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Research Paper

Effect of Selenium on Oxidative Stress Outcomes due to Cyclophosphamide Consumption in Rats' Submandibular Salivary Glands

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ABSTRACT

Background: This study aimed to evaluate the possible role of selenium in mitigating the toxic effect of cyclophosphamide on the oxidative parameters as well as the histology of submandibular salivary glands' tissues of albino male rats.

Methods: Twenty male albino rats (aged 3-4 months, 300-400 grams) were divided into four groups (n=5): the first group was administered with distilled water orally, the second group was administered with selenium (0.2 mg/kg) orally for 14 days, the third group was given (150 mg/kg) cyclophosphamide by i.p. injection on day eight, and the fourth group was given selenium (0.2 mg/kg) and cyclophosphamide (150 mg/kg) by i.p. injection on day eight. On day 15, all rats were anesthetized, blood samples were collected for total antioxidant capacity (TAC) and malondialdehyde (MDA) analysis, all rats were euthanized, and the submandibular salivary glands were collected.

Results: The biochemical analysis of serum TAC values and MDA levels revealed a significant reduction in the TAC levels and an elevation in MDA levels in the cyclophosphamide (CY) group in comparison with other groups, whereas, the cyclophosphamide with selenium (CY+Se) group showed an elevation in TAC values and a reduction in MDA levels in comparison with the CY group. The histopathological study revealed mucous acini necrosis, atrophy, vacuoles in the serous acini, with edema surrounding the striated ducts, degeneration signs in granular convoluted tubules, as well as an increase in fibrous tissue surrounding the interlobular ducts, while the CY+Se group showed an improvement in the histological architectures.

Conclusion: Cyclophosphamide caused oxidative stress, represented by a reduction in the antioxidant marker level, an elevation in the oxidative marker level, and structural alterations in the submandibular salivary glands of rats and selenium mitigated these effects, as seen by the biochemical analysis and histological investigation.

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1. Introduction

Oxidative stress is an imbalance between the reactive oxygen species (ROS) production and the anti-oxidant capacity inside the body, or overproduction of ROS that cannot be overwhelmed by the anti-oxidant defense mechanisms inside the body [1, 2], which can lead to many pathological disorders due to induction of apoptosis that in turn leads to necrosis and cell death [3].

Cyclophosphamide (CY) is considered a chemotherapeutic and immunosuppressive agent that is widely used to treat malignant diseases (leukemia, breast cancer, ovarian's cancer, as well as many other cancers). Furthermore, it is used to treat many non-malignant diseases, such as rheumatoid arthritis, and lupus erythematosus, and in organ transplantation [4, 5], but it can produce toxicities in many tissues and organs, including the heart, liver, lungs, kidneys, testes, ovaries, and the salivary glands [6], via oxidative stress by overproduction of free radicals that can lead to cell death [7].

Salivary glands have a vital role in maintaining the integrity of the oral cavity by producing saliva that has a pivotal physiological function inside the oral cavity, including protection, lubrication, and buffering effect [8].

In recent years, studies have focused on the role of antioxidants in mitigating the toxic effects induced by chemotherapy [9, 10].

Clinical trials have been carried out on some trace elements showing therapeutic activity. Zinc has been found to improve metabolic parameters associated with diabetes or oxidative dysmetabolism [11-13].

Selenium (Se) element is a trace element and antioxidant and has several pivotal physiological functions in the mammalian body, such as anti-inflammatory, antiviral [14], and chemoprotective properties [15]. These important properties of Se can be due to the presence of selenium element in some proteins called selenoproteins that have an essential role in the redox system inside the body, such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR), and iodothyronine deiodinases [16].

One of the main functions of most of these selenoproteins is the protective effect against ROS and oxidative stress that ultimately protect the cell against oxidative cell injury [17].

Total antioxidant capacity (TAC) is considered one of the parameters to measure oxidative stress. TAC can be defined as a total sum of antioxidants that counteract or scavenge free radicals [18], while malondialdehyde (MDA) is an end product that generates from the interaction between the ROS and the cell membrane [1]. It is a significant parameter to indicate the level of oxidative stress [19].

