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# Investigating the Ameliorative Effects of Various Doses of Cerium Dioxide on Adult Male Rates in Comparison to Acrylamide Toxic Effect

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**ABSTRACT**
Acrylamide one of most popular exposure chemicals which cause several pathological alterations involving liver through depletion of GSH and elevation of MDA. Giving of Cerium dioxide which has antioxidant and anti-inflammatory properties.Is expected to improved biochemical parameters and protect cell from oxidative stressinjury.This experiment aims to limitation of acrylamide exposure effect by using suitable dose of cerium dioxide.In current study 120 mature male rat are used were divided randomly for 6 groups, each one consistsfrom 20 animals. And they were consecutively: ACR (8 mg/kg), ACR +Ceo2 (8 and 35mg/kg), ACR +Ceo2 (8 and 15mg/kg), Ceo2(35mg/kg), Ceo2(15mg/kg), and D.W. group. Daily dosing for 100 days. Finally, the liver samples were collected for biochemical, histopathological and immunohistochemistry investigations**.**This study revealed significant elevation of oxidative stress with acrylamide treated group. Where MDA elevation and GSH diminished. With high dose of cerium dioxide treated groups show significant decrease in MDA level and significant elevation level of GSH, disappearance of inflammation and elevation of anti-apoptoticprotein expression. The ameliorative effect of cerium dioxide appears with high dose (35mg/kg)when compared with acrylamide treated group.

**Keywords:**Ameliorative effects; Cerium dioxide; Acrylamide toxicity.

## INTRODUCTION

Acrylamide(ACR) is a water-soluble, white, odorless, crystalline solid compound that is prepared through the filtration of the monomer from aqueous solutions (Meshram et al.2020). It is used in the production of paper, dyes, plastics, adhesives, sugar, and in food processing. It is also found in tobacco smoke (Dawood et al.2023), (Cazier et al.2024). Due to a combination of very different factors, such as a fast-food culture, the nutritive and sensory qualities of fried and oven-baked foods, and the consumption habits of those who consume them daily, exposure to acrylamide has recently been a concern(Timmermann et al.2021). The primary raw ingredients in foods high in acrylamide are carbohydrates, but heat above 120 °C is a necessary requirement for the Maillard reaction to take place. The cause of the formation of acrylamide in foods is almost the same in meat, fish, dairy, and grain products(Perera et al.2021). Acrylamide has been listed in group 2A by the International Agency for Research on Cancer(Koszucka et al.2020).In particular, attention was paid to acrylamide concentrations and exposure times suitable for studying the effects of food intake on oxidative stress and liver damage, because of the importance of oral exposure as a side path of potential occupational exposure (Abdulla & Al-Okaily, 2022)(Abbas & Jawad.2023).Crucial to acrylamide toxicity is its metabolism, leading to the formation of a variety of reactive compounds, including glycidamide, which is metabolized to glyceramide mercapturic acid (Kocadağlı& Gökmen, 2024).A systemic increase in pro-inflammatory cytokines, such as acute phase proteins like C-reactive protein or fibrinogen, has also been observed in response to exposure to acrylamide (Guo et al.2024). These findings clearly showed that toxicological assessment of inflammation should play an important role in determining the adverse liver and gastrointestinal tract effects of integrated acrylamide intake (Zhang et al.2023).Cerium oxide(Ceo2), or ceria, has attracted significant interest in the scientific community because of its unique group of properties (Wang et al.2023). The capability to accommodate multiple oxidation states creates opportunities for cerium oxide to serve as an antioxidant that is capable of scavenging free radicals and as active anti-inflammatory materials(hassan,.2019), (Fifere et al.2022). Furthermore, the capability to trap oxygen, particularly in the oxygen vacancies in both reduced and oxidized environments, serves as stores and transporters (Zhuang et al., 2020). This property is responsible for the highest ionic conductivity among the rare

