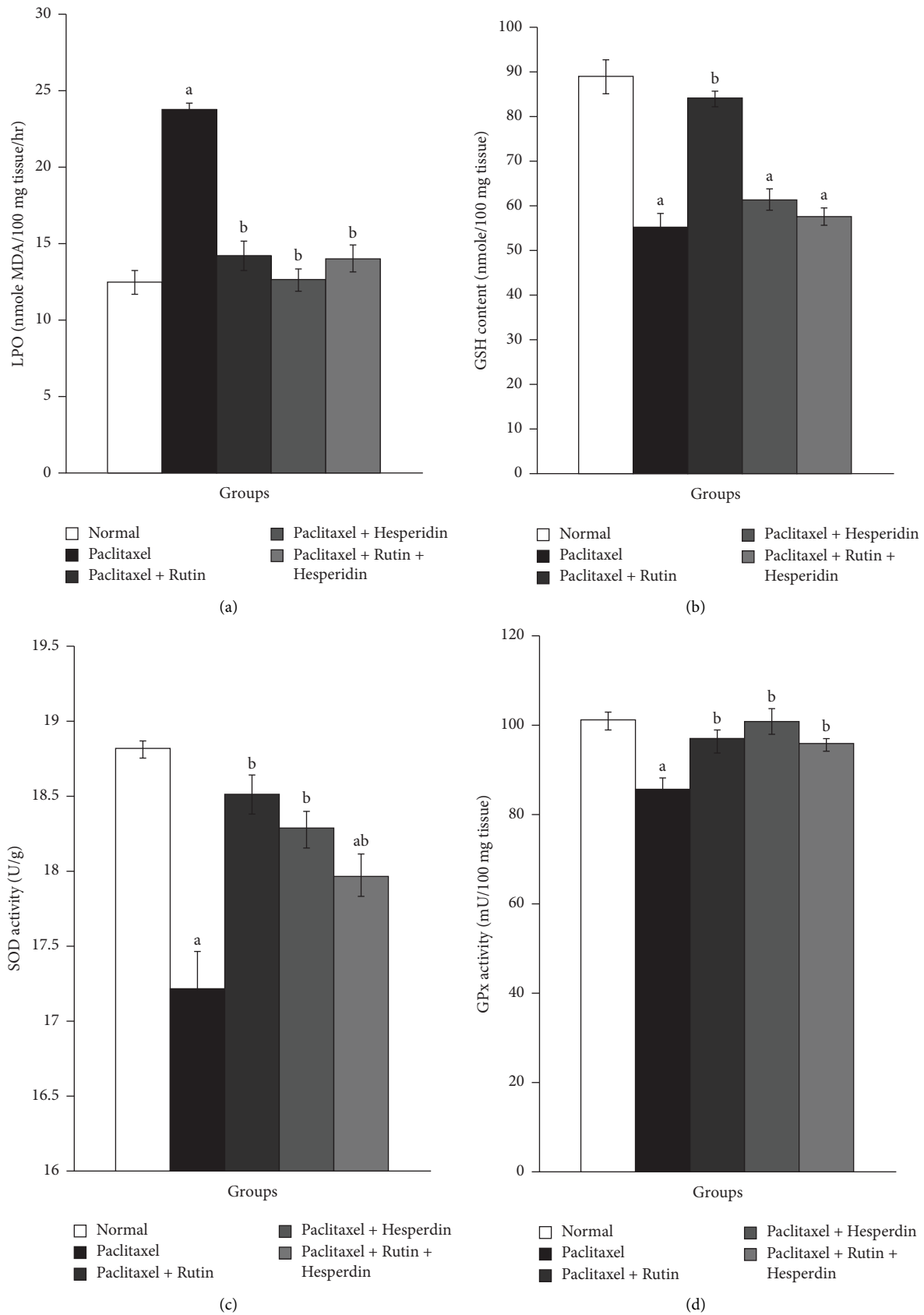


FIGURE 5: Graphs show the effects of rutin and hesperidin on heart LPO (a), GSH (b), SOD (c), and GPx (d) in paclitaxel-administered group. ^a $p < 0.05$: significant compared with normal group. ^b $p < 0.05$: significant compared with paclitaxel-administered group.

TABLE 1: Correlation between the kidney function biomarkers and oxidative stress bioindicators.

	Creatinine		Urea		Uric acid	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
LPO	0.633	$p < 0.001$	0.457	$p < 0.05$	0.721	$p < 0.001$
GSH	-0.588	$p < 0.01$	-0.489	$p < 0.01$	-0.780	$p < 0.001$
SOD	-0.601	$p < 0.001$	-0.542	$p < 0.01$	-0.686	$p < 0.001$
GPx	-0.570	$p < 0.01$	-0.536	$p < 0.01$	-0.623	$p < 0.001$

r: correlation value. $p > 0.05$, nonsignificant; significance was calculated at these levels: $p < 0.05$, $p < 0.01$, and $p < 0.001$.

TABLE 2: Correlation between the heart function biomarkers and oxidative stress bioindicators.

	CK-MB		LDH	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
LPO	0.664	$p < 0.001$	0.705	$p < 0.001$
GSH	-0.589	$p < 0.01$	-0.421	$p < 0.05$
SOD	-0.645	$p < 0.001$	-0.600	$p < 0.001$
GPx	-0.607	$p < 0.001$	-0.504	$p < 0.01$

r: correlation value. $p > 0.05$, nonsignificant; significance was calculated at these levels: $p < 0.05$, $p < 0.01$, and $p < 0.001$.

TABLE 3: Pathological renal lesion scores in different groups.

Groups	Parameters				
	Degenerative renal tubules	Necrosis of renal tubules	Congestion	Leucocytic infiltration	Glomerulonephrosis
Normal	—	—	—	—	—
Paclitaxel	++	++	+++	+++	+++
Paclitaxel + rutin	++	—	++	++	++
Paclitaxel + hesperidin	++	+	++	++	+++
Paclitaxel + rutin + hesperidin	++	+	+++	+	++

Lesion types are (—) absence, (+) minimal, (++) mild, (+++) moderate, and (+++++) severe.