Our study examined the possible role of Se on the oxidative parameters as well as the histology of submandibular salivary glands of albino male rats to mitigate the toxic effect of CY.

2. Materials and Methods

Drugs

CY, Endoxan® (500 mg) containing cyclophosphamide monohydrate (Baxter Oncology GmbH, Baxter International Inc.), diluted with normal saline (pioneer pharmaceutical, Iraq) for intraperitoneal injection, and Se (200 Mcg) tablets (AMS® American Medic & Science) were used. The tablet was ground using mortar, and dissolved in distilled water (DW), (shaken well -using Agitator Vortex Mixer)

Animals

Twenty adult male albino rats, weighted about 300-400 grams, and about 3-4 weeks old, were utilized in our study. All rats were obtained from the Animal House (College of Veterinary Medicine, University of Mosul. They were housed in plastic cages each cage containing six rats, and housed under standard environment conditions at 21±2°C and under a 12 h light/12 h dark cycle, and had access to standard diet and drinking water.

Experimental design

Twenty rats were randomly divided into four groups of five rats in each group (n=5), as described below:

Control (C) group: Rats that received 2 mL/kg b.w. of DW orally using oral needle gavage for 14 days, and 3 ml/kg b.w. of normal saline intraperitoneal (i.p) on day eight of the experiment.

Se group: Rats that received selenium at 0.2 mg/kg b.w./day orally dissolved in DW for 14 days via oral needle gavage and 3 mL/kg b.w. of normal saline (i.p) on day eight of the experiment.

CY group: Rats that received 2 mL/kg b.w of DW orally using oral needle gavage for 14 days, and only a single

dose of CY (150 mg/kg) diluted in normal saline (i.p) on day eight of the experiment.

Cyclophosphamide+selenium (CY+Se) group: Rats that received selenium (0.2 mg/kg b.w./day) orally dissolved in DW using oral needle gavage for 14 days, as well as, a single dose of CY (150 mg/kg of b.w.) diluted in normal saline on day eight of the experiment.

On the final day of our experiment, all rats were anesthetized with an injection of ketamine and xylazine. The blood samples were collected from rats' retro-orbital venous plexus for biochemical analysis. Then, submandibular salivary glands (SMG) were excised for histological examination.

Biochemical analysis

The blood samples were collected from the retro-orbital venous plexus using micro-hematocrit capillary tubes. The blood was collected inside plain gel tubes and kept for 30 min at room temperature. Then centrifuging was done for 20 min at 3000 rpm. The serum samples were removed and transferred to Eppendorf tubes for storing at -20°C until analysis using the Total Antioxidant Capacity Assay Kit (Elabscience®, E-BC-K136, Colorimetric method) that is used for the determination of TAC values in serum. The MDA Colorimetric Assay Kit (Elabscience®, E-BC-K025-S, Colorimetric method), was used to measure the MDA content in serum.

Histological study

The excised submandibular glands for all groups were taken and immersed in neutral buffer formalin 10% for 24h for fixation and the collected tissue blocks were serially sectioned by the microtome and placed on a glass slide to be stained with hematoxylin & eosin (H&E) and examined by light microscope.

Statistical analysis

Sigmaplot software, version 14 (Systal Software Inc.) was utilized for statistical analysis using one-way ANOVA and the Duncan post hoc test. Mean±SD was used for the results of serum total antioxidants and MDA. The $P<0.0$ was statistically significant.

3. Results

Biochemical analysis results: Serum TAC (U/m) in the CY group (1.96±0.86) showed a significant ($P\leq0.05$) reduction when compared to the control (4.88±2.54), Se (4.94±0. 5), and CY with Se (3.76±0.58) groups, while it showed no marked reduction in the CY with Se group in comparison with the control and Se groups. There was a great similarity between the TAC level in the Se group and in the control group (Table 1, Figure 1A).

Serum MDA MDA levels of the control (15.48±1.92), Se (14.96±3.58), and CY with Se groups (16.12±2.46) had remarkable similarities, with no significant differences between these groups, whereas, there was substantial increase in the MDA levels of the CY group ($P\leq0.05$) compared to other groups, while the co-administration of the Se with CY decreased its levels (Table 1, Figure 1B).

