Original Article

The Therapeutic Effect of the Alcoholic Extract of the Fruit of *Ziziphus spina-christi* L. in Reducing Oxidative Stress and Toxic Effects on the Liver Resulting from Exposure to Sodium Fluoride

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Abstract

Background: Sodium fluoride causes liver disorders in albino rats and can cause ischemia and increased oxidative stress. This requires *Ziziphus spina-christi* L. extract for its antioxidant and free radical scavenger properties. **Objective:** This research aims to ascertain whether the alcoholic extract of the fruit of the *Z. spina-christi* tree can reduce oxidative stress and toxic effects on the liver resulting from exposure to sodium fluoride in male albino rats. **Materials and Methods:** About 40 albino male rats were divided into four groups, each with 10 rats. The first group, Control: was given an oral dose of (5 mL/kg) distilled water. The second group, Ziziphus: was dosed orally with the alcoholic extract of *Z. spina-christi* L. (200 mg/kg) daily for 3 months at a dose of 3 mL). The third group, sodium fluoride: was injected intraperitoneally with a sodium fluoride solution (50 mg/kg) every day for 3 months at a dose of 0.1 mL. The fourth group, Ziziphus Naf+: was injected intraperitoneally with (50 mg/kg) of sodium fluoride solution (every other day) for a period of 3 months, after which it was dosed with (200 mg/kg) of the alcoholic extract of Sidr fruits, at the same dose for the second and third groups. **Results:** The experiment included injecting male rats with sodium fluoride (Naf) intraperitoneally. This resulted in a significant increase in liver enzyme activity and MDA concentration. However, the effectiveness of antioxidant enzymes decreased in the third group compared to the first group. The fourth group showed an increase in antioxidant enzyme activity. In the second group, the alcoholic extract of Ziziphus fruit increased antioxidant enzyme activity but decreased alanine aminotransferase, gamma-glutamyl transferase, and Malondialdehyde. The fourth group showed increased antioxidant enzymes, GSH, SOD, and CAT but all variables decreased. Histological examination showed extensive liver tissue damage, including irregularity of the hepatic cords, hyperemia, and degeneration. Combined treatment with sodium fluoride and *Z. spina-christi* L. extract improved liver tissue regulation and cell function. **Conclusion:** We conclude from our current study that the alcoholic extract of Ziziphus fruits is characterized by its high antioxidant activity, which works to mitigate and eliminate the effects of toxicity resulting from NaF injections on some functional and histological parameters of the liver of male albino rats.

Keywords: Alcoholic extract, antioxidant activity, liver enzyme, oxidative stress, Ziziphus

Introduction

Environmental pollution by chemical compounds is a significant health problem due to industrial and technological progress. Although beneficial in specific proportions, these compounds can cause acute or chronic toxicity in high doses, affecting vital organs and not just a particular organ. High doses can cause acute or chronic toxicity.[1]

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Fluoride, a chemical element, significantly affects environmental pollution due to its widespread presence in industries such as aluminum, battery, and iron production. It is necessary for humans and animals but accumulates in tissues.[2]

Fluoride poisoning damages soft tissues, bones, and teeth. This causes oxidative stress and increased ROS in cells, exceeding the antioxidant capacity and possibly leading to cell destruction.[3]

Recent studies explore using medicinal plants to treat diseases and eliminate toxins. The World Health Organization prioritizes this approach, being aware of the rare medicinal treasures in plants and the potential side effects of manufactured active ingredients.[4]

Pharmaceutical conferences encourage using medicinal plants as a safer source of medicines. They have been used to prevent diseases and inhibit ROS. This leads to an increasing preference for natural antioxidants.[5]

The Sidrtree is *Z. spina-christi* (L.). It is one of the perennial plants spread in most countries and is widely used in the therapeutic field because its fruits are rich in antioxidants.[6]