MB, LDH, and AST activity, indicating paclitaxel-induced cardiac damage. Notably, Zhang et al. [69] revealed that paclitaxel-induced heart toxicity in normal rats caused significant increases in serum CK-MB levels [70]. These alterations in biochemical parameters correlate with cardiac histopathological findings and lesions that include severe hyalinosis associated with focal lymphocytic infiltration. These results match those of Malekinejad et al. [71], Razzaq et al. [72], and Saad et al. [68], who also found that animals treated with paclitaxel showed severe congestion and necrosis in the heart. Moreover, previous articles have reported that paclitaxel is cardiotoxic [17, 18, 73]. Paclitaxel also was reported to induce apoptosis in cardiac tissue [74]. The heart function and histological integrity may deteriorate from increased oxidative stress, along with a decline in the heart GSH levels, GPx, and SOD activity.

This present article illustrates the ability of rutin and hesperidin to ameliorate elevated CK-MB and LDH activities and normalize cardiac histology in paclitaxel-administered rats. Siti et al. [75] and Xianchu et al. [76] showed that rutin is cardioprotective, and Wang et al. [77] reported that pretreatment with rutin attenuated pirarubicin-induced histopathological alterations and lowered serum LDH and CK-MB activities. An article by Abdel-Raheem and Abdel-Ghany [78] showed that pretreatment with hesperidin protected rats' cardiac tissues from cardiotoxicity caused by doxorubicin *via* reversing histological

alteration and reducing serum LDH and CK activities. Pretreatment with hesperidin conserved morphological and ultrastructural architecture of myocardium and reduced LDH and CK-MB activities, supporting a cardioprotective property for hesperidin [79].

Significant increases in the kidney and cardiac LPO, a significant decline in nonenzymatic antioxidant (GSH) concentration, and enzymatic antioxidant (GPx and SOD) activities are all related to detrimental biochemical and histological alterations in the current investigation. Similarly, Ren et al. [80] reported that paclitaxel exposure induced increased ROS and MDA concentrations, while the whole SOD activity declined. These results indicated that paclitaxel administration led to changes in protein expression associated with apoptosis and ROS generation. Also, according to an article, paclitaxel-triggered apoptosis in the renal tubular was linked to decreased mitochondrial membrane potential and a large rise in ROS production. In [81, 82], it was found that a reduction in SOD activity may cause a reduction in superoxide radical ion removal, which may be detrimental to the kidney [64]. An article of Malekinejad et al. [71] showed that paclitaxel administration produced a remarkable increase in the heart LPO and identified the critical role of oxidative and nitrosative stress. Paclitaxel has been recognized to produce reactive oxygen species (ROS) that trigger mitochondrial dysfunction to release cytochrome C into the cytoplasm and activate the

