

Original Article

Attenuating Effects of α -tocopherol on Cytarabine-Induced Toxicity in Parotid Salivary Gland of Rabbits: A Histological and Immunohistochemical Study



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ABSTRACT

Background: Cytarabine is considered a cornerstone of treating acute leukemia. Xerostomia is among the adverse effects that can dictate treatment cessation or the use of some agents that decrease its cytotoxic effects.

Objectives: This study aims to identify the histological effects of cytarabine on the rabbits' parotid gland and to assess the ameliorating α -tocopherol impact on these effects.

Methods: The study rabbits were separated into 4 groups. Group A (control) was given 1 mL of intraperitoneal (IP) injection of normal saline/day for 10 days. Group B received α -tocopherol (800 IU) by gavage for 10 days. Group C received cytarabine (60 mg/kg/d) IP for 10 days. Group D received α -tocopherol (800 IU) by gavage before injection of cytarabine (60 mg/kg) at the same time for 10 days. The rabbits were euthanized, and tissue preparation for analyzing microscopically and immunohistochemically for B-cell lymphoma 2 (Bcl-2) and tumor-necrosis-factor (TNF)- α was achieved.

Results: Microscopically, group B's parotid salivary gland sections revealed increased thickness of connective tissue of the trabeculae, degeneration, and necrosis of serous acini cells with aggregation of inflammatory cells. In contrast to the histopathological alteration of the glands in group C, which is characterized by intact serous acini, intercalated duct, and normal thickness of trabeculae, in the cytarabine group, TNF- α immunohistochemical expression was of grade 3 and in the cytarabine with α -tocopherol group was of grade 1. The Bcl-2 immunohistochemical expression in the cytarabine group was of grade 0, and in the cytarabine with α -tocopherol group was of grade 1.

Conclusion: α -Tocopherol decreases cytarabine toxicity in the rabbits' parotid salivary glands.

Keywords: α -Tocopherol, Bcl-2, Cytarabine, Parotid salivary gland, TNF- α

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Introduction

Cytarabine is an analogue of pyrimidine nucleoside. Cytarabine (Ara C) has been considered the cornerstone of treating acute leukemia since 1964 (Patel et al., 2012) besides viral infections (Dagenais et al., 2020; Kocarnik, 2020; Namuju & Chilaka, 2021). However, momentous aftermaths such as keratoconjunctivitis, neuronal damage, bone marrow suppression, and xerostomia require treatment cessation (Bilgin et al., 2020).

The triphosphate nucleotide that is included in the metabolism of cytarabine (Ara C) is responsible for its cytotoxic impact and takes action—as a competitive inhibitor of deoxycytidine triphosphate (dCTP)—and gets assimilated into deoxyribonucleic acid (DNA) in place of dCTP which hamper DNA polymerase. It inhibits DNA synthesis during replication and repair, which sooner or later brings out cell death (Zhang et al., 2016; Zhang et al., 2016). It has been reported that cytarabine generates genotoxicity and oxidative stress that originate apoptosis (Patel et al., 2012; Namuju & Chilaka, 2021).

Patients on cytarabine suffer from diminishing plasma values of total antioxidants (Kisaoglu et al., 2013). Reports suggest that some antioxidants may be a beneficial adjunct that minimizes the development of cytarabine-attendant cytotoxic effects (Namuju & Chilaka, 2021; Bilgin et al., 2020).

By the goodness of its mechanism, cytarabine damages DNA and hampers cell division in rapidly proliferating cells at the production phase. It generates oxidative stressing to accomplish its cytotoxic character and injury of organelles, DNA, and proteins (Guzmán et al., 2016; Hernández et al., 2018).

The major salivary glands secrete 90% of the daily saliva, and their malfunction changes the composition and decreases the amount of saliva, leading to dry mouth (xerostomia), manifested clinically by oral mucositis (Kurutas, 2016). Such malfunction was proven to occur with chemotherapy and aggravated its secondary mucotoxic effects (Omar et al., 2018). Many adverse effects have resulted from the usage of chemotherapeutic drugs, so protection against their toxicity is necessary (Al Allaf & Al Ashoo, 2021).

