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AMELIORATIVE EFFECTS OF BAICALIN AGAINST EXPOSURE TO FLUMETHRIN IN MALE RATS*
ERKEK RATLARDA FLUMETRİN MARUZİYETİNE KARŞI BAİKALİNİN İYİLEŞTİRİCİ ETKİLERİ

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ABSTRACT

Flumethrin is a pyrethroid insecticide, while baicalin is a flavonoid with antioxidant, anti-inflammatory, and anticarcinogenic properties. The aim of this study was to investigate the effects of baicalin on biochemical parameters and lipid peroxidation flumethrin-induced in rats. In the study, 42 rats were divided in to six groups with each group comprising seven rats. Flumethrin was administrated 15 mg/kg b.w. to second group, flumethrin+baicalin 50 mg/kg b.w. was administrated to third group, flumethrin+baicalin 100 mg/kg b.w. was administrated to fourth group, baicalin 50 mg/kg b.w. was administrated to fifth group, and baicalin 100 mg/kg b.w. was administrated to sixth group. After, blood and tissue samples were collected for biochemical and histopathological evaluations. According to obtained results, when flumethrin-induced group was compared to control, alkaline phosphatase, cholesterol, blood urea nitrogen, uricacid and total protein levels significantly decreased. Also, kidney catalase and plasma glutatione peroxidase, liver catalase and superoxide dismutase activities decreased, but both kidney and liver nitric oxide and melon dialdehyde levels increased in flumethrin-induced group. Flumethrin caused to histopathological alterations in tissues. On the other hand, statistically, kidney catalase and plasma glutation eperoxidase, liver catalase and superoxide dismutase activities increased, but nitricoxide and melon dialdehyde levels decreased in all groups given baicalin. In additionally, baicalin affected to some biochemical parameters ($p<0.05$) and regressed to tissue damage. The obtained biochemical results were consistent with histopathological results. In conclusion, this study suggests that Baicalin can ameliorate oxidative stress and tissue damage in flumethrin-induced subacutet oxication in rats.

Keywords: Antioxidant, baicalin, flumethrin, lipid peroxidation, toxicity.

ÖZ

Baikalin antioksidan, antiinflamatuar ve antikarsinojenik özelliklere sahip bir flavonoidken, flumetrin bir piretroid insektisittir. Bu çalışmanın amacı, flumetrin ile indüklenmiş ratlarda baikalinin biyokimyasal parametrelere ve lipid peroksidasyonuna etkilerini araştırmaktı. Çalışmada 42 adet rat, her grupta yedi adet rat olacak şekilde altı gruba ayrıldı. Flumetrin ve baikalin mısır yağı içinde tek doz oral gavaj yoluyla 28 gün boyunca verildi: Kontrol grubuna mısır yağı uygulandı. Flumethrin 15 mg/kg c.a. ikinci gruba, flumetrin+baikalin 50 mg/kg c.a. üçüncü gruba, flumetrin+baikalin 100 mg/kg c.a. dördüncü gruba, baikalin 50 mg/kg c.a. beşinci gruba, baikalin 100 mg/kg c.a. altıncı gruba verildi. Daha sonra kan ve doku örnekleri biyokimyasal ve histopatolojik değerlendirmeler için alındı. Elde edilen sonuçlara göre, flumetrin verilen grup kontrol ile karşılaştırıldığında kolesterol, alkalen fosfataz, total protein, üre ve ürik asit düzeyleri anlamlı seviyede azaldı. Ayrıca flumetrin alan grupta böbrek süperoksit dismutaz ve glutatyon peroksidaz ile karaciğer süperoksit dismutaz ve katalaz aktiviteleri azaldı, ancak hem karaciğer hem de böbrek melondialdehit ve nitrik oksit seviyeleri arttı. Flumetrin dokularda histopatolojik değişikliklere neden olmuştur. Öte yandan, baikalin verilen tüm gruplarda istatistiksel olarak böbrek süperoksit dismutaz ve glutatyon peroksidaz ile karaciğer süperoksit dismutaz ve katalaz aktiviteleri arttı, ancak nitrik oksit ve melondialdehit düzeyleri azaldı. Ayrıca baikalin bazı biyokimyasal parametreleri etkiledi ($p<0.05$) ve doku hasarını azalttı. Elde edilen biyokimyasal sonuçlar histopatolojik sonuçlarla uyumludur. Sonuç olarak, ratlarda flumetrin ile oluşturulan subakuttoksikasyonda, Baicalin oksidatif stresi ve doku hasarını iyileştirebilir.

