Research Article

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Fampridine Ameliorates Hepatic Oxidative Stress Caused by Cisplatin in a Rat Model

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Abstract

Cisplatin is one of the most potent and commonly used anticancer compounds to treat various tumors, but it causes many unwanted side effects that restrict its use. Hepatotoxicity is one of the common adverse effects that occur even when small amounts of cisplatin are used for short times. This study tested the ameliorative effect of fampridine, a compound used to treat multiple sclerosis, against cisplatin-induced hepatotoxicity. Forty rats were divided into four groups; Group 1 served as the negative control and did not receive any treatment; Group 2 was a positive control and administered a single intraperitoneal dose of cisplatin (5 mg/kg); Group 3 was given oral fampridine at 4 mg/kg for three consecutive days, starting from the day cisplatin was injected; Group 4 was given fampridine (4 mg/kg for three days) and cisplatin (5 mg/kg, single dose). After the experiments, animal weights, liver weights, serum creatinine, and levels of malondialdehyde (MDA) and oxidized (GSSG) and reduced glutathione (GSH) in the liver tissues were measured after three and five days of treatment. Cisplatin caused hepatotoxicity manifested by decreased body weight, liver weight, and liver-to-body weight ratios. It also elevated creatinine concentrations in the serum and MDA and GSSG in the liver tissue, while GSH concentrations decreased. Fampridine treatment ameliorated these toxic impacts from cisplatin. Hence, people who are taking cisplatin as an anticancer therapy and fampridine as a treatment for multiple sclerosis may benefit from the latter's protective effect against cisplatin-induced hepatotoxicity.

Keywords: hepatotoxicity, Wistar rats, antioxidant, glutathion

Introduction

Cisplatin is a potent anticancer compound that has been extensively used to treat various cancers in humans (1) and animals, such as cats (2), dogs (3), and equines (4), for many decades. It has been proven effective against many cancers, including bladder, blood, breast, esophagus, ovary, testes, bones, neck, and sarcoma (5). It is commonly used as a first-line treatment in cancer patients (6).

Cisplatin exerts its anticancer cytotoxic effects by interfering with deoxyribonucleic acid (DNA) synthesis and cell growth. It forms intra-strand adducts and inter-strand links between purine bases, inhibiting the G2 phase in the cell cycle and inducing apoptosis (7).

Cisplatin has been used for over four decades, effectively treating many cancers and improving the life expectancy of the treated individuals. It is one of the most commonly used anticancer compounds in 40–80% of cancer patients (8). However, it has been shown to cause toxicity to various tissues, such as hepatotoxicity and nephrotoxicity (9). Hepatotoxicity has been reported in about one-third of the treated individuals, and it has even been reported to occur in patients receiving low doses of cisplatin (10).

After administration, cisplatin rapidly distributes in the tissues, entering the cells by passive diffusion, and high concentrations reach the liver, where most metabolic reactions of drugs and xenobiotics occur (11). In the hepatocytes, cisplatin causes vacuolation, dilation of sinusoids, and cytoplasmic changes near the central vein (12). The cytochrome P450 (CYP450) enzyme complex metabolizes it in the hepatocytes, especially CYP2E1 (13). CYP2E1 is mainly expressed in hepatocytes, with lesser amounts in the brain, kidney, lungs, lymphocytes, and gastrointestinal tract. Cells overexpressing CYP2E1 show increased oxidative stress (14). Additionally, cisplatin generates reactive oxygen species (ROS). The combined effect of increased ROS by cisplatin and oxidative stress by CYP2E1 causes increased release of hydrogen peroxide (H_2O_2), superoxide radical (O_2.-), and hydroxyl radical (.OH), adding to tissue damage, apoptosis, and hepatic failure (15).

Few mechanisms have been identified for cisplatin-induced hepatotoxicity, and it was shown to start as the generation of ROS in excess amounts, leading to oxidative stress, inflammation, DNA damage, and apoptosis (9).

Cellular membrane transporters mainly mediate the entry and toxicological effects of cisplatin. The organic cation transporters (OCTs) have been shown to mediate cisplatin's entry into cells (1). For example, OCT2 is mainly involved in cisplatin's entry into renal cells, causing nephrotoxicity (16). Another example is the involvement of OCT6 in cisplatin entry into the pulmonary tissue cells (17). Moreover, OCT3 mediates cisplatin entry into hepatocytes (18). Hence, compounds that inhibit these transporters potentially reduce cisplatin's entry into cells and, consequently, reduce its toxic impacts.

Fampridine, also called dalfampridine or 4-aminopyridine, was approved by the United States Food and Drug Administration in 2010 for use in patients with multiple sclerosis to improve their walking ability (19). Fampridine inhibits many voltage-dependent potassium channels on cell membranes (20) and is a substrate and inhibitor of OCT2 (21). Based on fampridine's mechanism of action, it was used in this study to assess its ameliorative effect on cisplatin-induced hepatotoxicity in a rat model.

Materials and Methods

Animals and housing: Male albino Wistar rats aged 8–12 weeks and weighing 170–180 g at arrival were used in the study. They were kept at the Research Center's Animal House in the College of Veterinary Medicine, University of Sulaimani. The rats were put in polypropylene cages with dimensions of 40 × 30 × 20 cm^3, with water and feed provided *ad libitum.* Wood shaving was used for the cages' bedding, which was changed once every three days or as required. The room temperature was around 25°C, ventilation was controlled, and a 12-hour light/dark cycle was followed. The rats were kept for ten days before starting the experiment to adapt to the new environment, and each rat was tagged on its tail by a permanent marker when the experiment began.

Treatment procedures: Forty rats were divided equally into four groups as follows: Group 1 served as the negative control and was left without treatment throughout the study; Group 2 (cisplatin) was a positive control, and the rats were given cisplatin (produced by Pfizer, Canada) as one intraperitoneal dose at 5 mg/kg (22); Group 3 (fampridine) rats were given fampridine (produced by Sigma-Aldrich, USA) by oral gavage at 4 mg/kg daily for three days (23, 24); and Group 4 (fampridine + cisplatin) rats were intraperitoneally injected with 5 mg/kg cisplatin and orally given fampridine at 4 mg/kg for three days, one hour before and 24 and 48 hours after cisplatin administration.

The rats were weighed daily during the experiment, and the drugs were given according to the weight of each rat. The rats of each group were then divided into two subgroups, each containing five. The first subgroup was sacrificed after three days of treatment, while the second subgroup was killed after five days.

