Ind. J. Pharm. Edu. Res., 2026; 60(1):410-420.
https://www.ijper.org

Original Article

Investigatıon of the Protective Effect of Hydrogen Sulphide Donor Sodium Hydrosulphide and Sulfurized Apricot on Experimental Acute Kidney Injury Induced by Cisplatin in Rats

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ABSTRACT

Background: In the present study, we aimed to investigate the protective effect of Hydrogen sulfide (H_2S) donor Sodium Hydrosulphide (NaHS) and Sulfurized Apricot (SA) on experimental acute kidney injury induced by cisplatin in rats. **Materials and Methods:** Four groups of Wistar albino rats were formed with 10 rats in each group: Control group, Cisplatin group, Cisplatin+SA group, and Cisplatin+NaHS group. The activities of Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GPx) and Cystathione gamma-lyase (CSE), and the levels of Malondialdehyde (MDA), Glutathione (GSH) and total GSH were measured. Creatinine, urea, Sodium (Na), Chlorine (Cl), Potassium (K), Calcium (Ca), Aspartate aminotransferase (AST), and Alanine Aminotransferase (ALT) were also measured. **Results:** CAT activity increased in the cisplatin+SA and cisplatin+NaHS groups. CSE activity increased in the cisplatin+NaHS group. MDA levels increased in the cisplatin and cisplatin+NaHS groups. This increase was also observed in SOD and GPx activities but was not statistically significant. Serum ALT, AST, creatinine, and urea levels were higher in the cisplatin group. ADP activity was lower in the cisplatin group. The histological findings support the biochemical results obtained in our study. Red/total GSH was higher in the cisplatin, cisplatin+SA, and cisplatin+NaHS groups. **Conclusion:** SA and NaHS would have beneficial effects in preventing cisplatin-induced kidney damage.

Keywords: Acute kidney injury, Hydrogen sulfide, Sulfurized apricot, Cisplatin.

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Received: 02-05-2025;
Revised: 21-06-2025;
Accepted: 27-08-2025.

INTRODUCTION

Chemotherapy is a type of treatment used to prevent the spread of cancer, slow tumor growth, and destroy cancer cells. Antineoplastic drugs are commonly used in chemotherapy. Antineoplastic drugs are known to cause some damage to healthy cells as well as affect cancer cells that are growing in the body. As a result, many side effects have been reported with these drugs. These include neurotoxicity, hepatotoxicity, general pain, nausea, vomiting, hair loss, increased risk of infection, functional impairment, and nephrotoxicity.[1,2]

Cisplatin (cis-diamminedichloroplatinum II) is a clinically developed and effective anti-cancer drug used to treat many cancers such as cervical, ovarian, testicular, non-small cell lung, lymphoma, and head and neck.[3] It causes inhibition of cancer cell growth by interacting with DNA.[4] Cisplatin is associated with several side effects, including nephrotoxicity, hepatotoxicity, ototoxicity, and cardiotoxicity. Nephrotoxicity is the most important side effect of cisplatin, limiting its clinical use.[5] It is estimated that 20-35% of cancer patients treated with cisplatin are at risk of drug-induced nephrotoxicity.[6] Oxidative stress has been identified as the leading cause of cisplatin-induced nephrotoxicity.[7]

The renal effects of cisplatin include inhibition of GSH and Sulphhydryl (-SH) group-related antioxidant mechanisms, impaired reabsorption function, and alterations in electrolyte homeostasis. The relationship between cisplatin and nephrotoxicity is generally explained in terms of antioxidant

DOI: 10.5530/ijper.20261390

mechanisms. The impairment of the antioxidant defense mechanism by cisplatin may lead to the release of some markers at high levels. It has been reported that cisplatin causes changes in the levels of cellular antioxidant enzyme activities in renal tissue. It disturbs the intracellular redox balance in favor of oxidants. In addition, increased blood urea nitrogen and creatinine levels are strongly associated with oxidative damage-induced nephrotoxicity.[8,9]

To prevent the nephrotoxic effects of cisplatin, many natural and synthetic protective agents are being investigated. Sodium thiosulphate, a nucleophilic sulfur compound, is one of the chemicals often used to reduce the toxic effect. Such compounds have been reported to be effective through antioxidant and anti-inflammatory pathways by acting on caspase activity.[8,10] Sodium thiosulphate is also an important oxidation product of H_2S. Kidney tissue is one of the organs where H_2S is most abundant, as all four different pathways that produce H_2S are active in the kidney. H_2S has been reported to protect against cisplatin-induced nephrotoxicity. However, this effect is dose-dependent; H_2S, which is protective at physiological concentrations, exacerbates oxidative damage at high concentrations. NaHS, a known H_2S donor, has been reported to reduce the effects of cisplatin.[11,12]

Apricot is a plant from the rose family. Studies on this plant have reported that it has antitussive, antiasthmatic, and hepatoprotective effects. In addition, the vitamins and antioxidants in apricots have been found to support renal protection in radiation-induced kidney injury.[13] In the mechanism of methotrexate-mediated kidney damage, it has been highlighted that it may also act through antioxidant enzymes and prevent cell death through apoptotic pathways.[14]

It has been explained that apricot plays a role in increasing the antioxidant enzyme activities of SOD, CAT, and GPx in the liver and is also effective in reducing the levels of AST, ALT, and MDA.[15] In our study, we believe that the SA plant may be another donor that can be used in addition to NaHS to reduce the effects of cisplatin due to its H_2S content. It may protect against kidney damage due to the many different types of antioxidants, vitamins, and polyphenol biomolecules it contains.

It has been reported that the effects of cisplatin on the kidneys include antioxidant mechanisms related to GSH and Sulfhydryl (-SH) groups. In addition, cisplatin has been shown to cause changes in the levels of cellular antioxidant enzyme activities such as SOD, CAT, and GPx in kidney tissue, disrupting the intracellular redox balance in favor of oxidants, leading to oxidative damage and the development of nephrotoxicity. In this study, we focused on H_2S, which is found in high concentrations in the kidneys and has been reported to have a protective effect against cisplatin-induced nephrotoxicity. To this end, we planned to investigate the protective effects of NaHS, a donor of H_2S and sulfur-containing apricot, against kidney damage.