Anahtar kelimeler: Antioksidan, baikalin, flumethrin, lipid peroksidasyonu, toksisite.

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INTRODUCTION

Pyrethroids are the synthetic compounds derived of pyrethrins whic hare natural organic insecticides procured from the *Chrysanthemum cinerariaefolium* plant. They exhibit fewer toxic properties than other insecticides such as carbamate and organophosphate in mammals and are resistant to sunlight in the environment for a longtime. There fore, they are generally morepreferred to againstec to parasites. Pyrethroids affect the peripheral and central nervous systems. These insecticides cause inhibition of voltage-dependent sodium channels located in the cell membrane, showing rapid knock-down properties and cause temporary paralysis and death of insect. According to the differences in their chemical structures and their mechanism of action, pyrethroids are divided into two groups; Type I and Type II.[1] Flumethrin (FL) is, Type II synthetic pyrethroid,an oil-soluble insecticide used in veterinary medicine to control ectoparasites. Flumethrin is a neurotoxic substance, and its activity takes place on sodium and chloride channels of insects. Flumethrin inhibites to voltage-dependent Na channels and increases the passage of Na ions through the nerve membrane. Continuing ion permeability for a long time provides a permanent depolarization. In neurons cause repeated and prolonged stimulation on muscles and organs as sodium continues to enter the cell. This situation has a lethal effect on insects.[2,3]

The antioxidant enzymes that catalyse (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) arean essential defense against the harmful effects of free radicals. Superoxide radicalsare converted into hydrogen peroxide (H_2O_2) and molecular oxygen by SOD. The H_2O_2, a harmful metabolite, is converted to water and oxygenby CAT. The GSH-Pxuses glutathione as electron source and it prevents the formation of hydroxyl (OH) from H_2O_2. These reactions are antioxidant defense system for cells. Disruptionsin the antioxidant defence system may cause to the formation of oxidative stress. As a result of these disruptions, different aldehydes are formed. Malondi aldehyde (MDA) is the mostactive worker among these aldehydes. The amounts of MDA and nitricoxide (NO) are considered to be the most important indicator of membrane lipid peroxidation resulting from the interaction of cell membrane and the reactive oxygen species (ROS).[4,5] Pesticides may induce to oxidative stress, too.[6]

When previous studies on flumethrin are reviewed, there are only few studies reporting that it affects oxidant/antioxidant balance and hematological parameters.[7-10]

Flavonoids are polyphenolic compounds found in many fruits and vegetables.[11] Baicalin (BA), a flavonoid, is found in severalplantspecies in the *Scutellaria* genus, such as *Scutellariabaicalensis* and *Scutellarialateriflora*. In many studies, it has been stated that baicalin has anti-inflammatory, antibacterial, neuroprotective, antiapoptotic, and antioxidant properties.[12-18] Pharmacokinetic studies have shown that baicalin is hydrolyzed in the gastrointestinal tract,[19] enterohepatic recycling,[20] and transported across the cell membrane via a carrier.[21] Baicalin has a limited bioavailability of 2.2%. This leads to its limited clinical efficacy.[20] However, the absorption of baicalin in the stomach is moderate. Following its entry into metabolism, it is hydrolyzed to baicaleine, the aglycone form, bythe β glucuronidase enzyme produced by intestinal bacteria.[22]

In the present study, the effects of baicalin on blood biochemical parameters in serum and lipid peroxidation parameters in liver and kidney tissues were investigated on flumethrin-induced subacute toxicities in rats. In addition, histopathological evaluations were also performed on liver and kidney tissues.