earth mixed oxide solids (Li et al., 2021). As formed, ceria contains relatively lower exposed micro alkanes that can drive scavenging of free radicals. The Ce3+ plays an essential role in the capacity of the cerium oxide to protect the cells against oxidative stress (Deng et al.2022). The term antioxidants is widely used in the fields of agro- and food industries, environmental protection, as well as in the design of drugs. Natural antioxidants found in plants and animals are vitamins, minerals, enzymes, amino acids, or carotenoids (Akbari et al.2022). The valence of cerium can oscillate between +3 and +4 due to reversible reduction and oxidation processes characterizing ceria (Fifere et al.2022). In all of the above environments, further evidence has clarified the mechanisms of action of CeO2 nanoparticles. These mechanisms emerge from the fundamental redox reactions that CeO2 can undergo (Ahn et al., 2024).

**Materials and methods**

The current experimental study applied for 120 mature Albino male rats. animals aged four months with body weight range (220-240) grams. The chronic toxicity period extends for (100) days. Each mature and treatment was given daily by gavage feeding. Sterile Acrylamide obtained from CDH (India), dissolved in distilled water while cerium oxide obtained from HC (Canada).

**Experimental Protocol**

After one week of acclimatization, animals were divided in to (6) groups (20) rats for each, and dosing rats for each group as following.

Group 1: will be administration with 8 mg/kg of ACR.
Group 2: will be administration with 8 mg/kg of ACR + Cerium dioxide 35
Group3: will be administration with 8 mg/kg of ACR + Cerium dioxide 15
Group4: will be administration Cerium dioxide 35 mg/ kg.
Group5: will be administration Cerium dioxide 15 mg/ kg.
Group6: negative control, will be dosing with distilled water.

Finally, the rats were euthanized; and removed liver and intestine immediately for sample collection for histopathological and biochemical examination (Alshumary et al. 2024).

**Biochemical procedure**

Specimens of tissue were cut, sized, submerged in liquid nitrogen, and preserved at -80 degrees Celsius. After the addition of PBS solution with a pH of 7.4, the tissue samples were homogenized. The specimens have to be processed at a temperature of 4 degrees Celsius. After centrifugation, the liquid on top was gathered following a 20-minute processing time at a rotation speed of 3,000 rpm. The clarified supernatant was then used in the assays.The collected samples and standards were diluted in the 96-well plate reader of the Rat MDA and GSH ELISA kits. The optical density reading photometer used for this assay was a 96-well plate reader. Preparing various solutions, accurate sampling, performing standard curves, and making ELISA measurements of the Kit are explained in a step-by-step manner. These procedures can be used to determine MDA and GSH levels in different samples.

**Histopathological analyses**

After a twenty-seven-hour fixation period, the specimens were subjected to a tap water wash, followed by automatic processing. The process involved gradually raising the alcoholic concentration from 70% to 100% over two-hour intervals in order to remove water from the tissues. Xylol was subsequently used for tissue clearance. The specimens were subsequently infiltrated with semi-liquid paraffin wax at a temperature of 58°C in a two-stage process. In conclusion, blocks of specimens were fabricated using paraffin wax, and each tissue was cut into sections using a rotary microtome, with a uniform thickness of 5µm for all tissues. Application of Hematoxylin and Eosin (H&E) stain was made to all tissue samples, with a light microscope employed to observe the histopathological changes, as reported by (Sabaawy and Al-Kaisie, 2021).