MATERIALS AND METHODS

Materials

Preparation of diets containing SA and NaHS

Apricot samples containing 2000 ppm sulfur were obtained from a local market in Malatya, Turkey. The sulfur-containing apricots were mixed into the rats' feed at a ratio of 10-15%. A small amount of water was added to the mixture, which was kneaded until homogenized and then formed into pellets. The freshly made pellets were spread out on cardboard to dry and were dried in a well-ventilated, cool room. The rats in the sulfur apricot group were given pellet feed containing sulfur apricots instead of the standard pellet feed ad libitum.

NaHS was obtained from Sigma-Aldrich (CAS No: 207683-19-0). The total dose for the rats was calculated to be 100 µmol/kg and prepared by dissolving in deionized water for use.

Procurement and preparation of laboratory animals for experiments

This study complied with the "Ethical Guidelines for Animal Use" after receiving the approval of the İnönü University, Faculty of Medicine, Local Ethics Committee (decision date:17.12.2020 and number 2020/17-5). The power analysis was performed using G*Power 3.1 (Dusseldorf, Germany). The alpha error rate (type I error) is 0.05, the power of the test (1-beta) is 0.8, and the effect size is 1.82. Based on these values, the minimum required sample size to detect a significant difference using this test is 8 animals per group, for at least 32 animals. The laboratory animals used in the study were obtained from the Inonu University Laboratory Animal Production and Research Centre. A total of 40 adult male Wistar albino rats aged 3-5 months with an average weight of 250-350 g were used. All animals were housed in polypropylene cages (5 animals per cage) and fed ad libitum with tap water. They were kept on a 12-hr light/12-hr dark cycle, and the room temperature was maintained at 22-24°C. A total of 40 male rats were randomly divided into 4 groups of 10 animals each.

Methods

Experimental groups

Control group; this group was fed ad libitum with standard chow and water during the study period. A single intraperitoneal (i.p.) dose of 0.9% NaCl solution equal to the amount of cisplatin injection was injected.

Cisplatin group; this group was fed ad libitum with standard chow and water throughout the study. A dose of 20 mg/kg cisplatin was dissolved in 0.9% NaCl and injected i.p. as a single dose.[16]

Cisplatin+SA group; Rats in this group were fed an apricot pellet diet containing 10% 2000 ppm sulfur for 15 days, and 20 mg/kg cisplatin was injected i.p. at the end of the 15th day.

Cisplatin+NaHS group; this group was fed ad libitum with standard chow and water throughout the study. Rats were injected i.p. with 50 µmol/kg NaHS (total dose 100 µmol/kg) dissolved in 0.9% NaCl 1 hr before and 4 hr after cisplatin injection.[17]

Sample collection

All animals were anesthetized with ketamine+xylazine injection (0.5 mg/kg-1 mg/kg) 72 hr after cisplatin injection and sacrificed by cervical dislocation method after intracardiac blood sampling. Rat blood samples were centrifuged at 2000 g for 10 min to obtain serum. The plasma portion of the blood was separated for antithrombotic activity analysis. Both kidney tissues were removed, and the right kidney was preserved in 10% formaldehyde for histopathological examination. The left kidney tissues were rapidly perfused and stored in a deep freezer at -80ºC for biochemical measurements.

Kidney tissue was transferred to glass tubes, and 50 µm/L phosphate buffer (pH 7.4) was added at a 1:10 weight/volume ratio. The tissues were then homogenized in an UltraTurrax T25 homogenizer (IKA Werke GmbH, Staufen, Germany) at 6000 rpm for 5 min while keeping the tissues cold. After vortexing, the homogenates were transferred to Eppendorf tubes. The homogenates were centrifuged at 13,500 g for 15 min at 4ºC in a refrigerated centrifuge (Centrifuge 5415R, Eppendorf AG, Hamburg, Germany), and the supernatant was collected. The collected supernatants were used for biochemical analysis.

Biochemical analysis

The protein content of the samples was measured using the Lowry method. BSA (Bovine Serum Albumin) was used as a protein standard.[18] MDA levels (nmol/mg protein) were measured using Mihara and Uchiyama methods.[19] GPx activity (U/mg protein) was measured according to the method of Lawrence and Burk.[20] CAT activity (U/mg protein) was determined by the method of Luck H.[21] SOD activity (U/mg protein) was determined by the method of Sun *et al.*,[22] The amount of GSH (mmol/ml protein) was measured at 412 nm according to the method of Sedlak and Lindsay.[23] Total GSH (GSH+GSSG) level is measured by reacting with GSH, dithionitrobenzoic acid (DTNB), and reducing oxidized GSH (GSSG).[24] The amount of GSH in the tissue was expressed as mmol/ml protein, using a commercial GSH as a standard. Determination of CSE activity (U/mg protein) was determined by the method of Xu *et al.*[25]

Urea, creatinine, Na, K, Cl, Ca levels, ALT, and AST activities were measured in blood serum using a Biochemistry Autoanalyser kit (Abbott C 16000). Blood antiplatelet activity was measured using the Chrono Log Antiplatelet Analyser 200 system using the ristocetin and Adenosine Diphosphate (ADP) kit.

Histological examinations

Tissue samples collected for histopathological examination were fixed in 10% formaldehyde. Routine tissue processing procedures were applied to the fixed tissues, and tissue samples were embedded in paraffin blocks. Sections of 5 µm thickness were cut from the prepared blocks. The Hematoxylin-Eosin (H-E) staining method was used for histological light microscopic evaluation. Sections were analyzed and photographed using a Leica Q Win image analysis system and a Leica DFC 280 light microscope. We examined kidney sections for inflammatory cell infiltration, glomerular degeneration, hemorrhage, vascular congestion,

