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Assessment of lycopene as a protective agent against nickel sulfate-induced toxicity in Wistar rats*

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Summary

Nickel sulfate ($NiSO_4$) is widely used in industrial processes and is a common environmental pollutant. Exposure to nickel sulfate has been associated with various adverse health effects, including hepatotoxicity, nephrotoxicity, and oxidative stress. In this study, 24 Wistar albino rats were divided into four groups: Group I received daily saline intraperitoneally (i.p.) and corn oil (0.5 mL, oral gavage); $NiSO_4$ (20 mg/kg, i.p.) was administered 2 hr after administration of corn oil in Group II; Group III received lycopene (10 mg/kg, oral gavage) suspended in corn oil, followed by $NiSO_4$ (20 mg/kg, i.p.) 2 hr later; Group IV received lycopene (10 mg/kg, oral gavage) suspended in corn oil. The findings demonstrated that lycopene did not affect the final body weight and organ weights of rats exposed to $NiSO_4$. Lycopene reduced malondialdehyde (MDA) levels, a key biomarker of lipid peroxidation, in liver and kidney tissues. On the other hand, it increased the levels of reduced glutathione (GSH) and catalase (CAT), while exerting no measurable effect on superoxide dismutase (SOD). The semi-quantitative assessment of liver and kidney tissues according to histopathological criteria revealed a statistically significant difference ($p < 0.001$) between the $NiSO_4$ group and the groups where lycopene was administered alongside $NiSO_4$ for protective purposes. As a result, the protective effect of lycopene against $NiSO_4$ toxicity was confirmed. The fact that nickel did not alter certain biochemical parameters suggests that this effect may depend on the dose of lycopene and the duration of its use.

Keywords: lycopene, nickel, protective effect, rat, toxicity

The increase in nickel levels in the biosphere has led to environmental pollution due to its extensive use in various industrial sectors, including automotive, energy, electrical-electronic, chemical, and medical equipment industries (15, 20). As a result of environmental pollution and contaminated dietary intake, humans and animals are exposed to nickel through the atmosphere, water, and soil (43).

Nickel has a detrimental impact on human and animal health, leading to lung and nasal cancer, kidney and cardiovascular diseases, allergic dermatitis, pulmonary fibrosis, and reproductive issues (6). Nickel has teratogenic, carcinogenic, genotoxic, and immunotoxic effects. Nickel nanoparticles have toxic effects on the liver, kidneys, nerve cells, and reproductive system due to cellular apoptosis, lipid peroxidation, protein oxidation, DNA damage, and oxidative stress (12, 13). Although its toxicity varies depending on the solubility of nickel compounds and the route of exposure, nickel accumulates primarily in the liver, kidney, bone, lung, heart, and testicular tissues (3, 28).

It has been stated that antioxidant substances ingested with food can prevent cytotoxicity mechanisms and oxidative stress by scavenging reactive oxygen species (ROS), and free radicals mediated by environmental pollutants (45, 47). Lycopene is an isomer of β-carotene found in red fruits and vegetables, which lack vitamin A activity and is synthesized by plants and some microorganisms. Lycopene has antioxidant, anti-inflammatory, antidiabetic, and anticancer properties (48). Lycopene inhibits lipid peroxidation by scavenging peroxyl radicals with low levels of oxygen (39).

This study aimed to evaluate the protective effect of lycopene against $NiSO_4$ toxicity in liver and kidney tissues, through biochemical, antioxidant, oxidative stress, and accumulation level analyses, as well as histopathological examination.

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Material and methods

Ethical statement. Approval was obtained from the Animal Experiments Local Ethics Committee of Harran University (Harran-HADYEK) (Decision No. 01-11 Date: 16/12/2021).

Test chemicals. $NiSO_4$ (Acros Organics, 270552500) and lycopene (Redivivo, DSM, 5003792004) were used in the study. In addition, oxidative stress and antioxidant analyses were performed by measuring MDA (SunRed, 201-11-0157), GSH (SunRed, 201-11-5137), SOD (SunRed, 201-11-0169), and CAT (SunRed, 201-11-5106) with commercial analytical kits.

Animals. Harran-HDAM Laboratory Animal Unit supplied 24 male rats aged six weeks (Wistar albino rats weighing 200-220 g). The rats were acclimated to laboratory conditions for 7 days at a temperature of 23 ± 2°C and humidity of 60-65%, on a 12-hour light/dark cycle. They were fed pellet feed and consumed water *ad libitum*.

Experimental design. The treatment protocols and doses were modified according to previous studies and are presented below.

Group I (Control Group) (n = 6): Rats in this group were administered physiological saline intraperitoneally (i.p.) and corn oil (0.5 mL) by oral gavage daily for 21 days (9).