**Immunohistochemistry**

Protocol 1 (for BAX): After the sections were deparaffinized, the tissue was boiled in 0.01 M sodium citrate buffer (pH 6.0) in a microwave oven for antigen retrieval. Endogenous peroxidase activity and non-specific background were blocked with 3% hydrogen peroxide and 3% serum albumin in 0.05 M PBS, respectively. The sections were incubated with primary antibody (1:200) overnight at 4 °C. Biotinylated goat anti-rabbit secondary antibodies and avidin-biotin complex were used to detect bound BAX. The signal was visualized using a diaminobenzidine tetra hydrochloride substrate kit, and the sections were counterstained with hematoxylin. Protocol 2 (for BCL2): For the BCL2 protein, after dewaxing with xylene and hydrating through a series of decreasing alcohol concentrations, the sections were boiled in a microwave oven in 0.01 M sodium citrate solution (pH 6.0) for antigen retrieval. The sections were incubated with a rabbit polyclonal BCL2 antibody. The sections were then washed in PBS, and the bound antibodies were visualized using an avidin-

biotin complex detection system. The primary antibodies were incubated overnight at 4 °C, and the secondary antibodies were substituted for the primary antibodies during the control incubations. For each protocol, appropriate negative controls were prepared by substituting an equal volume of PBS for the primary antibodies. Avidin-biotin-peroxidase reagents were used, and all incubations were performed in a humid chamber at room temperature. Avidin fluorescein was used as the chromogen. The immunoreactivity was visualized using a light microscope. Specimens were examined and photographed under a light microscope. Control hematoxylin and eosin-stained tissue sections were used for the histologic examination (Abdel-Abbas and Hassan.2022).

**Statistical analysis**

statistical program SPSS and sigma stat program was used for data analysis. With variance $p \leq 0.05$ for both (wade,.2005).

**Ethical approval**

This study was carried out in the University of Baghdad – Collage of Veterinary Medicine and approved by the Ethical Committee (P.G/2197).

**RESULTS**

The results were variable according type of group treatment and dose. these results indicate significant differences in MDA levels between the various groups. The control group exhibited the highest MDA levels in liver tissues, suggesting baseline oxidative stress levels. The acrylamide group showed a marked reduction in MDA levels, indicating that acrylamide exposure reduces oxidative stress. The addition of cerium oxide at different dosages 35 mg and 15 mg resulted in varying effects on MDA levels, with the higher dosage 35 mg being more effective in mitigating oxidative stress compared to the lower dosage 15 mg. The cerium oxide alone group also showed reduced MDA levels, highlighting its potential anti-oxidative properties Table 1.

The finding substantial variations in GSH levels among the different groups. The control group had the highest GSH levels in both the gastrointestinal tract and liver tissue, indicating baseline antioxidant levels. The acrylamide group exhibited a significant decrease in glutathione levels, that exposure to acrylamide diminished antioxidant capacity. The addition of cerium oxide at different concentrations 35 mg and 15 mg led to different outcomes in terms of GSH levels, with the higher concentration 35 mg showing greater efficacy in reducing oxidative stress compared to the lower concentration 15 mg. The cerium oxide alone group demonstrated a rise in glutathione levels Table1.

**Table 1:** tissue level of MDA and GSH in of immature Group.

| Oxidative stress (MDA) (Group) | **Mean±SD** | |
|---|---|---|
| | **MDA** | **GSH** |
| Acrylamide | 64.808±1.950 A | 71.314±4.370 D |
| Acrylamide + Cerium oxide 35 mg | 46.859±1.826 C | 96.129±4.202 C |
| Acrylamide + Cerium oxide 15 mg | 53.205±1.942 B | 74.648±2.237 D |
| Cerium oxide | 27.436±1.491 D | 143.259±4.153 A |
| Cerium oxide | 28.782±1.350 D | 139.648±1.878 AB |
| Control | 30.192±2.306 D | 127.240±6.687 B |

The pathological sections exhibitedin first group a clear pathological changes, including dilation and congestion of central vein and other section show marked mononuclear cells aggregation mainly in portal area with hyperplasia figure 1 A. meanwhile the sections in the second group which treated with ACR and Ceo2 35mg /kg B.W. show vascular changes with mild infiltration of mononuclear cells figure1 B. But the third group exhibited moderate pathological changes, including edema, congestion figure 1 C. and infiltration of mononuclear cells, but to a lesser degree than in first group. Although the others two groups which treated with Ceo2 only but with different dose for each show no pathological evidence figure 1 D, E.