Antioxidants, including digestible types, effectively eliminate chemotherapy toxicity (Al Allaf & Al Ashoo, 2021). Vitamin E, peroxy radical scrounger, attenuates

oxidative cascades and rescues the injured organs (Faedmaleki et al., 2016; Hedayati et al., 2019; Bakr et al., 2021).

This work aims to identify the repercussions of cytarabine on the rabbits' parotid glands' structure and to define whether α -tocopherol has ameliorating effects on these changes using immunohistochemical technique (B-cell lymphoma 2 [Bcl2] and tumor necrosis factor [TNF- α]).

Materials and Methods

Experimental animals

After obtaining the Research Ethics Committee's permission at the College of Dentistry, University of Mosul, this study was conducted on 24 Albino rabbits (1.75-2.25 kg, 4 months old). The animals were divided into 4 groups: The first was the control group, and the second was treated by α -tocopherol alone. The third was a cytarabine-treated group, and the fourth was the cytarabine and α -tocopherol treated group.

Lab conditions

The animals were kept at a room temperature of $22\pm 2^\circ\text{C}$ with 12 hours of light and darkness, unrestricted access to food and water ad libitum for 10 days for adaptation within the superlative laboratory and nutritional status at 25°C (Dadashpour et al., 2022).

Experimental design

Four groups of 6 animals each were prepared as follows. Group A (control) was given 1 mL of intraperitoneal (IP) injection of normal saline daily for 10 days. Group B received α -tocopherol (800 IU) by gavage for 10 days. Group C received cytarabine (60 mg/kg/d) IP for 10 days (Al-Jammas & Al-Saraj, 2020). Group D received α -tocopherol (800 IU) by gavage prior to injection of cytarabine (60 mg/kg) for 10 days (Al-Jammas & Al-Saraj, 2020).

Rabbits were euthanized (Cicero, 2018) after 10 days with ether (Al Allaf & Al Ashoo, 2021), and their parotid tissues were prepared for histological study (Onwuama et al., 2022). Using paraffinized sections, immunohistochemical analysis was achieved for the expression of Bcl-2 and TNF- α according to some studies (Saleh et al., 2000; Meutia et al., 2021; Etemad-Moghadam et al., 2009).

Table 1. Immunohistochemical intensity scores of Bcl-2 and TNF- α expression in rabbits' parotid glands

Groups	Mean \pm SD				P
	Control Group (n=6)	Cytarabine Group (n=6)	Cytarabine+ α -tocopherol Group (n=6)	α -tocopherol Group (n=6)	
Scores of TNF- α	0.5 \pm 0.54 ^B	2.7 \pm 0.94 ^A	1.5 \pm 0.56 ^B	0.7 \pm 0.24 ^B	0.002
Scores of Bcl-2	2.2 \pm 0.2 ^A	0.4 \pm 0.24 ^B	1.4 \pm 0.24 ^C	2 \pm 0.5 ^{AC}	<0.001

A, B, C, AC: Significant variation among groups (P \leq 0.05).

Statistical analysis

The scores of the expression of Bcl-2 and TNF- α were recorded via grading of staining (0, 1, 2, and 3) to be analyzed by the Kruskal-Wallis test at a significant level of P<0.5 (Etemad-Moghadam et al., 2009; Meutia Sari et al., 2021; Taheri Mirghaed et al., 2023).

Results

Histopathological evaluations

Parotid gland plates of group A (control group) and group B (α -tocopherol) manifested a normal architec-

ture of the serous acini, intercalated duct, striated ducts, and excretory ducts (Figure 1, A, B, & C). While parotid gland plates of group C (cytarabine-treated group) illustrated a surge in the thickness of trabecular connective tissue, degeneration and necrosis of serous acini with aggregation of inflammatory cells (polymorph nuclear cells and Langhan's giant cells), and necrosis in the intercalated ducts (Figure 2, A & B). Also, the histopathological changes of the parotid glands of group C presented with the raised thickness of connective tissue surrounding ducts, interlobular edema, atrophy, degeneration, and necrosis of serous acini as well as necrosis of intercalated duct with aggregation of inflammatory cells. There