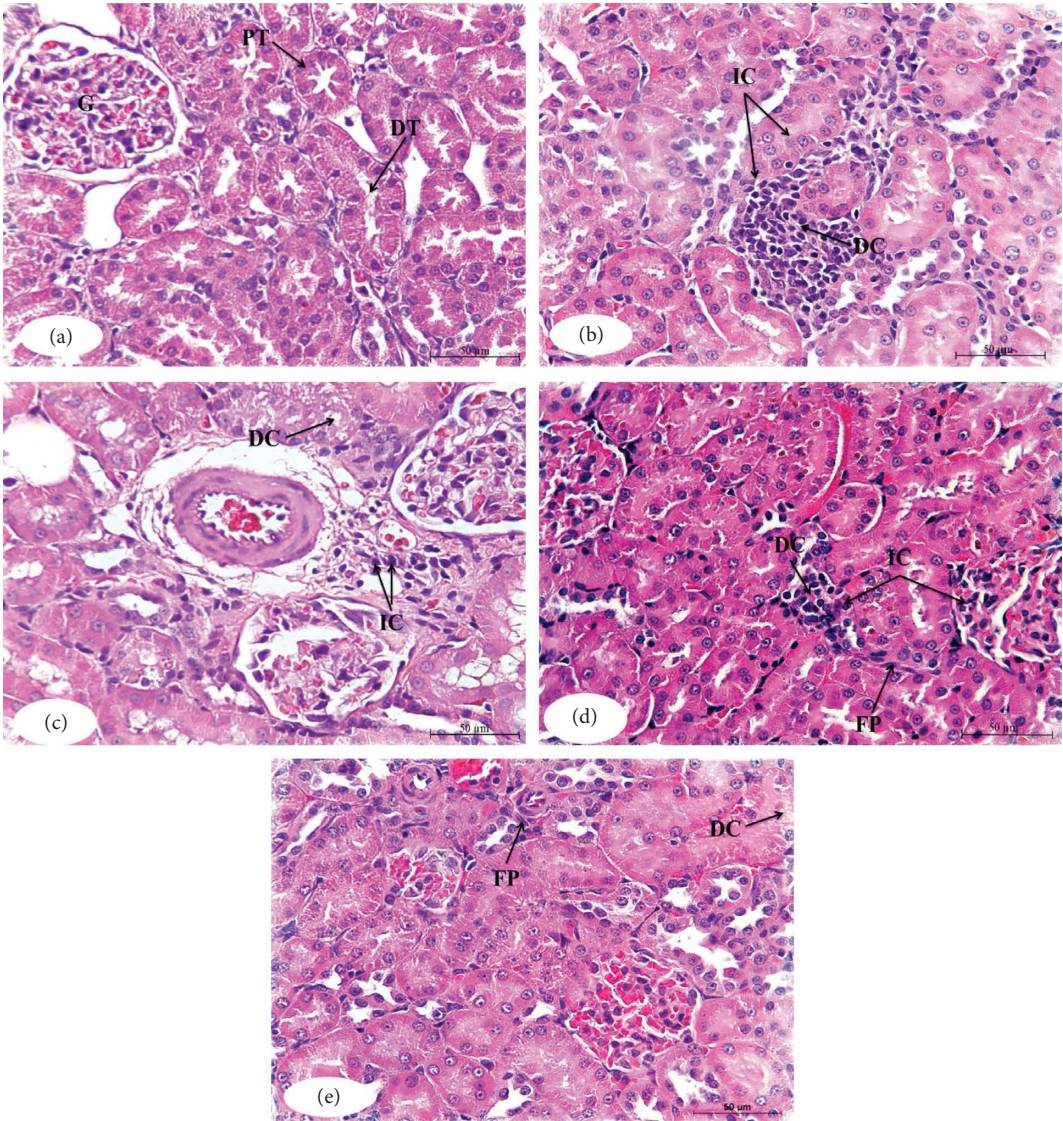


FIGURE 6: Photomicrographs of the kidney sections of the normal (a), paclitaxel-administered control group (b), and paclitaxel-administered groups treated with rutin (c), hesperidin (d), and their combination (e). G: glomeruli; PT: proximal tubules; DT: distal tubules; DC: degenerative changes; IC: inflammatory cells infiltration; FP: fibroblastic proliferation (H&E; ×400).

TABLE 4: Pathological cardiac lesion scores in different groups.

Groups	Parameters	
	Coagulative necrosis (hyalinosis)	Leucocytic infiltration
Normal	–	–
Paclitaxel	++	+++
Paclitaxel + rutin	+	+
Paclitaxel + hesperidin	++	–
Paclitaxel + rutin + hesperidin	+	–

Lesion types are (–) absence, (+) minimal, (++) mild, (+++) moderate, and (+++++) severe.

caspase cascade and apoptosis stimulation [83, 84]. As a result of this investigation and previous articles, we believe that paclitaxel-induced renal and cardiac dysfunction and histopathology are caused by increased oxidative stress and attenuation of antioxidant defenses.

