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Research Article

THE PROTECTIVE EFFECTS OF DILL (*Anethum graveolens* L.) IN PARACETAMOL-INDUCED ACUTE TOXICATION IN MICE

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ABSTRACT. The purpose of this study was to determine whether the protective effect of the AG (*Anethum graveolens*) extract against experimental liver acute toxication formed by PT in mice. For this purpose, 2 months old, 20-25 g weight Balb-c male mice of 50 divided into 5 groups which each contain 10. Applications were made by oral gavage. Group I is designated as the control group and isotonic NaCl given for 7 days, Group II of animals 400 mg/kg a single dose PT applicated orally, Group III is PT+AG1 (100 mg/kg AG given for 7 days and 1 hours after last extract application 400 mg/kg PT given, Group IV is PT+AG2 (200 mg/kg AG+PT 400 mg/kg), Group V. AG2 (200 mg/kg AG were given orally for 7 days. About 5 hours after these applications the blood was taken from heart under ketamin and xylazine anesthesia; liver and kidney tissue were taken after cervical dislocation. Assessments were performed serum cytokine levels (interleukin-1ß, interleukin-6, interleukin-10 and tumor necrosis factor-α), some biochemical enzymes (ALT, AST), lipid peroxidation levels in tissues (MDA, SOD, GSH) with liver and kidney histopathological examinations. In our study, it is determined that AST, ALT, cytokine and tissue MDA levels increased, SOD and GSH levels decreased in PT group. On the other hand, when we compare the groups received two different doses (100 and 200 mg/kg) of extract with only PT applied group, AG application significantly decreased IL-1β, IL-10, IL-6, TNF-α, ALT and AST levels in serum. It is determined that MDA level decreased, and GSH and SOD levels increased depending on dose. Histopathological findings are consistent with biochemical findings. As a result, AG applications can prevent organ damage via affected cytokine answer and oxidative stress in PT-induced acute liver and kidney toxications in mice.

Keywords: *Mice, Anethum graveolens, Paracetamol, Lipid peroxidation, Toxication*

INTRODUCTION

Paracetamol (PT), a paraaminophenol derivative, has been used in therapy as an antipyretic since the end of the 19th century. The drug is known to be a safe drug in treatment doses commonly used in mild to moderate pain and fever reduction [1]. Most of the PT taken at normal doses is metabolized by the sulfate and glucuronic acid coupling reactions; very few are exposed to oxidation reactions with liver cytochrome P-450 enzymes and cause the formation of toxic n-acetyl-p-benzoquinoneimines for the liver. Toxic oxidation metabolites in the liver are converted into non-toxic metabolites that are released into the urine, by combining with glutathione containing sulfhydryl groups [2]. The studies in experimental animal's report that when used at high doses, it causes liver necrosis, kidney toxicity, and even death [3]. As a result, PT taken in overdose limits the inactivation capacity of the n-acetyl-p-benzoin of glutathione and the glutathione stores in the liver are exhausted. PT is first converted to non-reactive metabolites in the liver by sulfation and glucuronidation reactions, but these metabolites are converted to a toxic reactive metabolite (n-acetyl-p-benzoquinonimine) on the liver by the liver cytochrome P-450 enzyme system. The resulting metabolite is covalently bound to the oxide lipids and sulfhydryl groups in the liver tissue, leading to severe damage to cell membranes

[4,5,6,7,8]. It has also been reported that paracetamol poisonings also deplete liver GSH deposits [9]. It has been shown that reduction of oxidation of paracetamol and induction of glutathione synthesis in mice, has been shown to reduce the toxicity of paracetamol [10]. Depletion of GSH deposits in the body may directly induce oxidative stress through GSH, and indirectly, decreasing the activity of antioxidant enzymes also has the same effect [11,12]. Literature studies have reported that GSH-Px and thiol transferase enzyme activities are reduced in paracetamol-induced liver injury in animals [13,14].

By neutralizing free radicals, plants prevent the progress of many chronic diseases associated with oxidative stress and reactive oxygen species [15,16]. As the side effects of medicines used in the treatment of diseases are so much, there is an increasing interest in plants with each passing day. The most important reason for preferring such plants as drugs is that they have fewer toxic effects than drugs.

Today, *Anethum graveolens* (AG) (dill) is a widely consumed plant both in the world and in our country. The aromatic plant AG is rich in terms of essential oils and antioxidants and has also positive effects on anti-inflammatory [17, 18], anti-ulcerative [19], antihyperlipidemic [20], antibacterial [21, 22, 23], antifungal [24, 25], antidiabetic [26, 27], antioxidant [28, 29], anticonvulsant [30] and female reproductive system [31]. When studies on Anethum graveolens are examined, it is reported that they contain antioxidants phytochemicals (high essential oils, flavonoids, phenolic compounds, etc.) and reduce oxidative stress in living organisms [28, 29, 15, 32].