Group II ($NiSO_4$ Group) (n = 6): Two hours after the administration of corn oil (0.5 mL) by oral gavage, $NiSO_4$ (20 mg/kg, c.a., daily, i.p.) was dissolved in physiological saline solution and administered for 21 days (16, 34, 41).

Group III (Lycopene Group) (n = 6): Lycopene was suspended in corn oil (0.5 mL) and administered by oral gavage at a dose of 10 mg/kg for 21 days (42).

Group IV (Lycopene + $NiSO_4$ Group) (n = 6): Lycopene was suspended in corn oil (0.5 mL) and administered by oral gavage at a dose of 10 mg/kg, and 2 hours later, $NiSO_4$ (20 mg/kg, c.a., daily, i.p.) was administered for 21 days.

The animals were weighed at the beginning and end of the experiment, and their weights were recorded. At the end of the experiment (day 22), approximately 2 mL of blood was drawn intracardially from the rats into blood serum gel separator tubes, and the animals were euthanised by decapitation without anaesthesia. Blood samples were centrifuged at 3000 rpm for 10 min, and the sera obtained were stored at –80°C until they were analysed. At necropsy, liver and kidney tissues were excised, placed in an ice-cold isotonic solution (pH 7.4), and weighed. Then, some of the liver and kidney tissues were excised and stored at –80°C until they were analysed.

Liver and kidney function parameters. The levels of ALT, AST, ALP, LDL-C, total protein, total cholesterol, urea, uric acid, creatine, and albumin in serum were determined spectrophotometrically using an autoanalyser (Siemens Healthineers Atellica) with commercial diagnostic kits (Siemens).

Oxidative stress and antioxidant analyses. Tissue samples of 200 mg were weighed with a precision balance (Precisa, 262SMA-FR, UK) and placed in Eppendorf tubes, to which 2 mL of cold PBS was added. They were disintegrated in a homogeniser (Qiagen tissuelyser LT, 85600, Netherlands) at 50 rpm for 20 min and then cold centrifuged at 12000 rpm for 10 min (25). The supernatants were put into other Eppendorf tubes. The protein content of liver and kidney tissue samples was measured in an autoanalyser (Siemens Healthineers Atellica) with a protein test kit (Siemens) after homogenisation. Analyses were carried out according to the kit protocols.

Biochemical analyses were run to determine MDA, GSH, SOD, and CAT levels in liver and kidney tissues (30). The level of MDA was identified as nmol/mg protein using a commercial assay kit according to a method used by Placer et al. (33). The level of GSH was identified as µg/mg protein using a commercial assay kit according to a method used by Sedlak et al. (37). The level of SOD was identified as U/mg protein using a commercial assay kit according to a principle described by Sun et al. (40). The level of CAT was identified as U/mg protein using a commercial assay kit based on a method used by Aebi (4).

Inductively coupled plasma-mass spectrometry analysis. ICP-MS (Agilent Technologies, 7700X, USA) was used to examine nickel concentration in tissues. The samples were pre-treated and gradually incinerated in a microwave oven as described by Ütme et al. (44). The amount of nickel in tissues was determined by the EPA 6020 method with Agilent 5188-6525-coded standard one ppm internal standard samples. The amount of nickel in the tissues was measured three times, and the results were determined based on the average values obtained from these measurements. The limit of quantification (LOQ), limit of detection (LOD), and repeatability (R) values (ppb) were set at 0.051975, 0.01575, and 1.0000 for nickel, respectively.

Histopathological analysis. Liver and kidney tissues were fixed in a 10% buffered formaldehyde solution. Paraffin blocks were subjected to a routine tissue follow-up, sectioned on 4 µm thick slides, and stained with Haematoxylin & Eosin (H&E). Histopathological criteria used for semi-quantitative evaluation included reticular and vascular degeneration, necrosis, dissociation, and inflammatory cell infiltration in the cytoplasm of hepatocytes in the liver as well as atrophy, reticular and vascular degeneration, necrosis in glomeruli and tubules in the kidney. Microscopic analysis of the tissues under a light microscope evaluated the lesions semi-quantitatively as none (0), mild (+), moderate (++), or severe (+++) in terms of histopathologic criteria (18, 49). Furthermore, areas with lesions meeting these criteria were counted in five randomly selected fields within a × 10 objective field, and semi-quantitative statistical analysis was carried out to compare the groups.

Statistical analysis. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. One-way analysis of variance (ANOVA) was used to evaluate differences between the groups for the normally distributed parameters and Kruskal-Wallis analysis was used for parameters that were not normally distributed. Intergroup pairwise comparisons were made with Duncan's test. The SPSS 21 software was used in statistical analyses, and differences between mean values for the groups were considered statistically significant at the level of $p < 0.05$. The parameters are presented in the tables as mean ± standard deviation (SD).

