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Preventive Effects of Silymarin on Diclofenac-induced Toxicity in the Domestic Pigeon (*Columba livia*)

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ABSTRACT

This study aimed to evaluate the effects of silymarin on diclofenac-induced acute liver and kidney poisoning in domestic pigeons (Columba livia). The use of NSAIDs leads to adverse drug effects, such as cardiovascular and gastrointestinal hemorrhage and renal side effects. The vast amount of pharmacological attributes possessed by silymarin describes the remarkable content of research aimed at understanding its effect in the remedy of diverse diseases. Fifteen pigeons were randomly assigned into three groups (1, 2, and 3). Group 1 pigeons served as the negative control group and only were given tap water. Groups 2 and 3 were administered diclofenac (15 mg/kg PO q12h) since the start of the study for 24 h. The third group of pigeons was treated with silymarin (35 mg/kg) plus diclofenac, beginning 12 hours after diclofenac exposure, with the silymarin treatment continuing q12h for 48 h. Blood samples were taken from the birds at times 0, 12 h, 24 h, and 48 h of the experiment for serum biochemistry analysis. The results indicated that the treatment of pigeons with silymarin reduced the serum level of AST, ALT, UA, and urea while increasing ALB and TP. Clinical observations also indicated the presence of toxication symptoms, including loss of appetite, diarrhea, and lethargy. These symptoms improved faster in the silymarin group. It can be concluded that silymarin reduces acute liver and kidney damage caused by diclofenac in pigeons.

Keywords

Diclofenac, Domestic pigeon, Serum biochemistry, Silymarin

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Abbreviations

NSAIDs: Nonsteroidal anti-inflammatory drugs
AST: Aspartate aminotransferase
ALT: Alanine transaminase
TP: Total protein
ALB: Albumin
UA: Uric acid

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Introduction

In animals, the liver is an organ in which poisons are widely accumulated.

Liver tissue is responsible for providing essential structures, such as protein, carbohydrate, fat, bile secretion, glycogen storage, and detoxification of various medications [1, 2].

NSAIDs are a class of medicines that reduce inflammation. play an important role in controlling and reducing fever and pain, and preventing blood clotting [3]. These agents are the most commonly used analgesics worldwide [4]. Adverse drug effects depend on the characteristics of the medication. Digestive system, cardiovascular, and kidney complications are among the common side effects of this pharmaceutical class [5]. Due to the arbitrary use of NSAIDs in human societies, we see drug side effects every year, which are 25% in the United Kingdom and 21% in the United States [4]. COX is an enzyme that converts arachidonic acid to prostaglandin. The main mechanism of action of NSAIDs is inhibiting this enzyme. As a result, a reduction in pain, inflammation, and fever occurs [6].

Diclofenac, sold under different names in the market, is an NSAID that is applied to treat pain and inflammatory diseases, such as gout. Oral, parenteral, or topical routes of application diminish pain within 30 minutes [3]. The most important side effects of this agent are heart disorders, kidney failure, and stomach ulcers. Moreover, its common adverse effects include abdominal pain, vomiting, gastrointestinal bleeding, headache, and dizziness. It should be noted that it is contraindicated in humans during the last three months of pregnancy [7]. As mentioned earlier, prostaglandin production from arachidonic acid through the COX pathway is inhibited by diclofenac [4]. The maximum plasma peak of diclofenac is observed 2 h after oral administration. Diclofenac is excreted through the liver and kidneys. It is metabolized in the liver to hydroxy diclofenac, which turns into sulfate and glucuronic acid, facilitating excretion through the renal system [4]. It is known so far that diclofenac causes toxicity due to the damage to the mitochondrial function and the creation of pro-oxidant radicals, which are metabolized by peroxidases [4].

In the past, several studies have been conducted on animals exposed to poisoning and their treatment with different herbal medicines [8, 9]. Silymarin is one of the plant-derived agents that has been studied many times due to its antioxidant, anti-inflammatory, immune system modulator, anti-fibrotic, antiviral, and liver-protective properties [10, 11]. Silymarin is a polyphenolic flavonoid extracted from the seeds of milk thistle (Silybum marianum), which belongs to the Asteraceae family [12]. Silymarin, as a liver-protective medication with detoxification properties, has shown good performance in studies on exposure to acetaminophen, carbon tetrachloride, arsenic, butyrophenones, and phenothiazines [7, 13]. This plant has been observed to repair the liver damage caused by sodium nitrate in rats [12].