When the studies were examined, no study determining the effects of AG extract on PT-induced acute liver toxicity in rats was conducted. In this study, it was determined whether the AG extract had a protective effect on the liver in PT-induced acute liver toxicity in mice.

MATERIALS AND METHODS

In the study totally 50 Balb-c male mice of 2 months weighing 20-25 g were used. The mice were obtained to evaluate from Erciyes University (ERAC-Experimental Research and Application Center) and the study was conducted there. Before the experiment, animals were kept in groups in the laboratory at normal room temperature (22ºC), under appropriate conditions, with adequate feed and water. Animal experiments were conducted in accordance with Erciyes University Experimental Animal Ethics Committee decisions (Ethics Report No: 15/128).

On the other hand, Chemicals materials; Xylazine (Rompun, Bayer), ketamine (ketals, Pfizer), paracetamol (99,99999 purity) (Doğa İlaç, İstanbul, Turkey). Mouse ELISA kits used for cytokine measurement; IL-1ß platinum (eBioscience, BMS 6002), IL-6 platinum (eBioscience, BMS 603/2), IL-10 platinum (eBioscience, BMS 614/2) (Farmasina, İstanbul,Turkey), mouse TNF-α ELISA kit (Invitrogen, KMC3011) (Lokus, Kayseri, Turkey) and kits for antiokxidant measurement, TBARS assay kit (elabscience, BC0184) and SOD assay kit (elabscience, BC0020) (Atlas Med, Ankara, Turkey), GSH assay kit (Oxford biomed res, GT20) (Ardi Med, İstanbul, Turkey) were supplied from relevant suppliers

Preparation of Extract

All parts of the fresh creek (leaf and root) supplied from the markets around Kayseri were dried in an airy environment. It was then powdered and extracted with methanol under cooling at 40ºC for 4 hours. The extract was filtered, and the filtrate concentrated on a rotary evaporator (Büchi rota vapor R-200). The extract obtained was stored at +4 ºC and dissolved in distilled water before being given to animals.

Experimental design and collection of samples; In the first group (control group), isotonic sodium chloride solution was given orally for 7 days. In the second group of mice, the isotonic sodium chloride solution was given orally for 7 days and after an hour from the last dose, a single dose of paracetamol PT 400 mg/kg c.a. was given orally. The mice in the third group received 100 mg/kg c.a. *Anethum graveolens* orally for 7 days and after an hour from the last extract 400 mg/kg paracetamol was given orally. The mice in the fourth group were given 200 mg/kg *Anethum graveolens* orally for 7 days and after an hour from the dose of the last extract 400 mg/kg PT was given by oral gavage. The mice in the fifth group received 200 mg/kg *Anethum graveolens* orally for 7 days. Five hours after the last dose, blood samples were taken from the mice in all groups with cardiac puncture and gliotema to gill tubes, then the mice were euthanized by cervical dislocation and their livers and kidneys were removed. Blood was centrifuged at 4000 rpm for 10 minutes at +4 °C and its serum was removed. Serum with ELISA kits were stored in deep freeze (-80 °C) until IL-1β, IL-6, IL-10 and TNF-α levels were measured and cytokine efficacy was assessed. Some serums were maintained at +4°C to determine the activity of liver function enzymes (ALT, AST). Some of the tissues (liver and kidney) were stored in deep freezing (-80°C) for antioxidant analysis by determining MDA, SOD, GSH levels. The other part was taken in 10% formaldehyde containers for histopathological examination.

Biochemical Analysis was conducted on the tissues (liver and kidney) washed with PBS. Then, the tissues were disintegrated in porcelain with liquid nitrogen and homogenized.

Lipid peroxidation analyzes were measured that MDA (TBARS), SOD and GSH assays were performed in accordance with kit procedures. Measurements were made in ELISA (Biotek Synergy H1 reader) at the appropriate wavelength.

Determination of Serum Cytokine Levels

IL-lß, IL-6, IL-10 and TNF-a analysis were performed according to kit procedures and levels were determined in an ELISA reader.

Determination of Serum ALT and AST Levels

ALT and AST were carried out in accordance with the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) on the Roche / Hitachi Cobas C 501 system to determine the numerical value of serum and plasma aminotransferase aspartate and alanine transferase.