Results and discussion

Body and organ weight. Table 1 shows the initial and final weights of the animals in the control and experimental groups, as well as their liver and kidney weights. At the end of the experiment, the liver and kidney weights were highest in the lycopene group, followed by the control group, the lycopene + $NiSO_4$ group, and the $NiSO_4$ group. The liver and kidney weights of the $NiSO_4$ groups decreased compared to the control group ($p < 0.001$). The difference in liver and kidney weights between the lycopene + $NiSO_4$ group and the $NiSO_4$ group was not statistically significant ($p > 0.05$).

Serum liver and kidney function parameters. Table 2 shows the results of serum liver and kidney function tests for the animals in the control and experimental groups. The increase in the amounts of AST, ALT, ALP, and total cholesterol in the $NiSO_4$ group was statistically significant compared to the control group ($p < 0.001$). The decrease in total protein levels in the $NiSO_4$ group was statistically significant compared to the control group ($p < 0.001$). The difference in AST and ALT levels when lycopene was used against $NiSO_4$ toxicity was not statistically significant. However, the difference in ALP levels was statistically significant ($p < 0.001$). The difference between total cholesterol levels in the lycopene group and the $NiSO_4$ group was statistically significant ($p < 0.001$). The difference between the $NiSO_4$ group and the lycopene + $NiSO_4$ group in terms of protein amount was significant ($p < 0.001$). The increase in the amounts of uric acid, urea, creatine, and albumin in the $NiSO_4$ group compared to the control group was statistically significant ($p < 0.001$). The difference in the amount of uric acid, urea, and albumin between the lycopene + $NiSO_4$ group

Tab. 1. Body and organ weight (g) of control and experimental groups

Groups	Control	$NiSO_4$	Lycopene	Lycopene + $NiSO_4$	p
Initial weight	205.50 ± 10.65^{ab}	200.66 ± 5.88^{ab}	209.00 ± 12.31^{a}	192.33 ± 16.26^{b}	$p > 0.05$
Final weight	281.66 ± 12.9^{b}	238.16 ± 6.55^{c}	309.66 ± 18.73^{a}	243.16 ± 5.87^{c}	***
Liver organ weight	12.13 ± 0.62^{b}	10.32 ± 1.13^{c}	14.13 ± 1.51^{a}	10.40 ± 0.54^{c}	***
Kidneyorgan weight	3.2 ± 0.25^{b}	2.66 ± 0.15^{c}	3.47 ± 0.21^{a}	2.74 ± 0.07^{c}	***

Explanations: Mean ± Std. deviation; no significant difference was found between the groups $p > 0.05$, *** $p < 0.001$; a, b, c – indicate intergroup differences in the same row

Tab. 2. Serum liver and kidney function tests of control and experimental groups

Groups	Control	$NiSO_4$	Lycopene	Lycopene + $NiSO_4$	p
AST IU/L	66.16 ± 1.16^{b}	125.50 ± 3.67^{a}	65.83 ± 2.63^{b}	125.33 ± 4.63^{a}	***
ALT IU/L	34.16 ± 1.47^{b}	52.00 ± 1.78^{a}	35.33 ± 1.96^{b}	51.83 ± 3.12^{a}	***
ALP IU/L	104.66 ± 2.16^{d}	157.50 ± 5.71^{a}	113.50 ± 1.87^{c}	151.00 ± 2.89^{b}	***
Total Cholesterol mg/dL	57.83 ± 3.97^{c}	103.00 ± 1.41^{a}	58.83 ± 7.35^{c}	74.83 ± 3.54^{b}	***
Total Protein g/dL	6.43 ± 0.37^{a}	3.51 ± 0.35^{d}	5.73 ± 0.34^{b}	5.28 ± 0.40^{c}	***
Uric acid mg/dL	1.61 ± 0.51^{b}	4.75 ± 0.21^{a}	1.60 ± 0.70^{b}	2.18 ± 0.32^{b}	***
Urea mg/dL	22.66 ± 0.81^{c}	35.33 ± 1.50^{a}	30.33 ± 5.27^{b}	31.33 ± 1.96^{b}	***
Creatine mg/dL	0.45 ± 0.09^{b}	1.35 ± 0.03^{a}	0.36 ± 0.05^{c}	1.29 ± 0.05^{a}	***
Albumin mg/dL	20.40 ± 1.35^{c}	31.65 ± 2.12^{a}	20.40 ± 0.97^{c}	24.00 ± 1.05^{b}	***