MATERIAL AND METHODS

Chemicals

Baicalin (98%, 5 g, Med Chem Express, HY-N0197), flumethrin (Bayticol, 1000 mLpour-on solution of 1%, Bayer), ketamine (Ketals, 500 mg, 10 mL solution for injection, Pfizer), xylazine (Rompun, 2%, 23.32 mg/mL, Bayer), TBA (Sigma, T5500), nitrate reductase (Sigma, N7265), TCAA (Sigma, T6399), Griess reagent (Sigma, G4410), phosphate buffer (Sigma, P3619), *n*-butanol (Sigma, 281549), EDTA (Sigma, E5134), H_2O_2solution (Sigma, 216763), xanthine oxidase (Sigma, X1875), NaN_3 (Sigma, S2002), $CuCl_2$ (Sigma, N5130), NADPH (Sigma, N7505), FAD (Sigma, F6625), glutation reductase (Sigma, G4251) were supplied from related to companies.

Animals

The this study was carried out with the ethics committee approval dated 09.10.2019 and numbered 19/171 given by the Erciyes University, Animal Experiments Local Ethics Committee.

The rats used in the study were obtained from Erciyes University, Experimental and Clinical Research Center (DEKAM). Forty-two male *Wistar Albino* rats, aged 16-18 weeks, and weighing 250-350 g, were used. The rats were divided into six groups, with seven animals in eachcage. Animals were fed with pelletfeed *ad-libitum.* They were housed under suitable conditions[(controlled temperature (21±2°C), humidity (%50±5), air change (12 cyclesperhour), light (12 hourlight, 12 hoursdark)] by the research center.

Experimental design and model

The animals were divided into six groups with seven animals in each group, and a total of 42 rats were used. The study continued for 28 days. Group 1 was used as the control group. This group was given cornoil by oral gavage. Group 2 was given FL 15 mg/kg b.w. in cornoil by oral gavage.[7]Group 3 was given FL 15 mg/kgb.w. and a single dose of 50 mg/kg b.w. incornoil by the same route. Group 4 was given FL 15 mg/kg and BA 100 mg/kg. Group 5 was given BA 50 mg/kg and group 6 was given BA 100 mg/kg.

Taking the samples

At the end of the experiment, ketamine + xylazine anesthesia was applied to all groups. After ward, blood samples were collected into gel tubes by cardiac puncture. The rats were euthanized, and tissue samples were taken. The blood samples were centrifuged at 4000 *rpm* for 10 minutes and kept at +4 ºC and -20 ºC throughout the experiment. Liver and kidney tissues were quickly removed and stored at -20 ºC for oxidants/antioxidants analysis.

Determination of serumbiochemical parameter levels

Some biochemical parameter levels (AST, ALT, ALP, LDH, total protein, cholesterol, triglyceride, BUN, uricacid and creatinine) were determined in the blood, and analyses were performed by A Roche Cobas kit and an auto analyzer.

Determination of lipid peroxidation parameters in liver and kidney tissues

Liver and kidney tissues were homogenized in ice-cold with a pH of 7.2 phosphate buffer at a ratio of 1:4 in a mechanical-tipped homogenizer for half a minute at 20000 *rpm* for the measurement of lipid peroxidation parameters. Next, the obtained mixture was homogenized for half a minute with an ultrasonic homogenizer. Then, the homogenates were centrifuged at 20000 *rpm* for one hour in a centrifuge set at +4 ºC, and the clear upper part was taken in to the Eppendorf tubes. The tubes were stored in the freezer at -20 ºCuntil the time of analysis.

Tissue protein,[23,24] MDA,[25] SOD,[26] NO,[27] GSH-Px,[28] and CAT[29] were analyzed according to the methods described.

Histopathological evaluation

Liver and kidney tissues were taken into 10% formaldehyde. Tissues detected in formaldehyde for at least 48 hours were trimmed and placed in tissue cassettes. The taped tissues were washed under tap water for eight hours and then dehydrated by passing through serial alcohols. Dehydrated tissues were made transparent by passing through xylene and then blocked in paraffin. Five-micron sections from each of the blocks were taken on a slide with a microtome. Tissues on the slide were stained with Hematoxylin-Eosin (H&E), and histopathological changes in the tissues were evaluated.