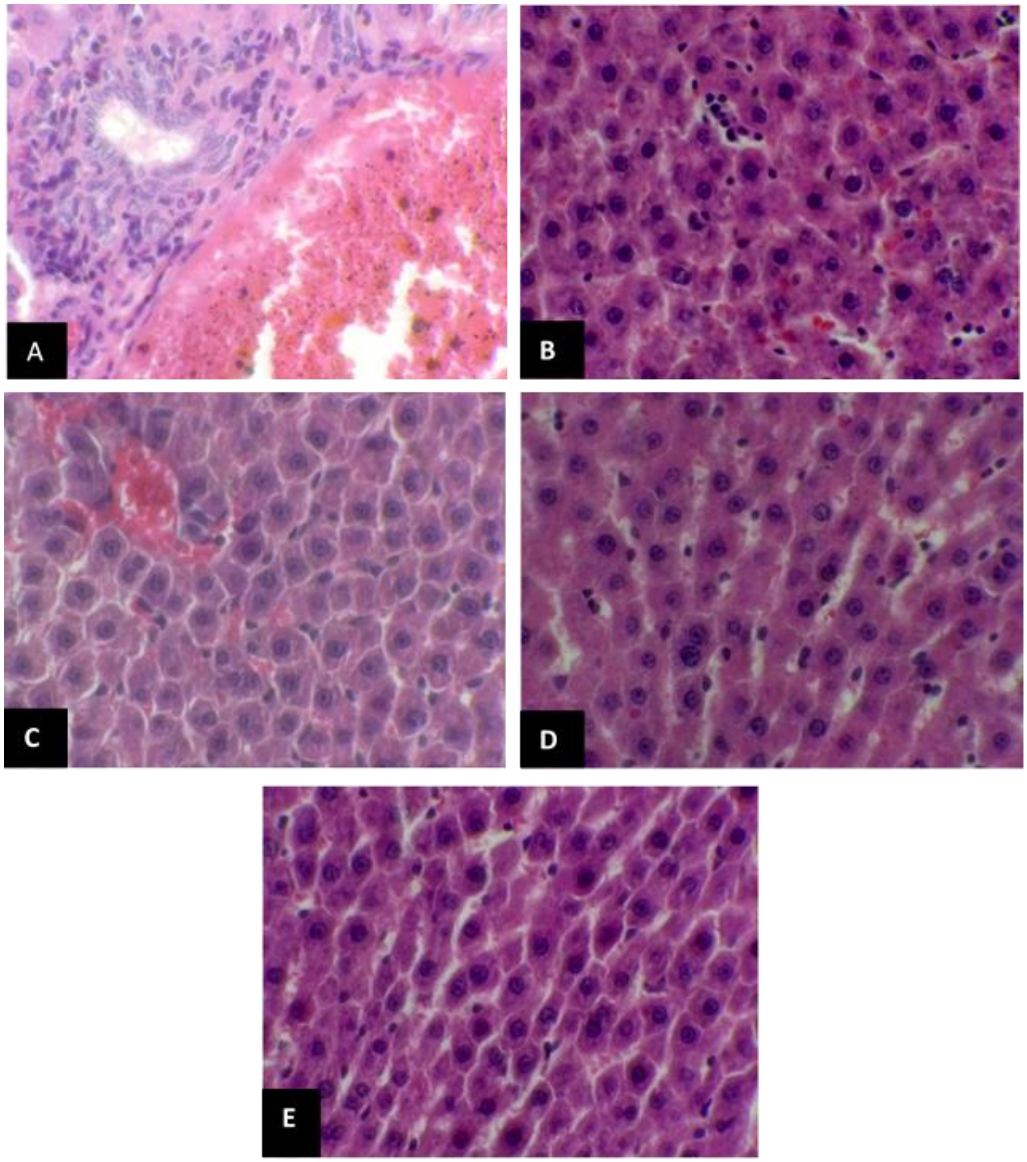


**Fig. 1:A**: Histopathological section showing dilated with congestion of portal vein and marked mononuclear cells aggregation (H&E stain X400),**B**: histopathological section 2$^{ed}$ group showing mild infiltration of mononuclear cells (H&E stain X400),**C:** Figure: Histopathological section 3$^{rd}$ showing congestion of blood vessels moderate mononuclear cells infiltrations proliferation of kupffers cells (H&E stain X400),**D**: Histopathological section 4$^{th}$ showing no clear pathological changes(H&E stain X400),**E**: Histopathological section 5$^{th}$ showing no clear pathological changes in the liver parenchyma (H&E stain X400).

Immunohistochemistry results indicate that different treatments significantly affect the expression levels of BAX and BCL2 proteins in liver tissues. in first group we show strong positive reaction for both BAX and BCL2(fig).and the levels were significant diminished in second group while in third group show high levels of excretion of both BAX and BCL2 but in fourth and fifth group significant decreased and become near from control group result, data in Table 2.