Animal euthanasia and collection of organs: The rats were anesthetized with 75 mg/kg ketamine (produced by Alfasan, Woerden-Holland, Netherlands) and 2 mg/kg xylazine (produced by Interchemie, Holland Co., Netherlands) (25). After opening the chest cavity, blood was taken from the heart and put into plain test tubes to collect serum samples to determine creatinine levels.

The livers were soaked with normal saline, dried with sterile gauze, and weighed using a digital balance. The liver samples were then frozen at -80°C until used to determine the levels of reduced glutathione (GSH), oxidized glutathione (GSSG), and malondialdehyde in the hepatic tissue.

Serum creatinine: The serum samples were centrifuged with a microcentrifuge (by Neuation iFUGE M24PR, India). Then, the serum creatinine levels were measured with Cobas c 311 (Roche/Hitachi, Switzerland).

Total, oxidized, and reduced glutathione levels in the hepatic tissue: GSH and GSSG concentrations were determined in livers using the Total Glutathione (T-GSH)/Oxidized Glutathione (GSSG) Colorimetric Assay Kit (by Elabscience Co./USA). The procedure was conducted following the manufacturer's instructions.

Determination of malondialdehyde concentrations in the liver tissues: MDA (Malondialdehyde) ELISA Kit (Elabscience Co./USA) was used to measure the production of thiobarbituric acid-reactive substances (TBARS) to assess lipid peroxidation. The kit manufacturer's instructions were followed to conduct the experiment.

Ethical statement: The scientific and ethical committees at the College of Veterinary Medicine, University of Sulaimani, approved the study protocol.

Statistical analysis: Data were represented as means of five rats per group ± standard error of the mean (SEM). Differences between groups were analyzed using a one-way analysis of variance (ANOVA), followed by Duncan's post hoc, and the differences at different times within the same group were compared using independent samples t-test. IBM's Statistical Package for Social Sciences (SPSS) software (version 24.0, USA) was used to conduct the analyses. Differences were considered statistically significant if the probability value was larger or equal to 0.05.

Results

The weights of the groups sacrificed after three days ranged between 194.0 g and 196.0 g when the experiment started, with no significant differences between the groups (Figure 1). After three days, the weights decreased in the positive control from 195.4 ± 2.2 g to 190.8 ± 2.4. In contrast, the rats' weights of the negative control increased from 195.5 ± 1.7 g to 198.5 ± 1.5 g. However, the differences between the positive and negative controls were not statistically significant ($p > 0.05$).

After five days, the pretreatment weights of the sacrificed rats ranged between 191.2 ± 3.4 g to 193.7 ± 1.3 g before treatment. After five days, the weights of the positive control rats decreased to 187.0 ± 3.4 g, while the negative control rats averaged 199.2 ± 1.4 g, significantly higher than the positive control (Figure 1). This outcome indicated that cisplatin treatment negatively impacted the rats' health.

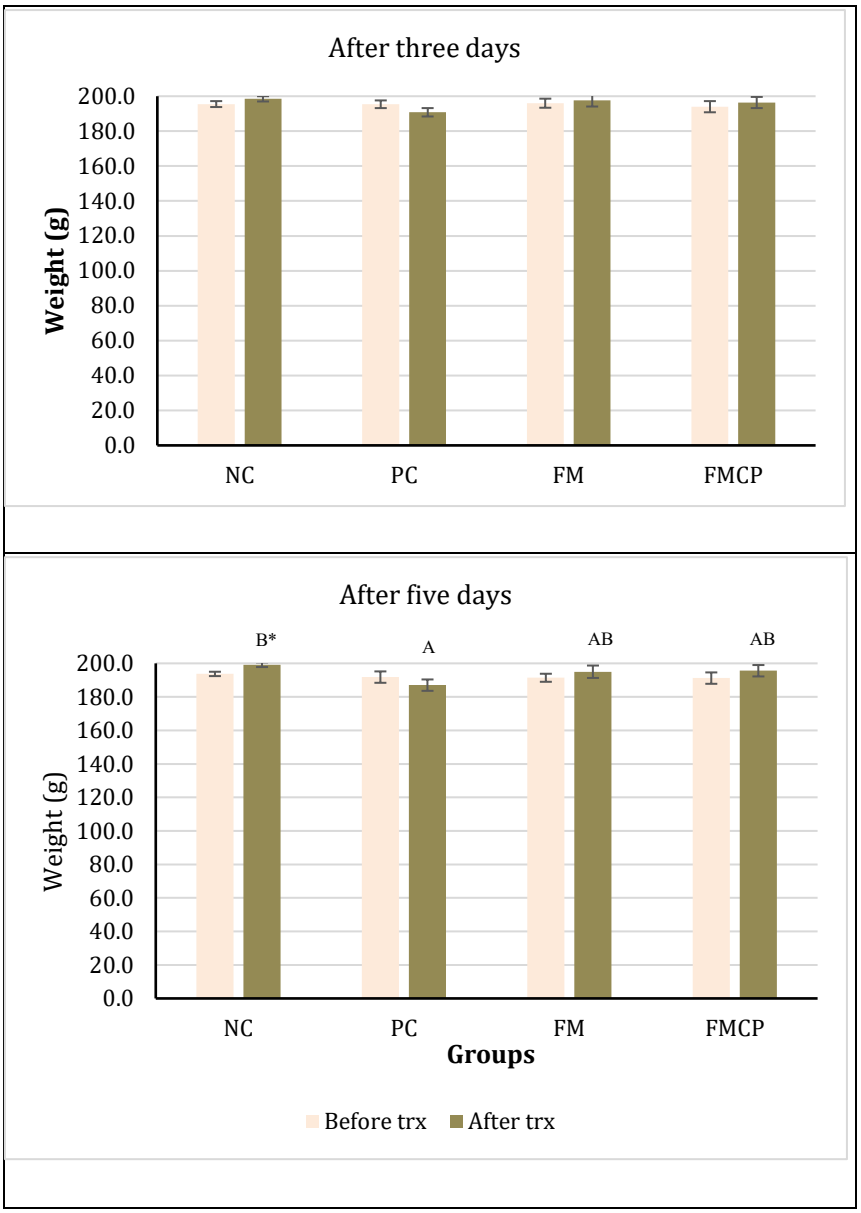

Figure 1. Weights of the rats after three and five days of cisplatin administration. Values represent the means of five rats (columns) per group ± SEM (error bars). Different letters denote significant differences between groups within the same time at $p < 0.05$ (test = one-way ANOVA, followed by Duncan's post hoc), while the asterisk indicates a significant difference between the values of before and after treatment (test = independent samples t-test). No differences were observed between the groups before and after three days of treatment.