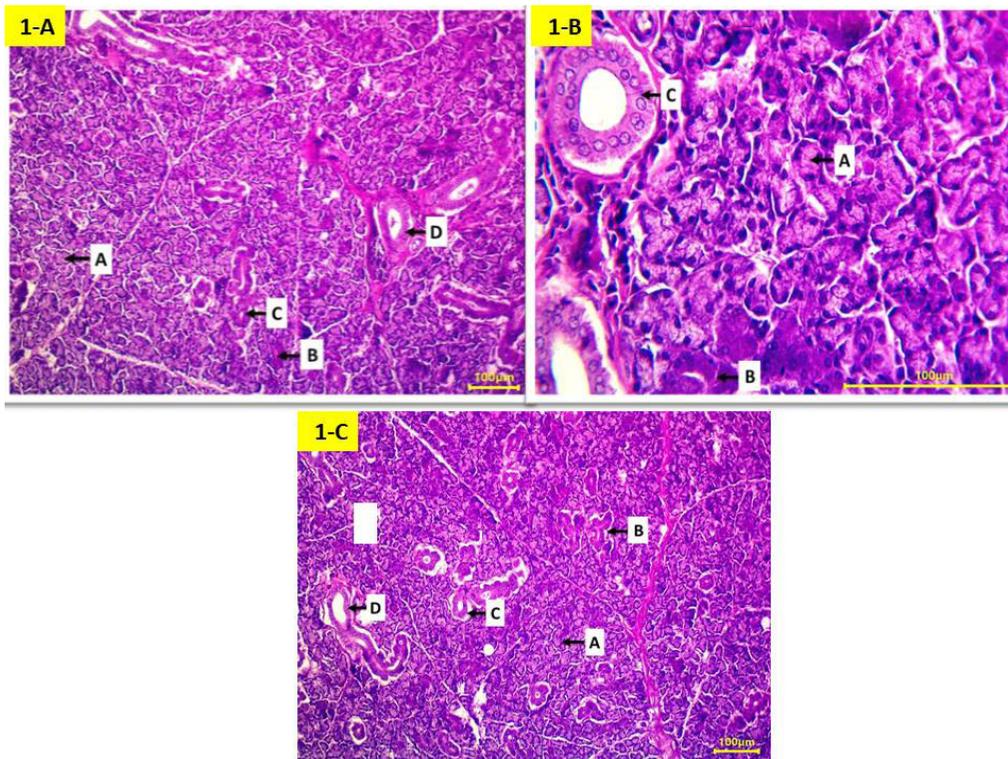


Figure 1. Photomicrographs of the rabbit parotid salivary gland

Group A (control group) (1-A & B), Group B (α -tocopherol) (1-C): Showing normal architecture of the serous acini (A), intercalated duct (B), striated ducts (C) and excretory ducts (D). H & E stain. (A & C: 100x, B: 400x).

