Received: 20 November 2020 | Accepted: 8 May 2021

DOI: 10.1002/bab.2198

ORIGINAL ARTICLE

WILEY

Examination of the effect of curcumin in experimental liver damage created by diethylnitrosamine in Swiss albino mice to superoxide dismutase and catalase activities and glutathione, malondialdehyde, and advanced oxidation protein products levels

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Abstract

In this study, the effects of curcumin, glutathione (GSH), malondialdehyde (MDA) levels, advanced protein oxidation products (AOPP), superoxide dismutase (SOD), and catalase (CAT) activities in experimental liver damage with diethylnitrosamine (DEN) in Swiss albino mice were investigated. The subjects ($n = 9$) used in the study were divided into 5 groups as tumor control 1, tumor control 2, curcumin protective, curcumin treatment and healthy control groups Curcumin oral gavage (in 150 mg/kg of ethylalcohol) was given to the protecting group for 19 days, 5 days before the administration of DEN, and 24 h after the administration of DEN. Hundred microliters of ethylalcohol oral gavage was given to the healthy group for 19 days. While MDA levels decreased significantly in the curcumin preservative group ($p < 0.05$), ($p = 0.002$), the decrease was not significant in the treatment groups ($p > 0.05$), ($p = 0.128$). AOPP levels decreased significantly in the curcumin protective group ($p < 0.05$), ($p = 0.009$) but the decrease in the treatment group was not found significant ($p > 0.05$), ($p = 0.073$). SOD activities increased significantly in both groups. It was found as ($p < 0.05$), ($p = 0.001$) and ($p < 0.05$), ($p = 0.002$), respectively. GSH levels decreased but these reductions were not found statistically significant. CAT activities increased significantly in both groups. It was determined as ($p < 0.05$), ($p = 0.001$) for both groups.

KEYWORDS
advanced protein oxidation products, curcumin, diethylnitrosamine, liver damage, malondialdehyde

1 | INTRODUCTION

The substances that prevent and delay the oxidation of biomolecules such as protein, lipid, carbohydrate, and

List of Abbreviations: GSH, glutathione; MDA, malondialdehyde; AOPP, advanced protein oxidation products; SOD, superoxide dismutase; CAT, catalase; DEN, diethylnitrosamine; DZM, dizyem

DNA in the organism are called antioxidants, and this event is called antioxidant defense.[1] Antioxidants prevent the formation of active oxygen in the organism or the active oxygen that is formed, and thus prevent cell damage.[2]

Antioxidants are classified as enzymatic (superoxide dismutase [SOD], glutathione peroxidase [GPx], catalase [CAT], glutathione S-transferase [GST]) and nonenzymatic (glutathione [GSH], vitamin E, vitamin C, vitamin A, melatonin) according to molecular structures. Reactive oxygen types (ROS) occur when oxygen is incremented during biochemical reactions in the organism and cause damage to many tissues in living things. They are called "free radical." After all, they have a radical structure or "oxidant substance" because they cause oxidative destruction.[3] "Oxidative stress" occurs as a result of the disruption of the oxidative balance between the formation of free radicals and the rate of neutralization in the organism. As a result of oxidative stress, tissue damage occurs in living things.[4]

Oxidative stress also occurs in many pathological conditions such as diabetes, Alzheimer's, kidney failure, in old age,[5] and intense exposure to biological oxidant substances such as pesticides, drugs, and radiation. Free radicals are associated with the pathology of more than 50 diseases in humans.[6]

Reactive oxygen types are divided into two groups as radical and nonradical ones. Superoxide radical (O_2-·), hydroxyl radical (OH·), peroxy radical (L2O·), alkoxy radical (LO·), and hydroperoxy radical (HO_2·) are radical reactive oxygen species (ROS). Reactive oxygen radicals and oxidative stress have been demonstrated by studies conducted to be associated with carcinogenesis. It has been suggested that free radicals are effective in the tumor development process.[6,7]

DNA damage plays an active role in carcinogenesis and is known to cause single-strand DNA damage and cause strand breaks with various modifications, especially oxidation. Oxidative damage occurring in DNA leads to the formation of DNA–protein cross-links and modifications in purine–pyrimidine bases.[8]

