An Antioxidant Combination Improves Histopathological Alterations and Biochemical Parameters in D-Galactosamine-Induced Hepatotoxicity in Rats

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ABSTRACT

The protective effects of a combination of antioxidants on histopathological changes and biochemical parameters were examined in D-galactosamine (D-GalN)-induced hepatotoxicity in rats. Physiological saline solution was injected intraperitoneally into the control group, while D-GalN (500 mg kg^{-1}) was administered intraperitoneally into the experimental animals. The combination of 100 mg/kg/day ascorbic acid, 100 mg/kg/day alpha tocopherol, 15 mg/kg/day beta carotene, and 0.2 mg/kg/day sodium selenate was administered orally to intact control rats for 3 days. The same antioxidant combination was given to the D-GalN group. Liver and blood samples were used for histopathological and biochemical assays. Liver tissues were significantly damaged by D-GalN administration based on the histopathological findings. Serum aspartate and alanine transaminase, gamma glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, sialic acid, and uric acid levels increased. Serum and liver glutathione levels decreased, and serum superoxide dismutase, glutathione peroxidase, and glutathione-S-transferase, catalase activities as well as lipid peroxidation values increased in the D-GalN group. In contrast, administration of the antioxidants reversed the histopathological and biochemical changes in the liver of animals administered D-GalN. In conclusion, the administration of a combination of antioxidants suppressed histopathological changes and biochemical parameters in rats given D-GalN.

Keywords: Vitamin C, β-carotene, D-galactosamine, sodium selenate, vitamin E, liver damage

INTRODUCTION

Acute liver failure is the rapid development of hepatocellular dysfunction triggering a cascade of events that damages multiple organs. Various agents, such as acetaminophen, hepa wash, and concanavalin cause acute liver damage in animal models, and D-galactosamine (D-GalN) is a well-established model in experimental animals, such as rats (1-6). Several compounds, such as dobutamine, scoparone, polydatin, proline, and triterpenoids are protective against liver failure (7-11) and the possible role of various antioxidants is under study.

Selenium is a trace element with a significant role in sustaining health. It is a cofactor of glutathione peroxidase (GPx) and protects cells against reactive oxygen species (ROS) (12,13). Vitamin C has endogenous antioxidant features, and it has synergistic effects in combination with vitamin E that protect low-density lipoprotein from oxidative stress induced by peroxyl radicals (14,15). Vitamin E serves as a free radical scavenger that protects fatty acids in bio-membranes and lipoproteins (16). Similarly, β-carotene is a major source of retinoids (vitamin A) in the human diet (17). The protective roles of selenium, vitamin C, and vitamin E either alone or in combination against hepatitis have been described previously (18,19). Poor selenium intake can lead to enhanced levels of ROS and oxidative stress, particularly in patients lacking other antioxidants (e.g., vitamins E and C) (20). However, the role of selenium and the antioxidant combination (vitamins A, C, and E) has not been studied in terms of biochemical and histological impact.

The effects of a combination of antioxidants on histological and biochemical parameters in D-GalN-induced liver injury were studied here. Serum aspartate (AST)

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and alanine transaminase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), catalase (CAT), and lactate dehydrogenase (LDH) activities, as well as serum sialic acid, uric acid, blood glutathione, liver glutathione, lipid peroxidation (LPO) levels, catalase (CAT), superoxide dismutase (SOD), glutathione-S-transferase (GST), and GPx activities, as well as histopathology of liver tissue were analyzed to understand D-GalN toxicity.

MATERIALS AND METHODS

Animals

Forty female Sprague-Dawley rats (age, 2-2.5 months) were obtained from the Experimental Medical Research Institute of Istanbul University (DETAE). All rats were clinically healthy and approximately the same weight. The rats were fed a standard rat chow and given water *ad libitum.*