Microscopic examination: Histological examination of the rats' submandibular salivary gland tissue section of the control and Se groups showed normal histological pictures representing intact mucous acini, granular convoluted tubules, and striated ducts (Figure 2), whereas, that of the CY group revealed several histological changes, represented by necrosis and atrophy of mucous acini and edema surrounding serous acini. Degeneration of striated ducts granular convoluted tubules, and epithelial cells are shown in Figure 3. In addition, fibrous tissue surrounding interlobular ducts and congestion of blood vessels increased. While, the CY+Se group revealed an improvement in the histological changes compared to the CY group represented by intact mucous acini, granular convoluted tubules, striated ducts, and interlobular ducts but with fibrous tissue between lobules (Figure 4).

4. Discussion

Oxidative stress is a state, in which the body's antioxidant defense system is unable to eliminate, neutralize, or detoxify the ROS, and occurs when there is an imbalance between the ROS formation and internal antioxidant defense system [20]. In a normal physiological state, there is a balance between ROS formation and elimination [21], and when this balance is disturbed and shifted toward ROS accumulation, oxidative stress occurs, which has an essential role in the pathogenesis in several diseases and toxicities [22].

Chemotherapeutic agents have been considered a cornerstone in the treatment of malignant diseases. However, most of these agents have non-specific action, which means they not only destroy or kill the cancer cells but also normal cells [23]. However, each chemotherapeutic agent, including CY has its particular side effects and toxicities [24].

CY belongs to the alkylating agent class, which is widely used in the treatment of malignant and nonma-

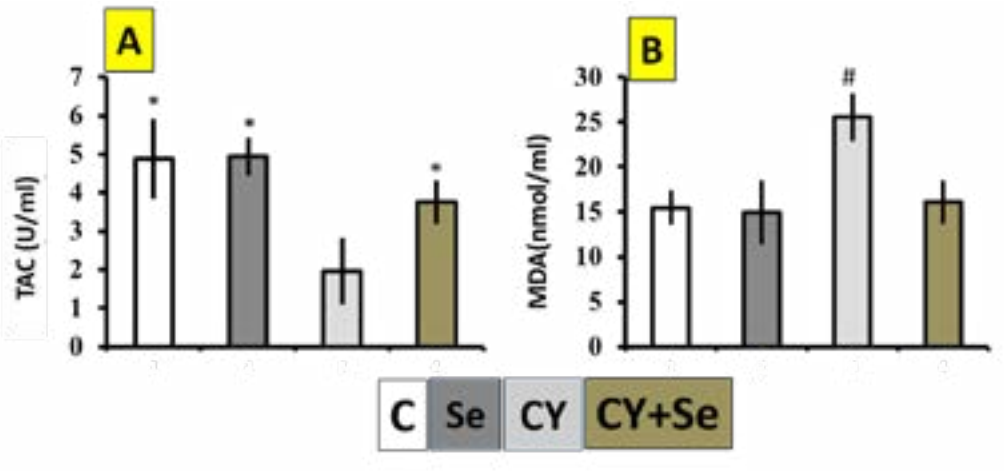

Figure 1. Oxidant/Antioxidant status of the studied groups A) Total antioxidant capacity, B) malondialdehyde.

Abbreviations: C: Control; Se: Selinium; CY: Cyclophosphamide; CY+Se: Cyclophosphamide+selenium.

Data are expressed as Mean±SD. *P<0.05 compared to the CY group, #P<0.05 compared to other groups.

Table 1. Serum total antioxidants capacity values and malondialdehyde levels.

Oxidative Stress Parameters	Mean±SD				P
	(C)	(Se)	(CY)	(CY+Se)	
TAC (U/mL)	4.88±2.54[a]	4.94±0.5[a]	1.96±0.86[b]	3.76±0.58[a]	0.033
MDA (nmol/mL)	15.48±1.92[a]	14.96±3.58[a]	25.56±2.66[b]	16.12±2.46[a]	0.043

Total specimens=5

[a, b]The different letters mean significant differences between groups at P≤0.05

lignant diseases including leukemia, lymphomas, breast cancer, organ transplantation, lupus erythematous, and rheumatoid arthritis [25]. It is a prodrug that undergoes a metabolic activation by the liver via the cytochrome P450 system to yield acroline and phosphamide mustard. One of these metabolites (acroline) is associated with toxicities of several tissues and organs [26], via the overproduction of ROS and lipid peroxidation that ultimately leads to oxidative stress and cell death [27].