Considering the lack of data in the literature, the present study aimed to investigate the therapeutic effects of silymarin on diclofenac-induced poisoning in pigeons and its protective role on the liver and kidney.

Result

As can be observed in Table 1 and figure 2, there was no significant difference in tested parameters between different treatment groups at the start of the experiment (hour 0). An increase in AST, ALT, and UA was found 12 h after exposure to diclofenac. The increase in AST, ALT, and UA was significantly higher in the positive control group ($p < 0.05$). In terms of these three parameters, no significant difference was observed between the treatment group and the negative control 24 and 48 h after treatment, but both groups had a significant difference with the positive control group ($p < 0.05$). Regarding urea, no significant difference was observed between the treatment group and the positive control in hours 12 and 24, but both groups showed a significant difference with the negative control group ($p < 0.05$), and 48 h after exposure to diclofenac, a significant difference was observed between silymarin and the positive control groups ($p < 0.05$).

The decrease in ALB and TP was found 12 h after exposure to diclofenac. The mean ALB level in hours 24 and 48 was not significantly different between the negative control and treatment groups, but both groups had a higher level of ALB than the positive control group and showed a significant difference ($p < 0.05$). In terms of TP in hours 12 and 48, no significant difference was observed between the treatment group and the negative control, but both groups had a significant difference with the positive control group ($p < 0.05$).

The trend of alteration in the measured parameters over time in each group showed no significant difference in the negative control group in terms of all the investigated parameters between the studied time points. On time 12, there was a rise in UA and urea, which was significant in the treatment and positive control groups between times 0 and 12. Then, the amount of UA and urea in the blood declined after 24 and 48 h in the Silymarin group, but in the positive control group, the concentration of UA was still high.

AST and ALT enzymes significantly increased in

Table 1.
Mean ± SD for kidney indices and liver enzyme concentration at different time points, post-exposure with Silymarin compared to control groups.of S. aureus in Iran.

	Treatment	0	12	24	48
Uric acid (mg/dL)	Negative control	3.93 ± 0.70 a,A	3.94 ± 0.60 a,B	3.86 ± 0.80 a,B	3.90 ± 0.78 a,B
	Positive control	4.63 ± 0.66 b, A	*17.30 ± 4.19 a, A*	*15.13 ± 3.80 a, A*	*12.20 ± 2.00 a, A*
	Silymarin	3.90 ± 0.81 b, A	12.03 ± 1.95 a, A	8.16 ± 1.95 b, B	5.70 ± 0.98 b, B
Urea (mg/dL)	Negative control	2.03 ± 0.73 a,A	2.26 ± 0.80 a,B	2.00 ± 0.81 a,B	2.50 ± 0.70 a,B
	Positive control	2.63 ± 0.66 b, A	9.73 ± 0.76 a, A	12.93 ± 3.10 a, A	10.76 ± 1.88 a, A
	Silymarin	2.83 ± 0.66 b, A	11.28 ± 1.03 a, A	8.16 ± 0.85 b, A	5.62 ± 0.61 b, B
AST (U/L)	Negative control	51.33 ± 3.21 a, A	52.33 ± 1.52 a, B	53.33 ± 5.03 a, B	53.35 ± 3.51 a, B
	Positive control	51.35 ± 1.52 b, A	149.66 ± 10.01 a, A	157.00 ± 17.08 a, A	147.66 ± 10.01 a, A
	Silymarin	51.66 ± 2.51 b, A	116.33 ± 35.92 a, A	75.33 ± 12.85 b, B	67.66 ± 2.51 b, B
ALT (U/L)	Negative control	9.33 ± 1.52 a,A	9.66 ± 2.52 a,B	10.00 ± 2.64 a,B	8.66 ± 1.52 a,B
	Positive control	10.00 ± 0.59 b, A	25.66 ± 9.29 a, A	28.33 ± 14.43 a, A	27.00 ± 14.73 a, A
	Silymarin	15.66 ± 4.04 a, B			11.33 ± 3.21 b, B
ALB (g/dL)	Negative control	1.71 ± 0.10 a, A	1.69 ± 0.10 a, A	1.71 ± 0.09 a, A	1.71 ± 0.09 a, A
	Positive control	1.21 ± 0.21 a, A	0.54 ± 0.23 b, B	0.66 ± 0.12 b, B	0.66 ± 0.12 b, B
	Silymarin	1.31 ± 0.41 a, A	0.69 ± 0.24 b, B	1.04 ± 0.05 a, A	1.22 ± 0.31 a, A
TP (g/dL)	Negative control	4.03 ± 0.45 a, A	3.93 ± 0.45 a, A	4.16 ± 0.50 a, A	3.93 ± 0.47 a, A
	Positive control	3.90 ± 0.45 a, A	2.50 ± 0.60 b, B	2.43 ± 0.49 b, B	2.46 ± 0.56 b, B
	Silymarin	3.93 ± 0.58 a,A	3.93 ± 0.58 a,A	3.00 ± 0.30 b,AB	3.60 ± 0.43 a,A