Experimental Design

The rats were separated into four groups of 10 rats each: 1) control animals (administered 0.9% NaCl intraperitoneally); 2) control animals given antioxidants (100 mg/kg/day ascorbic acid,100 mg/kg/day alpha tocopherol, 15 mg/kg/day beta carotene, and 0.2 mg/kg/day sodium selenate); 3) animals given only a single dose of D-GalN hydrochloride (500 mg/kg, Acros Organics, Pittsburgh, PA, USA) (dissolved in 0.9% NaCl); and 4) animals given D-GalN + antioxidants (same doses and time). D-GalN was administered on day 3, 1 hour after the antioxidant combination. The antioxidants were administered by gavage, and D-GalN was given intraperitoneally. Control and D-GalN animals were separated 6 hours after the injection. On day 3 of the experiment, all animals were fasted overnight, and rats were sacrificed 7 hours after the last antioxidant administration. Blood samples were collected and liver tissue samples were obtained for biochemical and histological analyses.

Histological Assays

Bouin's fixative was used to prepare the liver samples, which were embedded in paraffin. Masson's trichrome stain was used to stain tissue sections for histological observations using a light microscope (CX41; Olympus, Tokyo, Japan).

Biochemical Assays

Blood and liver samples were taken from the animals. Serum and liver tissue samples were frozen until use. The18 h-fasting blood and liver glutathione levels were assayed according to Beutler (1975) (21). AST, ALT (22), ALP (23), GGT (24), LDH (25), sialic acid, (26) and uric acid levels (27) were assayed in serum samples. Protein levels were estimated by the Lowry method (28).

Tissue samples were homogenized in cold 0.9% NaCl to prepare the 10% (w/v) homogenates. The homogenates were centrifuged, and the supernatants were removed. CAT (29), SOD (30), GST (31), and GPx (32,33) activities were assayed in appropriately diluted liver tissue homogenates. LPO levels in liver homogenates were assayed according to Ledwozyw et al. (34).

Statistical Analysis

The biochemical results were analyzed using NCSS statistical software (NCSS Inc.; Kaysville, UT, USA). All data are expressed as mean±standard deviation. A p-value <0.05 was considered significant.

RESULTS

Light Microscopic Results

Liver tissues from animals given saline or the antioxidants (groups 1 and 2, respectively) had normal histology except for vacuolization that was observed in liver cells from group 2 (data not shown). The D-GalN-injected rats (group 3) had significant histopathological changes in the liver (Figure 1). Increased hyperemia, moderate vacuolization, enlargement in the sinusoidal area, necrotic, and swollen cells with a light cytoplasm were observed in the D-GalN group vs. control groups 1 and 2. Administering selenium and the antioxidants reversed the histopathological changes in D-GalN-injected animals. A decrease in mononuclear cell infiltration and hyperemia was observed in group 4 animals. However, vacuolization was observed in group 2 animals. These results indicate that administering selenium and the antioxidants may suppress the histological changes, except vacuolization in the liver of D-GalN- injected rats.

Biochemical Results

Changes in serum AST, ALT, ALP, and GGT in the control and experimental groups are shown in Table 1. Serum AST ($p<0.0001$), ALT ($p<0.0001$), ALP ($p<0.0001$), and GGT ($p<0.0001$) activities were significantly higher in the D-GalN group compared to those in the control group. Administering the antioxidants significantly decreased serum AST ($p<0.005$), ALT ($p<0.05$), ALP ($p<0.05$), and GGT ($p<0.005$) activities in the D-GalN group (Table 1).

Blood GSH levels and serum LDH and CAT activities for all groups are shown in Table 2. Blood GSH values were significantly lower in the experimental group compared to those in the control group ($p<0.0001$), but CAT activity did not change. A significant increase in serum LDH activity was observed in the D-GalN group ($p<0.005$) compared with control rats. Administering antioxidants significantly increased blood GSH levels ($p<0.0001$) and CAT ($p<0.005$) activity, but decreased LDH activity in the D-GalN group ($p<0.0001$, Table 2).

Serum sialic acid and uric acid levels were significantly higher in the D-GalN group compared with those in the control group ($p<0.0001$) (Table 3). Antioxidant administration caused a significant decrease in mean serum sialic acid ($p<0.0001$) and uric acid ($p<0.005$) values in the D-GalN group compared with those in the control group (Table 3).