Antioxidant supplementation has been reported to have a promising role in ameliorating or alleviating chemotherapy-induced toxicities in the cells and tissues, via increasing the antioxidant defense mechanisms inside the body [28].

Se is a trace element and a powerful antioxidant and plays a pivotal role in the body's antioxidant defense system [29]. In addition, it has an important role in the growth, fertility, and immune system inside the body [30].

Recently, Se has been considered because it acts as an antioxidant, and is incorporated in many antioxidant selenoproteins to protect the body from the oxidative stress resulting from excessive ROS production [31]. Also, Se has been used to protect the cells from apoptosis and damage induced by ROS [32].

The present study aimed to investigate the possible role of Se in mitigating or alleviating the impact of the CY on the rats' submandibular salivary gland histology and the oxidative state parameters via using the total antioxidant capacity and oxidative stress markers, such as serum MDA.

In the present study, the biochemical analysis of the serum TAC and MDA revealed a reduction in the Mean value of TAC serum levels in the CY group that was administered (i.p. injection; 150 mg/kg) with CY, with significant differences at a P<0.05 in comparison with other groups, whereas, there was an elevation in the Mean value of serum MDA concentrations of the CY group

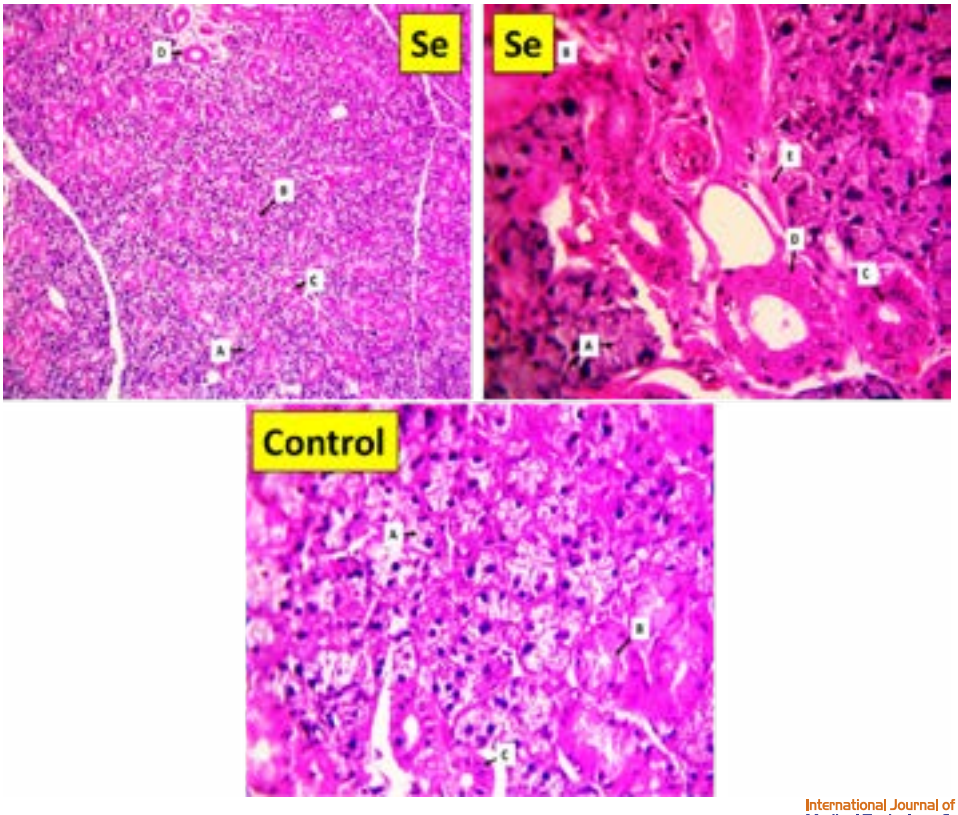

Figure 2. Representative image of rat submandibular salivary gland

A) The control group with normal histological pictures and intact serous acini, B) Mucous acini, C) Granular convoluted tubules, D) Striated ducts.