*Values are mean ± SD of three replicates.
a bThe different superscript letters in the same row indicate significant differences ($p < 0.05$).
A-BThe different superscript letters in the same column in each parameter indicate significant differences ($p < 0.05$).

the treatment group 12 h after exposure to diclofenac. AST enzyme decreased 24 h after treatment with silymarin compared to time 12 ($p < 0.05$), but ALT enzyme declined 48 h post-treatment. ALB showed a reduction after 12 h in the positive control and treatment groups. However, after 24 h, the ALB level rose in the silymarin group. Although TP decreased after 12 and 24 h in the positive control and treatment groups, it increased after 48 h in the silymarin group.

Clinical observations indicated toxication symptoms in the positive control and silymarin groups after 12 h from the onset of the experiment, which included the loss of appetite, diarrhea, and lethargy. These symptoms improved faster in the silymarin group as we did not find these symptoms 48 h after the onset of the experiment. On the other hand, the clinical signs of poisoning were still observed in the positive control group. There was no death in these groups.

Discussion

NSAIDs are utilized to treat different clinical conditions in animals. Although NSAIDs are essential to managing pain and inflammatory conditions in birds, their prescription is limited. One of the main

reasons for this issue is the shortage of research on NSAID usage in birds. NSAIDs, such as diclofenac, are applied as an antipyretic agent and a painkiller. If diclofenac is used once or several times but in a short period and a high dose, it will lead to acute poisoning [4]. In accidents and emergencies where the patient is injured and in pain, the possibility of acute diclofenac poisoning is high, especially if we do not have access to opioids and have to use a high dose of diclofenac to relieve pain [4]. Symptoms of acute poisoning include various side effects and even death within a few days [14].

The clinical signs of diclofenac poisoning include neurological symptoms, such as drowsiness, dizziness, vision problems, hearing problems, gastrointestinal problems (e.g., gastric ulcers and nausea), and renal issues (e.g., impaired urination) [15]. The results of this study showed that administering diclofenac caused some symptoms, including loss of appetite, diarrhea, and lethargy in groups II and III. However, it was observed that the symptoms in the birds in group III improved after the administration of silymarin, while the symptoms were more stable and resolved in a shorter period in comparison to the pigeons in group II. Similar results were reported in a previous study that investigated the protective effects of silymarin on hepatotoxicity and renal toxicity caused by acetaminophen in pigeons [1].

According to previous studies, it can be stated that diclofenac causes serious damage to the liver and kidneys by increasing liver enzymes and decreasing protein production, as well as increasing UA and urea [16, 17]. Diclofenac poisoning in vultures and chickens is characterized by significant increases in plasma UA and subsequent gout [17]. As mentioned in Table 1, hepatocyte injury markers (AST and ALT), were increased in diclofenac-administrated groups (II, III), while we observed a decrease in AST and ALT activities 24 h post-administration in the silymarin group (III). In line with the present study, researchers demonstrated that the administration of silymarin significantly improved the altered serum biochemical parameters [1].