Explanations: Mean ± Std. deviation; *** $p < 0.001$; a, b, c, d – indicate intergroup differences in the same row

Tab. 3. Liver and kidney MDA (nmol/mg protein), GSH (µg/mg protein), SOD (U/mg protein) and CAT (U/mg protein) levels of control and experimental groups

Tissue	Groups	Control	$NiSO_4$	Lycopene	Lycopene + $NiSO_4$	p
Liver	MDA	39.77 ± 6.52^{b}	78.1 ± 12.00^{a}	39.00 ± 3.3^{b}	43.97 ± 2.63^{b}	***
	GSH	21.46 ± 1.88^{b}	17.83 ± 0.95^{c}	25.43 ± 1.20^{a}	23.19 ± 2.25^{b}	***
	SOD	7.53 ± 0.65^{a}	5.96 ± 0.38^{b}	7.77 ± 1.20^{a}	6.36 ± 0.55^{b}	***
	CAT	88.30 ± 7.01^{a}	55.70 ± 3.93^{b}	86.74 ± 14.78^{a}	86.51 ± 6.95^{a}	***
Kidney	MDA	0.52 ± 0.10^{c}	0.73 ± 0.06^{a}	0.41 ± 0.04^{d}	0.62 ± 0.05^{b}	***
	GSH	2.89 ± 0.70^{a}	1.71 ± 0.08^{c}	3.00 ± 0.14^{a}	2.30 ± 0.10^{b}	***
	SOD	12.61 ± 1.04^{b}	8.78 ± 0.70^{c}	13.70 ± 0.61^{a}	9.25 ± 0.77^{c}	***
	CAT	5.86 ± 0.76^{b}	4.82 ± 0.38^{c}	6.68 ± 0.38^{a}	5.78 ± 0.63^{b}	***

Explanations: Mean ± Std. deviation; *** $p < 0.001$; a, b, c, d – indicate intergroup differences in the same row

and the $NiSO_4$ group was significant ($p < 0.001$). No statistically significant effect of protective lycopene on creatine levels against nickel toxicity was found ($p > 0.05$).

Oxidative stress and antioxidant analysis in liver and kidney tissues. Table 3 shows the levels of MDA, GSH, SOD, and CAT in the liver and kidney tissues of the animals in the control and experimental groups. In the lycopene-treated group, the level of MDA was lower than it was in the $NiSO_4$ group ($p < 0.001$). In the lycopene group, the levels of GSH and CAT were elevated ($p < 0.001$ and $p < 0.001$, respectively) and the level of SOD was similar compared to those in the $NiSO_4$ group.

The level of nickel accumulation in tissues. Table 4 shows the level of nickel accumulation in liver and kidney tissues. It was determined that nickel accumulation in liver and kidney tissues increased in the $NiSO_4$ group compared to the control group ($p < 0.001$). Nickel accumulation in liver tissues increased and was statistically similar in the $NiSO_4$ and Lycopene + $NiSO_4$ groups. Nickel accumulation in kidney tissues increased in the $NiSO_4$ and lycopene + $NiSO_4$ groups, and the difference between the groups was statistically significant ($p < 0.001$).

Histopathological findings. Table 5 and Figure 1 and 2 show the results of the histopathological examination and semi-quantitative analysis of the liver and kidney tissues in which areas with lesions were counted in five randomly selected fields within a × 10 objective field. No significant difference was seen between the control and lycopene groups in the histopathological examination. However, in the semi-quantitative evaluation of the liver and kidney tissues according to histopathological criteria, the difference between the $NiSO_4$ and lycopene + $NiSO_4$ groups was statistically significant ($p < 0.001$).

Adeyemi et al. (2) observe that assessing organ and body weight is a valuable method for evaluating exposure to toxic substances. Previous studies have documented a decrease in the final live weight of rats subjected to high doses of nickel because of a reduction in both water and feed intake (15, 17, 24). This study confirms the toxicity of nickel, as evidenced by a significant decrease in the final live weight, as well as reductions in liver and kidney weights observed in the groups exposed to nickel. Mahmoud et al. (27) reported that a significant loss in body weight due to low food intake and lower protein levels was noted in a nickel group. A recent study on nickel by Adeyemi et al. (2) associated this effect with various mechanisms, such as ROS production,

Tab. 4. Nickel accumulation level in liver and kidney dry mass tissues of control and experimental groups ICP-MS (ppb)

Groups	Control	$NiSO_4$	Lycopene	Lycopene + $NiSO_4$	p
Liver	28.36 ± 1.18^b	510.63 ± 13.79^a	26.99 ± 4.10^b	530.00 ± 48.72^a	***
Kidney	60.67 ± 4.61^c	5036.79 ± 362.80^b	70.21 ± 11.50^c	5593.43 ± 808.14^a	***