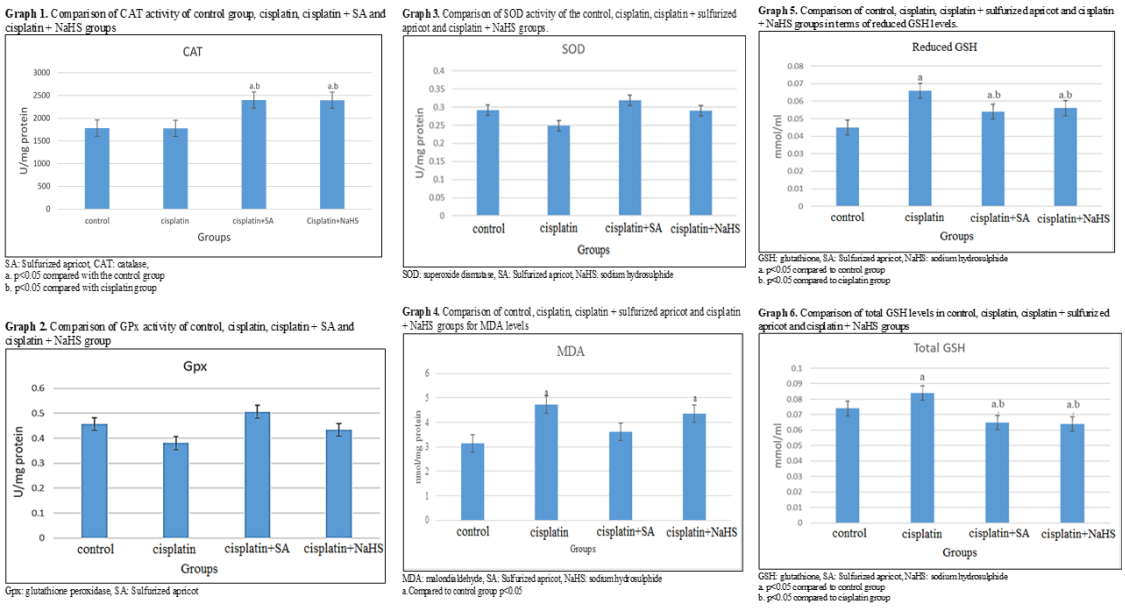


Figure 1: CAT, GPx, SOD activities, and MDA, Reduced GSH, Total GSH levels of the control, cisplatin, cisplatin+SA, and cisplatin+NaHS groups.

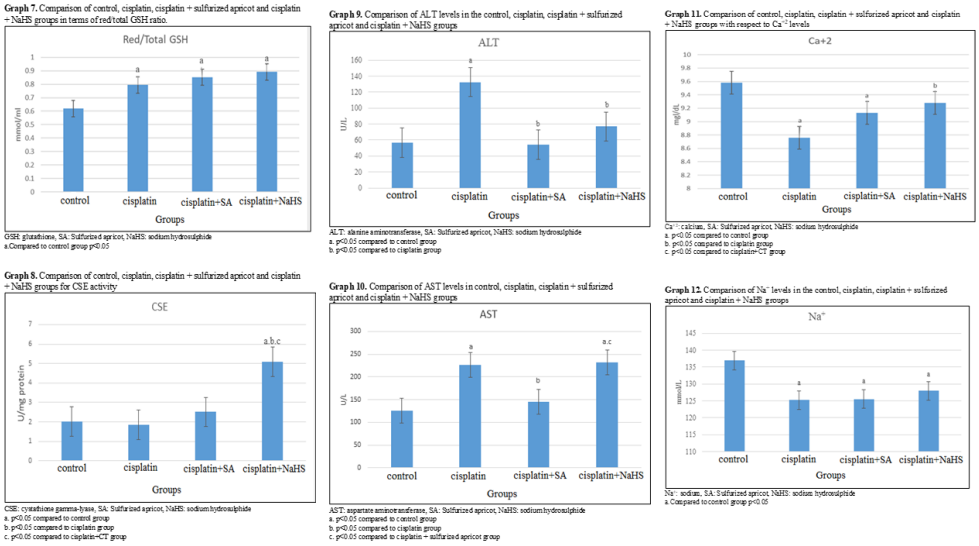


Figure 2: Red/Total GSH, CSE, ALT, AST, Ca^{+2}, and Na^{+} levels of the control, cisplatin, cisplatin+SA, and cisplatin+NaHS groups.

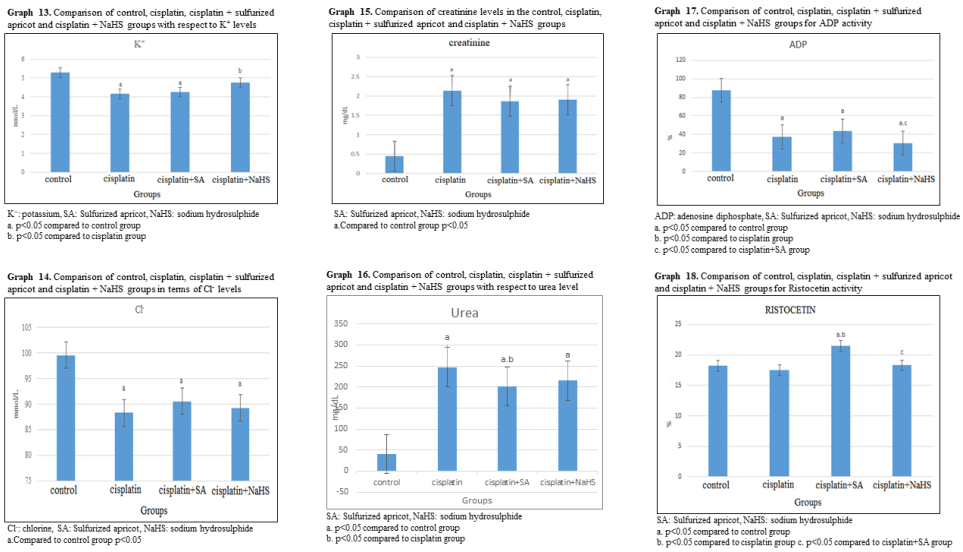


Figure 3: K^{+}, Cl^{-}, Creatinine, Urea, ADP, and Ristocetin levels of the control, cisplatin, cisplatin+SA, and cisplatin+NaHS groups.

Table 1: Averages and group comparisons of biochemical parameters.