Materials and Methods

Preparation of extracts

The alcoholic extract of *Z. spina-christi* fruit was prepared using a Soxhlet extraction apparatus. 25 g of powder was taken, and 500 mL of absolute ethanol alcohol was added. The solvent was absorbed for 10 min, with a 20:1 ratio between material and solvent. The device was operated at boiling temperature for 2.5–3 hours. The extracted solution was dried in an oven at 40°C–50°C and collected in a sterile vial.[7]

Experimental animals

The research presented here was conducted at Anbar University, College of Education for Pure Sciences, and Department of Biology. About 40 of adult rats were provided from the of Veterinary Medicine and Pharmaceutical Research Laboratory at the University of Baghdad. They were between 12 and 16 weeks old, and their average weight was 200–225 g. The animals were housed in clean, sterile environments, such as metal cages and bottles. During the entire study, participants had unrestricted access to food and drink. A total of 40 albino male mice were used and divided into 4 groups of 10:

- The first group, Control: was given an oral dose of (5 mL/kg) distilled water.
- The second group, *Ziziphus*: was dosed orally with the alcoholic extract of Sidr fruits (200 mg/kg) daily for 3 months at a dose of 3 mL).[8]
- The third group, Naf: was injected intraperitoneally with a sodium fluoride solution (50 mg/kg) every day for 3 months at a dose of 0.1 mL.
- The fourth group, *Ziziphus* Naf+: was injected intraperitoneally with (50 mg/kg) of sodium fluoride solution (every other day) for a period of 3 months and then dosed with (200 mg/kg) of the alcoholic extract of Sidr fruits at the same dose for the second and third groups.[8]

Blood solution preparation

The experiment lasted for 3 months. It included starvation, drugging, and sacrifice. Blood is drawn from the heart, which is called a heart stab stored in tubes, and centrifuged for 15 min. Serum was separated and stored at −20°C. The livers were washed with physiological saline and studied histologically in 10% formalin fixation solution. All information was recorded for biochemical tests.

Histological study

Live rat livers were removed, fixed in 10% formalin, and dehydrated with progressively higher ethanol concentrations. Tissue samples were dehydrated before washing in two types of xylene, impregnated in two different types of liquid paraffin wax, embedded, and blocked. Fore thick tissue slides were stained with hematoxylin and eosin.[9]

Statistical analysis

The results were statistically analyzed using GraphPad Prism V.8 software to extract the significant difference between the values of the treated groups. Analysis of variance was done using the ANOVA table, and the arithmetic mean and standard deviation were extracted at the probability level ($P \leq 0.05$) based on basic measurement methods in statistics, and statistical analyses were conducted.[10]

Ethical approval

The experimental protocol was approved under Order (197 on February 20, 2023) issued by the Ethical Committee for the Care and Use of Laboratory Animals in the Department of Biology—College of Education for Pure Sciences—Anbar University.

Estimation of oxidation balance - antioxidants in blood serum

The statistical results obtained regarding the oxidation balance in the current study show that there is a significant increase at the probability level ($P \leq 0.05$) in the effectiveness of MDA Malondialdehyde in animals of the third group 0.8489 ± 16.62 nmol/mL when compared with the group Control 1.014 ± 7.674 nmol/mL and respectively. The results of the analysis for our current study recorded a significant decrease at the probability level ($P \leq 0.05$) in the effectiveness of MDA for the animals of the second group, as follows: 5.826 ± 0.9459 nmol/mL, in comparison with the control group—appendix (4). We note from the statistical

results that there is a significant decrease in the probability level $P \leq 0.05$ of MDA in the animals of the fourth group, respectively 8.127 ± 1.141 nmol/mL, compared with the control group. Appendix (4). On the other hand, it is noted that there is a significant significant decrease in the level of MDA in the fourth group compared to the third group injected with sodium fluoride [Figure 1].

The results obtained regarding antioxidants in our current study show that there is a significant increase at the probability level ($P \leq 0.05$) in the activity capacity of the enzyme GSH, SOD, and CAT in the second group 0.9300 ± 13.79, 1.736 ± 14.58, and 4.459 ± 40.86 U/L, after comparing them with the control group 11.15 ± 0.3908, 14.10 ± 1.831, and 3.260 ± 37.77 U/L, on straight.