Histopathological Evaluation

Following routine alcohol-xylol follow-up procedures, all samples were embedded in paraffin blocks and serial sections with a thickness of 5 m were taken with a microtome. Received sections were photographed by staining with hemotoxylin-eosin (66) under

light microscopy (Olympus BX52 with DP72 camera system, Erciyes University, Faculty of Medicine, Department of Medical Pathology).

Statistical Evaluation

The normal distribution of the data was evaluated by a histogram, q-q graphs and Shapiro-Wilk test. The variance homogeneity was tested by the Levene test. In comparisons between more than two groups, one-way analysis of variance (ANOVA) was used when parametric assumptions were provided and Kruskal Wallis tests were used when these assumptions were not provided. Dunn-Bonferroni and Tukey tests were applied for multiple comparisons. The data was evaluated using the R Studio 3.2.2 program. Significance level was accepted as $p < 0.05$.

RESULTS AND DISCUSSION

Biochemical Results

Levels of tissue (liver and kidney), antioxidants (MDA, SOD and GSH), serum cytokines (IL-1β, IL-6, IL-10 and TNF-α) and liver enzymes (ALT and AST) amongst study groups are stated below in tabular form. The MDA, SOD and GSH levels of the groups are shown in Table 1 (liver) and Table 2 (kidney).

Table 1. *Effects of Anethum graveolens extract on MDA, SOD and GSH levels in rat liver tissues*

Liver	MDA (nmol/mg.prot)	SOD (U/mg.prot)	GSH (nmol/mg.prot)
Control	3.33±0.49[a]	3.33±1.50[a]	3.47±0.33[a]
PT	7.23±1.72[b]	0.95±0.09[b]	2.22±0.26[b]
PT+AG1	5.91±0.60[b]	3.37±1.56[a]	2.30±0.22[b]
PT+AG2	5.20±1.67[a]	3.51±0.66[a]	3.27±0.34[a]
AG2	4.26±0.70[a]	4.60±0.83[a]	3.70±0.44[a]

Data are expressed as mean ± standard deviation and median (1. quarter- 3. quarter). Same letters in the same column indicate similarity between groups, different letters indicate differences between groups.
[a] PT significantly different from the mouse group ($P < 0.05$),
[b] Significantly different from control group ($P < 0.05$).
AG1: 100 mg/kg. c.a.
AG2: 200 mg/kg. c.a.
PT: 400 mg/kg. c.a.

Table 2. *Effects of Anethum graveolens extract on MDA, SOD and GSH levels in mouse kidney tissues*

Kidney	MDA (nmol/mg.prot)	SOD (U/mg.prot)	GSH (nmol/mg.prot)
Control	5.68±0.38[a]	2.1 (1.5-2.6)	3.6(3.4-4.1)[a]
PT	7.01±0.50[b]	1.6 (1.0-2.2)	2.3(2.1-2.4)[b]
PT+AG1	5.94±0.32[a]	1.4 (1.1-2.2)	2.3(1,8-2,4)[b]
PT+AG2	5.98±0.21[a]	1.2 (0,6-2.9)	3.2(3.2-3.8)[a]
AG2	4.91±0.30	2.2 (0.9-3.6)	3.3(3.2-3.5)[a]

Data are expressed as mean ± standard deviation and median (1. quarter 3. quarter). Same letters in the same column indicate similarity between groups, different letters indicate differences between groups.
[a] PT significantly different from the mouse group ($P < 0.05$),
[b] Significantly different from control mouse group ($P < 0.05$).

The liver and kidney MDA levels of the experimental groups in the study were significantly increased in the PT group when compared to the other groups (p <0,05). PT group in multiple comparisons of MDA (liver) variant; control was significantly elevated with respect to PT + AG2 and AG2 groups and significant differences were determined between control group and PT and PT + AG2 groups. When comparing the PT group with the other groups in the binary comparison of the MDA (kidney) variables, the PT group was significantly higher than the other groups. In the study, the liver and kidney SOD levels of PT group animals decreased significantly compared to the other groups (p <0.05). There was an intergroup statistically significant increase in the liver SOD levels of the extract-receiving groups, but no significant distribution of SOD kidney levels was detected. PT group in multiple comparisons of SOD (liver) variant; control was significantly lower than PT + AG1, PT + AG2 and AG2 groups and there was a significant difference between PT group and other groups.

On the other hand, when an intergroup comparison is done in terms of GSH, GSH levels in liver and kidney tissue in PT and PT+AG1 groups decreased markedly compared to the other groups (p <0.05). PT group and PT + AG1 group in multiple comparisons of GSH (liver) and GSH (kidney) variables; control was significantly lower than the PT + AG2 and AG2 groups there was a significant difference between PT and PT + AG1 groups and the other groups. IL-1β, IL-6, IL-10 and TNF-α levels of the groups were shown in Table 3.