Explanations: Mean ± Std. deviation; *** $p < 0.001$; a, b, c – indicate intergroup differences in the same row

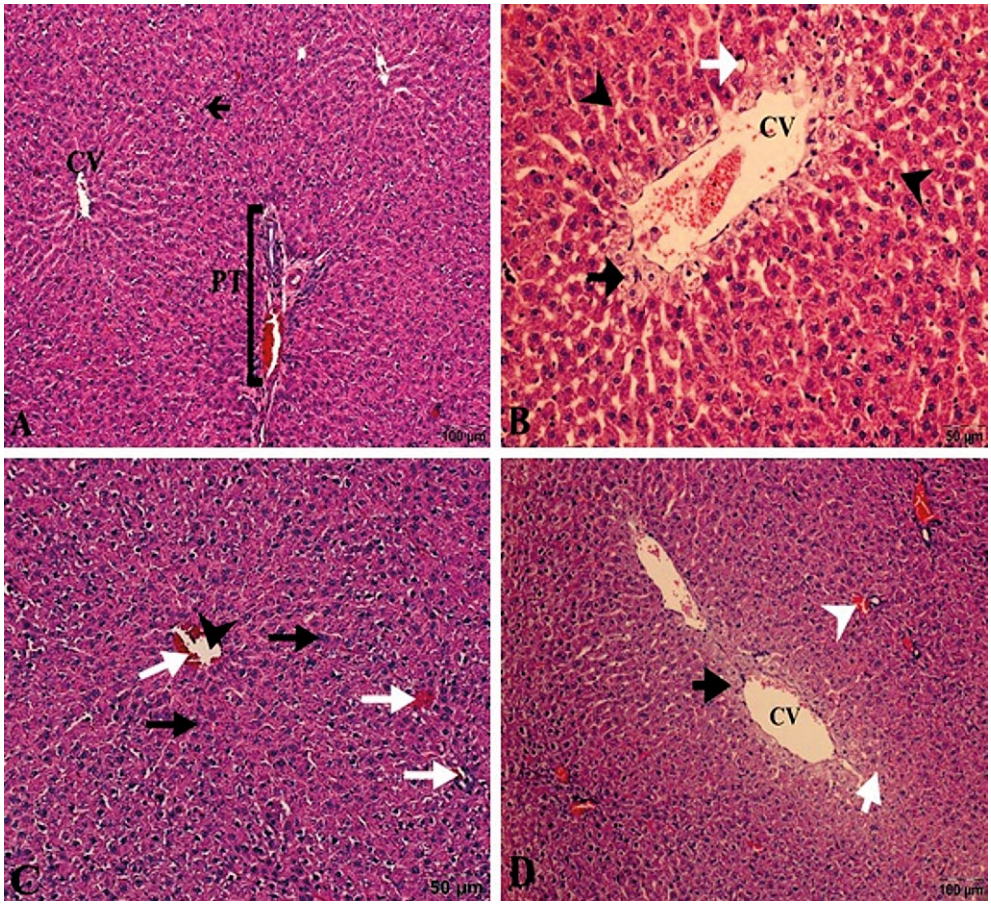

Fig. 1. Histopathological image of liver tissue
Explanations: A – Histopathological image of liver tissue in the control group, CV – central vein, PT – portal tract, black arrow: normal hepatocyte, H&E, × 10; B – Histopathological image of liver tissue in the $NiSO_4$ group, CV – central vein, black arrow: reticular degeneration, white arrow: vacuolar degeneration, arrowhead: necrotic hepatocyte, H&E, × 20; C – Histopathological image of liver tissue in the lycopene group, black arrowhead: vena centralis, black arrow: normal hepatocyte, white arrow: hyperaemic vessels, H&E, × 20; D – Histopathological image of liver tissue in the lycopene + $NiSO_4$ group, black arrow: reticular degeneration, white arrow: vacuolar degeneration, white arrowhead: hyperaemia, H&E, × 10