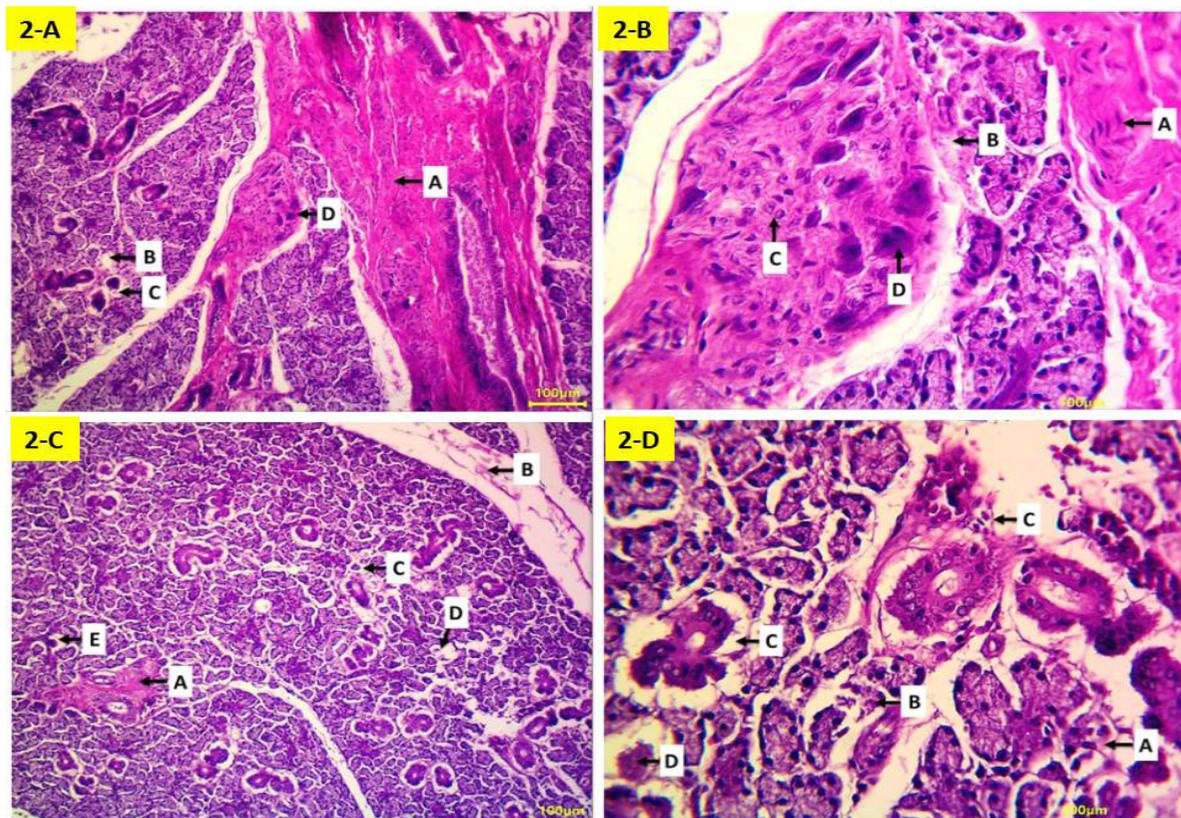


Figure 2. Photomicrographs of the rabbit parotid salivary gland

Group C (cytarabine treated group) (2-A & 2-B): Showing increased thickness of connective tissue of the trabeculae (A) degeneration and necrosis of serous acini (B) and intercalated duct (C), and aggregation of inflammatory cells as giant cells (D)

2-C & 2-D) Increased thickness of connective tissue surrounding ducts (A) edema (B), atrophy (C), degeneration and necrosis of serous acini (D) and necrosis of intercalated duct (E)

H&E stain. (A&C:100x, B&D: 400x).