An oxidant environment is known to increase tumor growth. Oxidants have been shown to stimulate cell proliferation, active oxygen radicals, and reactive aldehydes and peroxides that are formed are associated with tumor development by causing damage to genes that control the growth and differentiation of specific cells.[9,10,11] It is known that antioxidant enzyme activities increase with an adaptive mechanism in cases where oxidant stress increases such as cancer.[12]

Turmeric (*Curcuma longa*), a perennial herbaceous plant that belongs to the ginger family, is widely grown in southern and southeast tropical Asia. It is the active ingredient of curcumin and constitutes 2%–5% of the spice. Curcumin, which was first isolated by Vogel in 1842, has an orange-yellow crystal structure that is almost insoluble in water. In 1910, many studies show that curcumin is also a powerful anticancer agent and reveals that the skin, mammary gland, mouth, esophagus, stomach, intestine, colon, lung, and liver suppress tumor. It has been stated that curcumin has an anticancergenic effect on different tumors with a wide variety of mechanisms. A variety of suppressing inflammation inhibit cell proliferation, suppress certain oncogenes, suppress transcription factor NF-κB, inhibit the COX-2 enzyme, inhibit tumor implantation, activate the biotransformation of carcinogens, and activate the GST enzyme. It has been revealed with studies.[13,14]

Highlights

- The significant CAT activities were found in both the curcumin protective group and the curcumin treatment group
- AOPP values decreased in curcumin protective group
- MDA levels decreased significantly in the curcumin protective group

Diethylnitrosamine (DEN) is a carcinogenic substance; it is reported that it is formed from insecticides, pesticides, and nitrates found in cigarette smoke, and is formed as a result of the reaction of nitrate with secondary and tertiary amines in the stomach. Also found in alcoholic beverages and processed meat products, DEN may occur during the metabolism of therapeutic drugs in the liver.[15] DEN, which causes hepatic carcinoma, has been reported to cause oxidative damage by increasing 8-OH 2′ deoxyguanosine (8-OhdG). The amount of 8-OhdG increases 6 h after the administration of DEN. The relationship between lipid peroxidation, which is responsible for tumor formation, and DEN activation, and environmental radicals has been shown.[8]

DEN also induces inflammation through oxidative stress. Free radicals produced by DEN lead to NF-κB activation. Activation of NF-κB in liver macrophages called hepatocytes and Kupffer cells results in different effects.[10,16]

2 | MATERIALS AND METHOD

In this study, liver tissues of patients and control groups were used as material. GSH, malondialdehyde (MDA),

TABLE 1 Method

Groups	DEN (diethylnitrosamine)	Ethyl alcohol	Curcumin	Days	Number of mice
1	150 mg/kg (single dose)	100 μl (oral gavage)	–	19	9
2	150 mg/kg (single dose)	100 μl (oral gavage)	–	14	9
3	150 mg/kg (single dose)	–	150 mg/kg (dissolved in 100 μl of ethyl alcohol and the form of oral gavage)	19	9
4	150 mg/kg (single dose)	–	150 mg/kg (dissolved in 100 μl of ethyl alcohol and the form of oral gavage)	14	9
5	–	100 μl (oral gavage)		19	9

TABLE 2 Statistical results of all groups

Groups	MDA nmol/g tissue	AOPP nmol/mg prot.	SOD unit/mg prot.	GSH nmol/g tissue	CAT (U/gHb) $\times 10^4$
1	47.45 ± 9.58	207.84 ± 16.46	8.33 ± 1.12	0.010 ± 0.003	12.05 ± 3.09
2	44.91 ± 6.95	214.67 ± 1.66	7.42 ± 1.66	0.008 ± 0.003	10.2 ± 0.79
3	32.04 ± 4.92	184.57 ± 12.12	17.29 ± 1.96	0.009 ± 0.002	20.75 ± 2.57
4	37.99 ± 7.65	189.91 ± 19.01	11.75 ± 1.26	0.009 ± 0.002	22.1 ± 2.12
5	41.94 ± 6.77	190.66 ± 14.37	10.29 ± 1.54	0.013 ± 0.006	17.03 ± 2.92

advanced oxidation protein products (AOPP) levels, SOD, and CAT activities were examined in tissue and serum samples.

In the study, Swiss albino rats were arranged to have five groups in each group. Mice were obtained from the Experimental Medicine Research and Application Center (ÇÜTF-DETAUM) of Cukurova University Medical Faculty.