The negative control rats' livers weighed 6.17 ± 0.07 g after three days, but the positive control weighed 5.72 ± 0.12 g, significantly lower than the former. In the groups treated with fampridine and fampridine + cisplatin, the weights averaged 6.18 ± 0.14 g and 6.06 ± 0.09 g, respectively (Figure 2). The differences were not

significant compared to the negative control. This indicated the harmful effect of cisplatin on the rats' livers and that fampridine treatment reduced this negative impact. After five days, the negative control livers averaged 6.25 ± 0.05 g, while the positive control averaged 5.60 ± 0.03 g, significantly lower than the former. In contrast, there were no significant differences regarding liver weights between the fampridine-treated groups and the negative control (Figure 2).

When comparing the toxic effects of drugs and toxicants, the liver-to-body weight ratio offers a more accurate comparison. In this study, the ratio in the negative control three days posttreatment averaged 3.11% ± 0.01, but it was 3.00 ± 0.03% in the positive control. The positive control was significantly lower than the negative control, about 3.5%, indicating that cisplatin administration was harmful to the rats' livers. Fampridine-treated groups had liver-to-body weight ratios that were significantly higher than the positive control, confirming that the drug ameliorated the toxic effects of cisplatin, preventing a significant reduction in liver size (Figure 2). The same pattern was observed in the sacrificed rats after five days, confirming the preventive effect of fampridine.

Serum creatinine concentrations in the negative control after three days averaged 47.55 ± 1.61 mg/dL, but it was significantly higher in the positive control, averaging 62.58 ± 3.44 mg/dL. The fampridine-treated groups had creatinine concentrations that were markedly lower than the positive control but with no significant difference from the negative control (Figure 3). The picture was a bit different five days post-treatment. The serum creatinine increased in the fampridine + cisplatin-treated group to 53.64 ± 1.89 mg/dL, significantly higher than the negative control but lower than the positive control. This outcome indicated fampridine's preventive effect on cisplatin-induced toxicity, even if it did not prevent cisplatin's negative impact entirely.

After three days, the oxidized glutathione (GSSG) concentration in the liver tissue of the negative control was 0.41 ± 0.03 µmol/g, but it increased significantly in the positive control to 0.59 ± 0.03 µmol/g. This outcome demonstrates cisplatin's oxidizing effect in the hepatic tissue. The GSSG concentration in the liver of fampridine and fampridine + cisplatin-treated rats averaged 0.31 ± 0.03 µmol/g and 0.37 ± 0.03 µmol/g, respectively (Figure 4). These concentrations were significantly lower than the positive control, indicating that fampridine administration reduces the oxidative stress posed by cisplatin. The same outcome was observed after five days; cisplatin administration increased GSSG levels, while fampridine significantly decreased the concentration, confirming the hepatoprotective effect of this drug against cisplatin-induced oxidative stress in the liver.

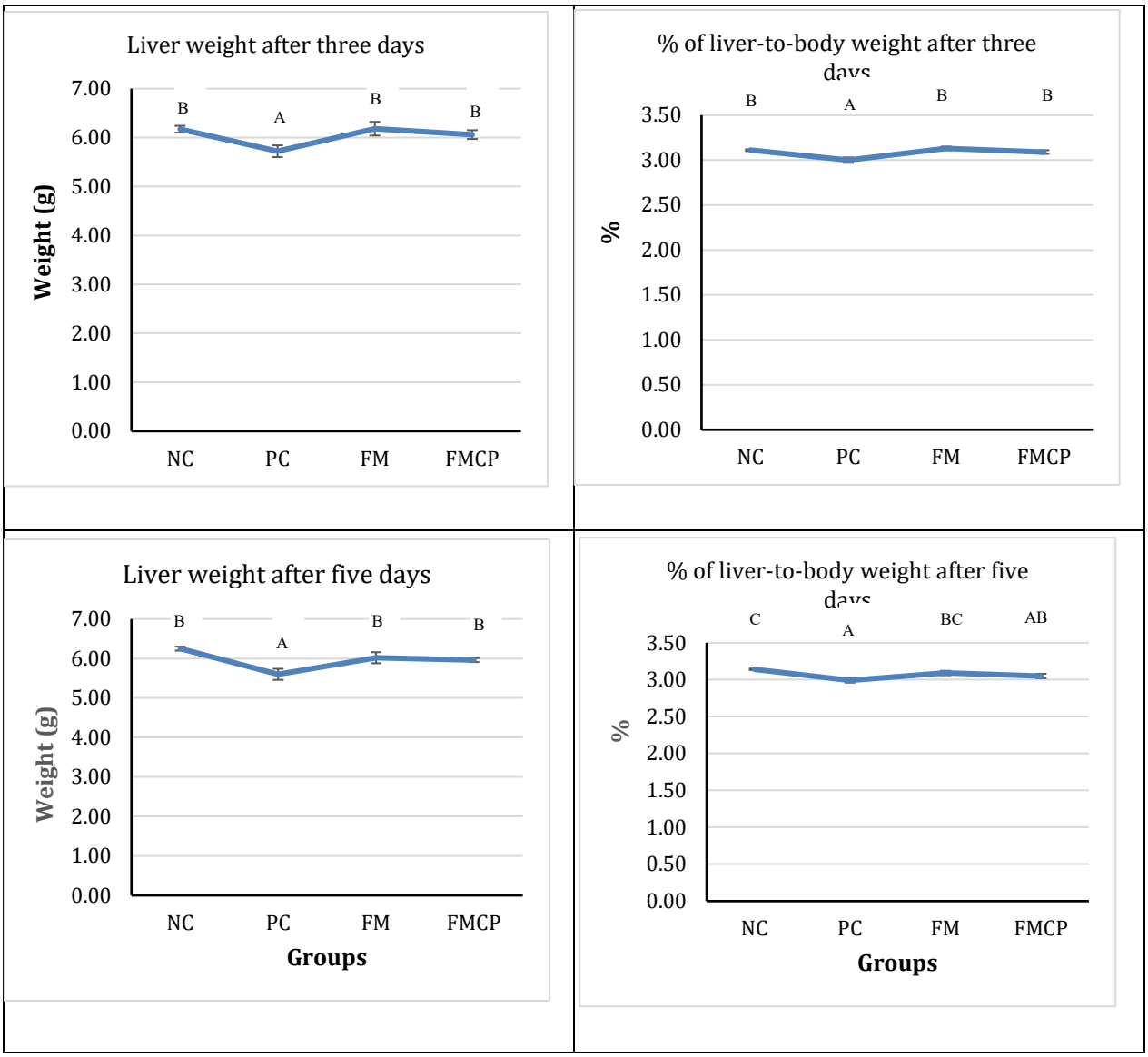

Figure 2. Liver weights and liver-to-body weight ratios. Values represent the means of five rats (columns) per group ± SEM (error bars). Different letters denote significant differences between groups within the same time at $p < 0.05$ (test = one-way ANOVA, followed by Duncan's post hoc), while no significant differences were observed between the same treatment group after three and five days (test = independent samples t-test).