Groups/Parameters	Control group	Cisplatin Group	Cisplatin+SA Group	Cisplatin+NaHS Group
	Mean±SE	Mean±SE	Mean±SE	Mean±SE
SOD	0.291±0.098	0.249±0.052	0.319±0.093	0.290±0.050
CAT	1783±652	1776±520	2397±643[a.b]	2396±321[a.b]
GPx	0.457±0.160	0.381±0.0870	0.506±0.195	0.434±0.213
MDA	3.155±1.193	4.720±1.101[a]	3.609±1.323	4.369±1.221[a]
Reduced GSH	0.045±0.004	0.066±0.010[a]	0.054±0.004[a,b]	0.056±0.003[a.b]
Total GSH	0.074±0.009	0.084±0.005[a]	0.065±0.011[a.b]	0.064±0.008[a.b]
Red/Total GSH	0.619±0.087	0.794±0.150[a]	0.852±0.118[a]	0.891±0.113[a]
CSE	2.013±0.913	1.859±0.696	2.514±1.400	5.094±0.911[a.b.c]

SA: Sulfurized apricot, SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase, MDA: Malondialdehyde, GSH: Glutathione, CSE: Cystathionine gamma-lyase.$p<0.05$ compared to control group.$p<0.05$ compared with cisplatin group.$p<0.05$ compared with cisplatin+SA group.

Table 2: Averages of biochemistry laboratory results and comparisons among the groups.

Groups/Parametetrs	Control group	Cisplatin Group	Cisplatin+SA Group	Cisplatin+NaHS Group
	Mean±SE	Mean±SE	Mean±SE	Mean±SE
ALT	56.60±7.84	132.5±60.02[a]	54.11±22.33[b]	76.87±29.18[b]
AST	125.6±11.65	225.88±60.76[a]	145±54.32[b]	231.62±49.04[a,c]
Ca	9.58±0.53	8.76±0.34[a]	9.13±0.37[a]	9.28±0.39[b]
Na	136.9±4.33	125.22±3.70[a]	125.5±5.61[a]	128±5.70[a]
K	5.28±0.55	4.15±0.65[a]	4.25±0.61[a]	4.76±0.424[b]
Cl	99.5±4.1	88.33±2.95[a]	90.55±5.98[a]	89.25±2.81[a]
Creatine	0.445±0.037	2.138±0.67[a]	1.86±0.50[a]	1.90±0.56[a]
Urea	39.94±4.76	247.2±56.38[a]	201.2±45.2[a,b]	215±65[a]

SA: Sulfurized apricot, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Ca: Calcium, Na: Sodium, K: Potassium, Cl: Chlorine.$p<0.05$ compared to control group.$p<0.05$ compared with cisplatin group.$p<0.05$ compared with cisplatin+SA group.

vacuolization of tubular epithelial cells, hemorrhage between the tubules, and epithelial atrophy, oedema between the tubules, and cell desquamation in the tubules and casts in the tubular lumen. Histopathologic damage score was calculated using these findings. Histopathologic damage score was calculated according to the degree of damage severity to 0 (none), 1 (mild), 2 (moderate), 3 (severe).

Statistical analysis

The one-sample Kolmogorov-Smirnov test was first used to test whether the data conformed to a normal distribution, and it was found that the data conformed to a normal distribution. The ANOVA test was used to compare groups of data that conformed to a normal distribution, and the LSD post hoc test was used to analyze which parameters belonged to which groups. All results are defined as mean±Standard Error (SE); $p<0.05$ values were considered statistically significant and presented in table and graphs. Statistical calculations were carried out using the SPSS 21.0 program package (SPSS Inc., Chicago, IL, USA).

The statistical analyses on the histological examinations were performed using SPSS 13 and MedCalc software. The means of all groups were compared using the non-parametric Kruskal-Wallis test. The significance of differences between groups was assessed by pairwise comparisons using the Mann-Whitney U test. All results are defined as mean±Standard Error (SE), and $p<0.0001$ values were considered statistically significant.

RESULTS

Biochemical Findings

CAT, GPx, SOD, and CSE activities and MDA, GSH, and total GSH levels were summarized in Figüres 1, 2 and Table 1. Serum urea, creatinine, ALT, AST, Na, K, Cl, and Ca levels were presented in Figures 2, 3, and Table 2, and antiplatelet activity was shown in Figure 3 and Table 3.

Results of oxidative stress parameters

When the results of CAT enzyme activity were analyzed in our study, no significant difference was observed between the control and cisplatin groups. However, a statistically significant increase was observed in the cisplatin+SA and cisplatin+NaHS groups compared to the control and cisplatin groups ($p<0.05$) (Table 1, Figure 1).

When GPx enzyme activity results were analyzed in our study, no statistically significant difference was observed between the groups (Table 1, Figure 1).

When the results of SOD enzyme activity were analyzed in our study, no statistically significant difference was observed between the groups (Table 1, Figure 1).

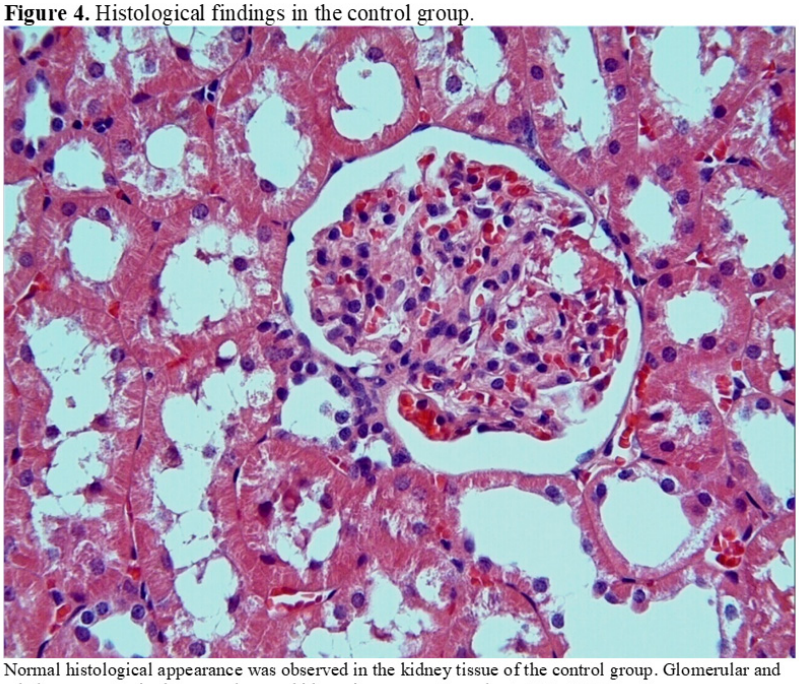
When the results of MDA levels were analyzed in our study, a statistically significant increase was observed in the results of the cisplatin and cisplatin+NaHS groups compared to the control group ($p<0.05$) (Table 1, Figure 1).