Hepatic degenerative changes by diclofenac cause cellular damage [18]. Diclofenac poisoning results in varying degrees of liver damage from mild to moderate and severe. In cases of mild damage, we observe elevated liver enzymes, while in moderate damage, in addition to the increase of liver enzymes and bilirubin, decreased ALB is found. In cases of severe damage, in addition to the mentioned changes, severe jaundice is also observed [19]. AST is a non-specific liver enzyme that is also produced in other tissues, but its increase can indicate hepatotoxicity. Both AST and ALT are present in the cytosol of hepatocytes. Liver cell damage leads to a rise in the cell membrane permeability, and cytoplasmic enzymes move out of the hepatocytes, causing their increased activity in the serum [20].

Oxidative stress can be mentioned among the tissue-damaging mechanisms that are the basis of diclofenac poisoning [21]. As a result, the active form of diclofenac, which is acyl glucuronide, mediates a large part of the poisoning events caused by this medicine, reminding the role and importance of antioxidants in preventing tissue changes [22]. The current remedy for diclofenac poisoning includes preventing further exposure and administering antioxidants. It was mentioned earlier that silymarin can be considered rich in antioxidative, anti-inflammatory, anti-fibrotic, anti-viral, and protective properties against the liver [10].

The greater the severity of the damage to the liver cells, the more ALB and TP will be inhibited [16]. A decline in the ALB level was found 12 h post-administration in both groups of birds administered diclofenac. ALB is produced mainly in the parenchymal cells of the liver [23]. Therefore, liver damage can change the level of ALB in the blood. Silymarin treatment significantly increased ALB levels, and similar findings were reported by Ihedioha et al. [1]. The reduction in TP is attributed to the initial damage to the endoplasmic reticulum, leading to the loss of cytochrome P-450 enzymes and its functional failure with reduced protein synthesis and accumulation of triglycerides, resulting in fatty liver disease [24]. Treatment of group II pigeons with silymarin could normalize diclofenac-induced reductions in serum TP, indicating hepatoprotective activity.

Several studies have shown that chronic use of diclofenac in high doses can cause pathological changes in the liver and kidney tissue [4]. Diclofenac interferes with renal arterial blood flow with a resultant diminished glomerular blood supply [17]. Birds are uricotelic and 60%–80% of the total nitrogen excreted by birds is in the form of UA. Therefore, it has been proposed to measure plasma UA concentration to assess renal function in birds [25]. An increase in UA and urea was found in the diclofenac-induced groups 12 h post-administration. Loss of appetite and vomiting in birds of these groups led to dehydration and increased levels of UA and urea. As seen in Table 1, UA and urea decreased in the silymarin-treated group 24 h post-administration. Our findings were in line with earlier research, where silymarin was utilized as a nephroprotective agent, and acetaminophen was used to cause kidney injury in pigeons [1].

Based on the results of the present study, silymarin can be useful in correcting abnormal biochemical changes in serum caused by diclofenac poisoning

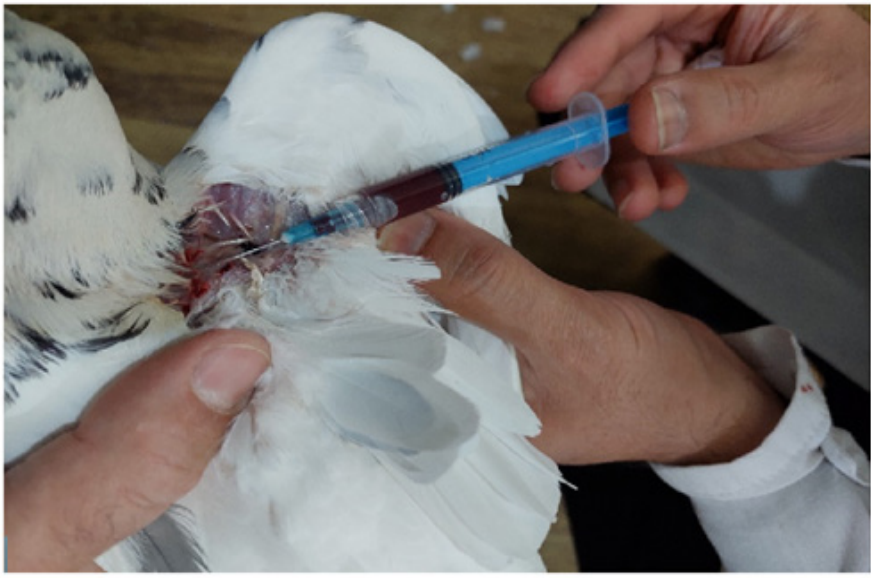

Figure 1.
Blood sampling from the wing vein

in pigeons and preventing its side effects. Therefore, it can be said that silymarin is a suitable treatment choice for pigeons and perhaps other birds affected by liver and kidney diseases.