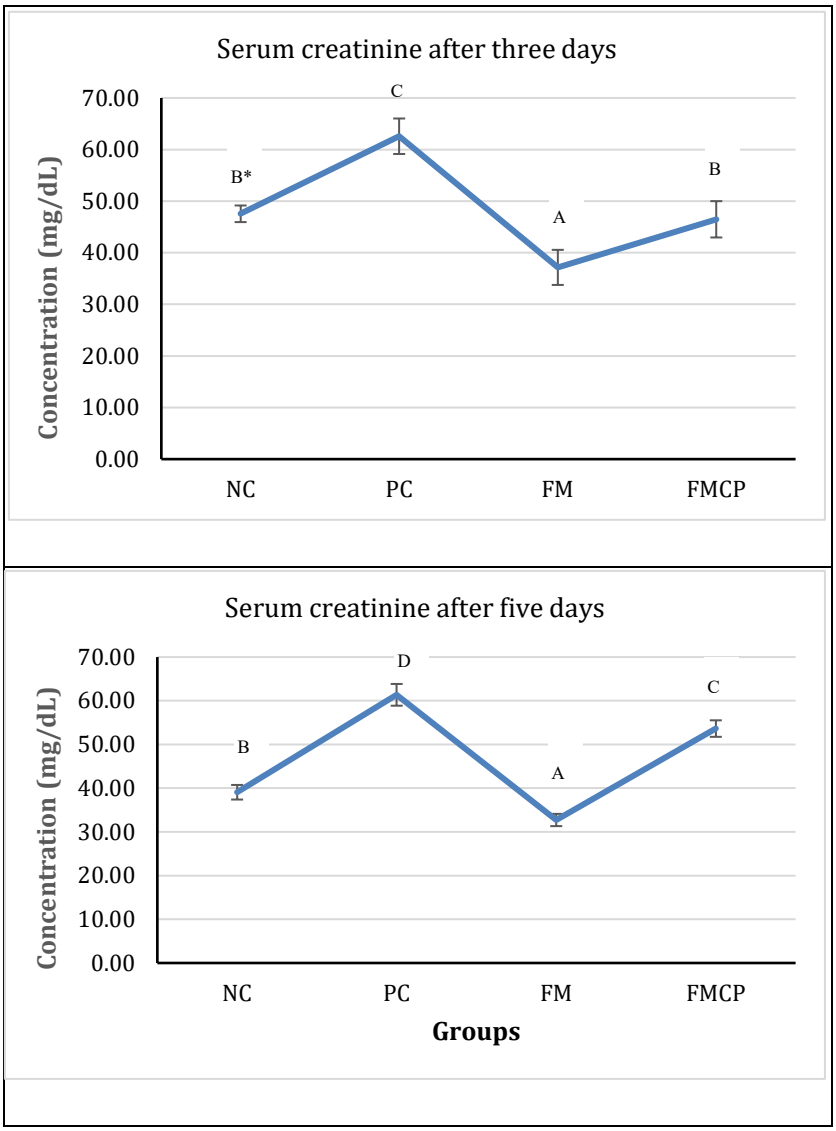

Figure 3. Serum creatinine levels. Values represent the means of five rats (columns) per group ± SEM (error bars). Different letters denote significant differences between groups within the same time at p < 0.05 (test = one-way ANOVA, followed by Duncan's post hoc). No significant differences were observed between the treatment groups after three days. * Denotes a significant difference between the values of three and five days within the same treatment group at p < 0.01 (test = independent samples t-test).

The reduced glutathione (GSH) concentration in the negative control's liver averaged 8.94 ± 0.67 µmol/g after three days, but it was significantly lower,6.53 ± 0.29 µmol/g, in the positive control (Figure 4). The livers of the groups treated with fampridine and fampridine + cisplatin contained a GSH concentration of 9.31 ± 0.44 µmol/g and 8.85 ± 0.19 µmol/g, significantly higher than that of the positive control. This outcome showed that fampridine prevents cisplatin-induced oxidative stress in the liver.