Statistical evaluation

The SPSS program (SPSS, version 21.0, IBM Corp.) was used for all statistical analyses. Statistical analysis of the data was calculated by one-way analysis of variance (ANOVA). Differences between groups were determined using the Tukey test. Analysis results were given as arithmetic mean±standard deviation. The value of $p<0.05$ was taken as the level of significance.

RESULTS

Effects of baicalin and flumethrin on biochemical parameters

Obtained results were shown in tables. Triglyceride, cholesterol, BUN, creatinine, and uricacid (Table 1); AST, ALT, ALP, LD Hand total protein levels (Table 2).

According to the obtained data from this study, compared to the groups in rats, the serum triglyceride levels were nostatistically significant change. However, cholesterol and BUN levels were statistically significantly lower in all groups compared to the control group ($p<0.05$). In addition, creatine level was similar to

Table 1. Effects of baicalin and flumethrin administration on serum triglyceride, cholesterol, BUN, creatinine and uricacid levels in rats

Groups	Triglyceride (mg/dL)	Cholesterol (mg/dL)	BUN (mg/dL)	Creatinine (mg/dL)	Uricacid (mg/dL)
G1	148.00±51.42	67.57±9.46^{b}	22.05±2.26^{d}	0.38±0.02^{a,b}	1.34±0.46^{b}
G2	110.42±34.84	57.00±5.91^{a,b}	18.27±1.81^{a,b,c}	0.37±0.03^{a,b}	0.92±0.09^{a,b}
G3	78.85±22.31	53.71±4.92^{a}	16.27±1.35^{a,b}	0.33±0.02^{a,b}	0.78±0.17^{a}
G4	83.42±28.61	57.42±4.96^{a,b}	16.04±2.3^{a}	0.33±0.01^{b}	0.81±0.16^{a}
G5	135.57±62.18	61.42±6.80^{a,b}	19.48±1.24^{c,d}	0.38±0.03^{a}	1.01±0.35^{a,b}
G6	119.57±53.12	56.42±7.80^{a}	19.07±1.59^{b,c}	0.37±0.04^{a,b}	1.00±0.22^{a,b}
P values	0.35	0.01	0.00	0.01	0.00

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b,c,d} The same letters in the same column in dicatesimilarity between groups, different letters indicate difference between groups ($p<0.05$).

Table 2. Effects of baicalin and flumethrin administration on serum AST, ALT, ALP, LDH, total protein and albümin levels in rats

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)	LDH (U/L)	Total protein (g/dL)
Group 1	124.00±30.33	63.00±15.73	313.85±78.70^{b}	1153.00±227.67	6.59±0.37^{b}
Group 2	120.28±22.44	62.57±7.04	203.57±48.51^{a}	1261.57±217.66	6.23±0.23^{a,b}
Group 3	121.57±17.36	62.85±2.60	227.28±47.78^{a}	1019.85±307.54	6.03±0.22^{a}
Group 4	101.00±7.18	63.71±6.82	201.14±49.41^{a}	979.42±240.52	6.07±0.24^{a}
Group 5	137.14±47.20	60.14±5.17	222.85±47.04^{a}	1253.14±390.16	6.36±0.26^{a,b}
Group 6	99.00±11.26	53.42±7.04	205.28±31.88^{a}	972.71±366.64	6.09±0.23^{a}
P values	0.08	0.22	0.00	0.25	0.00

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b} The same letters in the same column indicatesimilarity between groups, different letters indicate difference between groups($p<0.05$).

control in groups 2, 3 and 6. However, the uricacid level was statistically significantly decreased in all groups when compared to the control; this decrease was more pronounced in FL+BA groups (Groups 3 and 4) ($p<0.05$). When the uricacid level was compared between the groups, Groups 2, 5, 6, and Groups 3, 4 were similar (Table 1).

When the study results were evaluated, although there were changes in AST, ALT and LDH levels in the FL and BA groups compared to the control, there was nostatistically significant difference. However, when comparing the ALP levels between groups, it was statistically significantly lower in all groups compared to the control group ($p<0.05$). Also, total protein level was lower in all groups than the control ($p<0.05$) (Table 2).

