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Effects of Silymarin on Blood and Tissue Parameters in Sodium Fluoride-Induced Hepatotoxicity and Oxidative Stress in Rats

Ratlarda Sodyum Florid ile Oluşturulan Hepatotoksite ve Oksidatif Streste Silimarin'in Kan ve Doku Parametreleri Üzerine Etkileri

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ABSTRACT Objective: To investigate the protective and curative effect of silymarin against fluoride-induced hepatotoxity and oxidative degradation in rats. **Material and Methods:** Of the 45 rats, 9 were given only sodium fluoride (F); 9 were given only silymarin (S), 9 were given only tap water (K), 9 were given sodium fluoride and silymarin together (FS) and 9 were given silymarin after sodium fluoride was completed (T). **Results:** In Group F, serum AST level was significantly higher than in control group (p<0.001) and in Group FS and group T, serum AST and ALT levels were lower than in Group F, which was evaluated as improved toxic effect of sodium fluoride by silymarin. When compared with the control group; in Group F, a decrease in serum SOD and GSH-Px values and an increase in MDA levels showed oxidative deterioration in liver tissue; high SOD and GSH-Px levels and low MDA levels in Group S and Group T showed that silymarin prevents and improves tissue damage.Histopathological significant differences were found between Group F, Group S and Group T in terms of deterioration in remak cords (p<0.01 p=0,007). In addition, there was a significant difference between Group F, Group T and Group FS in terms of degenerative changes (p<0.001). **Conclusion:** It was concluded that sodium fluoride has toxic and destructive effects on liver tissue and silymarin has a protective and healing effect against these effects.

Keywords: Liver function tests, silymarin, sodium fluoride

ÖZET Amaç: Silimarinin sıçanlarda florür kaynaklı hepatotoksite ve oksidatif bozunmaya karşı koruyucu ve iyileştirici etkisini araştırmak amaçlandı.**Gereç ve Yöntemler:** Çalışmada kullanılan 45 ratın, 9'una sadece NaF (F); 9'una sadece silimarin (S), 9'una sadece çeşme suyu (K), 9'una NaF ve silimarin birlikte (FS) ve 9'una, NaF verilmesi tamamlandıktan sonra, silimarin (T) verildi. **Bulgular:** Grup F'de, serum AST düzeyinin kontrol grubuna göre önemli düzeyde yüksek (p<0,001) ve Grup FS'de ve Grup T'de, serum AST ve ALT düzeylerinin F grubuna göre düşük olması bulguları", sodyum floridin karaciğer dokusuna olan toksik etkisi ve buna karşı silimarinin koruyucu ve iyileştirici etkisi olarak değerlendirildi. Bu sonucun histopatolojik olarakta desteklendiği görüldü. Kontrol grubuyla yapılan karşılaştırmalarda; karaciğer dokusunda Grup F'de, SOD ve GSH-Px değerlerindeki düşüş ve MDA düzeyindeki artış karaciğer dokusundaki oksidatif yıkımı gösterirken; Grup FS'de ve Grup T'de SOD ve GSH-Px düzeylerinin yüksek, MDA düzeylerinin düşük bulunması, silimarinin oksidatif doku yıkımını önlediği ve bunu iyileştirdiğinin göstergesi oldu. Histopatolojik olarak remakerlerde bozulma açısından Grup F, Grup S ve Grup T arasında anlamlı fark bulundu (p<0,01 p=0,007). Ayrıca, Grup F, Grup T ve Grup FS arasında dejeneratif değişiklikler açısından anlamlı fark vardı. **Sonuç:** Bu çalışmada; sodyum floridin karaciğer dokusuna toksik ve yıkımlayıcı etki yaptığı; bu etkilere karşı silimarin'in koruyucu ve iyileştirici etkisinin olduğu sonucuna varıldı.