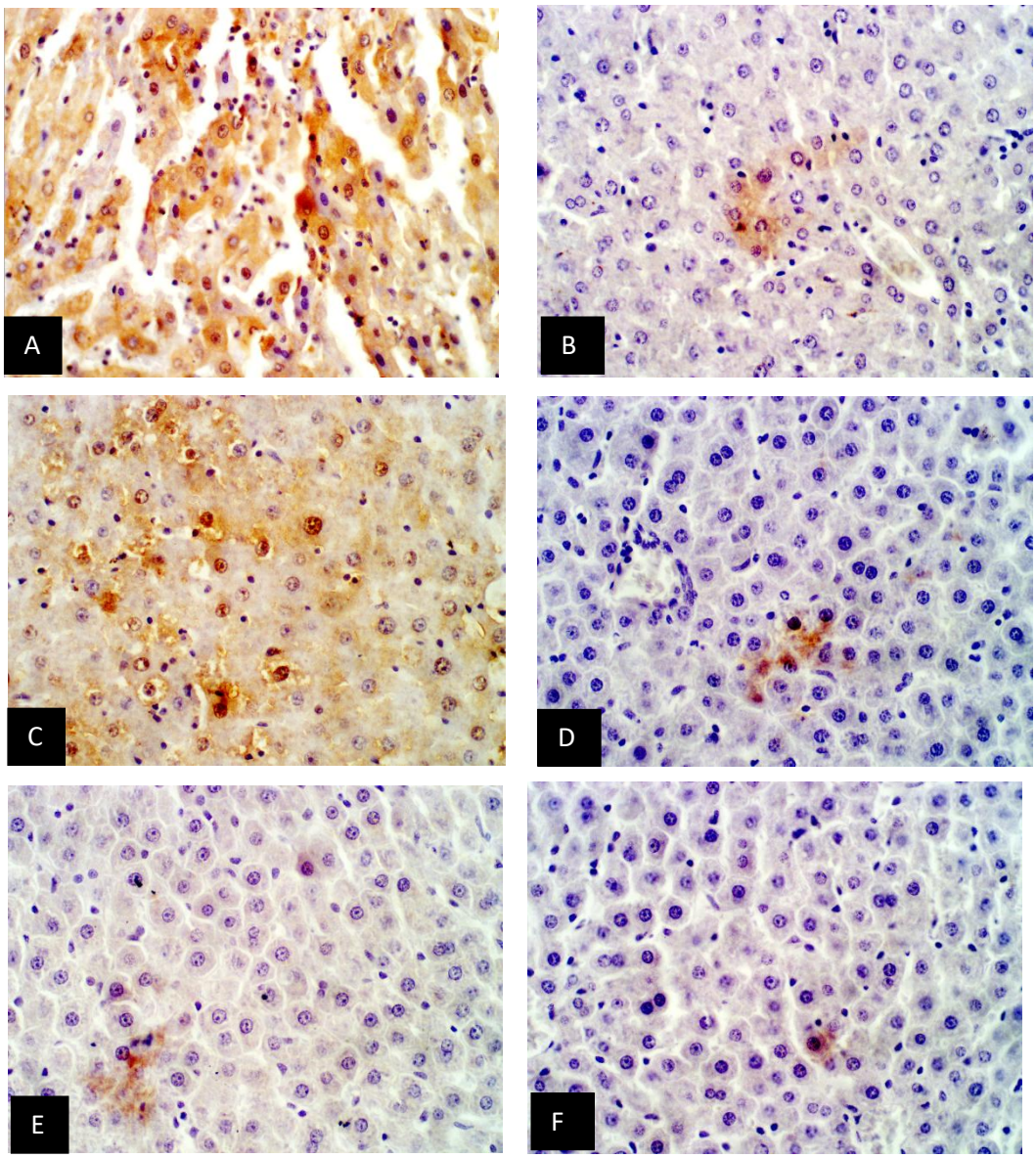


**Fig. 2A.**1st group BAX very strong positive reaction which appears as cytoplasmic golden-brown patches in hepatocytes. IHC-BAX. 400x., **B:** 2ed group BAX weak positive reaction which appears as cytoplasmic golden-brown granules in hepatocytes. IHC-BAX. 400x., **C:**3rd group BAX strong positive reaction which appears as cytoplasmic golden-brown granules in hepatocytes. IHC-BAX. 400x., **D:** 4th group BAX very weak positive reaction which appears as cytoplasmic golden-brown granules in three hepatocytes. IHC-BAX. 400x.,**E:** 5th group BAX very weak positive reaction which appears as cytoplasmic golden-brown granules in one hepatocyte. IHC-BAX. 400x.,**F:** Control group, BAX very weak positive reaction which appears as cytoplasmic golden-brown granules in one hepatocyte. IHC-BAX. 400x.