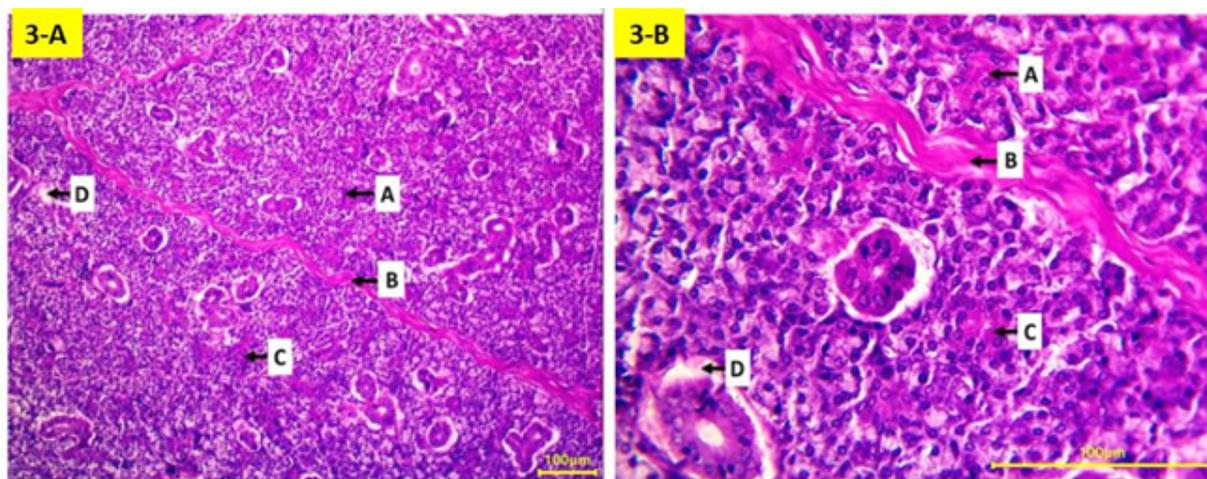


Figure 3. Photomicrograph of the rabbit parotid salivary gland

Group D (cytarabine with α -tocopherol treated group) (1-A & 1-B) Intact serous acini (A), intercalated duct (B) and normal thickness of trabeculae (B) with mild degeneration of epithelial cells of the striated duct (D). H&E stain. (A:100x, B: 400x).

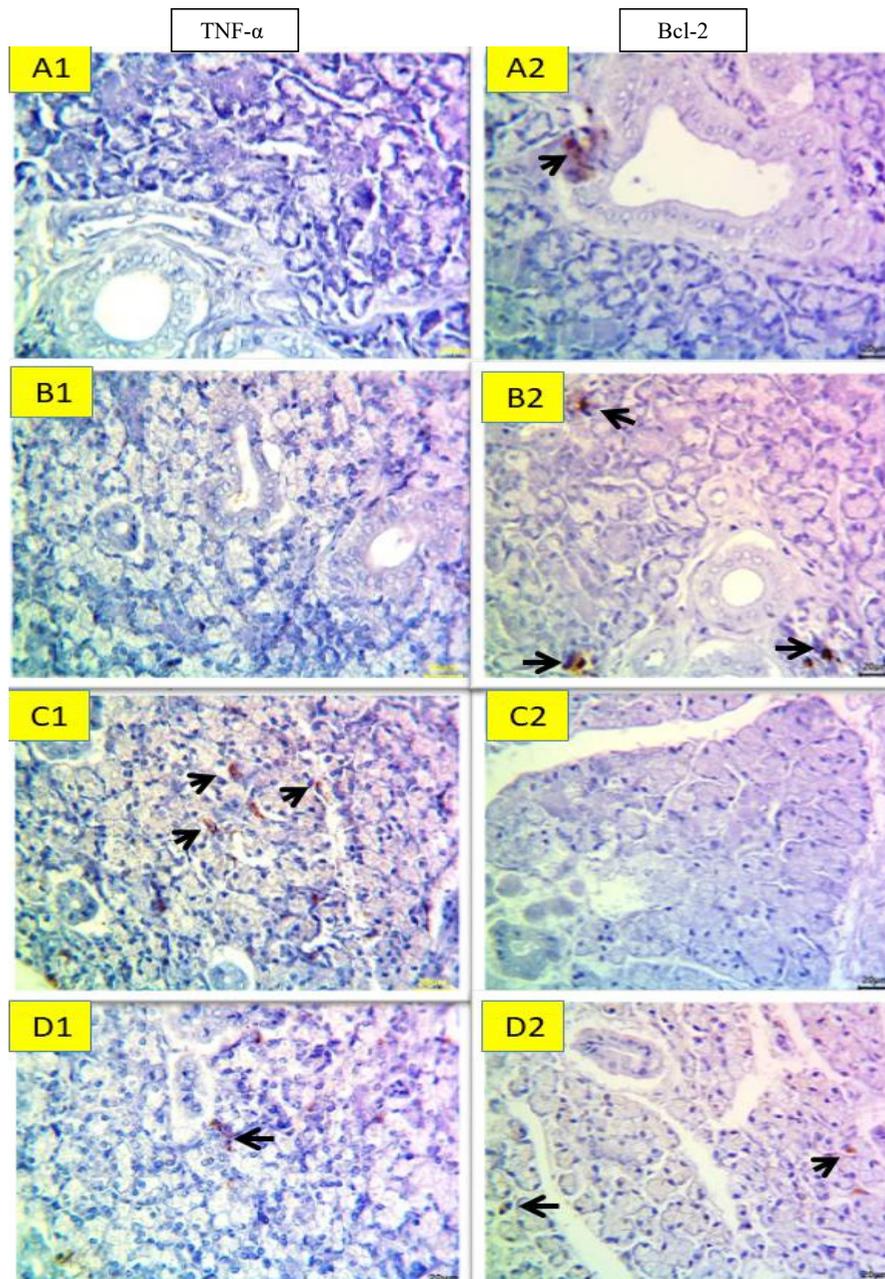


Figure 4. Immunohistochemical expressions *TNF- α* and *Bcl-2* for the rabbit parotid salivary gland in the epithelial cells cytoplasm