3 | METHOD

Of the Swiss albino rats that we divided into five groups. Mice in group 1 were given intraperitoneally, with a single dose of 150 mg/kg. Besides, 100 μl of ethyl alcohol oral gavage was given for 19 days (Table 1).

Mice in group 2 were given 100 μl of ethyl alcohol oral gavage 5 days before the administration of DEN intraperitoneally with a single dose of 150 mg/kg. At the end of the day, DEN was administered and 100 μl of ethyl alcohol oral gavage was given for the remaining 15 days (Table 1).

Mice in group 3 were dissolved in 100 μl of ethyl alcohol for 19 days, and 100 g/kg of curcumin was given, starting 5 days before a single dose of 150 mg/kg DEN intraperitoneally (Table 1).

Mice in group 4 were dissolved in 100 μl of ethyl alcohol, 14 days, 100 mg/kg of curcumin, starting 5 days after intraperitoneal administration of a single dose of 150 mg/kg DEN and oral gavage was given (Table 1).

The mice in group 5 were accepted as the control group, and 100 μl of ethyl alcohol oral gavage was given to these mice daily, apart from their daily food (Table 1).

4 | RESULTS

4.1 | Liver tissue MDA levels

When the damage control 1 group and healthy control group were compared (Table 2), an increase in MDA levels was observed, but this increase was not statistically significant ($p > 0.05$), ($p = 0.481$).

When the damage control group 2 and healthy control group were compared, an increase in MDA levels was observed, but this increase was not statistically significant ($p > 0.05$), ($p = 0.470$).

When the damage control group 1 and curcumin protective group were compared, it was observed that the MDA level decreased statistically ($p < 0.05$), ($p = 0.002$).

When the damage control group 2 and curcumin treatment group were compared, a decrease in MDA levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.128$).

When the curcumin protective group and healthy control group were compared, a statistically significant decrease in MDA levels was found ($p < 0.05$), ($p = 0.012$).

When curcumin treatment group and healthy control group were compared, a decrease in MDA levels was

found, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.295$).

4.2 | Liver tissue advanced protein oxidation levels

When the damage control 1 group and healthy control group were compared (Table 2), an increase in AOPP levels was observed, but this increase was not statistically significant ($p > 0.05$), ($p = 0.114$).

When the damage control group 2 and healthy control group were compared, a statistically significant increase in AOPP levels was observed ($p < 0.05$), ($p = 0.012$).

When the damage control group 1 and curcumin protective group were compared, it was observed that the AOPP level decreased statistically ($p < 0.05$), ($p = 0.009$).

When the damage control group 2 and curcumin treatment group were compared, a decrease in AOPP levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.073$).

When the curcumin protective group and healthy control group were compared, a decrease in AOPP levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.252$).

When curcumin treatment group and healthy control group were compared, a decrease in AOPP levels was found, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.837$).

4.3 | Liver tissue SOD activity

When the damage control 1 group and healthy control group were compared (Table 2), a statistically significant decrease in SOD levels was observed ($p < 0.05$), ($p = 0.011$).

When the damage control group 2 and healthy control group were compared, a statistically significant decrease in SOD levels was observed ($p < 0.05$), ($p = 0.004$).

When the damage control group 1 and curcumin protective group were compared, it was observed that the SOD level increased statistically significantly ($p < 0.05$), ($p = 0.001$).

When the damage control group 2 and curcumin treatment group were compared, it was observed that the SOD level increased statistically significantly ($p < 0.05$), ($p = 0.002$).

When the curcumin protective group and healthy control group were compared, a statistically significant increase in SOD levels was found ($p < 0.05$), ($p = 0.002$).

When the curcumin treatment group and healthy control group were compared, a statistically significant increase in SOD levels was found ($p < 0.05$), ($p = 0.001$).

4.4 | Liver tissue GSH levels

When the damage control 1 group and healthy control group were compared (Table 2), a decrease in GSH levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.481$).

When the damage control group 2 and healthy control group were compared, a decrease in GSH levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.370$).

When the damage control group 1 and curcumin protective group were compared, a decrease in GSH levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.279$).

When the damage control group 2 and curcumin treatment group were compared, a decrease in GSH levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.442$).