Anahtar Kelimeler: Karaciğer fonksiyon testleri, silymarin, sodyum florid

Fluorine is naturally abundant in some regions in our country, it is used in various concentrations in industrial products and intensive fluorine contamination occurs due to environmental pollution. Excess amount of fluorine entering the animal and human body through inhalation or digestion leads to acute and minor amounts to chronic disorders. In recent years, in some unidentified disorders in animals, fluorine is also considered among the possible causes of the disorder, considering the local conditions.[1-7]

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It has been reported that necrosis caused by fluoride in hepatocytes and changes in membrane lipids are associated with apoptosis and oxidative stress.[8,9] As a result of contact with fluorides; stress response factors, signal transduction compounds, proteins associated with apoptosis and organ-specific enzyme changes occur.[10]

Oxidative tissue destruction is caused by reactions of oxidant molecules on protein, lipid, carbohydrate, nucleic acid and enzymes, which are the cornerstones of the cell. Oxidative stress is determined by measuring parameters such as MDA, SOD, GSH-Px, alpha-tocopherol, ascorbic acid, glutathione, ubiquinone and cysteine.[11-13]

Against fluor-induced hepatotoxicity, the following were found to be effective caffeic acid; purple corn pigment extract against liver and kidney tissue destruction caused by sodium fluoride in rats; gallic acid against oxidative stress rising in toxicity caused by sodium fluoride; Epigallocatechin gallate against oxidative hepatic destruction caused by sodium fluoride in rats; Tamarindus Indica against oxidative destruction due to excess fluoride consumption in the rat liver.[9,14-17] In addition, it has been reported that resveratrol has a positive effect on reduction of oxidative stress caused by fluoride in rats.[18]

In this study, to investigate the protective and curative effects of silymarin against fluoride-induced hepatotoxicity and oxidative destruction in rats; serum AST and ALT levels, SOD, GSH-Px and MDA levels, which are indicative of oxidative stress, will be evaluated.

MATERIAL AND METHODS

Ethics committee approval was obtained from Ankara University Rectorate, Animal Experiments Local Ethics Committee, (decision date and number: 08.06.2016, 2016-15-153). This study was performed in accordance with the principles of Helsinki Declaration. The study was carried out on 45 Wistar albino male rats obtained from Ankara University Experimental Animal Breeding Unit, 8-12 weeks old, 180-240 gram live weight and 9 in each group. The animals were housed for 12 hours in a light/dark cycle and at appropriate humidity and temperature throughout the day. Rats were kept in quarantine for 5 days before starting the study. Standard feeding was applied to the rats, water was given as ad libitum.

The 45 rats used in the study were divided into 5 groups, each containing 9 rats. Sodium fluoride at a dose of 300 ppm/day was added to the drinking water of 9 rats (F) in the first group during the 30-day study. Sodium fluoride (300 ppm/day) was added to the drinking water of 9 rats (FS) in the second group during the 30-day study, and rats in this group were also given orally using 200 mg/day of silymarin for 30 days. After the addition of sodium fluoride at the dose of 300 ppm/day for 30 days in the drinking water of 9 rats (T) in the third group, rats in this group were given orally by using silymarin gavage at the dose of 200 ppm/day for the next ten days. In the fourth group, 9 rats (K) were given tap water only for a forty day study period. In the fifth group, 9 rats were given orally by gavage at a dose of 200 ppm / day of silymarin during a 30-day study.

At the end of the study period, blood samples were taken from all rats in the groups and rats were sacrificed and liver tissue samples were taken. Collected blood samples were centrifuged at 3000 rpm for 10 minutes, sera were removed and samples were numbered and stored at -80 ^{o}C in a freezer. Liver tissue samples obtained from sacrificed rats were enumerated and stored in deep freezer at -80^{0}C in sample boxes.