Note: *TNF- α* expressions are negative in the group A (control group) (A1) and group B (α -tocopherol) (B1). Group C (cytarabine-treated group) (C1): Strong positive and in the group D (cytarabine with α -tocopherol) (D1): Weak positive. *Bcl-2* expressions are strong positive in the group A (control group) (A2) and group B (α -tocopherol) (B2). Group C (cytarabine-treated group) (C): Negative, and in the group D (cytarabine with α -tocopherol) (D1): Weak positive. (Magnification 400x)

is detachment of acini and intralobular ducts from their basement membrane (Figure 2, C & D).

The histological sections of the parotid gland of group D (cytarabine administered group with α -tocopherol protection) exhibited intact serous acini, intercalated duct, normal trabecular thickness with degeneration of epithelial cells of the striated duct (Figure 3, A & 3B).

Immunohistochemical evaluations

The results of the immunohistochemical expressions *TNF- α* and *Bcl-2* for the rabbit parotid salivary gland in the epithelial cells cytoplasm. *TNF- α* expressions are negative in the group A (control group) (A1) and group B (α -tocopherol) (B1). group C (cytarabine treated group) (C1): Strong positive and in the group D (cytarabine

with α -tocopherol) (D1): Weak positive. Bcl-2 expressions are strong positive in the group A (control group) (A2) and group B (α -tocopherol) (B2). group C (Cytarabine treated group) (C): Negative, and in the group D (cytarabine with α -tocopherol) (D1): Weak positive. (magnification 400X) (Figure 4) (Table 1).

Discussion

Several microscopic alterations were noticed (in this work) via analyzing the parotid glands' sections of the cytarabine-treated group: Increased thickness of connective tissue of the trabeculae and degeneration and necrosis of serous acini with aggregation of inflammatory cells (polymorph nuclear cells and giant cells). An increase in connective tissue thickness surrounding ducts, edema, atrophy, degeneration and necrosis of serous acini, and necrosis of intercalated ducts were recorded. These findings are similar to those of Jensen et al. (2003), who attributed that to free radical damaging effects even in necrosis. These released free radicals merge with the cell's membrane, causing its lysis (Hsu et al., 2006).

On the other side, sections of the parotid gland of rabbits of group C (cytarabine administered group with α -tocopherol protection) showed a semi-normal appearance of parotid gland histology as there were intact serous acini, intercalated duct, normal thickness of trabeculae. Vitamin E possesses an antioxidant ability to battle the cytotoxic aftermath (Bakr et al., 2021).

To our knowledge, little research has been conducted on the ability of α -tocopherol to counteract the cytotoxic effect of cytarabine on rabbit parotid salivary gland.

The scavenging effect of α -tocopherol attenuates the cytarabine adverse effect on parotid gland histology. These findings are in accordance with those of others (Davari et al., 2012).

α -Tocopherol may be used as an adjuvant to curb these actions (Mukherjee et al., 2013; Delay et al., 2019; Namuju et al., 2014; Behrouz et al., 2022). However, there are reports regarding the possibility of antioxidants eliminating or raising anticancer potency and whether these agents rescue normal tissues and mitigate their toxicity (Singh et al., 2018; Esfahani et al., 2012). There is a criticism that co-administration with antioxidants (like vitamins C and E) may interfere with the anti-cancer efficacy (Suhail et al., 2012; Kaywanloo et al., 2022).

Among the usable inquiring tools to analyze the fundamental issues in pharmacology is the salivary gland

(Jensen et al., 2003; Sanguineti et al., 2015). There is a synchronized loss of glandular functions; however, they possess a low mitotic rate beyond the exposure to chemotherapeutic doses (Al-Refai et al., 2014).