Selenium (Se) group showed: A) Normal histological pictures represented by intact serous acini, B) Mucous acini, C) Granular convoluted tubules, D) Striated ducts, E) Interlobular ducts.

with significant differences at a $P<0.05$ in comparison with other groups.

These findings indicate the CY toxicities, which caused a depletion in the body's antioxidant system, via excessive production of ROS and lipid peroxidation [33]. Several studies are in agreement with the findings of the present study. El-Sebaey et al. (2019) found an elevation in the hepatic MDA levels and a significant depletion in the serum TAC values, in the CY-administered group [34]. Duggina et al. (2015) demonstrated similar results represented by a significant elevation in the MDA levels of the CY group in comparison with the control group [35]. In addition, our findings are similar to those of Cengiz et al. (2022), who revealed an elevation in the levels of oxidative stress markers, including MDA, and a reduction in the values of TAC in the CY-treated group in comparison with the control group [36].

On the other hand, was noticed an elevation in the values of TAC in the CY+Se group, and a reduction in the concentrations of MDA in comparison with the CY group. These findings were consistent with other studies, which explained the protective effect of Se via reducing the oxidative stress induced by the CY administration [37-39].

Hasani et al. (2019) reported that Se supplementation can be effective in ameliorating oxidative stress and inflammation via increasing TAC and glutathione peroxidase levels and decreasing MDA levels [40]. Ghosh et al. (2015) observed that oxidant parameters were considerably improved by Se [41]. Furthermore, several studies have found that the oxidative stress induced by CY treatment could lead to the accumulation of hydrogen peroxide (H_2O_2), and the Se elevated the TAC and antioxidant enzymes that in turn resulted in reducing the harmful accumulation of H_2O_2 via converting it to H_2O and O_2, and ultimately protecting the tissues from oxidative stress [42].