Materials and Methods

Ethical approval

The present research was approved by the Ethics and Animal Rights Committee, Faculty of Veterinary Medicine, Amol University of Special Modern Technologies (Ir.ausmt.rec.1402.15).

Animals

The pigeons in the present study were obtained from domestic bird breeding centers in the city of Amol, north of Iran. Fifteen adult pigeons of obscure sex, with an average weight of 310 g, were used for this experiment. Next, all selected pigeons were physically examined, and the birds were approved to be healthy. The birds were housed in steel birdhouses (100 cm × 60 cm × 60 cm dimensions) and were provided a standard pelletized bird diet and water. The birds were allowed to get accustomed to this condition for 14 days.

Medicine

Diclofenac sodium tablets were supplied from Tehran-darou Pharmaceutical Company, Tehran, Iran (DICOTARD®, 100 mg/kg). Silymarin tablets were supplied from Gol-darou, Esfahan, Iran, (LIVERGOL®, 70 mg/kg).

Study setting and design

Fifteen pigeons were accidentally divided into three groups (1, 2, and 3). Group 1 served as the negative control group and was given just tap water. Pigeons in groups 2 and 3 were administered diclofenac 15 mg/kg PO q12h at the onset of the experiment (hour 0) for 24 h. The third group of pigeons was further treated with silymarin 35 mg/kg, beginning 12 h after diclofenac consumption, with the silymarin treatment continuing every 12 h for 48 h. Blood samples were taken from birds at 0, 12, 24, and 48 h for serum biochemical analysis.

Sample collection

At first, 2 ml of blood from each bird in all groups was collected from the right-wing vein with a 2.5-ml syringe using a 23-gauge needle (Figure 1). Next, the collected blood was poured into test tubes to clot. To separate the clot from the serum, the samples were centrifuged for 10 min at 3000 rpm. After centrifugation, the serum supernatant was carefully separated from the clot and placed in clear and clean tubes until the analysis of biochemical factors. This operation was repeated 12, 24, and 48 h after diclofenac or water administration.

Biochemical analysis

The factors evaluated in blood serum for this study were AST, ALT, TP, ALB, UA, and urea. The preserved sera were utilized for spectrophotometric estimation (Cobas Mira Plus automatic analyzer, Roche, Switzerland) of the mentioned factors using commercial assay kits (AriaAzma, Babol, Iran).

Clinical assessment

Birds were closely monitored every 6 h for the clinical signs of acute drug poisoning (e.g., anorexia, vomiting, diarrhea, ruffled feathers, lethargy, sleeping, and death). If the mentioned clinical signs were observed in a pigeon, the cases were accurately recorded in its file.

Statistical analysis

Analysis of variance (ANOVA) with the Tukey-HSD test was used to assess significant differences in UA, urea, AST, ALT, ALB, and TP between different groups at each time point. Moreover, differences between the means of these parameters in distinct groups along exposure times were analyzed by repeated measures ANOVA and Tukey-HSD test. All results were expressed as mean ± SD. Statistical analyses were performed using SPSS Version 26 software (SPSS Inc., Chicago, IL, USA). For all analyses, $p < 0.05$ was considered statistically significant.