Liver GSH ($p<0.005$), CAT ($p<0.05$), SOD ($p<0.05$), and GPx ($p<0.05$) activities decreased significantly in the D-GalN group, compared to those in the control group. Liver GST activity also tended to decrease but not significantly. Tissue LPO levels increased in the D-GalN group compared to those in the control group ($p<0.005$). Administering the antioxi-

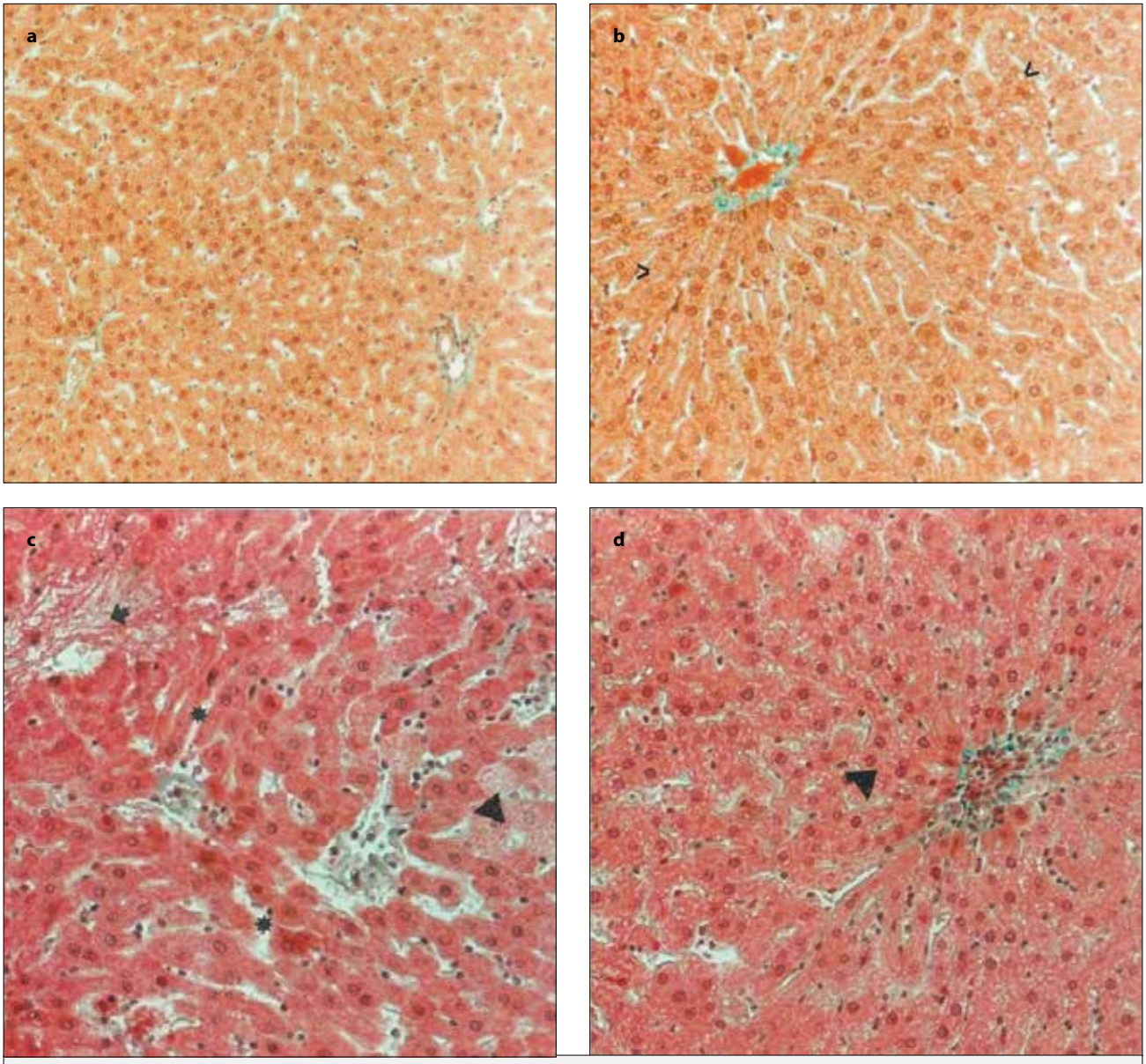

Figure 1. a-d. (a) Histological appearance of the liver of group 1 rats injected with physiological saline. (b) Histological appearance of the liver tissue of group 2 rats given selenium and the antioxidant combination. (c) Degenerative changes in the liver of the group 3rats injected with D-galactosamine (D-GalN). Enlarged sinusoidal spaces (*), necrotic areas (→), and swollen cells with light cytoplasm (▶). (d) Histological appearance of the liver tissue of group 4 rats given selenium and the antioxidant combination and injected with D-GalN. Cellular vacuolization (▶). Masson's trichrome (270×).

dants significantly increased tissue GSH level ($p<0.0001$) and CAT ($p<0.05$), SOD ($p<0.005$,) and GPx ($p<0.0001$) activities in the D-GalN group. Liver GST activity did not change. Liver LPO level decreased significantly in the D-GalN+antioxidant group ($p<0.005$) (Table 4).

DISCUSSION

Acute liver failure significantly affects many bodily functions (35). Animal models of liver injury have been used to study acute liver failure, and D-GalN administration is a good liver failure model (36). Other organs are affected by D-GalN administration (37). D-GalN accelerates oxidative stress by increasing ROS production (36,37). Administering D-GalN consumes antioxidant compounds in the liver (38).