Serum aspartate aminotransferase (AST), alanine transaminase (ALT), and total protein (TP) levels were measured in Ankara University Faculty of Veterinary Medicine Central Diagnostic Laboratory. For the measurement of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) levels in liver tissue. The liver was washed with phosphate buffer (PBS) before lysis. Tissue samples homogenized with homogenization buffer were then centrifuged to obtain supernatants and used for analysis. GSH-Px levels in liver tissue were measured using a commercial test kit (Cayman, 703102) which worked according to the method described by Paglia and Valentive (1967). SOD level was measured using the commercial test kit (Cayman, 706002), which worked according to the

method described by Sun et al. (1988). MDA level was measured using the MDA test kit (Cayman, 100009055) working according to the method indicated by Ohkawa et al. (1979) in the Laboratory of Biochemistry Department of Veterinary Faculty of Ankara University. Measurements were performed according to the kit protocols. In addition, protein content of all liver tissue samples were measured in autoanalyser (Erba XL 600) after homogenization and resolution of the tissues.

In the histopathological examination performed at Ankara University Faculty of Veterinary Medicine, Pathology Department liver samples of 45 rats were fixed in 10% neutral formaldehyde, then trimmed into cassettes and then washed in running water for 12 hours. The tissues were then transferred to the routine tissue tracking device (Leica TP1020) and blocked in paraffin (ThermoElectron Corp. Shandon Histocentre 3). Sections prepared with 5 µm thick microtome (Leica RM2255) from each block were stained with Harris's Hematoxylin-Eosin (HE) method after the deparaffinization and dehydration steps on an automatic staining machine (Leica Autostainer XL) and covered with a coverslip on an automatic capping machine (Leica CV5030). Histopathological evaluations of all preparations were performed under light microscope (Olympus BX51), the findings were graded and the required areas were photographed (Olympus DP71). Two pathologists evaluated the pathological findings according to the severity (hyperemia, remak cord deterioration, parenchymal degeneration, cell infiltration and bleeding), in 10 and 40 objective and 10 different sites. Accordingly, pathological findings; (-) negative, (+) mild, (++) moderate and (+++) severe.

All variables obtained from the study data were analyzed by Shapiro Wilk, one of the parametric test assumptions for normality, and Levene test for homogeneity of variance before the significance tests were carried out. Statistical analysis of variance between variables was performed by One-way ANOVA. Duncan test was used as the post-hoc test for the variables where the differences between groups were found to be significant. All statistical analyzes were examined with a minimum margin of 5%. Morphological parameters were evaluated by One-way ANOVA and Duncan test. SPSS 14.01 package program was used for statistical calculations.

RESULTS

In statistical evaluation of liver weights; the average liver weight changes in the Group F were different from the changes in the mean liver weights in the Group K, Group FS and Group S ($p<0.001$) (Table 1).

In terms of liver tissue SOD activity, the mean value obtained from the Group F that received sodium fluoride for 30 days was statistically significantly lower than the values in the Group K and Group S ($p<0.05$ $p=0.004$, $p=0.006$) (Figure 1, Table 2).

In terms of liver tissue MDA activity; the mean value obtained from the rats in the Group F given NaF for 30 days was statistically higher than the control values and the values in the other groups (Table 2).

In terms of liver tissue glutation peroxidase activity; the mean values of the rats in the Group F given NaF for 30 days were statistically significantly ($p<0.001$) lower than the values of the control and Group S given only silymarin (S) (Table 2).

There was no statistically significant difference between the mean values of serum ALT activity in the groups. In the Group F, Group FS and Group K, significant differences ($p<0.001$) were found between the mean serum AST activity values (Table 3).

TABLE 1: Mean liver weights.

Groups(n=9)	Liver weight (g) $\bar{X}\pm S_{\bar{X}}$
K	11.7±0.9[a]
F	7.8±1.7[b]
FS	10.2±1.6[a]
S	11.8±1.3[a]
T	10.9±1.3[a]

$\bar{X}\pm S_{\bar{X}}$: Mean ± standard error
a, b shows differences between groups in the same column ($p<0.05$).
F: Group given sodium fluoride for 30 days;
K: Control group with only tap water for 40 days;
FS: Group containing sodium fluoride and silymarin for 30 days;
S: Only silymarin-treated group for 30 days;
T: Group treated with silymarin for 10 days after sodium fluoride was given for 30 days.