When the reduced GSH results were analyzed in our study, a statistically significant increase was observed in the results of the cisplatin, cisplatin+SA, and cisplatin+NaHS groups compared to the control group ($p<0.05$). In addition, a statistically significant decrease was observed in the results of the cisplatin+SA and cisplatin+NaHS groups compared to the cisplatin group ($p<0.05$) (Table 1, Figure 1).

When analyzing the total GSH results in our study, a statistically significant increase was observed in the results of the cisplatin group compared to the control group ($p<0.05$). In addition, a statistically significant decrease was observed in the cisplatin+SA and cisplatin+NaHS groups compared to the cisplatin group ($p<0.05$). In addition, a statistically significant decrease was observed in the cisplatin+SA and cisplatin+NaHS groups compared to the control group ($p<0.05$) (Table 1, Figure 1).

When the red/total GSH results were analyzed in our study, a statistically significant increase was observed in the results of the

Figure 4. Histological findings in the control group.



Normal histological appearance was observed in the kidney tissue of the control group. Glomerular and tubular structures in the control group kidney tissue were normal. A: H-E; X40.

Figure 4: Histological findings in the control group.

cisplatin, cisplatin+SA, and cisplatin+NaHS groups compared to the control group (p<0.05) (Table 1, Figure 2).

When the CSE enzyme activity results of our study were analyzed, a statistically significant increase was observed in the results of the cisplatin+NaHS group compared to the control, cisplatin, and cisplatin+ SA groups (p<0.05) (Table 1, Figure 2).

Results of the biochemical serum parameters

When analyzing the ALT level results in our study, a statistically significant increase was observed in the cisplatin group compared to the control group (p<0.05). In addition, a statistically significant decrease was observed in the cisplatin+SA and cisplatin+NaHS groups compared to the cisplatin group (p<0.05) (Table 2, Figure 2).

When analyzing the AST level results in our study, a statistically significant increase was observed in the cisplatin and cisplatin+NaHS groups compared to the control group (p<0.05). A statistically significant decrease was observed in the cisplatin+SA group compared to the cisplatin group (p<0.05) (Table 2, Figure 2).

When analyzing the Ca^{+2} level results of our study, a statistically significant decrease in Ca^{+2} level was observed in the cisplatin and cisplatin+SA groups compared to the control group (p<0.05). A statistically significant increase in Ca^{+2} levels was observed in the cisplatin+NaHS group compared to the cisplatin group (p<0.05) (Table 2, Figure 2).

When the Na^{+} level results of our study were analyzed, a statistically significant decrease in Na^{+} level was observed in the cisplatin, cisplatin+SA, and cisplatin+NaHS groups compared to the control group (p<0.05) (Table 2, Figure 2).

When the results of blood K^{+} levels were analyzed in our study, a statistically significant decrease in blood K^{+} levels was observed in the cisplatin and cisplatin+SA groups compared to the control group (p<0.05). In addition, a statistically significant increase in blood K^{+} levels was observed in the cisplatin+NaHS group compared to the cisplatin group (p<0.05) (Table 2, Figure 3).

When the results of blood Cl^{-} levels were analyzed in our study, a statistically significant decrease in Cl^{-} levels was observed in the Cisplatin, Cisplatin+SA, and Cisplatin+ NaHS groups compared to the control group (p<0.05) (Table 2, Figure 3).

When the results of blood creatinine level were analyzed in our study, a statistically significant increase in blood creatinine level was observed in the cisplatin, cisplatin+SA, and cisplatin+NaHS groups compared to the control group (p<0.05) (Table 2, Figure 3).

When the blood urea level results of our study were analyzed, a statistically significant increase in blood urea level was observed in the cisplatin, cisplatin+SA, and cisplatin+NaHS groups compared to the control group (p<0.05). In addition, a statistically significant decrease in blood urea was observed in the cisplatin+apricot group compared to the cisplatin group (p<0.05) (Table 2, Figure 3).

Results of antiplatelet activity

When the results of blood ADP activity were analyzed in our study, a statistically significant decrease in blood ADP activity

Table 3: Mean results of antithrombotic activity and comparisons among the groups.

Groups/Parameters	Control group	Cisplatin Group	Cisplatin+SA Group	Cisplatin+NaHS Group
	Mean±SE	Mean±SE	Mean±SE	Mean±SE
ADP	87.67±13.08	37.28±17.68[a]	43.48±9.53[a]	30.43±4.08[a,c]
RISTOCETIN	18.22±1.91	17.53±2.79	21.46±3.22[a,b]	18.28±1.86[c]

SA: Sulfurized apricot, ADP: adenosine diphosphate.$p<0.05$ compared to control group.$p<0.05$ compared with cisplatin group.$p<0.05$ compared with cisplatin+SA group.

was observed in the cisplatin, cisplatin+SA, and cisplatin+NaHS groups compared with the control group ($p<0.05$) (Table 3, Figure 3).

When the results of blood ristocetin activity were analyzed in our study, a statistically significant increase in ristocetin activity was observed in the cisplatin+SA group compared to both the control and cisplatin groups ($p<0.05$) (Table 3, Figure 3).

Histological findings

Light microscopic examination of kidney tissue samples from rats in the control group (Figure 4) showed normal histological structure. Glomerular and tubular structures were normal in the kidney tissue of the control group. In the cisplatin group, hemorrhages (Figures 5A, 5B, 5E), edema (Figure 5A), disruption of glomerular structure (Figures 5B, 5C), mononuclear cell infiltration (Figures 5B, 5C), vacuolization in the tubules (Figures 5D, 5E), accumulation of a substance in the tubule lumen (Figures 5D, 5E, 5F), and desquamation of tubule epithelial cells (Figure 5F) were observed. In the cisplatin+sulphurized apricot group (Figures 6A, 6B, 6C, 6D), histopathological damage in the renal tissue was significantly reduced. A small amount of hemorrhage (Figures 6B, 6C) and a small amount of mononuclear cell infiltration (Figures 6C, 6D) were observed. A decrease in histopathological damage in the renal tissue was observed in the cisplatin+NaHS group (Figures 7A, 7B, 7C, 7D), A small amount of hemorrhage (Figures 7A, 7B) and a small amount of mononuclear cell infiltration (Figures 7A, 7B, 7C) and vacuolization (Figure 7D) were observed. The microscopic damage score was determined for each group, and the results are shown in Table 4.