When curcumin protective group and healthy control group were compared, a decrease in GSH levels was observed, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.174$).

When curcumin treatment group and healthy control group were compared, a decrease in GSH levels was found, but this decrease was not statistically significant ($p > 0.05$), ($p = 0.470$).

4.5 | Liver tissue CAT activities

When the damage control 1 group and healthy control group were compared (Table 2), a statistically significant decrease was observed in CAT activities ($p < 0.05$), ($p = 0.002$).

When the damage control group 2 and healthy control group were compared, a statistically significant decrease was observed in CAT activities ($p < 0.05$), ($p = 0.023$).

When the damage control group 1 and curcumin protective group were compared, CAT activity was observed to increase statistically significantly ($p < 0.05$), ($p = 0.001$).

When the damage control group 2 and curcumin treatment group were compared, it was observed that CAT activity increased statistically significantly ($p < 0.05$), ($p = 0.002$).

When the curcumin protective group and healthy control group were compared, a statistically significant increase in CAT activity was found ($p < 0.05$), ($p = 0.023$).

When the curcumin treatment group and healthy control group were compared, a statistically significant increase was found in CAT activity ($p < 0.05$), ($p = 0.002$).

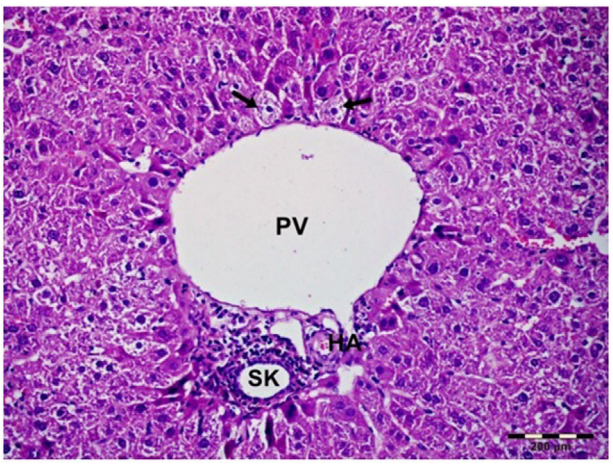

FIGURE 1 Group 1, light microscopic results

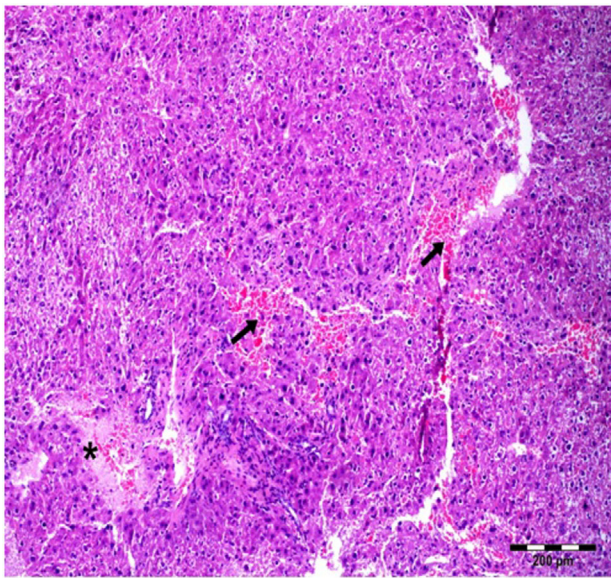

FIGURE 2 Group 2, light microscopic results

5 | LIGHT MICROSCOPIC RESULTS

5.1 | Group 1

In the histopathological examination of the liver sections belonging to the first group of subjects with an experimental liver injury with one dzm DEN, as a result of the hepatotoxic effect of DEN, single-cell necrosis characterized by balloon degeneration and pycnotic nucleus was observed in some of the hepatocytes that formed the parenchyma. It was noted that the central vein and portal triad maintain their integrity, but in the sinusoidal spaces in the periacinar and periportal areas, polymorphonuclear leukocyte infiltration occurs (Figure 1).

5.2 | Group 2

Liver fibrosis following severe tissue necrosis was observed in the histopathological examination of the liver sections belonging to the experimental liver injury with two dzm DEN. Forming the liver lobule, it was noted that the central vein and portal triad structures lost their integrity; however, many hepatocyte nuclei became picnotic and balloon degeneration severity increased. Also, it was determined that the amount of parenchymal connective tissue increased and severe lymphocyte infiltration occurred with sinusoidal congestion and hemorrhage (Figure 2).