While the results of the statistical analysis in this study recorded a significant decrease at the probability level ($P \leq 0.05$) in the activity of the enzyme GSH, SOD, and CAT in the animals of the third group, 0.9329 ± 5.980, 6.074 ± 0.9343, and 19.87 ± 2.997 U/L, compared to the control group.

And the enzymes GSH, SOD, and CAT in the fourth group, 9.465 ± 1.341, 12.01 ± 1.809, and 3.803 ± 33.71 U/L, the statistical results showed a significant increase. For these enzymes at the probability level ($P \leq 0.05$) compared to the third group, Figures 2-4, respectively.

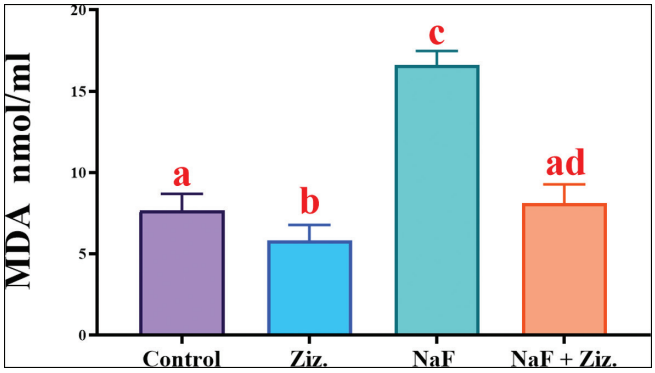

Figure 1: The effect of the alcoholic extract of the fruits of the Sidr plant, *Ziziphus spina-christi* (L.), on the level of the antioxidant agent (MDA) in the blood serum of male rats treated with sodium fluoride

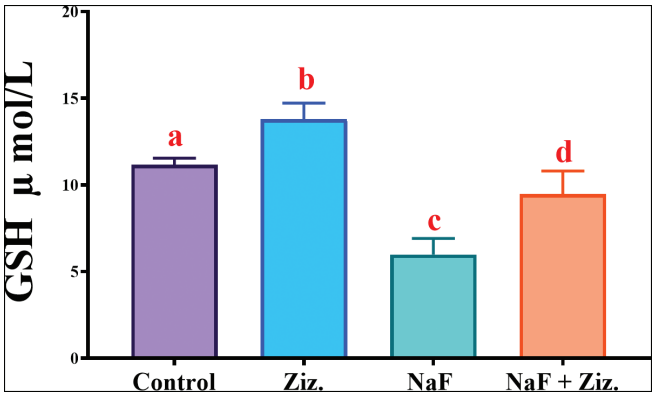

Figure 2: The effect of the alcoholic extract of the fruits of the Sidr plant, *Ziziphus spina-christi* (L.), on the activity of the enzyme (GSH) in the blood serum of male rats treated with sodium fluoride

Liver enzymes

The results obtained regarding liver function in the current study show that there is a significant increase in the level of probability ($P \leq 0.05$) in the level of activity of the enzymes ALT, AST, ALP, and GGT in the blood serum of the animals of the third group that were injected Peritoneally with sodium fluoride Naf, the U/L was (56.86 ± 4.580), (64.46 ± 4.699), (148.8 ± 8.150), and (5.826 ± 0.3623) U/L respectively compared to the control group (18.66 ± 3.272), (28.31 ± 2.380), (62.11 ± 6.112), (0.4000 ± 3.574) U/L.