Table 3. *Effects of Anethum graveolens extract on IL-1β, IL-6, IL-10 and TNF-α in mouse sera*

	IL-1β (pg/ml)	IL-6 (pg/ml)	IL-10 (pg/ml)	TNF-α (pg/ml)
Control	1.81±0.60[a]	52.67±7.12[a]	260.50±42.33[a]	3.37±0.73[a]
PT	40.69±3.12[b]	295.00±95.86[b]	410.83±123.54[b]	8.43±2.04[b]
PT+AG1	9.54±4.73	103.00±16.92[a]	333.00±43.56	3.96±0.70[a]
PT+AG2	5.53±2.12[a]	87.00±24.14[a]	272.83±46.37[a]	3.49±0.78[a]
AG2	1.54±0.76[a]	39.00±6.32[a]	239.33±23.63[a]	1.47±0.53[a]

Data are expressed as mean ± standard deviation and median (1. quarter- 3. quarter). Same letters in the same column indicate similarity between groups, different letters indicate differences between groups.
[a] PT significantly different from the mouse group (P <0.05),
[b] Significantly different from control mouse group (P <0.05).

In the study, serum IL-1β levels of the mice were significantly higher in the PT group compared to the other groups and distribution among the groups was statistically significant (p <0.05).

In the binary comparison of IL-1β according to the multiple comparison test, a significant increase in the PT group was observed when control group and PT were compared and there was a significant decrease in the extract groups.

Serum IL-6 levels of the animals were significantly higher in the PT group compared to the other groups and there was a decrease in all groups receiving extracts at different doses. The differences were statistically significant (p <0.05).

IL-10 levels of serum cytokines in rats were significantly higher in the PT group compared to the other groups (p <0.05). In the multiple comparison of interleukin 10 variants, PT group; the control group was significantly higher than the PT + AG2 group and the AG2 group, and the difference was significant.

In the study, measured TNF-α levels were also significantly increased in the PT group when compared with the other groups and the extracted groups were similar to the control group (p <0,05). Serum ALT and AST levels of the groups are shown in Table 4.

Table 4. *Effects of Anethum graveolens extract on ALT and AST in mouse serums*

	ALT (U/L)	**AST (U/L)**
Control	9.5(6.8-11.3)[a]	17.5(14.5-19.0)[a]
PT	172.0(42.8-1643.8)[b]	317.5(109.3-1436.8)[b]
PT+AG1	28.0(26.5-29.3)	64.0(63.8-66.0)
PT+AG2	26.0(22.3-28.0)	55.0(44.3-59.5)
AG2	9.5(6.8-12.5)[a]	19.5(14.5-25.5)[a]

Data are expressed as mean ± standard deviation and median (1. quarter - 3.quarter). Same letters in the same column indicate similarity between groups, different letters indicate differences between groups.
[a] PT significantly different from the mouse group (P <0.05),
[b] Significantly different from control mouse group (P <0.05).

The ALT and AST levels of the PT group animals were significantly higher than the other groups (p <0.05). Decreased levels of these enzymes were observed in the extract-receiving groups. The PT + AG1 group was similar to the PT + AG2 group and the control group was similar to the AG2 group. The results were statistically significant.

Histopathological Results

The histopathological findings of the experimental groups were given in the pictures (Figures 1-5). Pathological changes were shown on the pictures. The histological structure of the normal rat liver tissue from the control group was given in Fig. 1.