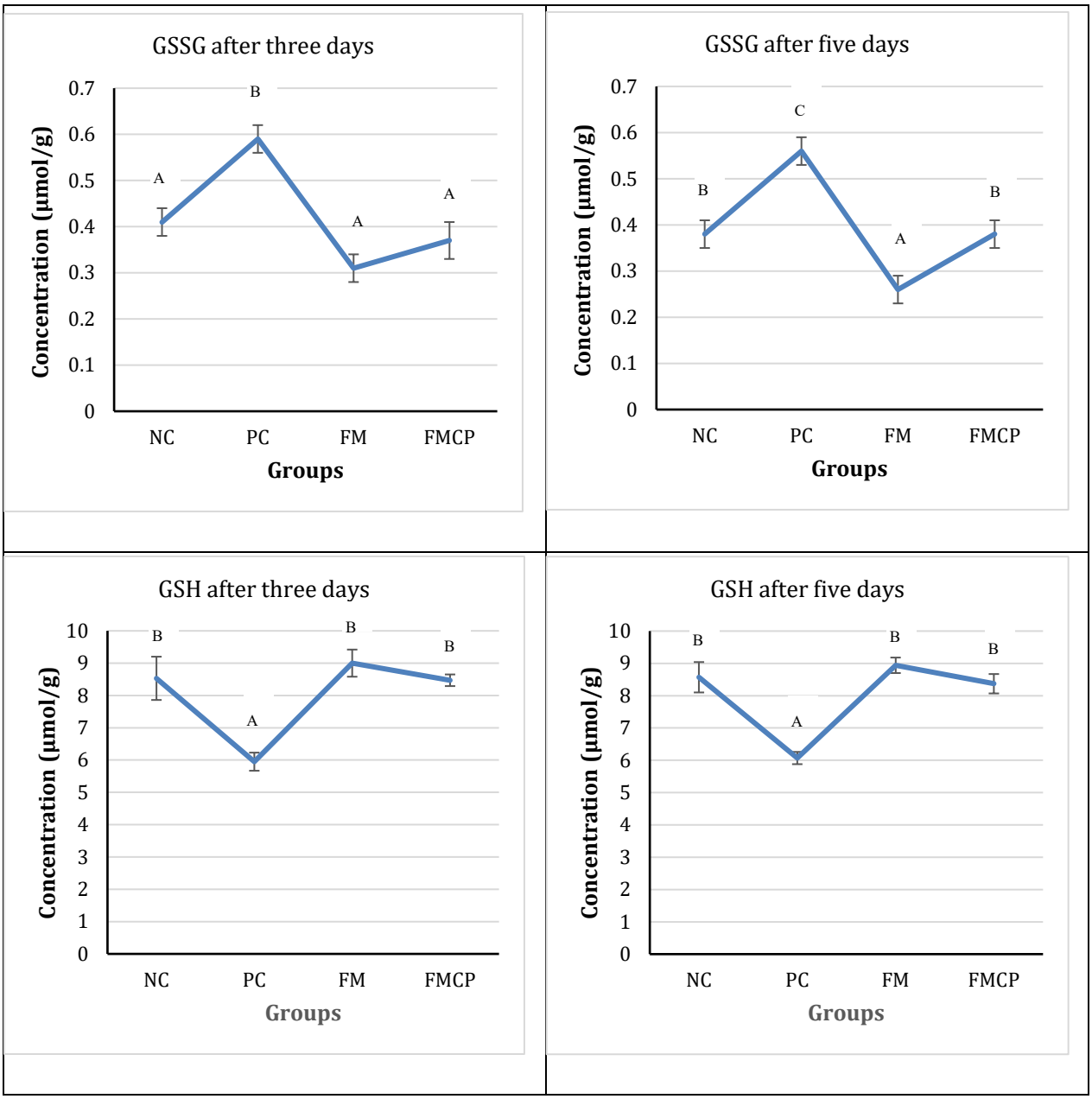

Figure 4. Concentrations of GSSG and GSH in the liver tissues. Values represent the means of five rats per group ± SEM (error bars). Different letters denote significant differences between treatment groups within the same time at $p < 0.05$ (test = one-way ANOVA, followed by Duncan's post hoc). No significant differences ($p > 0.05$) were observed when the values of three- and five-day post-treatment were compared (test = independent samples t-test). NC = negative control; PC = positive control; FM = fampridine; FMCP = fampridine + cisplatin.

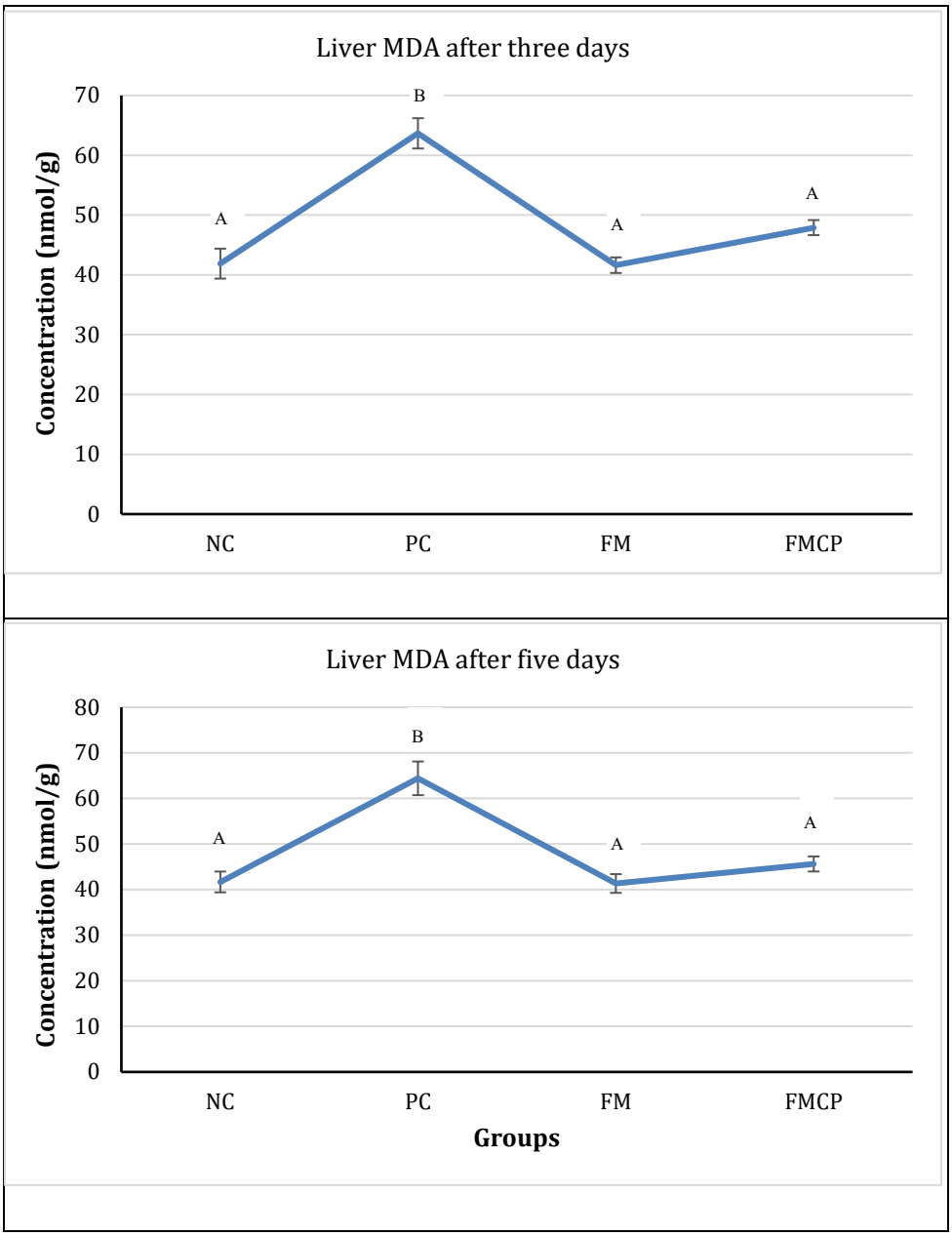

Figure 5. Malondialdehyde concentration in the liver tissues. Values represent the means of five rats per group ± SEM (error bars). Different letters denote significant differences between treatment groups within the same time at $p < 0.05$ (test = one-way ANOVA, followed by Duncan's post hoc). No significant differences ($p > 0.05$) were observed when the values of three- and five-day posttreatment were compared (test = independent samples t-test). NC = negative control; PC = positive control; FM = fampridine; FMCP = fampridine + cisplatin.