The animals of the second group were dosed orally with the alcoholic extract of the fruits *Z. spina-christi* L., which reduced the activity of the enzymes ALT and

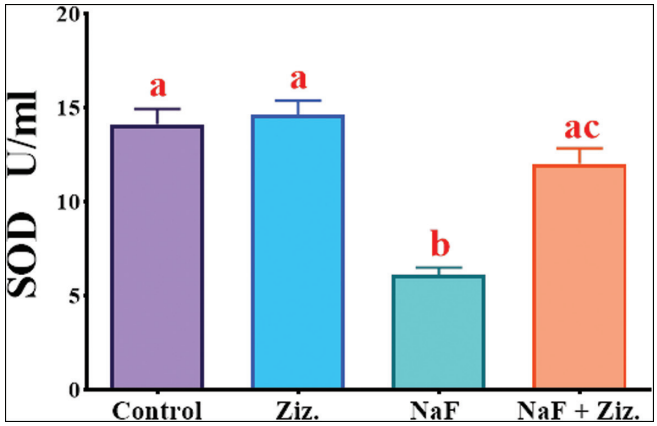

Figure 3: The effect of the alcoholic extract of the fruits of the Sidr plant, *Ziziphus spina-christi* (L.), on the activity of the CAT enzyme in the blood serum of male rats treated with sodium fluoride

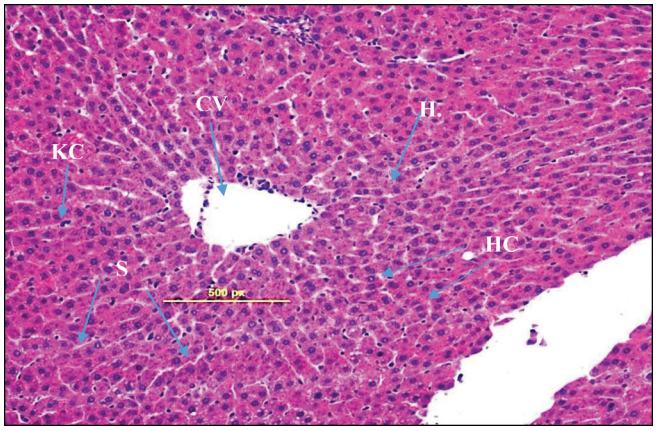

Figure 4: A cross-section of the liver tissue in the first group (control) treated with distilled water, showing hepatic cords in an organized manner, central vein (CV), sinusoids, liver cells and their nuclei (H) Hepatocytes, Kupffer Cells (H & E—40×)

GGT at the probability level ($P \leq 0.05$ in blood serum as follows: 17.84 ± 3.066 U/L and 2.942 ± 0.3669 U/L respectively, the same result was recorded for the fourth group that was injected intraperitoneally with sodium fluoride and dosed with Sidr fruit extract 24.82 ± 3.328 and 2.992 ± 0.3521 U/L, respectively when compared with the control group.

The results of the statistical analysis of the current study did not record a clear significant difference at the probability level ($P \leq 0.05$) for both ALP and AST in blood serum, as follows: 6.410 ± 61.28 and 34.10 ± 2.839 U/L, respectively, compared to the enzyme ALP and AST in the control group.

The results showed a significant decrease at the probability level ($P \leq 0.05$) in the activity of the enzymes ALT, AST, ALP, and GGT for the animals of the fourth group 24.82 ± 3.328, 32.74 ± 5.288, 68.12 ± 5.008, and 2.992 ± 0.3521 U/L, respectively, compared to the third group.

The results of the statistical analysis recorded a significant increase in the activity of the enzymes ALT, GGT, ALP, and AST at the probability level ($P \leq 0.05$) in the third group when compared with the fourth group, as follows 56.86 ± 4.580, 5.826 ± 0.3623, 148.8 ± 8.150, and 64.46 ± 4.699 U/L [Table 1].

Histological study

The results of the current study of the liver tissue of male rats from the first group showed Figure 4 of the typical structure of liver tissue. It consists of lobules shaped like polygonal prisms. The lobule appears in cross-section as a hexagonal shape resting on the central vein (CV). Hepatocytes are arranged within each lobule around the CV in the form of HC separated by adjacent sinusoids (sinusoids) interspersed with Kupffer cells. The changes specific to liver tissue were consistent with and supportive of the biochemical changes studied in the current study. The recent results of the histological study in the liver of the second group treated with alcoholic extract of Sidr fruits at a concentration of 200 mg/kg of body weight, as shown in [Figure 5], showed that the histological structure is similar to the first group in terms of the arrangement of cells, sinusoids, and HC around the CV.