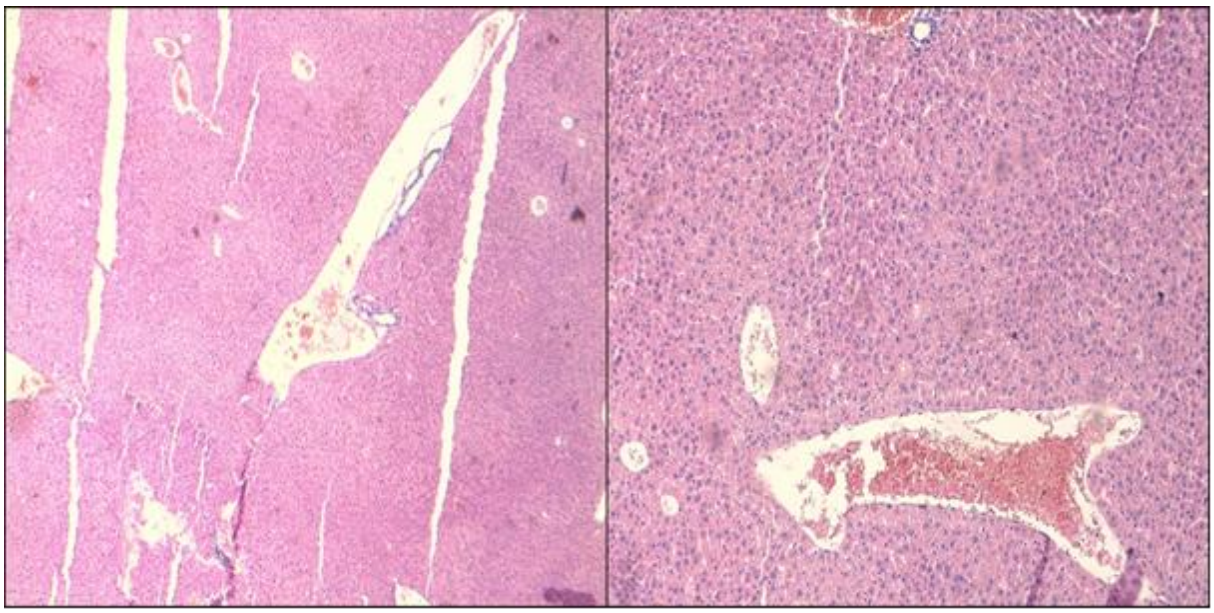

Fig. 1. *Control group normal histological appearance of rat liver tissue, HE, 100 µm, 200 µm*

When the liver tissues of paracetamol-treated mice were examined, there was a moderate increase in connective tissue, necrotic cells, necrosis of the lobule center,

moderate and severe inflammatory cell enlargement and confluent necrosis areas (Fig. 2). PT + AG1 (*Anethum graveolens* 100 mg/kg + Paracetamol 400 mg/kg) showed marked necrosis, bleeding areas and leucocyte accumulation in the liver of the animals. (Fig. 3).

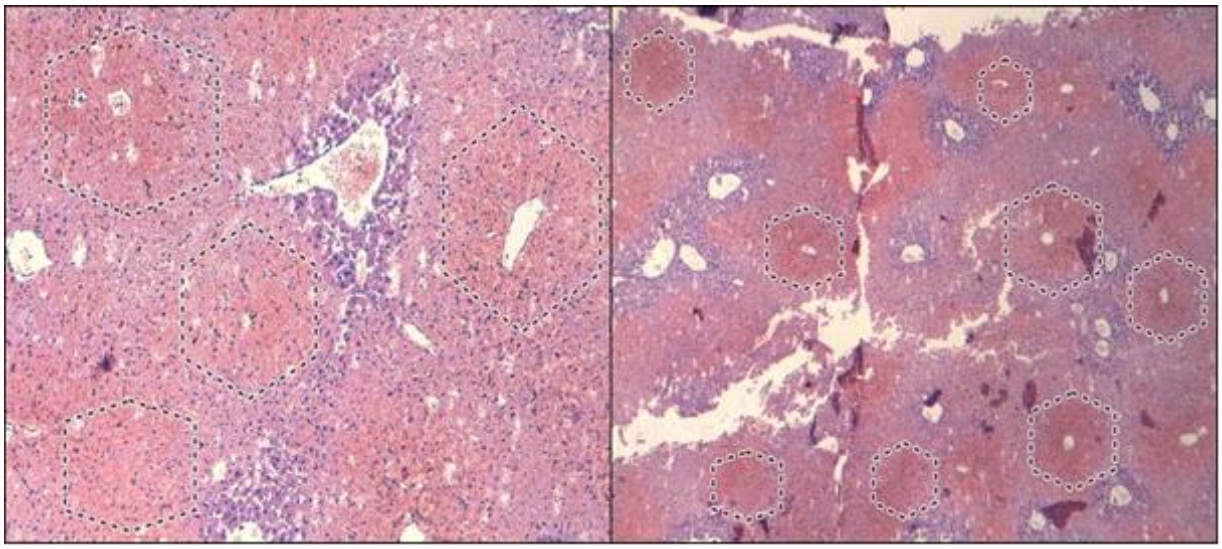

Fig. 2 *Confluent necrosis (hexagons) in mouse liver of PT (Paracetamol) group, HE, 100 µm, 200 µm*