Paclitaxel-induced oxidative stress in the kidney or heart was remarkably suppressed by rutin and hesperidin treatment with reduced LPO and elevated GSH content and activities of antioxidant enzymes. Both compounds enhance endogenous antioxidant activity beyond their ability to

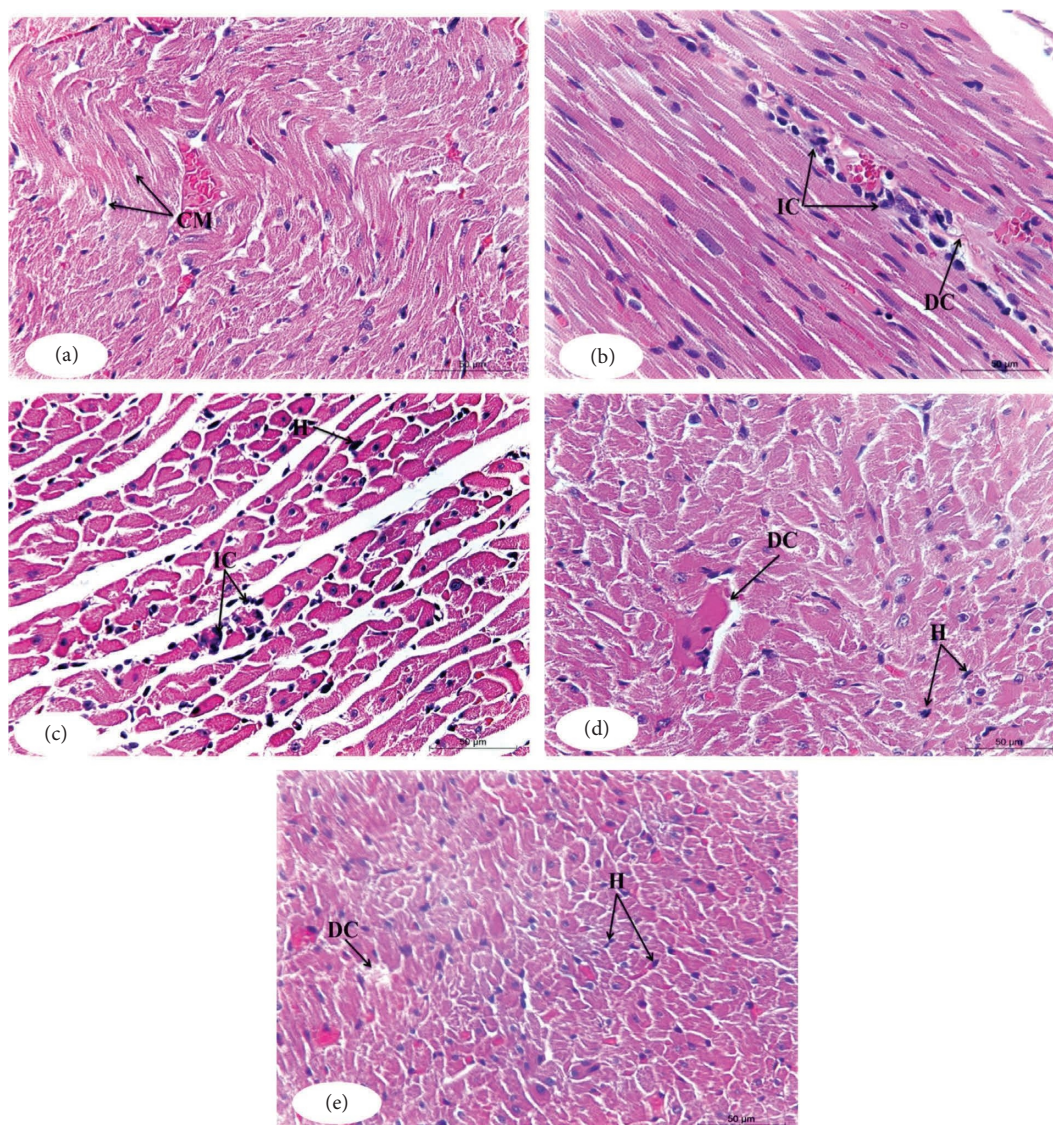


FIGURE 7: Photomicrographs of the heart sections of the normal (a), paclitaxel-administered control group (b), and paclitaxel-administered groups treated with rutin (c), hesperidin (d), and their combination (e). CM: cardiac muscles; DC: degenerative changes; IC: inflammatory cells infiltration; H: hyalinosis (H&E; $\times 400$).

scavenge free radicals and reduce the formation of lipid peroxide radicals. Remarkably similar results were mentioned by Geetha et al. [85], Huang et al. [86], and Xianchu et al. [76], who found that rutin suppressed oxidative stress *via* lowering production of ROS and MDA and by augmenting antioxidant status through increasing SOD, GSH, and GPx in several models of cardiovascular disease. An article of Qu et al. [27] showed that rutin suppressed oxidative/nitrosative stress, inflammation, and apoptosis in rats' kidneys. Rutin exhibited a significant level of protection against acrylamide-induced oxidative DNA damage, likely due to its antioxidant property [87].