The animals of the third group [Figure 6] that were injected with sodium fluoride showed liver tissue injury, which was represented by swelling and death of cells (HC), enlargement and congestion of the hepatic blood vessels, loss of the epithelial lining of the CV, and the presence of inflammatory infiltration around the blood vessels. Most hepatocytes showed severe degeneration and necrosis in the cytoplasm with frosted nuclei and infiltrated leukocytes were observed between the cells.

In the fourth group, treated with sodium fluoride and then with alcoholic Sidr fruit extract, it was observed that

Table 1: Activity of liver enzymes in the studied group

ALT U/L	Control	Ziz.	NaF	NaF + Ziz
Mean	18.66 a	17.84 a	56.86 b	24.82 c
± SD	3.272	3.066	4.580	3.328
AST U/L				
Mean	28.31 a	34.10 b	64.46 c	32.74 AD
± SD	2.380	2.839	4.699	5.288
ALP U/L				
Mean	62.11 a	61.28 a	148.8 b	68.12 ac
± SD	6.112	6.410	8.150	5.008
Mean	3.574 a	2.942 b	5.826 c	2.992 d
± SD	0.4000	0.3669	0.3623	0.3521

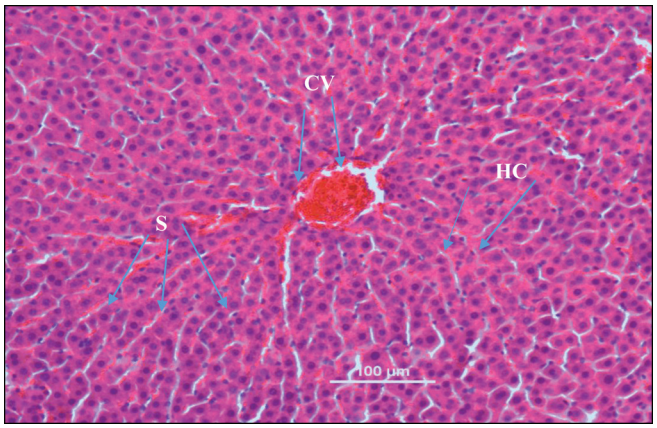

Figure 5: A cross-section of the liver tissue in the second group treated with alcoholic extract of Sidr fruits, administered orally, showing hepatic cords (HC) regularly, central vein (CV), hepatic sinusoids (S), and sinusoids (H&E—40×)

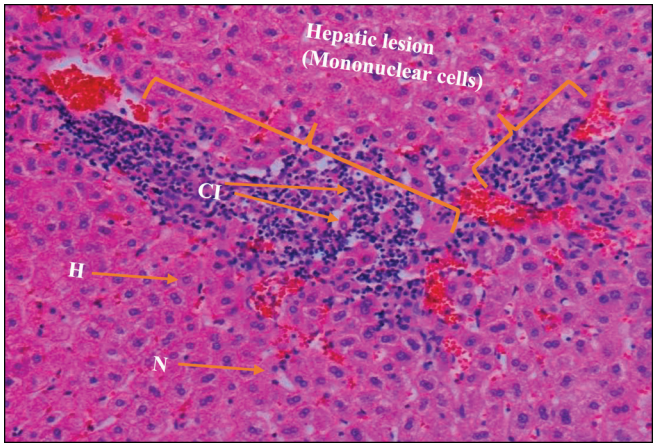

Figure 6: A cross-section of the liver tissue in the third group treated with sodium fluoride intraperitoneal injection, showing highly irregular hepatic cords, dilatation of the central vein (CV) with blood congestion, and significant dilatation of the sinusoids. Hepatitis (S) Sinusoids, severe necrosis of hepatocytes (N) Necrosis, and the presence of severe inflammatory cell infiltration (CI) Cellular infiltration (H & E—×40)