5.3 | Group 3

In the histopathological examination of the liver sections belonging to the third group of subjects investigating the protective effect of 150 mg/kg curcumin against experimental liver damage caused by DEN, it was determined that the central vein and portal triad structures maintain integrity, and sinusoidal congestion and hemorrhage decrease, but lymphocyte infiltration continues to some extent. However, hepatocytes with a pyknotic nuclei were observed in places (Figure 3).

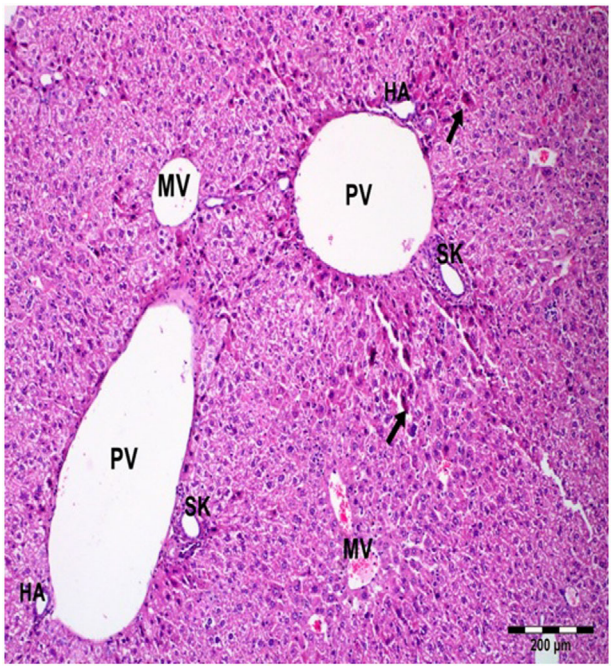

FIGURE 3 Group 3, light microscopic results

5.4 | Group 4

In the histopathological examination of liver sections belonging to the fourth group of subjects investigating the therapeutic effect of 150 mg/kg curcumin against

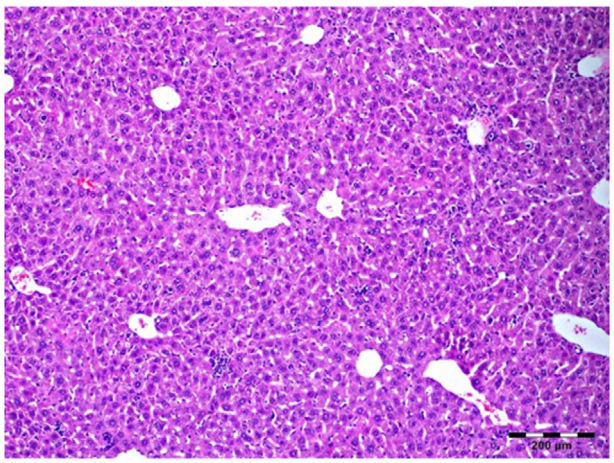

FIGURE 4 Group 4, light microscopic results

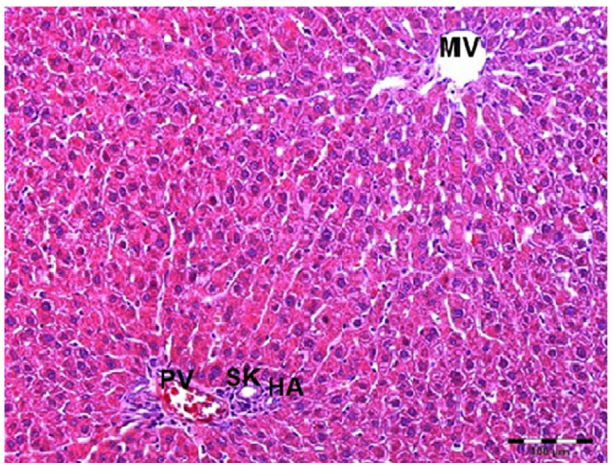

FIGURE 5 Group 5, light microscopic results

experimental liver damage caused by DEN, the central vein, portal triad, and hepatocyte cords that make up the liver lobule structure were determined to be similar to the control group. Reduced lymphocyte infiltration and hepatocytes with balloon degeneration with pycnotic nucleus were observed. Sinusoids open up to central veins as in the control group and congestion or hemorrhage was not observed (Figure 4).