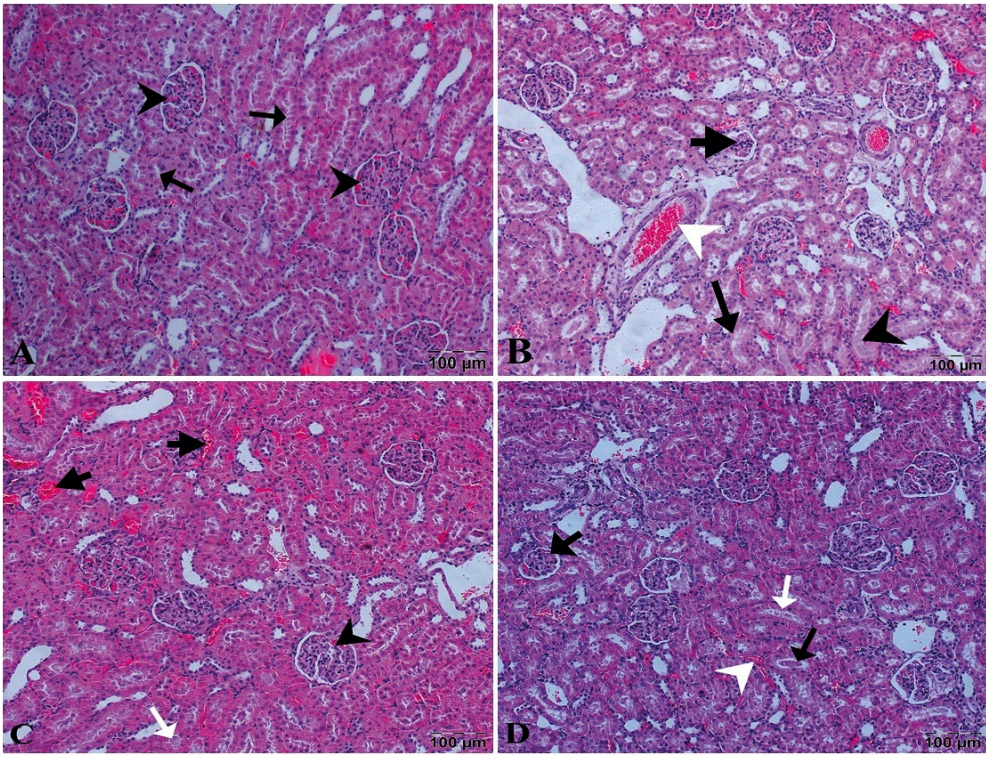

Fig. 2. Histopathological image of kidney tissue
Explanations: A – Histopathological image of kidney tissue in the control group; black arrowhead: normal glomerulus; black arrow: normal tubule; H&E, × 10; B – Histopathological image of kidney tissue in the $NiSO_4$ group, thick black arrow: atrophic glomerulus, black arrow: necrotic tubule epithelium, black arrowhead: hyaline cylinder, white arrowhead: hyperaemic vessels, H&E, × 10; C – Histopathological image of kidney tissue in the lycopene group; black arrowhead: normal glomerulus; white arrow: hyaline cylinder; black arrow: hyperaemic vessels; H&E, × 10; D – Histopathological image of liver tissue in the lycopene + $NiSO_4$ group; Vc – vena centralis, SC.; black arrow: reticular degeneration; white arrow: vacuolar degeneration; white arrowhead: hyperaemia, H&E, × 10

Tab. 5. Semi-quantitative evaluation of lesioned areas in liver and kidney tissues in control and experimental groups

Groups	Control	$NiSO_4$	Lycopene	Lycopene + $NiSO_4$	p
Liver	0 ± 0^c	9.83 ± 0.70^a	0.33 ± 0.21^c	4.33 ± 0.55^b	***
Kidney	0 ± 0^c	8.50 ± 0.42^a	0.16 ± 0.16^c	4.16 ± 0.60^b	***

Explanations: Mean ± Std. deviation; *** $p < 0.001$; a, b, c – indicate intergroup differences in the same row