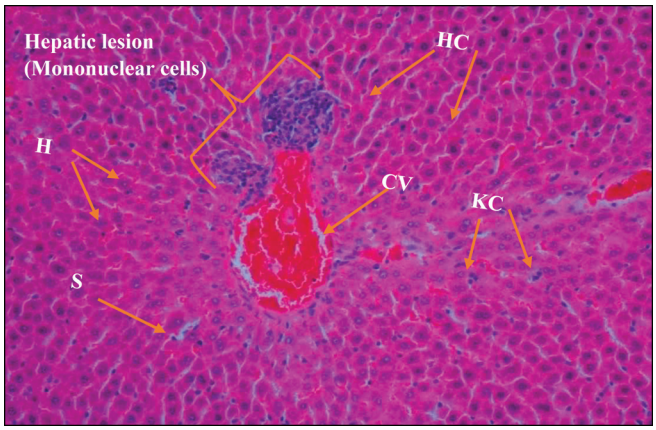

Figure 7: A cross-section of liver tissue in the fourth group treated with sodium fluoride, intraperitoneal injection and then dosing with Sidr fruit extract, showing liver cells (H), improvement in the organization of some hepatic cords (HC), expansion of the central vein (CV), dilatation of hepatic sinusoids (S), Kupffer cells (KC), (H & E—×40)

there was dilatation of the CV with the disappearance of blood congestion, an improvement in the organization of the HC, and an expansion of the hepatic sinusoids, some of which were interspersed with red blood cells. It was also observed that there was degeneration in some cells with a slight infiltration of inflammatory cells. Still, the tissue in this group appears closer to the control group [Figure 7].

Discussion

The MDA represents a marker for moderate free fats. The results of the current study confirmed an increase in the MDA level of groups treated with sodium fluoride due to its effect on stimulating the coenzyme Fatty-acetyl-COA. It is an essential part of metabolic processes and directs the oxidation of fatty acids, which leads to increased production of hydrogen peroxide (H_2O_2) of endogenous origin. This contributes to the production of lipid peroxidation.[11,12] Fluoride poisoning causes an increase in lipid peroxidation rate and membrane integrity loss, which may be a risk factor in the change in lipid metabolism and high blood lipid levels.

Sidr fruit extract works to inhibit the oxidation process of fats in cell membranes due to oxidative stress that leads to programmed cell death. Sidr fruits inhibit the process of fat oxidation through its active components, such as Rosmanol, carnosol, and Epirosmanol phenolic.

In addition, Sidr fruits protect against high blood sugar and hypercholesterolemia caused by oxidative stress, maintaining blood flow balance.[13]

Decrease in the level of antioxidants (GSH, SOD, and CAT) in albino rats treated with sodium fluoride compared to the control group. It may be attributed to the occurrence of a state of oxidative stress due to continuous treatment with sodium fluoride and as a result of the participation of effective antioxidants in preventing oxidation in cases of oxidative stress, either through the direct removal of free radicals or through enzymes that are an essential substance for them, such as glutathione peroxidase, which leads to increased consumption. Glutathione and its conversion to its inactive form, Glutathione dimercaptopropano.[14] The results of our study are consistent with the study of Yetuk and his group (2014). Who confirmed decreased antioxidant levels due to NaF injection in white rats.

The use of alcoholic Sidr fruit extract is characterized by its active ingredients, such as phenolic compounds, flavonoids, tannins, glycosides, and vitamins. It works to combat liver toxicity resulting from sodium fluoride (Naf) by removing free radicals, increasing the efficiency of the antioxidant defense system, and increasing the body's total antioxidant capacity. In addition, the plant contains the elements zinc (Zn) and manganese (Mn), which are involved in the chemical structure of GSH, SOD, and CAT. Zinc preserves the sulfhydryl group that makes up GSH.

The increase in antioxidant levels in single or combined treatments with fluoride is due to the alcoholic extract of Sidr fruits, which contains high percentages of active compounds, all characterized by their potent antioxidant properties.