5.5 | Group 5: control group

In the histological examination of the liver tissues belonging to the control group, hepatocyte cords consisting of polygonal-shaped hepatocytes extending radially toward the central vein and the periphery of the lobule in the center of the classical liver lobule were in normal appearance. Hepatocyte nuclei were of a vesicular type and even their nuclei could be distinguished. Sinusoids extending between the hepatocyte cords were opening to the central vein. Portal areas at the corners of the normal hepatic lobule contain portal vein, hepatic artery, and bile duct (Figure 5).

6 | ELECTRON MICROSCOPIC RESULTS

6.1 | Group 1

In the electron microscopic examination of the liver sections of the first group subjects who had an experimental liver injury with one dzm DEN, irregularities in hepatocyte nuclear membranes and increased electron density in the cytoplasm were observed. Besides, increased lipid droplets in hepatocyte cytoplasms attracted attention. Mitochondria were observed to be in normal appearance (Figure 6).

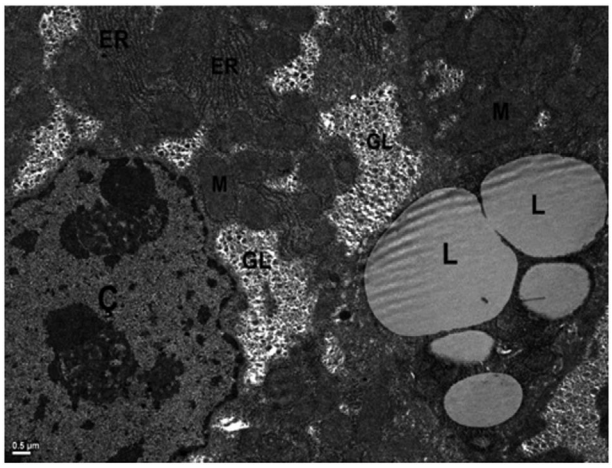

FIGURE 6 Group 1, electron microscopic results

6.2 | Group 2

In the electron microscopic examination of the liver sections of the second group subjects which had experiment a liver damage with 2 dzm Diethylnitrosamine; shrinkage and electron density in hepatocytenuclei, vacuolization in hepatocytecytoplasms were observed. In addition, apart from an increase in huge fat droplets in the cytoplasm, a significant decrease in glycogen particles was also observed (Figure 7).

6.3 | Group 3

In the electron microscopic examination of the liver sections of the third group of subjects investigating the protective effect of 150 mg/kg curcumin against experimental liver damage caused by DEN, it was noted that hepatocyte nucleus and cytoplasm were generally similar to control.