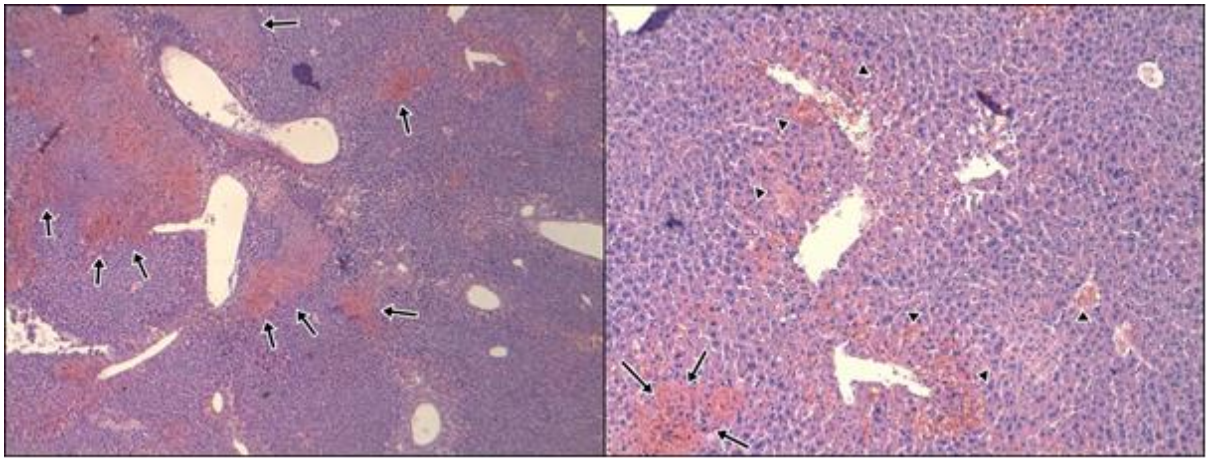

Fig. 3*. PT + AG1 (Anethum graveolens 100 mg / kg + Paracetamol 400 mg / kg) group showed significant areas of necrosis (arrows), bleeding areas (arrowheads) in the rat liver, HE, 100 µm, 200 µm*

PT + AG2 (*Anethum graveolens* 200 mg/kg + Paracetamol 400 mg/kg) necrosis areas were observed in the liver of the animals in the group (Figure 4).

Histopathological examination of the experimental groups given isotonic sodium chloride and AG2 alone (200 mg/kg) showed normal liver tissue without significant pathological findings. Liver cells were radially located, undamaged large spherical nuclei and granular cytoplasm were observed (Figure 5). No changes were observed in the histological examination of the kidney tissues, the histological appearance of the kidney tissue was generally the same and there were no significant differences between the groups.

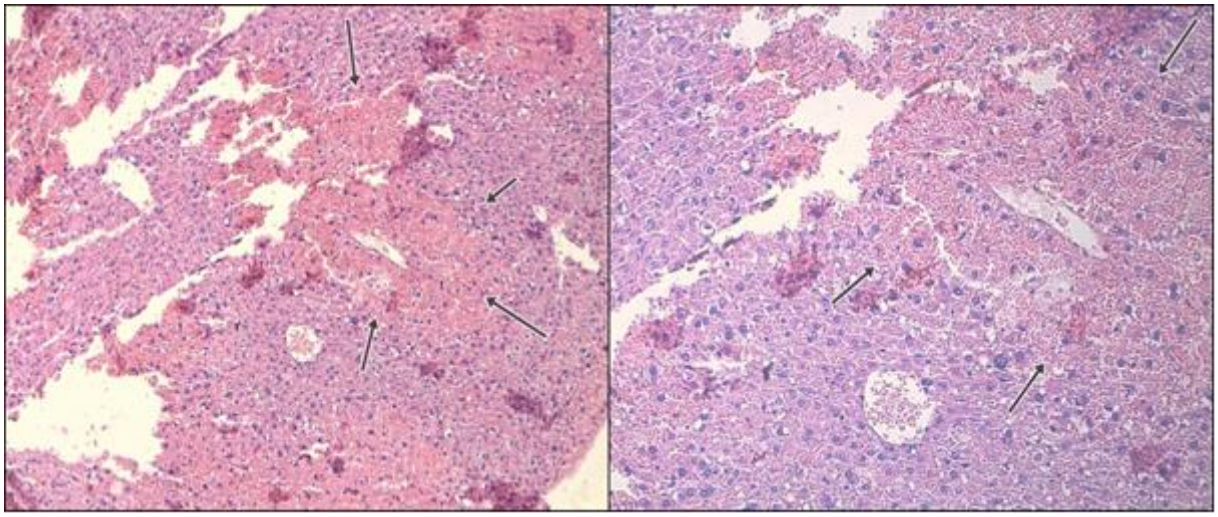

***Fig. 4**. PT + AG2 (Anethum graveolens 200 mg/kg + Paracetamol 400 mg/kg) group necrosis areas (arrows) in mouse livers, HE, 100 µm, 200 µm*