The MDA concentration in the negative control was 41.88 ± 2.50 nmol/g after three days and 41.68 ± 2.28 after five days. In the positive control, the concentrations after three and five days were 63.66 ± nmol/g and 64.4 ± 3.69 nmol/g, respectively. These values were significantly higher than the negative control, indicating that cisplatin increased lipid peroxidation in the liver tissue. The fampridine-treated groups had a considerably lower MDA than the positive control, suggesting that lipid peroxidation was less in these groups.

The results collected in this study, including animal and liver weights, serum creatinine, and the levels of GSH, GSSG, and MDA in the liver tissue, suggested that cisplatin administration increased oxidative stress in the treated animals and that treatment with fampridine ameliorated these effects even if they were not completely inhibited.

Discussion

Cisplatin is a potent anticancer compound used to treat various types of cancer despite having undesirable toxic effects on different tissues, especially the kidneys and liver (26). Many researchers have attempted to reduce these adverse effects by using drugs and natural compounds (27-29). This study demonstrated the hepatoprotective effect of fampridine when it was administered simultaneously with cisplatin in a rat model. Fampridine is an inhibitor of OCT2 (21) and several voltage-dependent potassium channels (20). OCT2 shares allosteric features with OCT1, which occurs abundantly on enterocytes and hepatocytes (30). High expression of OCT1 and OCT2 in the liver indicates their critical role in the hepatic elimination of many drugs, including cisplatin. Also, it was reported that cisplatin-mediated injury is partly through OCT2 (31). Hence, fampridine was selected based on its inhibitory effect on this transporter.

The cisplatin-induced hepatotoxicity in this study was through increased release of free radicals, and this was manifested by reduced malondialdehyde and GSH levels, while the GSSG and serum creatinine increased. Cisplatin administration reduced body weight, and other research reported similar results (32, 33). Also, a decrease in the relative liver-to-body weight indicates organ toxicity. In our study, the relative liver weight decreased, which was compatible with the results of previous studies regarding cisplatin's toxic effects (33, 34).

GSH is a crucial non-enzymatic antioxidant in mammalian cells. It is a tripeptide mainly concentrated in the liver, and the cysteine's thiol group mediates its biological activity (35). GSH acts as a direct antioxidant and cofactor for other enzymes, like glutathione peroxidase, which reacts with peroxides; this reaction converts GSH to GSSG(36). Afterwards, glutathione reductase and nicotinamide adenine dinucleotide phosphate (NADPH) convert GSSG back to GSH (37). GSH has various antioxidant effects inside the cell. For example, it can regenerate vitamin E after the latter reacts with lipid peroxy radicals (LOO·) and detoxifies them (38). GSH assists glutathione S-transferase in the detoxification of xenobiotics and electrophilic compounds(39). GSH participates in other cellular processes like

protein folding, protects the oxidation of protein thiols and crosslinking, regulates ascorbic acid's cell cycle and metabolism, and apoptosis (36). Cisplatin administration reduced the hepatic GSH concentration in this study, and other research reported similar results (29, 40). Glutathione is the most vital thiol-reducing compound in the liver involved in redox processes, and it is the most crucial defender against oxidative stress (35). Hence, reduced levels of GSH are indicative of cisplatin's oxidizing impact on the hepatic tissue. On the other hand, fampridine administration increased GSH and decreased GSSG concentrations, denoting the hepatoprotective effect of this compound by increasing the antioxidant levels.

Lipids are very susceptible to oxidation, and MDA is one of the principal biomarkers to assess lipid peroxidation (41). Polyunsaturated fatty acids containing many carbon-carbon double bonds are vulnerable to oxidative stress-induced damage. Oxidants extract a hydrogen atom, forming unstable lipid radicals. An oxygen atom will then be inserted, forming lipid peroxyl radicals and extracting another hydrogen atom. The reaction continues, leading to the formation of more stable compounds known as lipid hydroperoxides, and this process is called lipid peroxidation (42).

MDA is the most extensively studied lipid peroxidation-derived compound. It has mutagenic and toxic effects, and enzymes produce it as a byproduct when thromboxane A2 is synthesized (42). MDA can bind to proteins and nucleic acids by covalent bonds, forming DNA-protein crosslinks and compounds that impair biomolecules (43). It is used as a biomarker to evaluate oxidative stress caused by disease in different tissues, and its detection indicates that lipid peroxidation has a crucial role in this disease (44).

Serum creatinine levels also increased following cisplatin administration. Creatinine is an essential conventional biomarker for renal injury, and its elevation is suggestive of renal injury (45). Fampridine administration reduced the creatinine levels, indicating that it also reduced renal toxicity with cisplatin in this study.

In this study, cisplatin significantly increased the MDA concentration in the liver of the treated rats, indicating that the drug administration increased lipid peroxidation. On the other hand, fampridine administration reduced MDA significantly, compared to the positive control, denoting its hepatoprotective potential. Other studies also reported that cisplatin treatment increases MDA concentration in the hepatic tissues (46, 47), confirming our study's outcome.

Conclusions

Cisplatin induces oxidative stress and hepatic injury, which manifests as increased levels of oxidized glutathione and malondialdehyde and decreased levels of reduced glutathione in the hepatic tissue. Fampridine administration protected against oxidative stress in the treated rats. Cancer patients receiving cisplatin and using fampridine as a treatment for multiple

sclerosis would benefit from the hepatoprotective effect of the latter against cisplatin-induced oxidative stress and tissue damage.

Conflicts of interest

The authors declare that there is no conflict of interest.

Ethical Clearance

This work is approved by The Research Ethical Committee.

References

1.Romani AM (2022). Cisplatin in cancer treatment. *Biochemical pharmacology, 206*, 115323.

2.Spugnini EP, Vincenzi B, Carocci F, Bonichi C, Menicagli F, Baldi A (2020). Combination of bleomycin and cisplatin as adjuvant electrochemotherapy protocol for the treatment of incompletely excised feline injection-site sarcomas: A retrospective study. *Open Veterinary Journal, 10*(3), 267–271-267–271.

3.Knapp D, Henry C, Widmer W, Tan K, Moore G, Ramos-Vara J, Lucroy M, Greenberg C, Greene S, Abbo A (2013). Randomized trial of cisplatin versus firocoxib versus cisplatin/firocoxib in dogs with transitional cell carcinoma of the urinary bladder. *Journal of Veterinary Internal Medicine, 27*(1), 126-133.