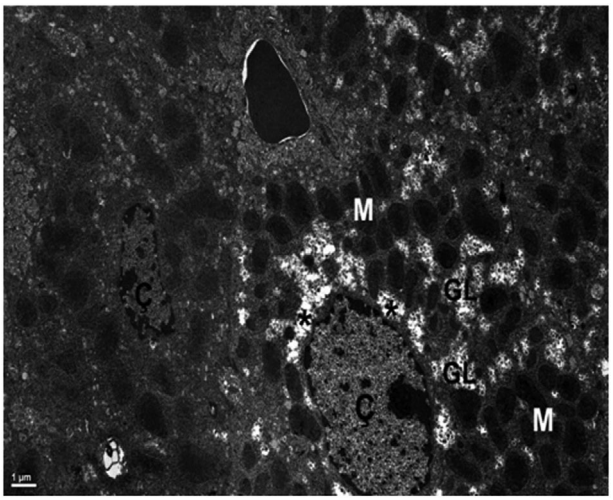

FIGURE 7 Group 2, electron microscopic results

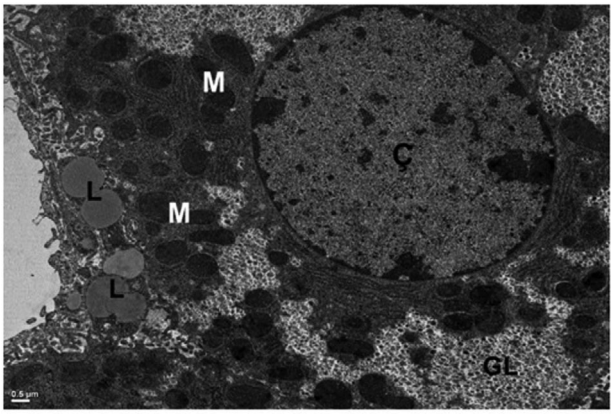

FIGURE 8 Group 3, electron microscopic results

As a protective effect of curcumin against cytoplasm liver damage, it was noted that the cytoplasm electron density has decreased, an increase in glycogen particles, and mitochondria have a normal appearance. However, it has been determined that increased lipid droplets remain (Figure 8).

6.4 | Group 4

In the electron microscopic examination of the liver sections of the fourth group of subjects who investigated the therapeutic effect of 150 mg/kg curcumin against experimental liver damage caused by DEN, hepatocytes with nuclei and cytoplasmic contents similar to the control group were seen. It has been observed that giant lipid droplets in the cytoplasms are reduced, and electron density and canalicular structures are in normal appearance (Figure 9).

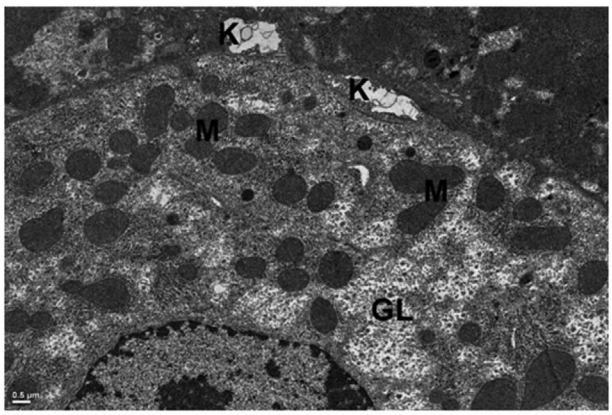

FIGURE 9 Group 4, electron microscopic results

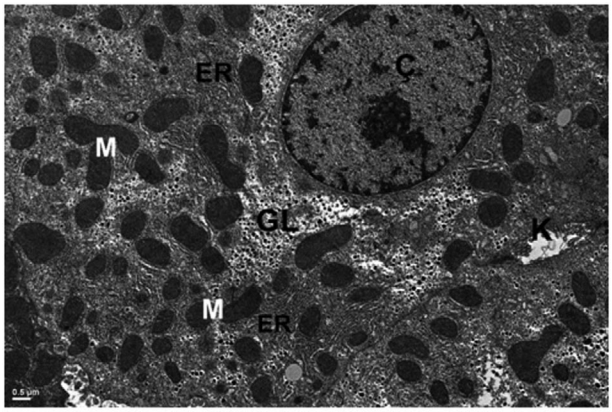

FIGURE 10 Group 5, electron microscopic results

6.5 | Group 5: control group

In electron microscopic examination of liver tissues belonging to the control group, it was observed that hepatocyte nuclei and cytoplasms were in normal morphology. In the cytoplasm of hepatocytes, there were many electron-dense mitochondria, granular endoplasmic reticulum, and glycogen particles. Between the basolateral faces of neighboring hepatocytes, canaliculus formed by plasma membranes were observed. Between the hepatocyte cords and sinusoidal capillary endothelial cells, there is a perisinusoidal space known as dissection space (Figure 10).

7 | DISCUSSION

Reactive oxygen species are produced as a result of metabolic and physiological events in the organism and harmful oxidative reactions may occur. Today, many researchers are investigating oxidative damage caused by

free radicals on DNA, proteins, lipids, and other components of the cell.

Free radicals are mutagenic and can act as mediators of phenotypic and genotypic changes. Carcinogenesis is a multistage condition that occurs following more than one mutation.[8] It is known that antioxidant enzyme activities increase with an adaptive mechanism in cases where oxidant stress increases, such as cancer.

It is not yet clear how the liver, which has a strong antioxidant defense mechanism in limiting free radical damage, has been defeated in this regard. While oxidative stress increases MDA and AOPP levels, SOD and GSH decrease.