Effects of baicalin and flumethrin on lipid peroxidation parameters in liver and kidney tissues

Lipid peroxidation parameter levels (MDA, SOD, NO, GSH-Px and CAT) in liver and kidney tissues are shown in Tables 3 and 4.

According to the present study results (Table 3), the MDA level in the liver tissues increased significantly in the flumethrin-administered toxication group compared to the other groups. Groups 5 and 6 were similar to the control group. Also, the MDA level decreased significantly in the groups that were given baicalin in addition to flumethrin. The SOD activity in the liver tissues was statistically significantly lower in the flumethrin toxication group compared to the other groups. The results of the two groups, in which only baicalin was administered in two different doses, were similar to those of the control. The SOD level in all groups given baicalin was statistically significantly higher than in the toxication group receiving only flumethrin (Group 2). When the results were evaluated in terms of the NO level in the liver tissues, there was a statistically significant increase in the NO level in the group given only flumethrin compared to all other groups. The NO levels of all groups that were given baicalin were similar to the control. The liver GSH-Px enzyme activity was not statistically different in all groups. The CAT activity showed a statistically significant decrease in the flumethrin group (Group 2) compared to the control when comparing groups. The CAT activity was similar to the control group in the groups that were given baicalin (Groups 3, 4, 5, and 6) ($p<0.05$).

In kidney tissue (Table 4), it was ascertained that, when the MDA level was compared between the groups, the MDA level of the group that received only flumethrin (Group 2) showed significantly higher than the control and all other groups. The results of the two groups that were given only baicalin in two different doses (Groups 5 and 6) were similar to the control group's results. In the groups where flumethrin and baicalin were administered together (Groups 3 and 4), the MDA level was lower than in Group 2. The changes in activities of the SOD were not statically crucial in allgroups. According to the data, the NO level in the kidney tissues increased statistically in the flumethrin group compared to all other groups. The NO level was similar to the control in the groups that were given baicalin. The GSH-Px activity decreased significantly in Group 2 compared to all other groups, including control. The results of the rat group in which only baicalin was administered at high doses were similar to the control group. Flumethrin administration in rats significantly decreased the CAT activity

Table 3. Effects of baicalin and flumethrin administration on liver MDA, SOD, NO, GSH-Pxand CAT levels in rats

Groups	MDA (µmol/g)	SOD (U/g protein)	NO (nmol/mg protein)	GSH-Px (nmol/dk/mg protein)	CAT (k/g protein)
Group 1	2.21±0.33 ^{a}	0.056±0.009 ^{a}	2.45±0.27 ^{a}	17.43±5.57	1233.22±165.80 ^{a}
Group 2	3.33±0.47 ^{b}	0.041±0.004 ^{b}	3.30±0.17 ^{b}	13.69±4.47	811.82±127.70 ^{b}
Group 3	2.84±0.31 ^{a,b}	0.048±0.008^{a,b}	2.68±0.33 ^{a}	14.90±4.20	1005.95±193.83^{a,b}
Group 4	2.69±0.55 ^{a,b}	0.047±0.002^{a,b}	2.57±0.30 ^{a}	13.25±4.53	1029.09±281.09^{a,b}
Group 5	2.30±0.35 ^{a}	0.054±0.005 ^{a}	2.58±0.18 ^{a}	15.96±6.61	1126.89±247.49^{a,b}
Group 6	2.39±0.32 ^{a}	0.053±0.008 ^{a}	2.36±0.33 ^{a}	17.71±6.02	1182.63±263.78 ^{a}
P values	0.00	0.00	0.00	0.51	0.01

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b} The same letters in the same column indicate similarity between groups, different letters indicate difference between groups ($p<0.05$).