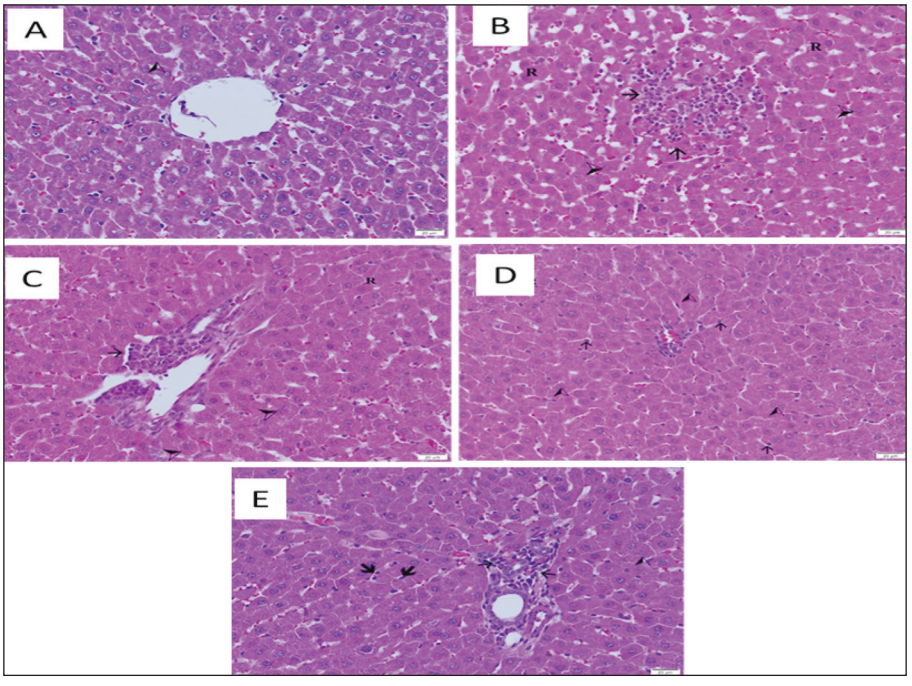

FIGURE 1: A. Slightly degenerated hepatocytes (arrowhead), HE staining (K group), B. Inflammatory cell infiltration (arrows), degenerative hepatocytes (arrowheads) and irregular remark cords (R). HE staining (group F), C. Irregular remark cords (R), inflammatory cell infiltrations (arrow), and degenerative hepatocytes (arrowheads). HE staining (F + S group), D. Degenerated hepatocytes (arrowheads), swollen Kupffer cells (arrows) and irregular remark cords (R). HE staining (S group), E. Mild degenerated hepatocytes (arrowhead), mild inflammatory cell infiltration in the portal region (arrows) and swollen Kupffer cells (thick arrows). HE staining (T group).

TABLE 2: Mean liver SOD, GSH-Px and MDA levels.

Groups (n=9)	SOD (U/g protein) $\bar{X}\pm S_{\bar{X}}$	MDA (nmol/g protein) $\bar{X}\pm S_{\bar{X}}$	GSH-Px (nmol/g protein) $\bar{X}\pm S_{\bar{X}}$
K	72.1±10.1[a]	68.7±13.1[a]	63.6±12.7[b]
F	63.6±7.1[b]	83.8±10.3[b]	52.6±9.0[a]
FS	77.6±10.3[a]	67.9±11.3[a]	80.6±11.4[c]
S	77.0±6.1[a]	67.5±8.6[a]	81.0±15.2[c]
T	72.4±7.3[a]	67.8±13.0[a]	63.6±12.1[b]

$\bar{X}\pm S_{\bar{X}}$: Mean ± standard error

a, b, c indicate differences between groups in the same column ($p < 0.001$).

F: Group given sodium fluoride for 30 days; K: Control group with only tap water for 40 days; FS: Group containing sodium fluoride and silymarin for 30 days;
S: Only silymarin-treated group for 30 days; T: Group treated with silymarin for 10 days after sodium fluoride was given for 30 days.

TABLE 3: Mean serum ALT and AST levels.