cytotoxicity, oxidative stress, and apoptosis (31). The present study also found that $NiSO_4$ caused a reduction in liver and kidney weights and final live weights ($p < 0.001$) in the $NiSO_4$ groups, which is compatible with other studies. In their study, Çavuşoglu et al. (8) determined that a positive control (lycopene 20 mg/kg) group of albino mice had the highest body weight among groups receiving different doses of lycopene (5, 10, 15, and 20 mg/kg by oral gavage for 20 days) against mercury-induced toxicity. Ramadan et al. (35) observed that lycopene administered at different doses (10, 15, and 20 mg/kg by oral gavage for 14 days) to albino mice against arsenic-induced nephrotoxicity increased their live weight depending on the dose. However, the increase in live weight for the 10 mg/kg dose was statistically insignificant. Similarly, the present study revealed no statistically significant difference in the final body weight, liver weight, and kidney weight in the lycopene + $NiSO_4$ group, which may be attributed to the oxidative stress produced by $NiSO_4$, the dose of lycopene, and the duration of its use. Serum biochemical markers are mostly used when monitoring the nephrotoxicity and hepatotoxic effects caused by chemical substances in the liver and kidneys (50). Some liver studies report that while nickel elevated the levels of ALT, AST, ALP, and total cholesterol, it reduced the amount of total proteins ($p < 0.001$) (1, 26). According to Das et al. (14), nickel caused cellular death and functional losses by competing with calcium inside cells, producing free radicals, causing lipid peroxidation, and damaging the bio-membrane integrity. They also concluded that the decreased body weight in nickel-treated groups was caused by the increased degeneration of proteins and lipids (7). This finding is confirmed by the fact that body weight decreased with reduced protein amounts in the present study. Pari et al. (32) reported that $NiSO_4$ administered to Wistar albino rats (20 mg/kg, for 20 days, i.p.) elevated their levels of AST, ALT, and ALP as well as the amount of bilirubin and the levels of total cholesterol, which may be attributed to hepatic dysfunction. In the present study, vacuolar degeneration, hyperaemia, and cell infiltrations, which were observed in the histopathological analysis, were consistent with the elevated serum biochemical markers. The elevated levels of AST, ALT, ALP, and total cholesterol combined with the reduced amount of total protein ($p < 0.001$) in the $NiSO_4$ groups are compatible with other studies. The present study revealed that lycopene did not change the levels of AST and ALT among serum liver parameters, but reduced the levels of ALP and total cholesterol as well as increased the levels of total protein. The failure of lycopene to change the levels of AST and ALT may be associated with the synthesis of AST and ALT enzymes in many organs and tissues, including the heart, skeletal muscle, and liver. Das et al. (13) found that nickel affected

many tissues, including the liver, kidney, bone, lung, heart, and testis. The present study showed that total cholesterol levels dropped in the lycopene + $NiSO_4$ group ($p < 0.001$). Wang et al. (46) offer valuable insights on the antioxidant and nutraceutical potential of lycopene in combating obesity. According to their study, lycopene demonstrated efficacy in reducing body weight gain through various mechanisms, which position it as a promising agent for addressing obesity-related concerns. Dahdouh et al. (10) reported that there was a significant increase in the levels of serum uric acid, urea, and creatinine in mice receiving $NiSO_4$ (2.7 mg/kg for four weeks, orally), and the amount of uric acid increased, since pyrimidines and purines were degraded and not excreted. The elevated levels of urea, uric acid, creatine, and albumin in the $NiSO_4$ groups in the present study were consistent with other studies. Ramadan et al. (35) observed that lycopene administered at different doses of (10, 15, 20 mg/kg by oral gavage for 14 days) to albino mice reduced their serum levels of urea and creatine and could be used as a promising drug against arsenic-induced nephrotoxicity. In the present study, lycopene reduced the levels of uric acid, urea, and albumin among renal parameters, but did not change creatinine levels. In the lycopene group, the decrease in urea, which is secreted following the breakdown of proteins in the liver, was confirmed by the decrease in histopathological findings in the semi-quantitative analysis of the kidney. Uric acid is the end product of purine metabolism. Therefore, the reduction in uric acid levels in the lycopene group given as a preservative is thought to be due to the DNA-protective and oxidative stress-reducing effects of lycopene (23). The present study suggests that lycopene did not significantly lower creatinine levels, which may be attributed to elevated nickel accumulation in the kidney and a decrease in the glomerular filtration rate after lycopene penetrated the renal epithelium and consequently impaired renal function.

The mechanism of nickel toxicity at the molecular level is not yet fully understood, but it is believed to be related to oxidative stress. Nickel may increase the amount of free radicals and reduce activities of antioxidant enzymes by consuming them through direct binding of the metal to the active site of the enzyme (20).

Many studies on experimental animals found that in groups to which $NiSO_4$ (20 mg/kg, for 20 days, i.p.) was administered, lipid peroxidation levels in liver and kidney tissue increased, whereas the levels of GSH, SOD, and CAT decreased due to ROS production (19, 26). Consistent with other studies on nickel, the present study showed that the level of MDA in the liver and kidney tissues of rats from the $NiSO_4$ groups increased, while the levels of GSH, SOD, and CAT decreased. Ramadan et al. (35) found that the administration of different doses of lycopene (10, 15, and 20 mg/kg by oral gavage for 14 days) against nephrotoxicity induced by arsenic protected albino mice against oxidative stress by reducing lipid peroxidation and increasing antioxidant enzymes (GSH, CAT, and SOD) in kidney tissue in a dose-dependent manner. A study conducted by Rencuzogullari et al. (36) on Wistar albino rats indicates that lycopene (10 mg/kg, 20 days, oral gavage) may alleviate damage caused by cadmium by reducing renal MDA levels. Dai et al. (11) determined that the administration of different doses of lycopene (5 and 20 mg/kg for 7 days) against nephrotoxicity induced by colistin increased the levels of SOD, CAT, and GSH, alleviated oxidative stress, and was effective, especially at the 20 mg/kg dose, according to histopathological findings. The same study revealed that lycopene at a dose of 5 mg/kg did not change the level of SOD, but increased the levels of GSH and CAT. In the present study, the administration of lycopene to the $NiSO_4$ group for protective purposes decreased the level of MDA and increased the levels of GSH and CAT in the kidney tissue, but did not change the level of SOD, which may have been related to the dose of lycopene.