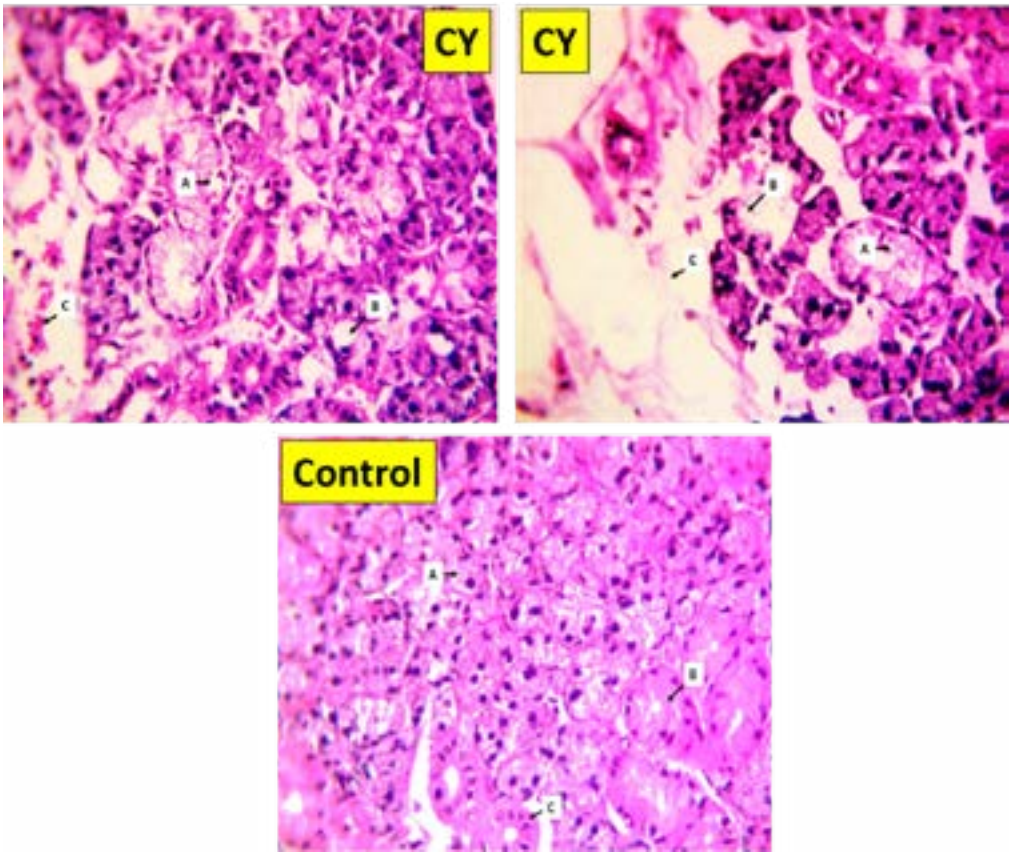

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Figure 3. Representative image of the rat submandibular salivary gland of the cyclophosphamide (CY group) group showed: A) Degeneration of epithelial cells of granular convoluted tubules, B) Mucous acini cells, C) With congestion of blood vessels. The control negative group showed: A) Normal histological pictures represented by intact mucous acini, B) Granular convoluted tubules, C) Striated ducts.

In this work, the light microscopic examination of the rats' submandibular salivary glands of the CY group revealed several histological changes represented by atrophy and necrosis signs in the mucous acini, degeneration of epithelial cells of granular convoluted tubules, striated ducts, and signs of edema around the mucous acini and vacuoles in the serous acini. While the C and the Se groups showed intact histological images.

These changes can be explained by the possible toxic effect of the CY due to the oxidative damage in this tissue, which is in agreement with a study that demonstrated a coincidence between the CY treatment and oxidative stress causing damage in the biosystem [43]. Also, our findings are consistent with those of Moawad et al. (2022) and Amin (2017) who reported that cisplatin caused abnormal architecture in the submandibular salivary gland acini, and intracellular vacuoles [44, 45].

The causes of cellular damage in the salivary glands induced by CY treatment have been explained by Yahyazadeh (2021) who stated that this damage is due to lipid peroxidation in the cell membranes resulting in excessive ROS production and oxidative stress [46]. The causes of the vacuolization are in agreement with those reported by Elsayed (2019) who stated that the acinar and ductal cell vacuolizations may be due to edematous changes replacing the degenerated or atrophic cells or fatty degeneration of these cells [24].

In addition, in our study, the CY group showed edema around the acini and vacuoles in the acini. These findings were confirmed by the studies published by Alghamidi et al. (2022), and Abo El-Yazed et al. (2018) who demonstrated that edema and vacuoles in the acini could be due to excessive ROS formation, leading to damage in the cell membrane that ultimately resulted in the accumulation of the sodium ion inside these cells and entry of water that results in swelling and vacuolization [47, 48].

In our study, the CY+Se group showed an improvement in the histological changes in comparison with the CY