In recent years, studies on the anticarcinogenic properties of curcumin have increased. Curcumin is a powerful antioxidant, anti-inflammatory, inhibiting carcinogen DNA damage, and tumor genesis, and has been shown on animal models by experiments.[13]. Curcumin is thought to suppress tumor genesis in cancer types such as skin, mammary gland, mouth, esophagus, stomach, intestine, colon, lung, and liver. While explaining the anticancer mechanism of action on different types of tumors, it has been suggested that one of these can occur by inhibiting TNF-dependent NF-$_K$B and COX-2, and by activating GST.

Thus, curcumin cell proliferation can suppress tumor invasion and angiogenesis while promoting apoptosis of tumor cells.

Our study aimed to examine the effect of curcumin on oxidative stress parameters and determine the effect of the time to start curcumin treatment besides determining its effect on liver damage. For this reason, apart from the control group, four different groups were selected ($n = 9$) and DEN was applied to the mice in group 1; in parallel, the curcumin was dissolved in ethyl alcohol and given as an oral gavage, provided that it was started 5 days before the administration of DEN to the mice in group 3. Feature has been checked. Again, mice in group 2 were given DEN, and in parallel, mice in group 4 were given oral gavage by dissolving curcumin in ethyl alcohol 24 h after the DEN application, and therapeutic properties were observed.

When we look at the MDA, AOPP, SOD, GSH, and CAT values of these two groups, it was determined that curcumin intake was much more effective before giving DEN to the body. While oxidative stress increases MDA and AOPP levels, SOD and GSH decrease. In parallel, when we look at the mice in groups 1 and 2, where the DEN application was performed, MDA values increased compared with the mice in the control group.

When the liver MDA levels of mice in the curcumin-treated group (3 and 4) were analyzed, it was found that this decrease was significantly more effective in the third group, which was the protective group ($p < 0.05$), ($p = 0.002$). In group 4, which is the treatment group, MDA levels decreased but it was not found statistically significant.

Superoxide dismutase is an antioxidant metalloproteinase that catalyzes the conversion of anion radicals to hydrogen peroxide and molecular oxygen.

The Mn-SOD mitochondria are delocalized to the matrix. Mn-SOD is involved in regulating the cellular concentration of O_2, a highly reactive oxidant, a product of cellular metabolism, and in protecting against oxidative cell damage. The Mn-SOD expression is low in many tumor cells. Overexpression of Mn-SOD in breast cancer cells and glioma cells in human melanoma cells suggested that it may be a tumor suppressor gene that suppresses tumor formation.

In our study, SOD activities decreased in mice in groups 1 and 2 compared with the mice in the healthy control group. SOD activities showed a statistically significant increase in curcumin protective group ($p < 0.05$) and curcumin treatment group ($p < 0.05$).

In cells, GSH is present in high concentrations, it is protective against reactive oxygen products and toxins. The redox status of the cells depends on the GSH maintained in a reduced state.

GSH is the most nonenzymatic antioxidant found in cells that plays a critical role in defending against oxidative stress caused by cell injury. Decreasing GSH levels may affect disease development. Finishing the GSH causes the inhibition of GPx, which exposes the cells more to oxidative stress. GSH is an important antioxidant that protects cells against ROS. It is also a very important element that provides detoxification of cells.

In our study, GSH levels were found to be lower in mice in groups 1 and 2 than in the healthy control group. GSH levels decreased in mice treated with curcumin in groups 3 and 4, but these reductions were not statistically significant.

When AOPP values were examined in our study, the decrease in curcumin protective group was found to be statistically significant ($p < 0.05$), ($p = 0.009$).

Besides, it was observed that there was a significant decrease in the fourth group, which is the curcumin treatment group, but this was not statistically significant ($p > 0.05$), ($p = 0.073$).

Finally, when CAT activities were evaluated, the increase in CAT activities was found statistically significant in both the curcumin protective group and the curcumin treatment group. It was determined as ($p < 0.05$), ($p = 0.001$) for both groups.

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How to cite this article: Seriner R, Dağlıoğlu K, Coşkun G, & Bilgin R. Examination of the effect of curcumin in experimental liver damage created by diethylnitrosamine in Swiss albino mice to superoxide dismutase and catalase activities and glutathione, malondialdehyde, and advanced oxidation protein products levels. *Biotechnology and Applied Biochemistry*. 2022;69:1217–1225. https://doi.org/10.1002/bab.2198