Table 4: Effects of SA and NaHS on cisplatin-induced renal injury (Mean±SE).

Groups	Histopathological score
Control	0.36±0.08[a]
Cisplatin	2.76±0.06[b]
Cisplatin+ SA	1.40±0.09[c]
Cisplatin+NaHS	1.83±0.10[d]

Small letters a, b, and c in the same column indicates differences between groups. ($p<0.0001$).

DISCUSSION

Cisplatin is widely used in the treatment of various types of cancer, including testicular, ovarian, head, neck, and lung cancers. Cisplatin primarily exerts its effect on living organisms by interacting with purine bases, thereby blocking DNA replication, transcription, and repair mechanisms, inhibiting tumor cell proliferation. On the other hand, cisplatin exhibits similar effects on healthy cells as well. As a result, the use of cisplatin inevitably leads to significant side effects. Among these, nephrotoxicity due to its tendency to accumulate in kidney tissue and bone marrow suppression are two of the most important side effects.[26,27] In this study, we utilized NaHS, a donor of H_2S, and sulfur apricot to counteract cisplatin-induced nephrotoxicity.

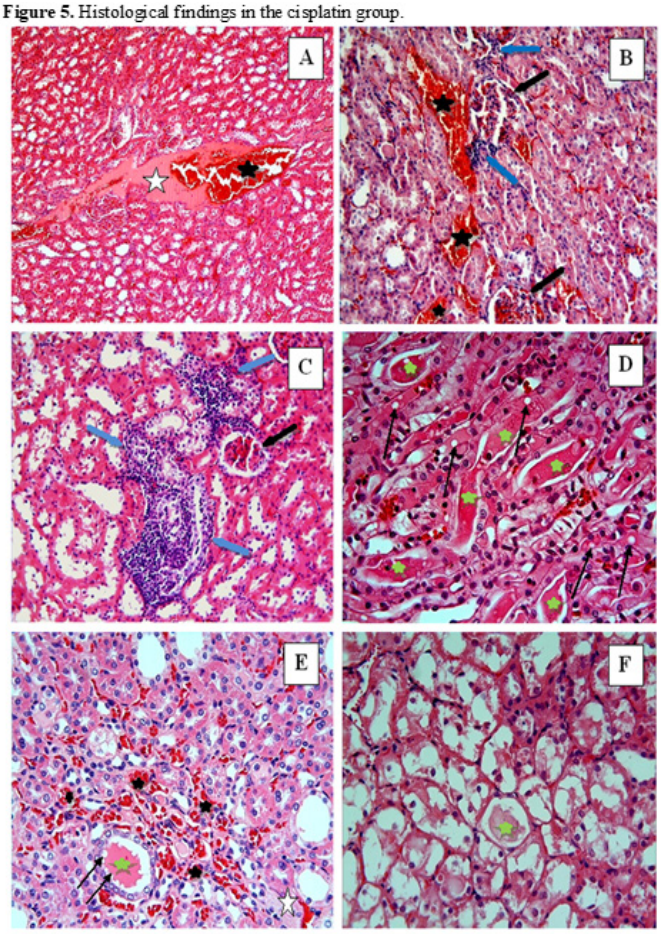
Apricot is a type of fruit that is grown mainly in the Malatya province of Turkey and has a geographical indication. Numerous studies have been conducted on apricots. These studies have identified trace elements, vitamins, polyphenols, and carotenoid derivatives as various bioactive compounds present in apricots, and it has been reported that these compounds provide protective effects against many diseases.[28] Recent publications in the literature have shown that the consumption of sulfur apricot increases the production of H_2S, a gasotransmitter described as a new type of signaling molecule, after nitric oxide and carbon monoxide, which is synthesized by three different enzyme systems in the body.[29,30] H_2S acts as an important signal molecule in cells and regulates many various biological functions. It has been reported that H_2S at low concentrations exhibits antioxidant, anti-inflammatory, antithrombotic, anti-apoptotic, and vasodilatory effects.[31] We chose sulfur apricot in our study to determine the protective effect that can be provided through H_2S. In this context, NaHS, a commonly used H_2S donor, was used as a positive control. Our literature search revealed a limited number of studies investigating the effects of H_2S in reducing the side effects of chemotherapeutic agents, but we found no studies using SA. Therefore, in this study, we aimed to evaluate whether sulfur apricot, whose sulfur content is within the limits permitted by the Turkish Food Codex, together with NaHS can prevent cisplatin-induced nephrotoxicity.

Sharma *et al.*, measured kidney tissue antioxidant system parameters (SOD, CAT, GPx, MDA) and DNA oxidation levels in rats treated with cisplatin. Cellular oxidant/antioxidant balance was disturbed in favor of oxidants, and *Exacum lawii* extract, which is given for protective purposes and is known to have antioxidant potential, significantly prevented this impairment.[32]

Ale *et al.*, investigated the renoprotective effects of *Cucumeropsis mannii* seed oil in cisplatin-induced nephrotoxicity in rats. The results of the study reported significant outcomes in the group receiving 5000 mg/kg of seed oil, showing increased enzyme activities of SOD, CAT, and GPx, as well as significant changes in MDA and GSH levels.[33] In a study where *Gymnema sylvestre* leaf extract was used against cisplatin-induced nephrotoxicity in rats, it was reported that the extract group showed significant results in SOD and CAT enzyme activities as well as MDA levels compared to the cisplatin group.[34] Two mechanisms are likely to be involved in preventing the nephrotoxic effects of cisplatin by antioxidants. The first is that some of these radicals, which increase in concentration in the cell as a result of cisplatin-induced reactive oxygen radical production, have an extremely short half-life and are highly reactive, are scavenged by antioxidant molecules, and their interaction with cellular macromolecules is prevented. The other possible mechanism is the inhibition by antioxidant molecules of the conversion of cisplatin into metabolites with a much more significant nephrotoxic effect. The enzyme GST catalyzes the first step in the metabolism of cisplatin to toxic metabolites, and glutathione-cisplatin conjugates are formed. In the next step, reactive cysteine thiols are formed by transpeptidases (GGT and APN) and cysteine S-conjugate beta-lyase.[35] Such free thiol-containing structures are primarily responsible for nephrotoxicity. As a first step, antioxidants and chelating agents containing free thiol groups can inhibit the conjugation of cisplatin with glutathione, blocking the process from the outset and reducing nephrotoxicity. As can be seen, how classical antioxidant biomolecules prevent cisplatin-induced nephrotoxicity is different from how H_2S acts. Although it has been suggested that H_2S has similar effects to antioxidant molecules, H_2S inhibits cellular pathways by preventing the phosphorylation of enzymes whose activity is regulated by covalent modification via persulphuration. The SA used in this study is expected to act as a potential H_2S donor because it contains many different types of biomolecules with antioxidant properties and because of its sulfur.