Groups	n	AST (IU/L) $\bar{X}\pm S_{\bar{X}}$	ALT (IU/L) $\bar{X}\pm S_{\bar{X}}$	Serum protein (g/dl) $\bar{X}\pm S_{\bar{X}}$
K	9	96.2±27.0[a]	68.0±37.6	4.8±0.7
F	9	200.9±70.5[d]	128.3±71.9	5.0±0.9
FS	9	102.6±35.2[a]	54.9±21.2	4.9±0.4
S	9	117.0±36.1[ab]	59.1±12.2	4.7±0.4
T	9	149.9±38.2[c]	88.9±48.9	4.8±0.8

$\bar{X}\pm S_{\bar{X}}$: Mean ± standard error

*a,b,c,d shows differences between groups in the same column ($p<0.001$).

F: Group given sodium fluoride for 30 days; K: Control group with only tap water for 40 days; FS: Group containing sodium fluoride and silymarin for 30 days;
S: Only silymarin-treated group for 30 days; T: Group treated with silymarin for 10 days after sodium fluoride was given for 30 days.

In the statistical evaluation, a difference was found between the Group F that was given fluoride in terms of disruption in the remark cords and the Group S and the Groups T ($p<0.01$). In addition, when degenerative changes were evaluated, the difference between fluorine group and Group T and Group SF was significant ($p<0.001$). In the evaluation of hyperemia a statistical difference was found between fluorine group and Group SF and Group S ($p <0.001$). There was a significant difference between Group F, Group SF, Group S and Group T in terms of cell infiltration ($p<0.05$) (Figure 1).

DISCUSSION

As a result of the widespread use of fluoride in the industrial field as well as its presence in nature, the rate of fluoride to which living things are exposed is increasing. With increasing amount of fluorine in the organism, various degenerations occur in various organs through oxidative stress, DNA degradation, ion channel modulations and intracellular protein degradation. One of the most typical indicators of metabolic reflection of these fluorine reactions is the increase in oxidative stress parameters. Research on the regression of oxidative stress caused by various stimulants entering the body by using exogenous antioxidants has been the most popular studies of recent years.[19,20]

In studies conducted to date, treatments that can be effective in alleviating or eliminating the effects of fluoride toxicity have been searched but not found. In recent years, studies with antioxidants have gained importance in fluoride toxicity. Silymarin, which is known to be an antioxidant substance, is said to be useful in the correction of functional and morphological disorders in the liver.[21,22] Silymarin has been reported to protect the liver from toxins such as acetaminophen, ethanol, carbon tetrachloride, doxorubicin.[23-25] Silymarin is referred to as a hepatoprotective substance due to its antioxidant properties, lipid peroxidation inhibitory effect, and activating effect of hepatic glutation production mechanisms. Silymarin can also be used for mast cell stabilization, anti-inflammatory, immune function regulator effects and as antifibrosis inducer.[22,26-33] Because of its free radical scavenging and stabilizing membranes, silymarin is also used to remove lipid peroxidation and hepatotoxic effects.[27]

The aim of this study was to investigate the hepatotoxicity and oxidative stress induced by sodium fluoride in rats and to evaluate the prophylactic and therapeutic effects of silymarin against this condition. For this purpose, changes in the activities of antioxidative enzymes such as SOD, GSH-Px, and changes in MDA levels indicative of lipid peroxidation, were evaluated.

In this study, the liver weights of the rats in the Group F which were given NaF alone for 30 days, when compared with the values determined in other groups, showed significant difference and was evaluated as the toxic effect of fluorine (Table 1). Perera et al., similar to the results of this study, stated that the liver weights determined in the fluorine-treated group were lower than those in the other groups.[34]

Statistically significant differences were found between sodium fluoride and sodium fluoride and silymarin treated and control groups in the serum AST activity in the groups in this study (Table 3). In several studies, it was stated that serum AST and ALT values were higher in fluorine treated group than those found in other groups.[34-36] The same investigators have demonstrated that antioxidant applications can eliminate the effect of fluorine on said enzyme activities. Perera, et al.[34] found no statistically significant difference in serum ALT value on the 30th day of the study compared to the pre-study value, but found that the value determined on the 60th day of the study was statistically different. Similarly, on the 30th day of the study, there was no statistically significant difference in the mean ALT value in the Group F compared to the value in the control group. In the study, the increase in ALT and AST values in Group F (Table 3) showed liver destruction. In the group that was administered fluoride together with silymarin (FS), and in the group treated with silymarin following fluoride application (T); the fact that ALT and AST values were lower than those in the Group F were interpreted as the protective and curative efficacy of silymarin in fluoride toxicity.