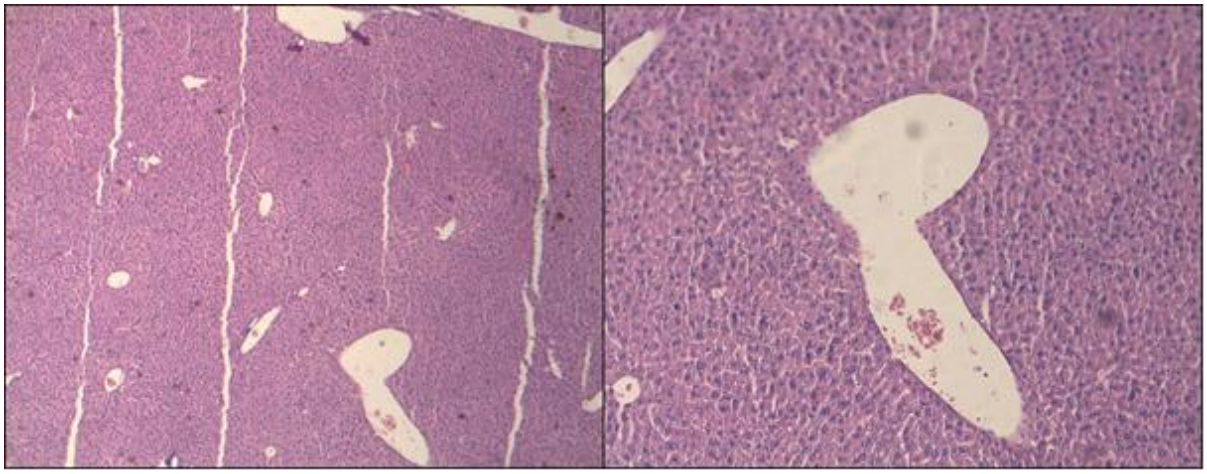

***Fig. 5**. AG2 (Anethum graveolens 200 mg/kg) group normal histological appearance of rat liver tissue, HE, 100 µm, 200 µm*

CONCLUSION

Paracetamol is safe when taken at the treatment dose, but when taken at high doses, paracetamol is at the top of the drugs causing poisoning and causes extensive tissue damage, mainly the liver [33,34]. Oxidative stress is an imbalance between oxidants and antioxidants in cells and causes oxidative damage [35]. SOD and GSH are important antioxidants in the intracellular protective mechanism of reactive oxygen species such as peroxides and free radicals [36]. Malondialdehyde (MDA) is one of the most important indicators of oxidative stress resulting from peroxidation of polyunsaturated fatty acids. The level of lipid peroxidation can be estimated according to the amount of MDA[37,38]. When the PT is taken at high doses, the metabolite n-acetyl-β-benzoinone (NAPQI) consumes the glutathione deposits in the liver and binds to the released NAPQI intracellular proteins, resulting in tissue damage by binding to sulfhydryls in membranes and proteins [39,40]. In PT toxication, the formation of free radicals increases, leading to the destruction of unsaturated fatty acids, resulting in cell damage due to endogenous antioxidant capacity decline, oxidant / antioxidant imbalance and oxidative stress, which

is reported to result from increased free radicals in this process [41,42]. Highly available polyphenols in AG plant exhibit antioxidant effects by neutralizing free radicals and destroying peroxides [43,44,45].

In previous studies, n-acetyl cysteine was used as an antidote in PT toxication, and many pharmacological agents (Vit C, E, melatonin, etc.) and plant extracts were investigated by researchers in different animal species for protection purposes [46,47,48]. In this study, the experimental PT toxicity model generated in vivo in mice was used.

The effects of antioxidant/oxidant balance and histopathological changes on serum cytokine and enzyme levels were investigated in vital organs such as liver and kidney, which were most affected by PT toxication of AG extracts administered by two different doses of oral gavage.