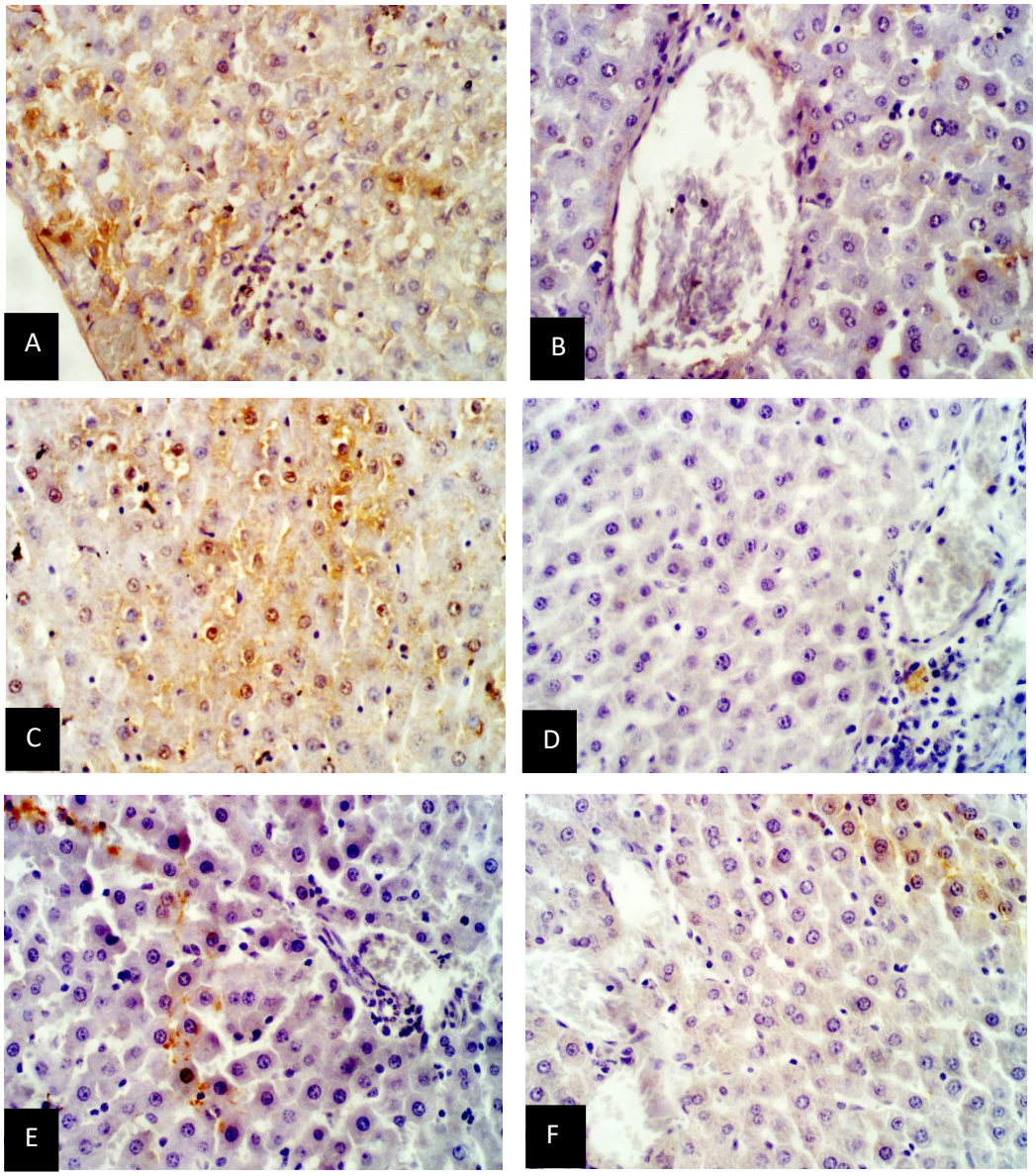


**Figure 2:A:** 1st BCL2 strong positive reaction which appears as cytoplasmic golden-brown patches in hepatocytes. IHC-BCL2. 400x., **B:** 2ed group BCL2 weak positive reaction which appears as cytoplasmic golden-brown granules in hepatocytes. IHC-BCL2. 400x., **C:** 3ed group BCL2 positive reaction which appears as cytoplasmic golden-brown granules in hepatocytes. IHC-BCL2. 400x., **D:** 4th BCL2 very weak positive reaction which appears as cytoplasmic golden-brown granules in hepatocytes. IHC-BCL2. 400x., **E:** 5th BCL2 very weak positive reaction which appears as cytoplasmic golden-brown patch in hepatocytes IHC-BCL2. 400x., **F:** control group BCL2 very weak positive reaction which appears as cytoplasmic golden-brown granules in hepatocytes IHC-BCL2. 400x.

**Table 2:** Expression of BAX and BCL2 in liver by immunohistochemistry.

| Parameters | Acrylamide (ACR) | ACR+ 35 mg | ACR+ 15 mg | Ceo2 (35) mg | Ceo2 (15) mg | Control |
|---|---|---|---|---|---|---|
| BAX | 2.78±0.20 B/a | 0.62±0.05 A/c | 1.69±0.11 A/b | 0.16±0.02A/d | 0.16±0.03A/d | 0.16±0.03A/d |
| BCL2 | 3.09±0.33 B/a | 0.23±0.01 B/c | 2.19±0.17 A/b | 0.15±0.02 A/d | 0.14±0.03 A/d | 0.16±0.01 A/d |

## DISCUSSION

Acrylamide is a potent compound that induces oxidative stress, and in several studies, this has been suggested to interfere with redox balance and increase the markers of oxidative stress and associated liver damage (Zhang et

al.2023).In animal models, acrylamide has been shown to affect several systems, including hepatic and extrahepatic systems (Lindeman et al.2021).An alteration in the different antioxidant enzyme levels after different means of acrylamide administration in the animals indicated that the liver is a direct target organ of acrylamide toxicity (Ibrahim & Ibrahem, 2020). In this study we have been estimated the productive and positive impact of cerium dioxide to reducing toxic effect of acrylamide.