Table 4. Effects of baicalin and flumethrin administrations on kidney MDA, SOD, NO, GSH-Px and CAT levels in rats

Groups	MDA (µmol/g)	SOD (U/g protein)	NO (nmol/mg protein)	GSH-Px (nmol/dk/mg protein)	CAT (k/g protein)
Group 1	1.36±0.23 ^{a}	0.083±0.006	2.38±0.49^{a,b}	21.22±6.18 ^{a}	229.77±48.03^{a,b}
Group 2	2.11±0.14 ^{c}	0.075±0.002	2.83±0.23 ^{b}	13.28±3.21 ^{b}	187.00±26.03 ^{a}
Group 3	1.71±0.28 ^{b}	0.078±0.003	2.29±0.16 ^{a}	15.01±4.66^{a,b}	211.98±18.43^{a,b}
Group 4	1.75±0.19 ^{b}	0.078±0.008	2.35±0.25 ^{a}	19.00±4.54^{a,b}	219.04±20.96^{a,b}
Group 5	1.35±0.13 ^{a}	0.084±0.005	2.22±0.28 ^{a}	20.80±5.25^{a,b}	228.27±56.24^{a,b}
Group 6	1.32±0.12 ^{a}	0.081±0.008	2.10±0.16 ^{a}	21.61±4.17 ^{a}	267.80±69.17 ^{b}
P values	0.00	0.10	0.00	0.00	0.04

Group 1 (Control), Group 2 (Flumethrin, 15 mg/kg b.w.), Group 3 (Flumethrin, 15 mg/kg b.w. + Baicalin 50 mg/kg b.w.), Group 4 (Flumethrin, 15 mg/kg b.w. + Baicalin 100 mg/kg bw), Group 5 (Baicalin 50 mg/kg bw), Group 6 (Baicalin 100 mg/kg b.w.).
Data are expressed as mean ± standard deviation. ^{a,b,c} The same letters in the same column indicate similarity between groups, different letters indicate difference between groups ($p<0.05$).

in the kidney tissues compared to all other groups, including the control. This enzyme activity in Groups 3, 4, and 5 did not change compared to the control. The group results that received only baicalin at a high level were statistically significantly higher than all groups, including the control ($p<0.05$).

Histopathological evaluation of tissues

Histopathological lesions were depicted on Figures 1 and 2.

As seen in figures (Figure 1 and 2), in the group that was given flumethrin (Group 2), it was noted that there was severe vacuolar degeneration in hepatocytes in liver tissues (Fig1b). As a result of the histopathological evaluation of the kidneys, severe degeneration was observed in the tubulusepithelium (Fig2b). In Group 3 and Group 4, lesions in all tissues regressed (Fig 1c and 2c). It was observed that the degree of recovery in tissues (1d and 2d). No histopathological lesions were found in the groups that were given only baicalin (Group 5 and 6).

DISCUSSION

Flumethrin is an insecticide frequently used in agriculture and in veterinary medicine to combat ectoparasites. In our study, flumethrin toxicity occuredin rats, and baicalin was administered in different doses for 28 days. The aim was to determine lipid peroxidation parameters in liver and kidney