Oxidative stress causes cell death, usually associated with lipid peroxidation (LPO). There is oxidative degeneration of lipids in LPO. The status of LPO is demonstrated by the identification of the LPO's

by-product MDA.[11] The average MDA value determined in the Group F was higher than the values determined in other groups (Table 2). Iano et al., contrary to the results obtained in this study and other studies, reported that MDA levels in the fluorine-treated groups were found to be lower than pre-trial values.[37-39]

O_2^- is destroyed by superoxide dismutase (SOD), resulting in H_2O_2 and O_2. For the natural elimination of O_2^-, H_2O_2, which is considered less reactive but potentially more dangerous, is formed.[40]

The average SOD value obtained from the Group F was lower than the average values obtained from the Group K and Group S (Table 2). Iano et al.[37] found that the SOD level in the fluorine group was lower than the values determined in the other groups. This finding was consistent with the data in this study.

In this study, in the evaluation of liver tissue GSH-Px activity, in comparison with the values obtained from Group K and Group S; mean value obtained from the Group F was found to be significantly lower (Table 2). Mean GSH-Px values in Group FS and Group S were calculated to be higher than the values in other working groups (Table 2). Iano et al. and Vasant and Narasimhacharya found high GSH-Px activity in the fluorine-treated group, while Kanagaraj et al. stated that they found low GSH-Px activity level in the fluoride group.[14,37,38] In this study; The decrease in SOD and glutathione peroxidase values and increase in MDA levels in the fluorine treated group showed oxidative degradation in the liver tissue, whereas the levels of SOD and glutation peroxidase levels were higher in the fluoridated (FS) group with silymarin and in the cured silymarin (T) group following fluoride administration. It was interpreted as an indicator of the protection of liver against fluoride toxicity due to its antioxidant properties.

Histopathological changes were more severe in the Group F (+++) and their severity in Group FS, Group S and Group T were found to be lightened (Figure 1). Significant differences were found between the Group F, Group S and Group T in terms of deterioration in remak cords. In addition, there was a significant difference between Group F, Group T and Group FS in terms of degenerative changes. In the evaluation of hyperemia, there was a significant difference between Group F, Group FS and Group S. In terms of cell infiltration, the difference between Group F, Group FS, Group S and Group T was significant. Perera et al. noted that the inflammatory changes detected in the cells in the portal region of the liver were similar to the findings in this study.[34] Samanta et al. found that moderate fat, cellular infiltration, and bleeding areas were formed in the liver of the fluoride-treated group and were consistent with the changes found in this study.[41]

Only fluorine treated group; that may be caused by oxidative destruction, cellular stress. Based on these data, it was concluded that silymarin affects fluoride-induced cellular differentiation is effective in preventing and correcting histopathological changes due to fluorine uptake.

CONCLUSION

In rats with toxic effects given sodium fluoride; it was expected that this toxic effect could be lessened or the severity of the toxic effect would occur less with silymarin. According to the analysis results in the study; it is noteworthy that cell destruction markers, enzyme values and histopathological changes appear to be milder than expected, especially in the group given fluorine together with fluorine only compared to the group given fluorine. In addition, the same parameters are compared. As expected in the evaluation between only the fluorine-treated group and the fluorine-only group for 40 days, and then 10-day fluorine only, it was observed that slymarin alleviates the toxic effect of fluorine. Considering the hepatoprotective effect of silymarin, it was thought that it would be beneficial in terms of elucidating the effect pathways at systemic and cellular levels in fluorosis events.

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Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or

members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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