Oxidative stressoutcome in the first group show significant elevation in MDA level and reduced in GSH when comparing with control group and this result was agreeingwith (Ahmed & Mohammed.,2022) who conclude The presence of heightened MDA levels in conjunction with acrylamide exposure highlights the pressing need for further investigation to better comprehend and mitigate the harmful consequences associated with this compound. In addition to (Firouzabadi et al.2022) investigation that recorded The acrylamide group exhibited a significant decrease in glutathione levels, indicating that exposure to acrylamide diminished antioxidant capacity. Meanwhile the another groups which treated with (acrylamide8 mg kg /B.W. and cerium dioxide 35 mg kg /B.W.) and (acrylamide8 mg kg /B.W. and cerium dioxide 15 mg kg /B.W.)showdiminish in MDA levelrespectively and, increase in GSH when comparing with acrylamide treating group and this observation parallel with (Pansambal et al.2023). who investigate The potent anti-oxidative property of cerium dioxide comes from the ability of $Ce^{3+}$ to efficiently scavenge the highly reactive radicals such as $O_2^{\bullet-}$, $H_2O_2$, •OH, and peroxyl radicals in living systems. The soft electrophilic nature of the $Ce^{3+}$ ion allows for many different metals to be comprised in this site at one time. Consequently, much more oxygen (relative to hydrogen) adsorbs or gets catalytically converted on Ce atoms, disrupting lipid peroxidation of cell membranes. As a result, $CeO_2$ would also be effective against non-radical reactions, further preventing the increase of MDA and decreasing GSH levels.

Acrylamide toxicity can lead to the induction of an inflammatory response mediated by immunological dysfunction (Kopańska et al.2022). our pathological finding was in agreement with (Schumacher et al., 2021) and they evidence The degree of liver injury is determined by levels, cellular type, and range of Kupffer cell activation, the infiltrating mononuclear cells, all of which are a result of the severity of liver damage. acrylamide has both hepatotoxic effects on liver morphology and histopathology parameters and on the biochemical level, causing significant damage to its functions (Uthra et al.2022) (Kandemir et al.2020). and this finding may be due to detoxification function of hepatocyte. The another groups which treated with acrylamide combination with cerium oxide show less pathological injury suggested to antioxidant function to cerium oxide and this finding was in agreement with biochemical evidence. While in cerium oxide groups show no evidence of pathological changes and this finding support antioxidant properties of ceria (Fifere et al.2022).

The imbalance between pro- and anti-apoptotic proteins BAX and BCL2, have a crucial role in the modulation of mitochondrial apoptosis(Saddam et al.2024).daily ACR treatment caused apoptotic cell death in the target organ by affecting the expressions of BCL2 and BAX proteins in rats (Adebayo et al.2020). And this result was agreement with our study where significant upregulation in BAX and BCL2.in second and third groups we show elevation in BCL2 expression and down regulation BAX expression and this investigation was parallel with (Yang et al.2024) who show The administration of cerium dioxide alone increased the expression of BCL2 and decrease BAX expression. while in fourth and fifth groups show excellent improvement result and this agree with (Ifijen&Omonmhenleb, 2023) they investigate that vitamin E and $CeO_2$NPs mitigated damage, apoptosis. And this ability come from ability of cerium dioxide to act as scavenger (Matussin et al., 2023).

## CONCLUSION

This study concluded the Acrylamide can cause hepatic injury through enhance BAX expression with depression of BCL2.and, MDA elevation companied with GSH depletion. Cerium dioxide has protective effect against Acrylamide intoxication through minimize the oxidative stress and inflammation in hepatic tissue.

### Conflict of Interest

The authors confirm that there are no conflicts of interest**.**

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