4.Tamzali Y, Borde L, Rols M, Golzio M, Lyazrhi F, Teissie J (2012). Successful treatment of equine sarcoids with cisplatin electrochemotherapy: a retrospective study of 48 cases. *Equine veterinary journal, 44*(2), 214-220.

5.Hamaya S, Oura K, Morishita A, Masaki T (2023). Cisplatin in liver cancer therapy. *International Journal of Molecular Sciences, 24*(13), 10858.

6.Tchounwou PB, Dasari S, Noubissi FK, Ray P, Kumar S (2021). Advances in our understanding of the molecular mechanisms of action of cisplatin in cancer therapy. *Journal of experimental pharmacology,* 303-328.

7.Ranasinghe R, Mathai ML, Zulli A (2022). Cisplatin for cancer therapy and overcoming chemoresistance. *Heliyon, 8*(9).

8.Mezencev R (2014). Interactions of cisplatin with non-DNA targets and their influence on anticancer activity and drug toxicity: the complex world of the platinum complex. *Current cancer drug targets, 14*(9), 794-816.

9.Abd Rashid N, Abd Halim SAS, Teoh SL, Budin SB, Hussan F, Ridzuan NRA, Jalil NAA (2021). The role of natural antioxidants in cisplatin-induced hepatotoxicity. *Biomedicine & Pharmacotherapy, 144*, 112328.

10.Al-Malki AL, Sayed AAR (2014). Thymoquinone attenuates cisplatin-induced hepatotoxicity via nuclear factor kappa-β. *BMC complementary and alternative medicine, 14*, 1-8.

11.Quintanilha JCF, de Sousa VM, Visacri MB, Amaral LS, Santos RMM, Zambrano T, Salazar LA, Moriel P (2017). Involvement of cytochrome P450 in cisplatin treatment: implications for toxicity. *Cancer chemotherapy and pharmacology, 80*, 223-233.

12.Hesham AA, Ghobara MM (2013). Histological study of the effect of cisplatin on the liver of adult male albino rat. IJASR

International Journal of Academic and Scientific Research ISSN, 1(1), 22-33.
13.Kamble P, Bhiwgade D (2011). Cisplatin induced histological and ultrastructural alterations in liver tissue of rat. *J Cytol Hist, 2*, 128.
14.Lu Y, Cederbaum AI (2006). Cisplatin-induced hepatotoxicity is enhanced by elevated expression of cytochrome P450 2E1. *Toxicological Sciences, 89*(2), 515-523.
15.Kurutas EB (2015). The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutrition journal, 15,* 1-22.
16.Ciarimboli G (2014). Membrane transporters as mediators of cisplatin side-effects. Anticancer research, 34(1), 547-550.
17.Kunii E, Oguri T, Kasai D, Ozasa H, Uemura T, Takakuwa O, Ohkubo H, Takemura M, Maeno K, Niimi A (2015). Organic cation transporter OCT6 mediates cisplatin uptake and resistance to cisplatin in lung cancer. *Cancer chemotherapy and pharmacology, 75*, 985-991.
18.Guttmann S, Chandhok G, Groba SR, Niemietz C, Sauer V, Gomes A, Ciarimboli G, Karst U, Zibert A, Schmidt HH (2018). Organic cation transporter 3 mediates cisplatin and copper cross-resistance in hepatoma cells. *Oncotarget, 9*(1), 743.
19.Valet M, Quoilin M, Lejeune T, Stoquart G, Van Pesch V, El Sankari S, Detrembleur C, Warlop T (2019). Effects of fampridine in people with multiple sclerosis: a systematic review and meta-analysis. *CNS drugs, 33*, 1087-1099.
20.Dunn J, Blight A (2011). Dalfampridine: a brief review of its mechanism of action and efficacy as a treatment to improve walking in patients with multiple sclerosis. *Current medical research and opinion, 27*(7), 1415-1423.
21.Xiao G, Rowbottom C, Boiselle C, Gan L-S (2018). Fampridine is a Substrate and Inhibitor of Human OCT2, but not of Human MATE1, or MATE2K. *Pharmaceutical research, 35*(8), 1-8.
22.de Oliveira Mora L, Antunes LMG, Francescato HsDC, Bianchi MdLP (2003). The effects of oral glutamine on cisplatin-induced nephrotoxicity in rats. *Pharmacological research, 47*(6), 517-522.
23.Goodman A, Brown T, Cohen J, Krupp L, Schapiro R, Schwid S, Cohen R, Marinucci L, Blight A (2008). Dose comparison trial of sustained-release fampridine in multiple sclerosis. *Neurology, 71*(15), 1134-1141.
24.Nair AB, Jacob S (2016). A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm, 7*(2), 27.
25.Dodelet-Devillers A, Zullian C, Beaudry F, Gourdon J, Chevrette J, Hélie P, Vachon P (2016). Physiological and pharmacokinetic effects of multilevel caging on Sprague Dawley rats under ketamine-xylazine anesthesia. *Experimental animals, 65*(4), 383-392.
26.Salem EA, Attia YA, Salem NA, Fathallah AM, Keshta AT (2024). Selenium nanoparticles effects of in reducing hepatotoxicity brought on by cisplatin. *Biochemistry Letters, 20*(1), 1-11.
27.Un H, Ugan RA, Kose D, Bayir Y, Cadirci E, Selli J, Halici Z (2020). A novel effect of Aprepitant: Protection for cisplatin-induced nephrotoxicity and hepatotoxicity. *European journal of pharmacology, 880*, 173168.

28.El-Gizawy MM, Hosny EN, Mourad HH, Abd-El Razik AN (2020). Curcumin nanoparticles ameliorate hepatotoxicity and nephrotoxicity induced by cisplatin in rats. *Naunyn-Schmiedeberg's Archives of Pharmacology, 393*, 1941-1953.

29.Doğan D, Meydan I, Kömüroğlu AU (2022). Protective Effect of Silymarin and Gallic Acid against Cisplatin-Induced Nephrotoxicity and Hepatotoxicity. *International journal of clinical practice, (1),* 6541026.

30.Nies AT, Koepsell H, Winter S, Burk O, Klein K, Kerb R, Zanger UM, Keppler D, Schwab M, Schaeffeler E (2009). Expression of organic cation transporters OCT1 (SLC22A1) and OCT3 (SLC22A3) is affected by genetic factors and cholestasis in human liver. Hepatology, 50(4), 1227-1240.