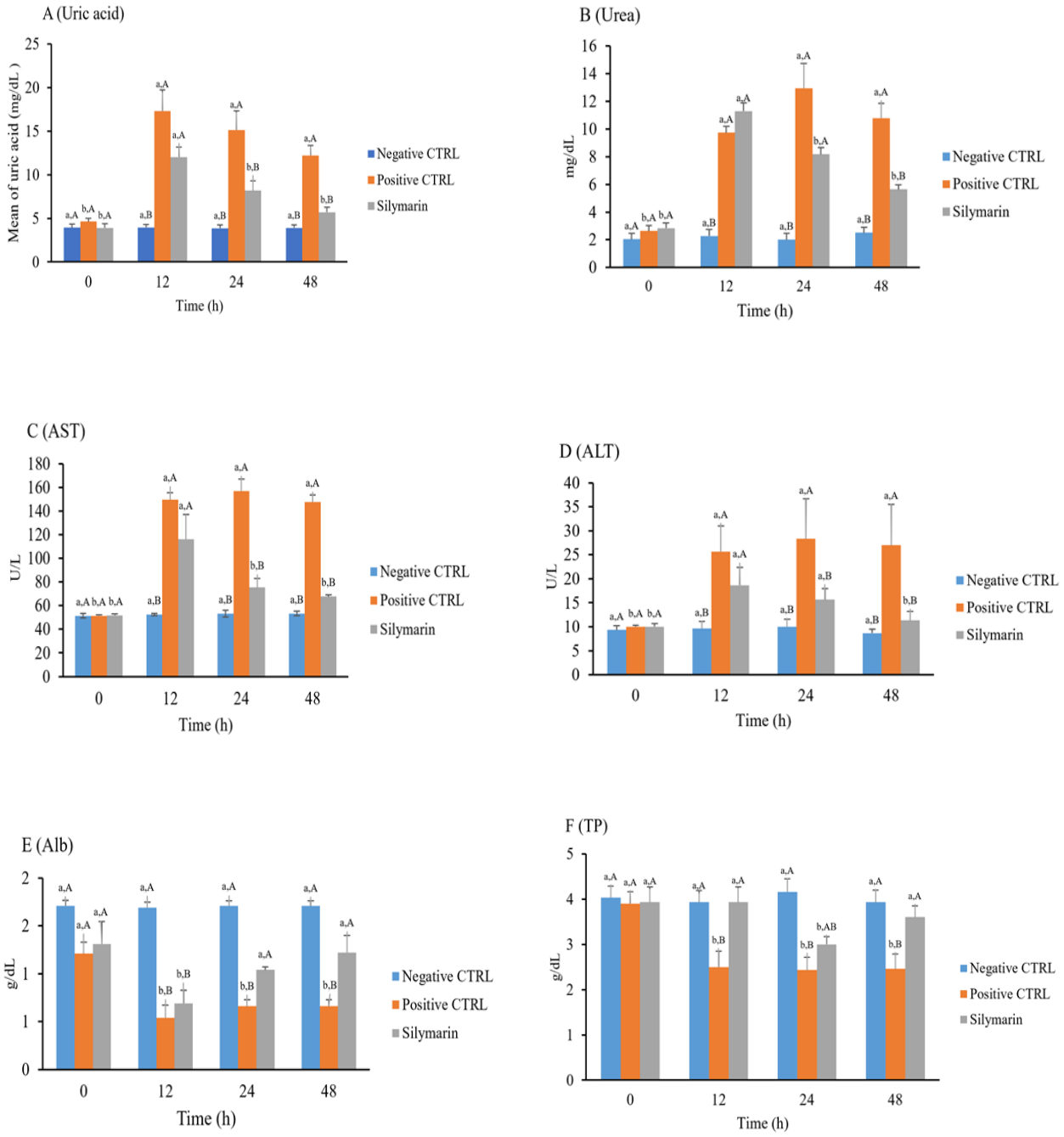

Figure 2.
Diagrams A to F indicate kidney indices and liver enzyme concentration at different time points, pre-and post-treatment with Silymarin in pigeons poisoned with diclofenac drug compared to a control group.
*Values are mean ± SE of three replicates.
a bThe different lowercase letters indicate significant differences in each group between tested times ($p < 0.05$).
A-BThe different capital letters indicate significant differences at each time point between the tested groups ($p < 0.05$).

Authors' Contributions

Nasser Vajdi, Saeed Seifi, and Shohreh Alian Samakkhah conceived and planned the experiments. Nasser Vajdi and Saeed Seifi carried out the experiments. Nasser Vajdi and Saeed Seifi contributed to sample preparation. Shohreh Alian Samakkhah contributed to the interpretation of the results. Nasser Vajdi took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis, and manuscript.

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Competing Interests

The authors declare that they have no conflict of interest.

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