Vitamin E improves the cytoplasmic vacuolization in both ductal and acinar zones due to its efficient action against the oxidation of fat and reactive oxygen species propagation besides the neutralization of the formed radicals (Rizvi et al., 2014; Bakr et al., 2021). So, vitamin E attenuates the cytotoxicity induced by anti-cancers. Vitamin E stabilizes the cells and increases the cells' membrane lipid with efficiency in membrane repair by turning away oxidized phospholipids, which are fundamental in membrane fusion affairs (Howard et al., 2011).

Like many anticancer agents, cytarabine drops Bcl-2 levels (Al-Rasheed et al., 2018).

Immunohistochemical analysis of the expression of Bcl-2 in the present work concluded that vitamin E combats the apoptotic impact of cytarabine as the expression of Bcl-2 increased by exposure to vitamin E as reported previously (Al-Refai et al., 2014; Al-Rasheed et al., 2018).

The analysis of the Bcl-2 expression in this study indicated an alteration by cytarabine as the synthesis of DNA is inhibited, and this cytotoxic agent initiates apoptosis. So, any agent against the Ara C with increased Bcl-2 may be useful (Zhang et al., 2019; Nishi et al., 2013). However, routine vitamin E prescription as prophylaxis has not been endorsed (Chen et al., 2021; Miao et al., 2021).

A hallmark of malignant cells is the discouragement of programmed death-apoptosis guided by proteins (Bcl-2). As this marker is raised, there is more cancer cell survival. The issue of identifying the anticancer potency of these protein inhibitors is under investigation, but there is a possibility of termination due to the aftereffects (Sharma et al., 2020).

Concerning the TNF- α , a cornerstone in immunity regulation, this study exhibited that cytarabine induced more expression of this marker. These observations agree with those of others as this marker correlated with inflammatory and oxidative processes via its impact on neutrophils (Al-Rasheed et al., 2018).

Furthermore, the expression of TNF- α was decreased among sections of rabbits in the cytarabine+tocopherol group. These observations agree with those of other researchers (Al-Rasheed et al., 2018; Bilgin et al., 2020), who reported a relationship between the endogenous an-

tioxidant agents and the low expression of TNF- α with a significant pro-inflammatory role (Al-Jammas & Al-Hubaity, 2011).

TNF- α is produced by the lymphocytic cells and macrophages to suppress the cellular proliferation of cancer cells besides its role in immunity (natural and acquired), cellular differentiation, and apoptotic processes. Its cytotoxic actions involved only the tumor cells (Sklavounou et al., 2000).

Several agents may be beneficial to attenuate the cytarabine-related toxicity, including antioxidants via decreasing the TNF- α . Few successful trials have employed anti-TNF- α agents to treat some clinical cases, such as psoriasis and inflammatory bowel disease (Saral et al., 2019). Selective novel agents that target the TNF- α receptors are recommended to be checked in experimental works.

The analysis of this work showed that TNF- α is highly expressed with exposure to cytarabine. The authors concluded a relationship between this indicator of inflammation and organ toxicity via the production of interleukin (IL)-1 and IL-6 with the role of TNF- α inhibitors to mitigate these effects (Saral et al., 2019).

High expression of inflammatory mediators raises the extent of tissue damage, so this damage can be prevented by inhibiting these mediators. In addition, diagnosing and following up on organ function may require measuring mediators, including TNF- α (El-Sheikh et al., 2017).

In conclusion, there is a protective role of α -tocopherol on cytarabine-induced toxicity in parotid salivary glands of rabbits via analyzing the histological outcomes and immunohistochemical analysis data (TNF- α and Bcl-2).

Ethical Considerations

Compliance with ethical guidelines

All ethical permissions were received, and all transactions were conducted in accordance with the guidelines established by the University of Mosul's College of Veterinary Medicine and Dentistry (Code: UM.VET.2023.65).

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Authors' contributions

Conceptualization: Saif Al-Jammas; Investigation: Luma Ibrahim Khalel Al-Allaf; Statistical analysis, writing and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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