31.Sprowl JA, Lancaster CS, Pabla N, Hermann E, Kosloske AM, Gibson AA, Li L, Zeeh D, Schlatter E, Janke LJ (2014). Cisplatin-induced renal injury is independently mediated by OCT2 and p53. *Clinical Cancer Research, 20*(15), 4026-4035.

32.Gholami Jourabi F, Yari S, Amiri P, Heidarianpour A, Hashemi H (2021). The ameliorative effects of methylene blue on testicular damage induced by cisplatin in rats. *Andrologia, 53(*1), e13850.

33.Okafor IA, Nnamah US, Nnaka J (2020). Liver Function Analyses and Spleen Histology Assessment Following the Co-administration of Cisplatin and Methanolic Extract of Portulaca Oleracea in Wistar Rats: An Experimental Study. *Natural Product Sciences, 26*(3), 252-258.

34.Aboraya DM, El Baz A, Risha EF, Abdelhamid FM (2022). Hesperidin ameliorates cisplatin induced hepatotoxicity and attenuates oxidative damage, cell apoptosis, and inflammation in rats. *Saudi journal of biological sciences, 29*(5), 3157-3166.

35.Vairetti M, Di Pasqua LG, Cagna M, Richelmi P, Ferrigno A, Berardo C (2021). Changes in glutathione content in liver diseases: an update. *Antioxidants, 10*(3), 364.

36.Averill-Bates DA: The antioxidant glutathione. In: *Vitamins and hormones. Volume 121*, edn.: *Elsevier; 2023:* 109-141.

37.Georgiou-Siafis SK, Tsiftsoglou AS (2023). The key role of GSH in keeping the redox balance in mammalian cells: mechanisms and significance of GSH in detoxification via formation of conjugates. *Antioxidants, 12*(11), 1953.

38.Recknagel RO, Glende EA, Britton RS: Free radical damage and lipid peroxidation. In: *Hepatotoxicology.* edn.: CRC press; 2020: 401-436.

39.Cooper A, Hanigan M (2018). Metabolism of glutathione S-conjugates: multiple pathways. *Comprehensive toxicology, 363*.

40.Akcakavak G, Kazak F, Yilmaz Deveci MZ (2023). Eucalyptol Protects against Cisplatin-Induced Liver Injury in Rats. *Biology Bulletin, 50*(5), 987-994.

41.Mas-Bargues C, Escriva C, Dromant M, Borras C, Vina J (2021). Lipid peroxidation as measured by chromatographic determination of malondialdehyde. Human plasma reference values in health and disease. *Archives of biochemistry and biophysics, 709*, 108941.

42.Cordiano R, Di Gioacchino M, Mangifesta R, Panzera C, Gangemi S,

Minciullo PL (2023). Malondialdehyde as a potential oxidative stress marker for allergy-oriented diseases: an update. *Molecules, 28(16*), 5979.

43.Marnett LJ (1999). Lipid peroxidation—DNA damage by malondialdehyde. Mutation Research/Fundamental and *Molecular Mechanisms of Mutagenesis, 424*(1-2), 83-95.

44.Busch CJ, Binder CJ (2017). Malondialdehyde epitopes as mediators of sterile inflammation. *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1862*(4), 398-406.

45.Slocum JL, Heung M, Pennathur S (2012). Marking renal injury: can we move beyond serum creatinine? *Translational Research, 159*(4), 277-289.

46.Pınar N, Çakırca G, Hakverdi S, Kaplan M (2020). Protective effect of alpha lipoic acid on cisplatin induced hepatotoxicity in rats. *Biotechnic & Histochemistry, 95*(3), 219-224.

47.Kurt N, Türkeri ÖN, Suleyman B, Bakan N (2021). The effect of taxifolin on high-dose-cisplatin-induced oxidative liver injury in rats. *Advances in Clinical and Experimental Medicine, 30*(10), 1025-1030.

فامبريدين يخفف من الإجهاد التأكسدي الكبدي الناجم عن السيسبلاتين في نموذج الجرذان

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الخلاصة

السيسبلاتين هو أحد أقوى المركبات المضادة للسرطان وأكثرها استخدامًا لعلاج الأورام المختلفة، ولكنه يسبب العديد من الآثار الجانبية غير المرغوب فيها التي تحد من استخدامه. تعد السمية الكبدية واحدة من الآثار الضارة الشائعة التي تحدث حتى عند استخدام كميات صغيرة من السيسبلاتين لفترات قصيرة. اختبرت هذه الدراسة التأثير المحسن للفامبريدين، وهو مركب يستخدم لعلاج التصلب المتعدد، ضد السمية الكبدية الناجمة عن السيسبلاتين. تم تقسيم أربعين جرذا إلى أربع مجموعات؛ عملت المجموعة الأولىك كمجموعة سيطرة سلبية ولم تتلق أي علاج؛ كانت المجموعة الثانية بمثابة مجموعة سيطرة إيجابية وأعطيت جرعة واحدة داخل الصفاق من السيسبلاتين (5 مجم/كجم)؛ أعطيت المجموعة الثالثة فامبريدين عن طريق الفم بجرعة 4 مجم/كجم لمدة ثلاثة أيام متتالية، بدءًا من اليوم الذي تم فيه حقن السيسبلاتين؛ أعطيت المجموعة الرابعة فامبريدين (4 مجم/كجم لمدة ثلاثة أيام) وسيسبلاتين (5 مجم/كجم، جرعة واحدة). بعد إجراء التجارب، تم قياس أوزان الحيوانات وأوزان الكبد والكرياتينين في المصل ومستويات المالونديالدهيد (MDA) والجلوتاتيون المؤكسد (GSSG) والجلوتاثيون المختزل (GSH) في أنسجة الكبد بعد ثلاثة وخمسة أيام من العلاج. تسبب السيسبلاتين في سمية الكبد التي تجلت في انخفاض وزن الجسم ووزن الكبد ونسبة وزن الكبد إلى الجسم. كما رفع تركيزات الكرياتينين في المصل وMDA وGSSG في أنسجة الكبد، في حين انخفض تركيز GSH. خفف علاج فامبريدين هذه التأثيرات السامة من السيسبلاتين. وبالتالي، فإن الأشخاص الذين يتناولون السيسبلاتين كعلاج مضاد للسرطان والفامبريدين كعلاج للتصلب المتعدد قد يستفيدون من التأثير الوقائي للأخير ضد السمية الكبدية الناجمة عن السيسبلاتين.

الكلمات المفتاحية: السمية الكبدية، جرذان ويستار، مضادات الأكسدة، الكلوتاثيون.