By alleviating the oxidative stress, endoplasmic reticulum stress, inflammation, apoptosis, and autophagy-induced by valproic acid, rutin administration ameliorated liver and kidney damage [88]. It was found that the protective effects of hesperidin were associated with

countering oxidative/nitrosative stress, inflammation, and apoptosis, thus, preserving renal structure and function in mice intoxicated with cyclophosphamide [89]. Moreover, hesperidin reduced the heart LPO and increased antioxidant enzyme activities in ischemic myocardial rats [90]. Hesperidin's anticancer potential is controlled by ROS-dependent apoptotic pathways in certain cancer cells, despite the fact that it can be an excellent ROS scavenger and could operate as a powerful antioxidant defense mechanism [91, 92].

5. Conclusion

Coadministration of rutin, hesperidin, or their combination with paclitaxel in male Wistar rats might diminish the incidence and severity of detrimental effects of paclitaxel (Taxol)-induced toxicity in the kidney and heart. These

protective effects are likely mediated by suppressing oxidative stress and enhancing antioxidant defenses. Moreover, a combination of rutin and hesperidin treatment of paclitaxel-administered rats was most efficacious in preventing renal and cardiac dysfunction and adverse histological impacts. Before using rutin and hesperidin in patients and receiving FDA approval, more clinical trials are required to evaluate their effectiveness and safety.

Abbreviations

ANOVA:	One-way analysis of variance
AST:	Aspartate aminotransferase
CK:	Creatine kinase
CK-MB:	Creatine kinase-MB
CMC:	Carboxymethylcellulose
CrEL:	Cremophor/ethanol
DNA:	Deoxyribonucleic acid
FDA:	Food and Drug Administration
GPx:	Glutathione peroxidase
GSH:	Reduced glutathione
GSSG:	Oxidized glutathione
H&E:	Hematoxylin and eosin stain
H ₂ O ₂ :	Hydrogen peroxide
b. wt:	Body weight
LDH:	Lactate dehydrogenase
LPO:	Lipid peroxidation
MDA:	Malondialdehyde or 1,1,3,3-tetramethoxypropane
rpm:	Round per minute
ROS:	Reactive oxygen species
SEM:	Standard error of the mean
SPSS:	Statistical package for social sciences
SOD:	Superoxide dismutase
TBA:	Thiobarbituric acid
TCA:	Trichloroacetic acid.

Data Availability

All data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflict of interest.

Acknowledgments

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through large Groups Project under grant number RGP. 2/38/43.

References

- [1] T. M. Abu Samaan, M. Samec, A. Liskova, P. Kubatka, and D. Büsselberg, "Paclitaxel's mechanistic and clinical effects on breast cancer," *Biomolecules*, vol. 9, no. 12, p. 789, 2019.
- [2] S. Ezrahi, A. Aserin, and N. Garti, "Basic principles of drug delivery systems—the case of paclitaxel," *Advances in Colloid and Interface Science*, vol. 263, pp. 95–130, 2019.
- [3] B. Gorain, H. Choudhury, M. Pandey, and P. Kesharwani, "Paclitaxel loaded vitamin E-TPGS nanoparticles for cancer therapy," *Materials Science and Engineering: C*, vol. 91, pp. 868–880, 2018.
- [4] N. P. Staff, J. C. Fehrenbacher, M. Caillaud, M. I. Damaj, R. A. Segal, and S. Rieger, "Pathogenesis of paclitaxel-induced peripheral neuropathy: a current review of *in vitro* and *in vivo* findings using rodent and human model systems," *Experimental Neurology*, vol. 324, Article ID 113121, 2020.
- [5] L. Zhu and L. Chen, "Progress in research on paclitaxel and tumor immunotherapy," *Cellular and Molecular Biology Letters*, vol. 24, no. 1, pp. 40–11, 2019.
- [6] S. M. Swain, S. F. Honig, M. C. Tefft, and L. Walton, "A phase II trial of paclitaxel (Taxol®) as first line treatment in advanced breast cancer," *Investigational New Drugs*, vol. 13, no. 3, pp. 217–222, 1995.
- [7] F. Gelsomino, M. Tiseo, F. Barbieri et al., "Phase 2 study of NAB-paclitaxel in SensiTivE and refractory relapsed small cell lung cancer (SCLC) (NABSTER TRIAL)," *British Journal of Cancer*, vol. 123, no. 1, pp. 26–32, 2020.
- [8] A. Hernández-Prat, A. Rodriguez-Vida, N. Juanpere-Rodero et al., "Novel oral mTORC1/2 inhibitor TAK-228 has synergistic antitumor effects when combined with paclitaxel or PI3K α inhibitor TAK-117 in preclinical bladder cancer models," *Molecular Cancer Research*, vol. 17, no. 9, pp. 1931–1944, 2019.
- [9] A. Y. Kilcar, O. Yildiz, T. Dogan, E. Sulu, G. Takan, and F. Z. B. Muftuler, "Bitter melon (*Momordica charantia*) extract effect against 99mTc labeled paclitaxel: *in vitro* monitoring on breast cancer cells," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 20, no. 12, pp. 1497–1503, 2020.
- [10] D. Qu, M. Jiao, H. Lin et al., "Anisamide-functionalized pH-responsive amphiphilic chitosan-based paclitaxel micelles for sigma-1 receptor targeted prostate cancer treatment," *Carbohydrate Polymers*, vol. 229, Article ID 115498, 2020.
- [11] L. Della Corte, F. Barra, V. Foreste et al., "Advances in paclitaxel combinations for treating cervical cancer," *Expert Opinion on Pharmacotherapy*, vol. 21, no. 6, pp. 663–677, 2020.
- [12] A. M. Cirrincione, A. D. Pellegrini, J. R. Dominy et al., "Paclitaxel-induced peripheral neuropathy is caused by epidermal ROS and mitochondrial damage through conserved MMP-13 activation," *Scientific Reports*, vol. 10, no. 1, pp. 1–12, 2020.
- [13] M. L. Costa, J. A. Rodrigues, J. Azevedo, V. Vasconcelos, E. Eiras, and M. G. Campos, "Hepatotoxicity induced by paclitaxel interaction with turmeric in association with a microcystin from a contaminated dietary supplement," *Toxicon*, vol. 150, pp. 207–211, 2018.
- [14] M. J. Gil-Gil, M. Bellet, S. Morales et al., "Pegylated liposomal doxorubicin plus cyclophosphamide followed by paclitaxel as primary chemotherapy in elderly or cardiotoxicity-prone patients with high-risk breast cancer: results of the phase II CAPRICE study," *Breast Cancer Research and Treatment*, vol. 151, no. 3, pp. 597–606, 2015.
- [15] G. I. Harisa, "Blood viscosity as a sensitive indicator for paclitaxel induced oxidative stress in human whole blood," *Saudi Pharmaceutical Journal*, vol. 23, no. 1, pp. 48–54, 2015.
- [16] E. Adikwu, N. Ebinyo, and D. O. Orakpor, "Coenzyme Q10 and resveratrol protect against paclitaxel-induced