Lee H *et al.*, reported that cisplatin used for lung cancer showed severe hepatotoxic and nephrotoxic effects. The herbal mixture consisting of 8 species, including apricot fruit and seed extract coded PM014, significantly reduced these effects.[36] Eslamifar Z *et al.*, reported that cisplatin showed dose-dependent nephrotoxic effects in their study in rats, and the use of gallic acid showed significant protection against these effects. In their study, the investigators demonstrated renal damage by showing that blood creatinine and urea levels increased rapidly after cisplatin injection. They also demonstrated oxidative damage by similarly increasing renal tissue MDA levels and decreasing antioxidant enzyme levels.[37] Similarly, in our study, creatinine increased from 0.445±0.037 to 2.138±0.67 and urea increased from 39.94±4.76 to 247.2±56.38 after cisplatin injection, and electrolyte homeostasis was disturbed. In support of the biochemical findings, renal damage was also evident in the histological images. MDA, antioxidant enzymes, and CSE were the parameters that most dramatically demonstrated cisplatin-induced oxidative damage in renal tissue. MDA levels increased dramatically after cisplatin injection; this increase was significantly reversed in the SA group, but no improvement was achieved in the NaHS group. Levels of the antioxidant enzymes CAT, SOD, and GPx were also reduced by cisplatin injection, but this reduction could not be defined as significant in our statistical analyses. In the SA group, the decrease observed in all three enzymes was reversed, and activities above the control were obtained. In particular, CAT activity showed an increase of 74.09%. Similar to the effect of SA, a 74% increase in CAT activity was obtained in the NaHS group compared to the cisplatin group. While CSE activity showed a non-significant decrease in the cisplatin group and a similar increase in the SA group, a statistically significant and dramatic increase was observed in the NaHS group. This increase in the levels of cystathionine γ-lyase, one of the three main enzymes responsible for H_2S production, in the NaHS group suggests that NaHS may have acted as a substrate for this enzyme. NaHS is the most commonly used H_2S donor in experimental studies

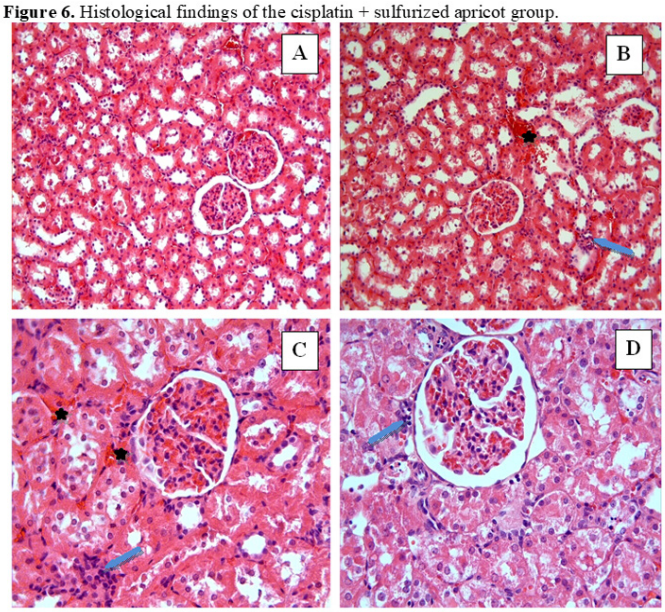
Figure 5. Histological findings in the cisplatin group.



In the cisplatin group, haemorrhage (black star) (A, B, E), oedema (white star) (A), disruption of glomerular structure (black arrows) (B, C), mononuclear cell infiltration (blue arrows) (B, C), vacuolization in tubules (thin black arrows) (D, E), accumulation of substance in the tubule lumen (D, E, F), shedding of tubule epithelial cells (F) were observed. A: H-E; X10, B, C: H-E; X20, D, E, F: H-E; X40.

Figure 5: Histological findings in the cisplatin group.

Figure 6. Histological findings of the cisplatin + sulfurized apricot group.



In the cisplatin + sulfurized apricot group (A, B, C, D), histopathological damage in the kidney tissue was significantly reduced. A small amount of haemorrhage (black stars) (B, C) and a small amount of mononuclear cell infiltration (blue arrows) (C, D) were observed. A, B: H-E; X20, C, D: H-E; X40.

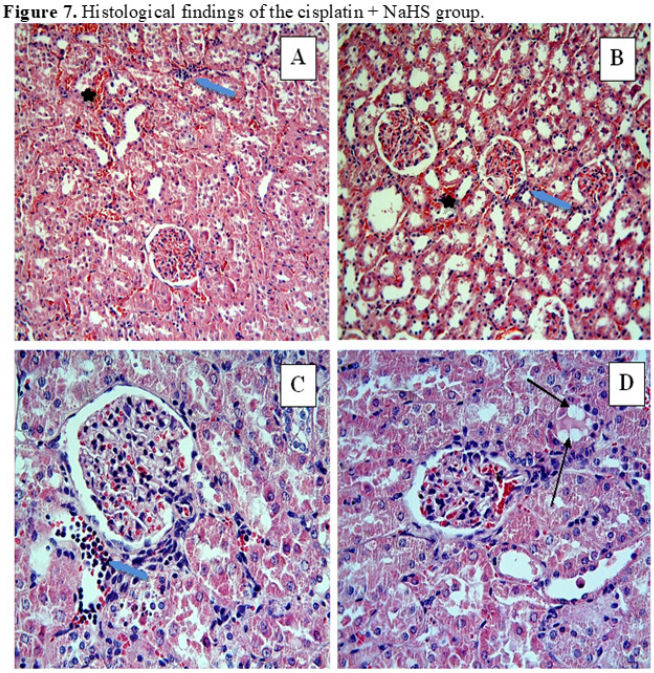
Figure 6: Histological findings of the cisplatin+SA group.