Administering D-GalN generated free radicals that stimulated LPO. D-GalN in combination with lipopolysaccharide treatment induces hepatotoxicity and significantly increase all markers of liver injury and LPO (39). Several researchers have suggested that various compounds, such as flavonoids, lycopene, and magniferin, ameliorate D-GalN-induced acute liver injury due to their antioxidant activities (40-42). Therefore, it can be in-

Table 1. Serum AST, ALT, ALP, and GGT activities for all groups

Group	AST (U/L)*	ALT (U/L)*	ALP (U/L)*	GGT (U/L)*
Control	51.63±6.77	9.26±2.90	29.78±7.75	4.77±0.41
Control + Antioxidant	56.10±34.94	57.89±8.58	42.30±15.09	2.41±1.11
D-GalN	97.46±12.08[a]	71.16± 7.65[a]	65.88±5.83[a]	13.24±1.70[a]
D-GalN + Antioxidant	67.88±20.99[b]	46.85±5.66[c]	48.28±12.84[c]	3.19±2.23[b]
p_{ANOVA}	0.0001	0.0001	0.0001	0.0001

*Mean±standard deviation
[a]p<0.0001compared with the control group
[b]p< 0.005 compared with the D-GalN group
[c]p< 0.05 compared with the D-GalN group

Table 2. Blood GSH levels and serum LDH and CAT activities for all groups

Group	GSH (mg%)*	LDH (U/L)*	CAT (U/L)*
Control	26.31±3.41	1085.00±575.08	22.92±2.27
Control + Antioxidant	20.68±3.91	617.14±111.09	28.85±12.45
D-GalN	17.18±3.14[a]	2902.50±846.33[c]	20.65±5.13
D-GalN + Antioxidant	24.82±2.82[b]	810.00±434.24[b]	38.89±6.17[d]
p_{ANOVA}	0.0001	0.0001	0.006

*Mean±standard deviation
[a]p <0.0001 compared with the control group
[b]p <0.0001 compared with the D-GalN group
[c]p < 0.005 compared with the control group
[d]p < 0.005 compared with the D-GalN group

Table 3. Serum sialic acid and uric acid levels for all groups

Group	Sialic acid (mmol/L)*	Uric acid (mg/dL)*
Control	0.81±0.31	1.06±0.12
Control+ Antioxidant	0.59±0.15	0.92±0.30
D-GalN	1.91±0.35[a]	1.84±0.36[a]
D-GalN + Antioxidant	0.69±0.34[b]	0.63±0.32[c]
p_{ANOVA}	0.0001	0.0001

*Mean±standard deviation
[a]p <0.0001 compared with the control group
[b]p <0.0001 compared with the D-GalN group
[c]p <0.005 compared with the D-GalN group

ferred that selenium and antioxidant supplements can prevent D-GalN-induced hepatic damage.