MDA is the end product of lipid peroxidation and is one of the most widely used determinants of lipid peroxidation. In tissues exposed to oxidative stress, the increase in MDA level is considered biomarker for oxidative stress [37,38]. In a similar study, rats were given toxic doses of acetaminophen (500 mg/kg) and aspirin (200 mg/kg). In conclusion, acetaminophen and aspirin have been reported to cause a significant increase in MDA levels in plasma and liver [49]. In another study, rats were given high dose acetaminophen (400-600 mg/kg), MDA level increased, GSH decreased, and massive centrilobular hepatocyte necrosis was noted in the liver [50]. In a study conducted by Curhan et al. [51] in rats, acetaminophen and alcohol application of rats resulted in pathophysiological changes in the rat liver, resulting in increases in serum MDA and ALT levels [51]. One of the non-enzymatic antioxidants is GSH; chemically reactive toxic compounds or the most important molecules that play a role in cellular defense against the oxidative stress. Glutathione can be found in the form of reductase and oxides. In its reduced form, the thiol group of cysteine has the ability to deliver reducing eq values to non-stabilizing molecules such as reactive oxygen species. Protective effect occurs with this mechanism. In situations such as reduced cellular GSH levels and GSH synthesis capacity, cells become susceptible to radiation and certain drugs [7,47,50]. When paracetamol is taken at high doses it is known that NAPQI as a mediator of oxidative stress leads to a decrease in GSH level and an increase in lipid peroxidation due to this decrease. This toxic metabolite binds to cellular proteins and causes necrosis in cells [8,52]. It has been reported that GSH levels in tissues are decreased in toxicities produced by PT at high doses in different animal species [48,50,53]. In organism, antioxidant enzymes such as SOD are easily inactivated by lipid peroxidases or reactive oxygen products. For this reason, the activity of these enzyme activities in paracetamol toxicity also declines [54]. In another study conducted by Slater et al. [55], it was determined that SOD decreased with paracetamol in toxic mice [55].

High-antioxidant AG extract was effective in Type II diabetes induced by corticosteroids in female rats both antidiabetic (affecting serum glucose and insulin levels) and antioxidants (correcting hepatic LPO, SOD, CAT and GSH levels affected by corticosteroids) [26]. As in the above studies, in our study, it was also seen that there was a significant increase in MDA level, a decrease in GSH and SOD levels in the same PT group. When we compared AG groups that received extract at two different doses with the groups that received PT only, it was seen that the MDA level decreased and GSH and SOD levels increased in a statistically significant manner.

The results of the study are similar in terms of changes in PT toxicized animals and in MDA, SOD and GSH levels of the materials used for protective purposes. When studies on high doses of PT in different animal species are examined, it is reported that PT not

only affects lipid peroxidation markers but also elevates levels of ALT, AST, IL-1β, TNF-α, IL-10 and IL- 6) [56,57,58,59,60,61].

The ethanolic extract of AG has been reported to have hepatoprotective effect in liver damage induced by administration of carbontetrachloride in rats [62]. Another study in rabbits reported that AG affected biochemical values and lowered ALT, AST levels [63].

In the above studies, it is understood that in living organisms toxicised by high levels of PT, cytokines (IL-1β, TNF-α, IL-6 and IL-10) and enzymes such as ALT and AST increase, both enzymes and cytokines decrease as a result of the substances considered as protective. In our current study, a significant increase in levels of ALT, AST, IL-1β, TNF-α, IL-6 and IL-10 was observed in the PT administered toxicity group. In a study with AG, LPS-induced inflammation showed anti-inflammatory properties by inhibiting nitric oxide synthase (iNOS) and mRNA expression of cytokines such as IL-1 and IL-6. Polyphenols and flavonoids in AG have been effective in this respect [18]. A study of the anti-inflammatory properties of Anethum graveolens in type II diabetes, a favorable decrease in serum IL-6, TNF-α and CRP levels was determined [27]. In the current study, it was seen that ALT, AST, ILieww-1β, TNF-α, IL-6 and IL-10 levels were significantly lower in the groups receiving AG extract when compared to the patient groups. The results of the study are similar to previous studies.

As a result of this study, it has been determined that administration of Anethum graveolens against paracetamol toxicity in rats prevents free radicals and increases antioxidant enzymes and prevents damage to the liver and kidney, thus contributing to antioxidant activity and creates anti-inflammatory effects decreased cytokine levels. The results of antioxidant capacity, liver enzymes and cytokines are compatible and support each other in liver tissues with histopathologic evaluations. Histopathologically, no significant findings were found for the kidneys. When taken in combination with AG paracetamol, it may be clinically beneficial because it is thought to contribute both to the inhibition of free radical formation and to the improvement of antioxidant levels. The most important advantage is that as this plant can be procured easily by everyone and consumed more frequently in our country, it can be consumed not only at events related to paracetamol toxicity, but also can be consumed more frequently, taking into consideration the positive contribution to all oxidative stress-producing events.

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Compliance with ethical standards The research does not involve any human participants and/or animals.

Conflicts of Interest: The authors declare no conflict of interest

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