in the literature. Li N. *et al.*, reported that exogenous H_2S treatment after myocardial infarction increased the production and activity of all three enzymes responsible for endogenous H_2S production.[38] Our results show that SA provides better protection against cisplatin-induced kidney damage than the NaHS-treated group. While NaHS only contributes as an H_2S donor through the biochemical activity of H_2S, SA both increases H_2S production through the sulfur it contains and shows beneficial effects through the bioactive molecules in the composition of apricots. Another point to consider here is that while trying to minimize the side effects caused by cisplatin in the treatment processes carried out with the cisplatin regimen, care should be taken not to reduce the treatment efficacy of cisplatin. In particular, high concentrations of H_2S can interfere with the metabolism of cisplatin and thus interrupt the treatment process. The aim is to protect organs and tissues outside the tumor without reducing the effectiveness of the treatment, which is administered with highly sensitive dose adjustments. Another major handicap in cancer treatment is drug resistance, which develops over time. For many anticancer drugs, tumor cells can protect themselves from the cytotoxic effects of the drug by developing various defense mechanisms. Ma Y *et al.*, reported in their study of cisplatin-resistant lung cancer cells that the administration of cisplatin together with H_2S stopped tumor cell proliferation and significantly reduced cell density.[39] The researchers emphasized that these effects were mediated by activation of p53, increased caspase-3, p21, MMP-2, and Bax, and suppression of Bcl-xL.

Some drugs inhibit platelet activation, whereas others may stimulate aggregation.[40] Jafri and Prothero reported that cisplatin may cause direct endovascular damage through free radical-induced lipid peroxidation in endothelial cells. They reported that this may lead to platelet aggregation and intimal thickening.[41] Ma *et al.*, reported that platelet-derived particles increased with cisplatin treatment in patients with small-cell lung cancer.[42] Our results showed no statistically significant difference between the groups in ADP-induced platelet aggregation. However, we can say that aggregation occurred with ristocetin induction of platelet aggregation, and this aggregation formation was inhibited in the Pt-complex group compared to the control and was above the control in the SA group. Aggregation was induced by preventing inhibition in the NaHS group, which was equivalent to the control. Zagli *et al.*, reported that NaHS, the donor of H_2S, could inhibit platelet aggregation induced by ADP, epinephrine, thrombin, arachidonic acid, thromboxane, and collagen.[43] Nishikawa *et al.*, aimed to determine the platelet aggregation of NaHS using platelet-rich plasma and washed platelets in rabbits. It was reported that NaHS attenuated cytosolic Ca^{+2} mobilization induced by ADP or collagen in washed platelets and also reduced platelet aggregation induced by ionomycin, a Ca^{+2} ionophore. This effect of NaHS was reported to be inhibited by an adenylyl cyclase inhibitor and potentiated by a phosphodiesterase inhibitor. Thus, H_2S has been reported to suppress rabbit platelet aggregation by interfering with downstream and upstream signals of cAMP-dependent cytosolic Ca^{+2} mobilization.[44] Both studies provide results that are compatible with our findings.

In our study, the biochemical data we obtained are consistent with and support our histological findings. In the cisplatin group, tissue damage manifested as hemorrhage, edema, glomerular degeneration, mononuclear cell infiltration, and tubular vacuolization, whereas these findings were significantly less observed in the sulfur apricot and NaHS groups. Wen *et al.*, demonstrated that cisplatin treatment causes tubular cell

Figure 7. Histological findings of the cisplatin + NaHS group.



In the cisplatin + NaHS group (A, B, C, D), a decrease in histopathological damage in the renal tissue was observed. A small amount of haemorrhage (black stars) (A, B) and a small amount of mononuclear cell infiltration (blue arrows) (A, B, C) and vacuolization (thin black arrows) (D) were observed. A, B: H-E; X20, C, D: H-E; X40.

Figure 7: Histological findings of the cisplatin+NaHS group.

death, while Zhou *et al.*, showed that cisplatin induces edema, inflammation, and glomerular degeneration in kidney tissue through microscopic findings.[39,40] Numerous studies in the literature have reported similar findings.

CONCLUSION

Chemotherapeutic drugs used in cancer treatment cause serious side effects. These drugs exhibit cytotoxic effects by both inhibiting cell proliferation and interfering with the vital functions of the cell, resulting in adverse effects on multiple systems. Minimizing these effects can be considered one of the primary goals of cancer treatment. Cisplatin, a platinum complex, also has serious undesirable side effects, with nephrotoxicity being one of the prominent ones. Based on the data obtained from our study, it is suggested that consumption of apricots containing sulfur may be effective in reducing the nephrotoxic effects of cisplatin together with the beneficial effects of the antioxidant components they contain.

ACKNOWLEDGEMENT

We would like to thank Inonu University Scientific Research Projects Unit for financially supporting our study. We would also like to thank Inonu University Faculty of Pharmacy for their support in carrying out the experimental processes of the study.

ABBREVIATIONS

SA: Sulfurized Apricot; **H_2S:** Hydrogen sulfide; **NaHS:** Sodium Hydrosulphide; **ADP:** Adenosine diphosphate; **CSE:** Cystathione gamma-lyase; **CAT:** Catalase; **SOD:** Superoxide Dismutase; **GPx:** Glutathione Peroxidase; **GSH:** Glutathione; **MDA:** Malondialdehyde; **ALT:** Alanine Aminotransferase; **AST:** Aspartate aminotransferase; **GST:** Glutathione S-transferase; **GGT:** Gamma-glutamyl transferase; **APN:** Alanyl aminopeptidase.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships.

FUNDING

This study was supported by the Inonu University Scientific Research Projects Unit (project number TYL-2021/2561).

ETHICS STATEMENT

All animal experimental procedures were performed with the approval of the İnonu University Local Animal Ethics Committee (dated 17.12.2020 and number 2020/17-5).

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Cite this article: Celikoz N, Yilmaztaekin Y, Cankaya O, Taslidere A, Datli RH, Uyumlu AB, *et al*. Investigation of the Protective Effect of Hydrogen Sulphide Donor Sodium Hydrosulphide and Sulfurized Apricot on Experimental Acute Kıdney Injury Induced by Cisplatin in Rats. Indian J of Pharmaceutical Education and Research. 2026;60(1):410-20.