Our results show that administering selenium and the antioxidants prevented histopathological liver damage in the D-GalN group. Similarly, the use of antioxidant compounds, such as vitamin E ameliorated oxidative damage in tissues including the liver. Gezginci-Oktayoglu et al. (43) reported that a combination of selenium and vitamins C and E has a curative effect on hepatic damage. Ghrelin also improves the histopathological changes in the liver (44). Wild ginseng cambial meristematic cells protect the liver against GalN-induced inflammation, and sesamin ameliorates D-GalN/lipopolysaccharide-induced hepatic damage (45,46). Forsythiaside has also been reported as a protective compound against lipopolysaccharide (LPS)/D-GalN-induced liver injury (47). Genistein maintains the redox potential and improves the antioxidant defense system of cells to prevent hepatic and inflammatory diseases (48). Aristatile et al. (49) reported that carvacrol has hepatoprotective effects and alleviates liver injury caused by D-GalN-induced hepatotoxicity in rats. Li et al. (50) determined that linalool protects against liver damage induced by LPS/D-GalN through induction by antioxidants.

Various researchers have demonstrated enhanced antioxidant enzymatic activities in livers damaged by D-GalN. Ai et al. (51) showed increased liver enzymatic activities, including SOD, GPx, and CAT caused by the phenolics obtained from *Oenanthe javanica*. Similarly, one study showed that rats injected with D-GalN/LPS develop hepatic damage, and AST and ALT levels increase significantly (36). Blood urea nitrogen also changes in the liver of rats after treatment with D-GalN/LPS (52). Ozden et al. (53) reported that vitamin E and taurine treatment significantly decreases tissue LPO levels.

Gezginci-Oktayoglu et al. (54) determined that oxidative stress decreases and antioxidant enzyme systems increase in response to administration of a *Beta vulgaris* L. var.*cicla* extract to injured rats based on decreased malondialdehyde formation (LPO), CAT activity, SOD, myeloperoxidase, and increased GSH levels in the liver. Similar biochemical results were reported in other organs, such as lungs injured by D-GalN. The lung tissue damage occurred in D-GalN/tumor necrosis factor-alpha administered animals. Lung damage improves with the administration of Z-FA. FMK (55). Similarly, our results indicate that increased levels of serum AST, ALT, ALP, GGT, LDH, LPO, serum sialic acid, and uric acid were due to D-GalN administration, which decreased liver CAT, SOD, GST, and GPx activities as well as blood and liver GSH levels. Liver LPO levels increased in the D-GalN group. Treat-

Table 4. Liver GSH and LPO levels and CAT, SOD, GST, GPx activities for all groups

Group	GSH (nmol GSH/ mg prot.)*	CAT (U/mg prot.)*	SOD (U/g prot.)*	GST (U/mg prot.)*	GPx (U/mg prot.)*	LPO (nmol MDA/ mg prot.)*
Control	54.61±17.10	29.80±5.70	17.45±7.62	0.72±0.27	1.76±0.59	0.31±0.11
Control + Antioxidant	38.76±11.83	69.05±11.86	4.39±3.40	0.64±0.14	0.52±0.004	0.36±0.09
D-GalN	32.41±5.06[a]	16.21±4.18[c]	4.79±0.15[c]	0.45±0.27	0.80±0.48[c]	0.72±0.28[a]
D-GalN + Antioxidant	65.08±8.16[b]	157.52±57.29[d]	25.15±5.06[e]	0.60±0.22	11.32±0.98[b]	0.40±0.10[e]
p_{ANOVA}	0.0001	0.0001	0.0001	0.478	0.0001	0.0001

*Mean±standard deviation
[a]p <0.005 compared with the control group
[b]p <0.0001 compared with the D-GalN group
[c]p <0.05 compared with the control group
[d]p <0.05 compared with the D-GalN group
[e]p <0.005 compared withthe D-GalN group

ment with selenium and the antioxidant combination reversed these effects. We conclude that the antioxidant combination suppressed some histopathological changes and biochemical parameters in D-GalN-hepatotoxicity of rats.

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