- nephrotoxicity in rats,” *Trends in Pharmaceutical Sciences*, vol. 7, no. 1, pp. 49–58, 2021.
- [17] M. Ashrafzadeh, A. Zarrabi, F. Hashemi et al., “Curcumin in cancer therapy: a novel adjunct for combination chemotherapy with paclitaxel and alleviation of its adverse effects,” *Life Sciences*, vol. 256, Article ID 117984, 2020.
 - [18] M. Osman and M. Elkady, “A prospective study to evaluate the effect of paclitaxel on cardiac ejection fraction,” *Breast Care*, vol. 12, no. 4, pp. 255–259, 2017.
 - [19] S. Ince, D. Arslan Acaro, O. Neuwirth et al., “Protective effect of polydatin, a natural precursor of resveratrol, against cisplatin-induced toxicity in rats,” *Food and Chemical Toxicology*, vol. 72, pp. 147–153, 2014.
 - [20] E. Sengul, V. Gelen, and S. Gedikli, “Cardioprotective activities of quercetin and rutin in Sprague Dawley rats treated with 5-fluorouracil,” *JAPS: Journal of Animal and Plant Sciences*, vol. 31, no. 2, pp. 423–443, 2021.
 - [21] E. Sengul, V. Gelen, S. Yildirim, S. Tekin, and Y. Dag, “The effects of selenium in acrylamide-induced nephrotoxicity in rats: roles of oxidative stress, inflammation, apoptosis, and DNA damage,” *Biological Trace Element Research*, vol. 199, no. 1, pp. 173–184, 2021.
 - [22] M. Addi, A. Elbouzidi, M. Abid, D. Tungmunthum, A. Elamrani, and C. Hano, “An overview of bioactive flavonoids from citrus fruits,” *Applied Sciences*, vol. 12, no. 1, p. 29, 2021.
 - [23] K. Borowiec and A. Michalak, “Flavonoids from edible fruits as therapeutic agents in neuroinflammation: a comprehensive review and update,” *Critical Reviews in Food Science and Nutrition*, vol. 62, no. 24, pp. 6742–6760, 2021.
 - [24] C. Del Bo, S. Bernardi, and M. Marino, “Systematic review on polyphenol intake and health outcomes: is there sufficient evidence to define a health-promoting polyphenol-rich dietary pattern?” *Nutrients*, vol. 11, no. 6, p. 1355, 2019.
 - [25] R. K. Sharma, N. Sharma, U. Kumar, and S. S. Samant, “Antioxidant properties, phenolics and flavonoids content of some economically important plants from North-west Indian Himalaya,” *Natural Product Research*, vol. 36, no. 6, pp. 1565–1569, 2021.
 - [26] A. Satari, S. Ghasemi, S. Habtemariam, S. Asgharian, and Z. Lorigooini, “Rutin: a flavonoid as an effective sensitizer for anticancer therapy; insights into multifaceted mechanisms and applicability for combination therapy,” *Evidence-based Complementary and Alternative Medicine*, vol. 2021, Article ID 9913179, 10 pages, 2021.
 - [27] S. Qu, C. Dai, F. Lang et al., “Rutin attenuates vancomycin-induced nephrotoxicity by ameliorating oxidative stress, apoptosis, and inflammation in rats,” *Antimicrobial Agents and Chemotherapy*, vol. 63, no. 1, Article ID e01545-18, 2019.
 - [28] R. Cannataro, A. Fazio, C. La Torre, M. C. Caroleo, and E. Cione, “Polyphenols in the mediterranean diet: from dietary sources to microRNA modulation,” *Antioxidants*, vol. 10, no. 2, p. 328, 2021.
 - [29] Q. Li, D. Xu, Z. Gu, T. Li, P. Huang, and L. Ren, “Rutin restrains the growth and metastasis of mouse breast cancer cells by regulating the microRNA-129-1-3p-mediated calcium signaling pathway,” *Journal of Biochemical and Molecular Toxicology*, vol. 35, no. 7, Article ID e22794, 2021.
 - [30] M. Qin, Q. Li, Y. Wang et al., “Rutin treats myocardial damage caused by pirarubicin via regulating miR-22-5p-regulated RAP1/ERK signaling pathway,” *Journal of Biochemical and Molecular Toxicology*, vol. 35, no. 1, Article ID e22615, 2021.
 - [31] M. Zhou, G. Zhang, J. Hu et al., “Rutin attenuates sorafenib-induced chemoresistance and autophagy in hepatocellular carcinoma by regulating BANCER/miRNA-590-5P/OLR1 Axis,” *International Journal of Biological Sciences*, vol. 17, no. 13, pp. 3595–3607, 2021.
 - [32] A. M. Ali, M. A. Gabbar, S. M. Abdel-Twab et al., “Antidiabetic potency, antioxidant effects, and mode of actions of *Citrus reticulata* fruit peel hydroethanolic extract, hesperidin, and quercetin in nicotinamide/streptozotocin-induced Wistar diabetic rats,” *Oxidative Medicine and Cellular Longevity*, vol. 2020, Article ID 1730492, 21 pages, 2020.
 - [33] S. Moustafa, R. Hashish, and R. Abdel-Karim, “The possible ameliorative effect of hesperidin administration in aluminum phosphide induced acute nephrotoxicity in adult albino rats,” *Ain Shams Journal of Forensic Medicine and Clinical Toxicology*, vol. 38, no. 1, pp. 46–56, 2022.
 - [34] P. Pandey and F. Khan, “A mechanistic review of the anticancer potential of hesperidin, a natural flavonoid from citrus fruits,” *Nutrition Research*, vol. 92, pp. 21–31, 2021.
 - [35] A. Mangaiarkkarasi, S. Rameshkannan, and R. M. Ali, “Effect of gabapentin and pregabalin in rat model of taxol induced neuropathic pain,” *Journal of Clinical and Diagnostic Research: Journal of Clinical and Diagnostic Research*, vol. 9, no. 5, pp. FF11–FF14, 2015.
 - [36] S. L. Patil, H. Somashekarappa, and K. Rajashekhar, “Radiomodulatory role of rutin and quercetin in Swiss albino mice exposed to the whole body gamma radiation,” *Indian Journal of Nuclear Medicine*, vol. 27, no. 4, pp. 237–242, 2012.
 - [37] L. Xu, Z. L. Yang, P. Li, and Y. Q. Zhou, “Modulating effect of Hesperidin on experimental murine colitis induced by dextran sulfate sodium,” *Phytomedicine*, vol. 16, no. 10, pp. 989–995, 2009.
 - [38] O. M. Ahmed, S. R. Galaly, M. Raslan, and M. A. M. A. Mostafa, “Thyme oil and thymol abrogate doxorubicin-induced nephrotoxicity and cardiotoxicity in Wistar rats via repression of oxidative stress and enhancement of antioxidant defense mechanisms,” *Biocell*, vol. 44, no. 1, pp. 41–53, 2020.
 - [39] D. L. Fabiny and G. Ertingshausen, “Automated reaction-rate method for determination of serum creatinine with the CentrifiChem,” *Clinical Chemistry*, vol. 17, no. 8, pp. 696–700, 1971.
 - [40] A. Tabacco, F. Meiattini, E. Moda, and P. Tarli, “Simplified enzymic/colorimetric serum urea nitrogen determination,” *Clinical Chemistry*, vol. 25, no. 2, pp. 336–337, 1979.
 - [41] P. Fossati, L. Prencipe, and G. Berti, “Use of 3,5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urine,” *Clinical Chemistry*, vol. 26, no. 2, pp. 227–231, 1980.
 - [42] D. S. Young, *Effects of Drugs on Clinical Laboratory Tests*, The American Association for Clinical Chemistry, Washington, DC, USA, 4th edition, 1995.
 - [43] A. Pesce, “Lactate dehydrogenase,” in *Clinical Chemistry*, 1124, The CV Mosby Co, Toronto, Canada, 1984.
 - [44] H. G. Preuss, S. T. Jarrell, R. Scheckenbach, S. Lieberman, and R. A. Anderson, “Comparative effects of chromium, vanadium and *Gymnema sylvestre* on sugar-induced blood pressure elevations in Spontaneously hypertensive rats (SHR),” *Journal of the American College of Nutrition*, vol. 17, no. 2, pp. 116–123, 1998.
 - [45] E. Beutler, O. Duren, and B. M. Kelly, “Improved method for the determination of blood glutathione,” *The Journal of Laboratory and Clinical Medicine*, vol. 61, pp. 882–888, 1963.
 - [46] B. Matkovics, M. Kotorman, I. S. Varga, D. Q. Hai, and C. S. Varga, “Oxidative stress in experimental diabetes induced by streptozotocin,” *Acta Physiologica Hungarica*, vol. 85, no. 1, pp. 29–38, 1997.