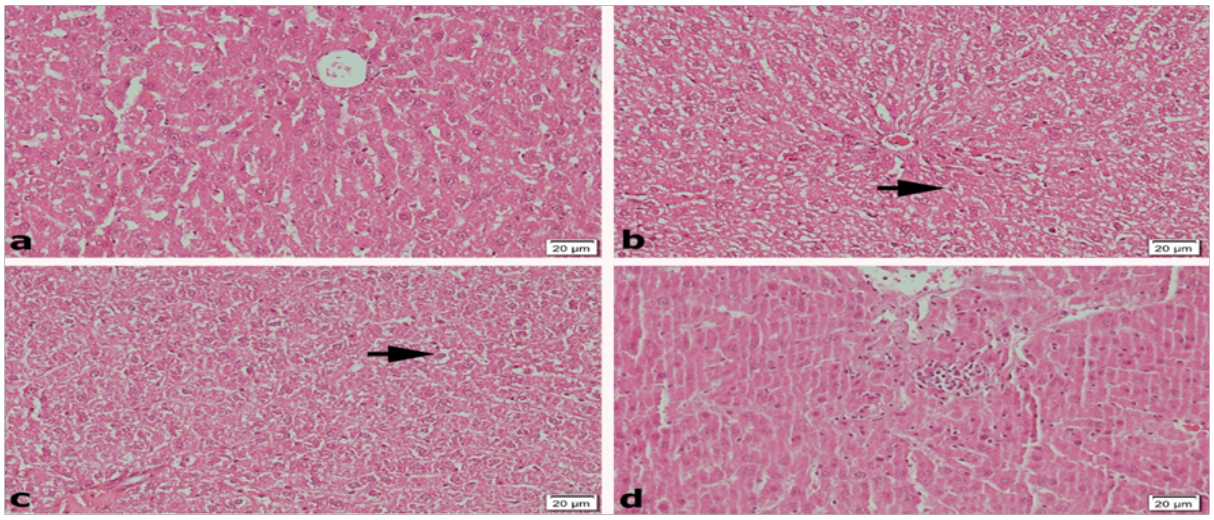

Figure 1: Histopathological evaluation of liver tissue

a) Control liver tissue. H&E, Bar: 20µm
b) Severe degeneration of hepatocytes (arrow). Group 2. H&E, Bar: 20µm
c) Moderate degeneration of hepatocytes (arrow). Group 3, H&E, Bar: 20µm
d) Regressed liver degeneration (arrow). Group 4, H&E, Bar: 20µm

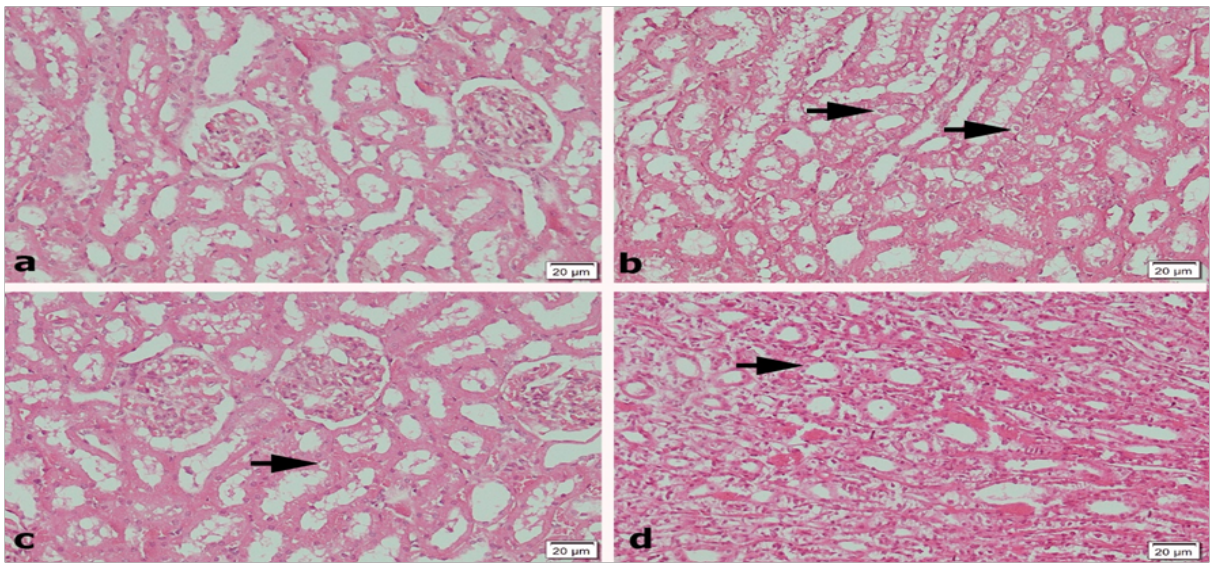

Figure 2: Histopathological evaluation of kidney tissue

a) Control group kidney tissue. H&E, Bar: 20µm
b) Severe degeneration of tubulusepithelium (arrows). Group 2, H&E, Bar: 20µm
c) Mild degeneration of tubulusepithelium (arrow). Group 3, H&E, Bar: 20µm
d) Mild degeneration of tubulusepithelium (arrow). Group 4, H&E, Bar: 20µm

tissues and the biochemical enzyme levels in the blood and evaluate the histopathologica lchanges in liver and kidney tissues.