A previous study Nacaia *et al*.[15] indicated the effect of sidr extract against liver fibrosis resulting from carbon tetrachloride (CCl4). It showed that sidr extract restored the normal levels of internal control activities SOD, CAT, and GSH to the normal level, and our current study also confirms this. The increase in antioxidants may be due to the chemical content of Sidr fruit extract is rich in antioxidant compounds, all of which work to remove free radicals. They also work to increase the activity of antioxidant enzymes such as CAT, SOD, and GSH, which can protect against oxidative stress by absorbing free radicals, especially ROS, and activating lipid peroxidation.

The liver is a major organ of detoxification and the leading site of metabolism in general. It is subject to various disturbances due to exposure to toxins. When liver cells are damaged, cellular enzymes leak into the bloodstream, where they can be measured through blood tests. ALT and AST are enzymes. The central liver, as a simultaneous rise in their levels in the blood, indicates a high probability of liver damage.[16]

These results agreed with a study Weerasinghe and Buja,[17] which indicated a significant increase in the levels of GGT, ALT, AST, and ALP enzymes in groups of male rats treated with sodium fluoride, which means changes in the liver of rats treated with sodium fluoride compared to the control group.

The increase in the levels of liver enzymes under study is attributed to the formation of free radicals resulting from NaF injections,[18] which attack the plasma membranes of liver cells, leading to the leakage of these enzymes into the blood. The state of oxidative stress resulting from increased influential oxygen groups results from DNA breakdown. Proteins and fats in the liver cells lead to degeneration or necrosis of these cells, and then their destruction and the excretion of their contents into the bloodstream, including liver enzymes.

The decrease in the activity of liver enzymes after dosing animals with the alcoholic extract of the Sidr plant in the current study indicates that the section has a therapeutic effect against toxins, as it works to reduce and inhibit hepatotoxicity caused by sodium fluoride in male rats, perhaps by removing or preventing the formation of free radicals generated during Naf metabolism. These enhanced effects of Sidr fruits can be attributed to the bioactive components that mitigated the harmful effect of fluoride, either through scavenging processes or antioxidant properties that prevent lipid peroxidation, stabilize reactive free radicals, and maintain cellular integrity.

The results of the histological examination were identical to,[19] as their study showed that when rats were dosed with the alcoholic extract of Sidr fruits, there were no harmful effects of the Sidr fruit extract on the histological structure of the liver. This is due to the plant's compounds that do not cause any toxic effects on tissues and do not induce the generation of free radicals or oxidative stress.

Sodium fluoride injection led to liver tissue injury, represented by swelling and HC, enlargement and congestion of the hepatic blood vessels, loss of the CV's epithelial lining, and inflammatory infiltration around the blood vessels. Most of the liver cells showed severe degeneration and necrosis in the cytoplasm with frozen nuclei, and white blood cells were observed infiltrating between the cells, as the cells affected by the action of sodium fluoride injection may have injected chemotactic factors to attract immune cells and thus increase their infiltration into the liver tissue, in addition to fatty infiltration of different sized fatty droplets. The results of a study[20] agree with the current study. It was reported that rats treated with sodium fluoride with water showed clear tissue changes leading to liver damage. Cellular necrosis with infiltration of mononuclear cells occurred in the portal channels, especially in the hepatic lobules, with the expansion of the hepatic sinusoids. These changes could be the result of fluoride-induced membrane distribution.

The results of measuring MDA indicated a significant increase in MDA, which is an indicator of peroxidation of lipids in liver cell membranes due to the formation of free radicals resulting from NaF injection, which makes us confirms that the degenerative effects in liver cells in the current study are due to the formation of free radicals, as The latter is characterized by its ability to interact with phosphorylated lipids of hepatic cell membranes, resulting in lipid peroxidation, which stimulates a series of membrane lytic reactions with a decrease in the vitality of the mitochondrial membrane and the destruction of lysosomal membranes, which works to activate programmed death enzymes (apoptosis). Thus, our study has proven that liver cell damage. It is associated with increased MDA as a marker of lipid peroxidation.[21]

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Conflicts of interest
There are no conflicts of interest.

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