- [47] S. Marklund and G. Marklund, "Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase," *European Journal of Biochemistry*, vol. 47, no. 3, pp. 469–474, 1974.
- [48] J. D. Bancroft, A. Stevens, and D. R. Turner, *Theory and Practice of Histological Techniques*, Churchill Living Stone, London, UK, 4th edition, 1996.
- [49] A. H. El-Far, M. A. Lebda, A. E. Noreldin et al., "Quercetin attenuates pancreatic and renal D-galactose-induced aging-related oxidative alterations in rats," *International Journal of Molecular Sciences*, vol. 21, no. 12, pp. 4348–48, 2020.
- [50] A. M. Zaazaa, "Studying the anticancer properties of bone MarrowDerived mesenchymal stem cells against hepatocellular carcinoma induced by N-nitrosodiethylamine in male rats," *Biointerface Research in Applied Chemistry*, vol. 13, no. 1, pp. 1–13, 2022.
- [51] I. Klein and H. C. Lehmann, "Pathomechanisms of paclitaxel-induced peripheral neuropathy," *Toxics*, vol. 9, no. 10, p. 229, 2021.
- [52] Y. Wang, Y. Zhou, Z. Zheng, J. Li, Y. Yan, and W. Wu, "Sulforaphane metabolites reduce resistance to paclitaxel via microtubule disruption," *Cell Death & Disease*, vol. 9, no. 11, pp. 1134–1149, 2018.
- [53] A. Grigorian and C. B. O'Brien, "Hepatotoxicity secondary to chemotherapy," *Journal of Clinical and Translational Hepatology*, vol. 2, no. 2, pp. 95–102, 2014.
- [54] P. D. King and M. C. Perry, "Hepatotoxicity of chemotherapy," *The Oncologist*, vol. 6, no. 2, pp. 162–176, 2001.
- [55] N. Lameire, "Nephrotoxicity of recent anti-cancer agents," *Clinical Kidney Journal*, vol. 7, no. 1, pp. 11–22, 2014.
- [56] G. Miolo, N. La Mura, P. Nigri et al., "The cardiotoxicity of chemotherapy: new prospects for an old problem," *Radiology and Oncology*, vol. 40, no. 3, pp. 149–161, 2006.
- [57] D. T. Al-Gabri, A. J. Al-Naely, and H. A. Alghanmi, "Using of nanocomposite loading klisinema persicum for reducing the damage of the liver and kidneys in female rats caused by taxol (paclitaxel)," *Turkish Journal of Physiotherapy and Rehabilitation*, vol. 32, no. 3, 2021.
- [58] Y. Zhang, Z. Wu, H. Yu et al., "Chinese herbal medicine *Wenxia Changfu* Formula reverses cell adhesion-mediated drug resistance via the integrin β 1-PI3K-AKT pathway in lung cancer," *Journal of Cancer*, vol. 10, no. 2, pp. 293–304, 2019.
- [59] O. M. Ahmed, T. M. Ali, M. A. Abdel Gaid, and A. A. Elberry, "Effects of enalapril and paricalcitol treatment on diabetic nephropathy and renal expressions of TNF- α , p53, caspase-3 and Bcl-2 in STZ-induced diabetic rats," *PLoS One*, vol. 14, no. 9, Article ID e0214349, 2019.
- [60] B. Ali, "A study of the physiological effects of the anticancer paclitaxel in men," *Al-Qadisiyah Journal of Pure Science*, vol. 21, no. 4, pp. 33–38, 2016.
- [61] H. Choudhury, B. Gorain, R. K. Tekade, M. Pandey, S. Karmakar, and T. K. Pal, "Safety against nephrotoxicity in paclitaxel treatment: oral nanocarrier as an effective tool in preclinical evaluation with marked *in vivo* antitumor activity," *Regulatory Toxicology and Pharmacology*, vol. 91, pp. 179–189, 2017.
- [62] X. Guo, W. Li, J. Hu, E. C. Zhu, and Q. Su, "Hepatotoxicity in patients with solid tumors treated with PD-1/PD-L1 inhibitors alone, PD-1/PD-L1 inhibitors plus chemotherapy, or chemotherapy alone: systematic review and meta-analysis," *European Journal of Clinical Pharmacology*, vol. 76, no. 10, pp. 1345–1354, 2020.
- [63] S. O. Rabah, "Acute taxol nephrotoxicity: histological and ultrastructural studies of mice kidney parenchyma," *Saudi Journal of Biological Sciences*, vol. 17, no. 2, pp. 105–114, 2010.
- [64] H. S. Abou Seif, "Protective effect of rutin and hesperidin against doxorubicin induced nephrotoxicity," *Journal of Applied Sciences*, vol. 1, no. 2, pp. 1–18, 2012.
- [65] N. O. Al-Harbi, F. Imam, M. M. Al-Harbi et al., "Rutin inhibits carfilzomib-induced oxidative stress and inflammation via the NOS-mediated NF- κ B signaling pathway," *Inflammopharmacology*, vol. 27, no. 4, pp. 817–827, 2019.
- [66] H. T. Emam and A. G. Madboly, "Ameliorative effects of hesperidin and melatonin against acetaminophen-induced nephrotoxicity in adult albino rats," *The Egyptian Journal of Forensic Sciences and Applied Toxicology*, vol. 21, no. 1, pp. 31–46, 2021.
- [67] A. Rauf, M. A. Shariati, M. Imran et al., "Comprehensive review on naringenin and naringin polyphenols as a potent anticancer agent," *Environmental Science and Pollution Research*, vol. 29, no. 21, pp. 31025–31041, 2022.
- [68] S. Y. Saad, T. A. O. Najjar, and M. Alashari, "Cardiotoxicity of doxorubicin/paclitaxel combination in rats: effect of sequence and timing of administration," *Journal of Biochemical and Molecular Toxicology*, vol. 18, no. 2, pp. 78–86, 2004.
- [69] K. Zhang, F. M. Heidrich, B. DeGray, W. Boehmerle, and B. E. Ehrlich, "Paclitaxel accelerates spontaneous calcium oscillations in cardiomyocytes by interacting with NCS-1 and the InsP3R," *Journal of Molecular and Cellular Cardiology*, vol. 49, no. 5, pp. 829–835, 2010.
- [70] C. Panis, R. Binato, S. Correa et al., "Short infusion of paclitaxel imbalances plasmatic lipid metabolism and correlates with cardiac markers of acute damage in patients with breast cancer," *Cancer Chemotherapy and Pharmacology*, vol. 80, no. 3, pp. 469–478, 2017.
- [71] H. Malekinejad, S. Ahsan, F. Delkhosh-Kasmaie, H. Cheraghi, A. Rezaei-Golmisheh, and H. Janbaz-Acyabar, "Cardioprotective effect of royal jelly on paclitaxel-induced cardiotoxicity in rats," *Iranian Journal of Basic Medical Sciences*, vol. 19, no. 2, pp. 221–227, 2016.
- [72] S. Razzaq, A. Rauf, A. Raza et al., "A multifunctional polymeric micelle for targeted delivery of paclitaxel by the inhibition of the P-glycoprotein transporters," *Nanomaterials*, vol. 11, no. 11, p. 2858, 2021.
- [73] H. M. Babiker, A. McBride, M. Newton et al., "Cardiotoxic effects of chemotherapy: a review of both cytotoxic and molecular targeted oncology therapies and their effect on the cardiovascular system," *Critical Reviews in Oncology*, vol. 126, pp. 186–200, 2018.
- [74] J. Li, T. Yin, L. Wang, L. Yin, J. Zhou, and M. Huo, "Biological evaluation of redox-sensitive micelles based on hyaluronic acid-deoxycholic acid conjugates for tumor-specific delivery of paclitaxel," *International Journal of Pharmaceutics*, vol. 483, no. 1–2, pp. 38–48, 2015.
- [75] H. N. Siti, J. Jalil, A. Y. Asmadi, and Y. Kamisah, "Roles of rutin in cardiac remodeling," *Journal of Functional Foods*, vol. 64, Article ID 103606, 2020.
- [76] L. Xianchu, Z. Lan, L. Ming, and M. Yanzhi, "Protective effects of rutin on lipopolysaccharide-induced heart injury in mice," *Journal of Toxicological Sciences*, vol. 43, no. 5, pp. 329–337, 2018.
- [77] Y. D. Wang, Y. Zhang, B. Sun, X. W. Leng, Y. J. Li, and L. Q. Ren, "Cardioprotective effects of rutin in rats exposed to pirarubicin toxicity," *Journal of Asian Natural Products Research*, vol. 20, no. 4, pp. 361–373, 2018.