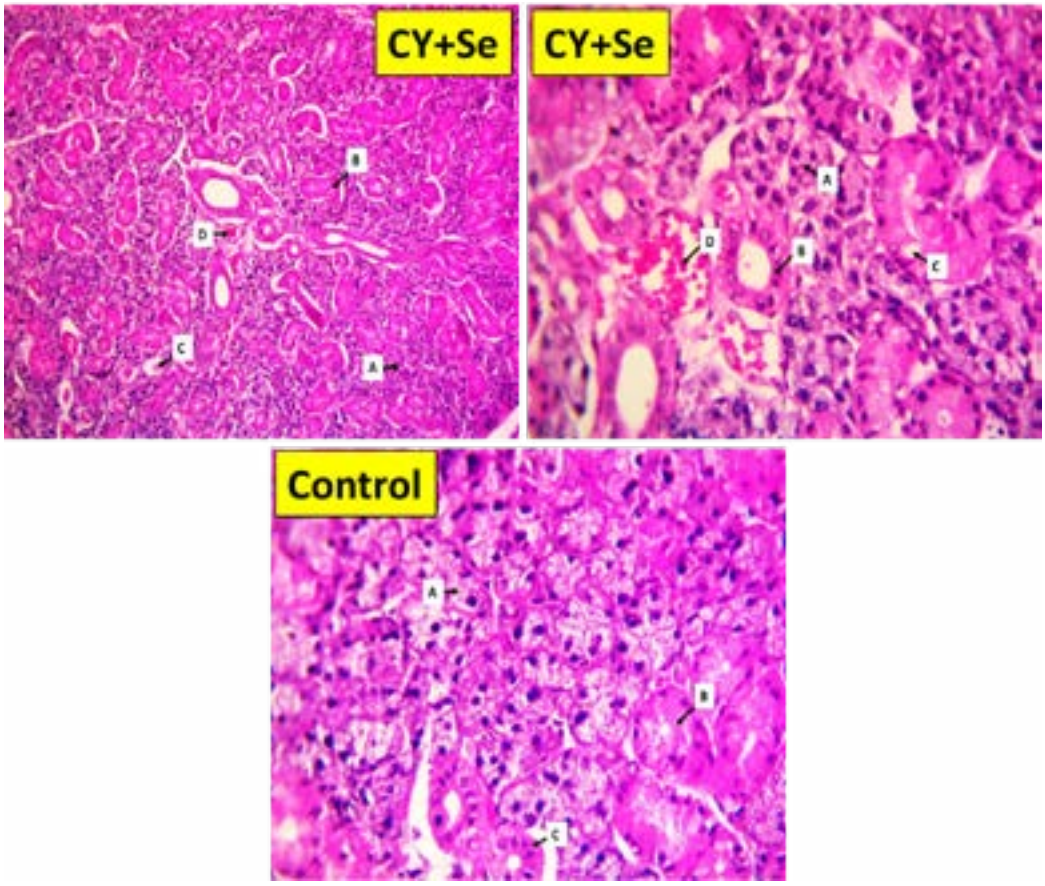

Figure 4. Representative image of rat submandibular salivary gland of the cyclophosphamide and selenium-treated group (CY+Se group) showed: A) Intact mucous acini, B) Striated duct, mild degeneration of granular convoluted tubules, C) Epithelial cells, D) Congestion of blood vessels.

The control negative group showed: A) Normal histological pictures represented by intact mucous acini, B) Granular convoluted tubules, C) Striated ducts.

group. The histological results indicated intact mucous acini, granular convoluted tubules, striated ducts, and interlobular ducts but with fibrous tissue between lobules. This improvement in the histological findings agreed with the findings of Zhang et al. (2021) who reported that these improvements could be due to the role of Se in curbing the toxic effect of CY on the submandibular salivary glands via the cytoprotective effect of Se against oxidative stress induced by CY [25].

Several recent studies have confirmed our findings. Moreover, Li et al. reported that Se can ameliorate oxidative stress in the liver, and reduce necrosis in hepatocytes and DNA damage induced by CY treatment in geese, besides reversing liver marker enzyme activity [49]. Another study that was published by Sengul et al. (2021) stated that Se can suppress the nephrotoxicity induced by acrylamide in rats, via the antioxidant, anti-inflammatory, anti-apoptotic, and renoprotective effects [50]. Ayhanci et al. demonstrated the role of Se as a protective pharmacological agent by decreasing the side effects of CY-induced kidney toxicity [51]. In addition, Bhattacharjee et al. (2017) [52] and Elshater (2018) [53] demonstrated the potential role of Se in ameliorating the CY-induced toxicity as well as improving the chemotherapeutic effect of CY.

Our study limitation was the difficulty in collecting the saliva from the rats in order to measure the effect of CY (with and without Se) in tested laboratory animals.

5. Conclusion

The histological and biochemical findings in our study suggest that the pre- and co-administration of Se with CY has a positive effect by improving the histological architecture and attenuating the oxidative damage induced by CY treatment via increasing the TAC values and decreasing the MDA levels.

Suggestion

We suggest that further studies should be carried out using special stains for the detection of the changes in the content of acini (mucus and serous), besides using the electron microscope to find the changes at the subcellular level.

Ethical Considerations

Compliance with ethical guidelines

The Ethics Committee University of Mosul, College of Dentistry (Code: UoM.Dent/A.L.10/22) approved this study.

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Authors' contributions

Investigation: Osama Adnan; Writing the original draft and final version: All authors.

Conflict of interest

The authors declared no conflict of interest.

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