In a study conducted by Pari et al. (31), nickel concentration in the liver tissue of Wistar rats from a $NiSO_4$ group (20 mg/kg, for 20 days, i.p.) amounted to 400000-500000 ppb. The present study revealed that the nickel concentration in the livers of rats from the $NiSO_4$ group was 510.63 ± 13.79 ppb. Kadi et al. (22) reported that the accumulation of nickel in the kidney tissue of mice to which $NiCl_2$ was administered i.p. at 3, 5, and 10 mg/kg for 1 day amounted to 3 mg/kg, 4000 ppb; 5 mg/kg, 4000-5000 ppb; and 10 mg/kg, 6000-8000 ppb, respectively. In the present study, the accumulation of nickel in the kidneys of the $NiSO_4$ group was 5036.79 ± 362.80 ppb. The reason for this difference in accumulation levels are believed to be the differences in methods used in the analyses, as well as the dose and route of administration of nickel. Nwokocha et al. (29) reported that the addition of 10% tomato extract – a source of lycopene – to the feed of rats drinking water containing lead, mercury, and cadmium provided more protection against cadmium and mercury toxicity and less protection against lead toxicity in liver tissue. They concluded that tomato extract may reduce heavy metal toxicity because of its ability to synthesise metal-chelating proteins and its antioxidant and anti-inflammatory properties. Hernayanti et al. (21) determined that the addition of 1.08 mg/kg tomato extract as a lycopene source to the feed of rats lowered their blood cadmium levels. In the present study, lycopene did not cause a statistically significant change in nickel accumulation in liver tissue. Ramadan et al. (35) reported that the administration of different doses of lycopene (10, 15, 20 mg/kg by oral gavage for 14 days) against nephrotoxicity

induced by arsenic in albino mice reduced arsenic accumulation in kidney tissue in a dose-dependent manner. Bouhalit et al. (7) found that the level of lipid peroxidation increased in Wistar albino rats receiving $NiSO_4$ (20 mg/kg, 21 days, i.p.). They also suggested that nickel accumulated in kidneys mainly because of their richness in metallothionein, a metal-binding protein with a high nickel affinity, and that kidneys produced ROS through Haber-Weiss and Fenton's reaction. Agarwal et al. (5), reported that lycopene accumulated in human kidneys at 0.15-0.62 nmol/g. The present study suggests that the accumulation of nickel increased upon the administration of lycopene to the $NiSO_4$ group for protective purposes, which may be caused by the fact that lycopene penetrates the epithelium of kidneys, and the excretion of nickel is reduced by impaired renal function. Various toxicity studies using different sources of lycopene have also shown that lycopene may affect the accumulation of metals in the liver depending on the type of metal.

In their study on albino Wistar rats, Derbal et al. (17) correlated biochemical parameters with histopathological changes, such as vacuolisation, inflammation, and necrosis, due to the administration of $NiSO_4$ (800 mg/L orally for 21 days). Other studies are compatible with the histopathological findings of the liver analysis in the $NiSO_4$ group in the present study. Çavuşoglu et al. (8) concluded that the administration of different doses of lycopene (5, 10, 15, and 20 mg/kg by oral gavage for 20 days) against mercury-induced cytotoxicity in albino mice reduced histopathological changes in the kidneys and liver, especially at doses of 15 and 20 mg/kg, because of its antioxidant potential. In the present study, the semi-quantitative analysis of liver and kidney tissues according to histopathological criteria confirmed the protective effect of lycopene, which is compatible with other studies.

In conclusion, the protective effect of lycopene against $NiSO_4$-induced toxicity was demonstrated. The importance of lycopene in the diet of patients with various chronic diseases, such as type 2 diabetes mellitus, obesity, cancer, as well as cardiovascular and neurodegenerative diseases, has been demonstrated. The fact that lycopene given as a protective against nickel toxicity did not cause changes in some biochemical parameters suggests that nickel has an effect on more than one organ and that it may be dependent on the dose and duration of lycopene application. It is important to investigate hepatoprotective and renoprotective antioxidants to prevent the adverse effects of heavy metals and chemicals on liver and kidney tissues. Further molecular and clinical studies are needed to determine the potential protective effect of lycopene against drug or xenobiotic toxicity, especially at the cellular level, and its effect on cell signalling pathways.

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