- [78] I. T. Abdel-Raheem and A. A. Abdel-Ghany, "Hesperidin alleviates doxorubicin-induced cardiotoxicity in rats," *Journal of the Egyptian National Cancer Institute*, vol. 21, no. 2, pp. 175–184, 2009.
- [79] P. Bhargava, D. Arya, and J. Bhatia, "Cardioprotective effect of hesperidin in an experimental model of cardiac hypertrophy," *Journal of Hypertension*, vol. 37, pp. e183–e184, 2019.
- [80] X. Ren, B. Zhao, H. Chang, M. Xiao, Y. Wu, and Y. Liu, "Paclitaxel suppresses proliferation and induces apoptosis through regulation of ROS and the AKT/MAPK signaling pathway in canine mammary gland tumor cells," *Molecular Medicine Reports*, vol. 17, no. 6, pp. 8289–8299, 2018.
- [81] D. Selimovic, M. Hassan, Y. Haikel, and U. R. Hengge, "Taxol-induced mitochondrial stress in melanoma cells is mediated by activation of c-JunN-terminal kinase (JNK) and p38 pathways via uncoupling protein 2," *Cellular Signalling*, vol. 20, no. 2, pp. 311–322, 2008.
- [82] G. Varbiro, B. Veres, F. Gallyas, and B. Sumegi, "Direct effect of taxol on free radical formation and mitochondrial permeability transition," *Free Radical Biology and Medicine*, vol. 31, no. 4, pp. 548–558, 2001.
- [83] V. Annamalai, M. Kotakonda, and V. Periyannan, "JAK1/STAT3 regulatory effect of β -caryophyllene on MG-63 osteosarcoma cells via ROS-induced apoptotic mitochondrial pathway by DNA fragmentation," *Journal of Biochemical and Molecular Toxicology*, vol. 34, no. 8, Article ID e22514, 2020.
- [84] A. W. Kwak, J. S. Choi, K. Liu et al., "Licochalcone C induces cell cycle G1 arrest and apoptosis in human esophageal squamous carcinoma cells by activation of the ROS/MAPK signaling pathway," *Journal of Chemotherapy*, vol. 32, no. 3, pp. 132–143, 2020.
- [85] R. Geetha, C. Sathya Priya, and C. V. Anuradha, "Trolox abrogates mitochondrial oxidative stress and myocardial apoptosis in mice fed calorie-rich diet," *Chemico-Biological Interactions*, vol. 278, pp. 74–83, 2017.
- [86] R. Huang, Z. Shi, L. Chen, Y. Zhang, J. Li, and Y. An, "Rutin alleviates diabetic cardiomyopathy and improves cardiac function in diabetic ApoEknockout mice," *European Journal of Pharmacology*, vol. 814, pp. 151–160, 2017.
- [87] C. Uthra, M. S. Reshi, A. Jaswal et al., "Protective efficacy of rutin against acrylamide-induced oxidative stress, biochemical alterations and histopathological lesions in rats," *Toxicology Research*, vol. 11, no. 1, Article ID tfab125, pp. 215–225, 2022.
- [88] F. M. Kandemir, M. Ileriturk, and C. Gur, "Rutin protects rat liver and kidney from sodium valproate-induced damage by attenuating oxidative stress, ER stress, inflammation, apoptosis and autophagy," *Molecular Biology Reports*, vol. 49, no. 7, pp. 6063–6074, 2022.
- [89] A. A. Fouad, S. A. Abdel-Gaber, and M. I. Abdelghany, "Hesperidin opposes the negative impact of cyclophosphamide on mice kidneys," *Drug and Chemical Toxicology*, vol. 44, no. 3, pp. 223–228, 2019.
- [90] P. Selvaraj and K. V. Pugalendi, "Hesperidin, a flavanone glycoside, on lipid peroxidation and antioxidant status in experimental myocardial ischemic rats," *Redox Report*, vol. 15, no. 5, pp. 217–223, 2010.
- [91] M. S. Antunes, F. V. L. Ladd, A. A. Ladd, A. L. Moreira, S. P. Boeira, and L. Cattelan Souza, "Hesperidin protects against behavioral alterations and loss of dopaminergic neurons in 6-OHDA-lesioned mice: the role of mitochondrial dysfunction and apoptosis," *Metabolic Brain Disease*, vol. 36, no. 1, pp. 153–167, 2021.
- [92] S. S. Khaled, H. A. Soliman, M. Abdel-Gabbar et al., "The preventive effects of naringin and naringenin against paclitaxel-induced nephrotoxicity and cardiotoxicity in male wistar rats," *Evidence-based Complementary and Alternative Medicine*, vol. 2022, Article ID 8739815, 11 pages, 2022.