In the literature review, some studies have been reported about the effects of flumethrin in animals. In a seven-day study performed by Küçükkurt et al. (2010) on the effects of flumethrin in sheep, it was found that there was no significant difference in blood MDA and NO levels, while GSH, CAT and SOD activities decreased.[30] Kanbur et al. (2010) showed that NO and MDA levels in plasma and all tissues increased CAT and SOD activities decreased in all tissues. Also, GSH-Pxenzymeactivity decreased significantly in erythrocytes, while increased in tissues of flumethrin-induced rats.[7] Salama et al. (2019) indicated that MDA level increased, SOD, CAT and GSH activities decreased in brain and liver tissues induced by flumethrin in rat.[10] In another 14-day study about the effects of flumethrin in rats, it was observed that flumethrin caused to increase in MDA level which is an important indicator of lipid peroxidation. Since the production of free radical sincreases with the effect of flumethrin, it is expected that an increase in the level of endogenous antioxidant enzymes (CAT and SOD) involved in cleansing these radicals may be to occurinitially. They reported that to be thereason for the increase in SOD and CAT activities in acute studies.[8] Mishra et al., (2012) revealed that flumethrin increased MDA level, but decreased SOD, and CAT activities in tissue of rat.[9] In the present study, when flumethrin-induced group compare to control group, MDA and NO level sincreased in kidney and liver tissues. On the other hand, CAT level decreased in both kidney and liver tissues, while SOD in the liver and GSH-Px in kidney tissue. Thus, flumethrin toxication caused to significantly an increase in the level of free radicals. The results of our study were consistent with the results of previous studies.

In literatures, it was reported that ALT and AST levels increased in flumethrin-induced toxication.[8,9] In our study, there was no statistically significant difference for AST and ALT levels in serum. However, when comparing the ALP levels between groups, it was determined that there was a statistically significant decrease in all groups compared to the control. Also, flumethrin expose led to a significant decrease in the levels of total protein, cholesterol, BUN, and uric acid in serum in rats ($p < 0.05$).

In a hydrogenperoxide-induced oxidative stress study in rats conducted by Zheng et al. (2014),[31] it was reported that the administration of baicalin decreased the MDA level while it increased the SOD and GSH-Px activities. Jang et al. (2003) revealed that hepatoprotective effects of baicalin on acetaminophen-induced liver damage in mice.[32] Su et al. (2017) demonstrated that baicalin have the all eviation effect to the liver and kidney damage induced-cinnabar in rat.[33] As known that, SOD, CAT, and GSH-Px enzymes form an antioxidant defense against oxidative stress. In the present study, flumethrin administration caused a decrease in SOD enzyme activity in liver tissue, GSH-Px enzyme activity in kidney tissue, and CAT enzyme activity in both tissues. On the other hand, when baicalin-received groups compare to flumetrin-induced group, these antioxidant enzymes were increased in baicalin-received groups.

The previous studies about flumethrin were examined, but there was not enough literature on histopathological findings. Salama et al. (2019) reported that flumethrin caused to minor histopathological lesions in liver and kidney tissues.[10] When the histopathological findings in our study were examined, the observation of severe degeneration in the liver and kidney tissues was in line with the findings in the literature. It was also observed that the tissue damage regressed in the groups treated with flumethrin and baicalin together.

When the experimental data were evaluated, the present study suggests that flumethrin effected some parameters (ALP, cholesterol, BUN, uricacid and total protein) levels in serum and kidney CAT and GSH-Px, liver CAT and SOD activities. Histopathological evaluation revealed that there were some alterations in tissues, when flumethrin administration. Baicalinaltered some parameters (cholesterol, ALP, total protein, BUN, uricacid), NO and MDA levels; it increased kidney CAT and GSH-Px, liver CAT and SOD activities in flumethrin-induced groups. It was determined that the lesions in tissues regressed in the groups where baicalin was applied in flumethrin-induced rats. Biochemical results were consistent with histopathological results.

CONCLUSION

In conclusion, it was observed that alterations in lipid peroxidation parameters and the histopathology of the tissues resulted from the toxic effects of flumethrin. It was concluded that the application of baicalin contributes to the antioxidant defense system, supports tissue healing by reducing oxidation, and plays a constructive role in reversing the negative effects of flumethrin. Thus, baicalin can alleviateoxidativestress and tissue damage in flumethrin-induced subacute toxication in rats. The findings of this study suggest that baicalin might be used as a pharmacological agent in flumethrin toxications.

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