Original Article

Ferulic Acid and Submandibular Salivary Gland in Rats Exposed to Methotrexate

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ABSTRACT

Background: Widely used in chemotherapy, methotrexate (MTX) is known to induce oxidative stress and cell death in non-target organs, such as salivary glands.

Objectives: This study investigates the preventive and therapeutic effects of ferulic acid (FA), a naturally occurring antioxidant and anti-inflammatory compound, on the histological and biochemical alterations induced by MTX in the submandibular salivary glands of rats.

Methods: A total of 24 mature male rats were divided into 4 groups (6 rats in each group): Group I (control) received a normal saline solution for 18 days during the study. On the 15th day of the study, group II (MTX-treated) rats got a single intraperitoneal (IP) injection of MTX (40 mg/kg). They were left untreated for three days. Group III was the protective group (FA+MTX). The rats were given FA (60 mg/kg/d, orally) for 14 days before receiving a single IP injection of MTX (40 mg/kg) on day 15. Group IV was the therapeutic group (MTX+FA). After three days of MTX administration (days 15, 16, and 17), they received FA (60 mg/kg/day, orally).

Results: FA significantly attenuated MTX-induced biochemical and histological anomalies, as demonstrated by decreased levels of IL-1β and caspase 3, elevated levels of IL-10, and attenuated degenerative alterations in the granular convoluted tubule, mucous acini, and striate duct.

Conclusion: The study revealed that MTX induces inflammation and cellular death in the submandibular salivary glands of rats, as evidenced by increased levels of IL-1β and caspase 3, along with decreased levels of IL-10, thereby impairing tissue architecture. FA, given either prophylactically or therapeutically, significantly reduced inflammation and apoptosis.

Keywords: Apoptosis, Ferulic acid (FA), Inflammation, Methotrexate (MTX), Submandibular gland

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Introduction

Salivary glands are important for oral and systemic health because they produce saliva that helps with digestion, maintains the mucosal barrier, and protects against germs. The submandibular glands are very important for unstimulated salivary flow, and systemic diseases and chemotherapy medicines can easily hurt them (Al-Moula et al., 2012; Al-Allaf et al., 2022; Ahmed & Mammdoh, 2022; Chibly et al., 2022; Taghyan et al., 2025).

Methotrexate (MTX) is a folate antagonist often used to treat several malignancies, autoimmune diseases, and inflammatory disorders. Despite its clinical efficacy, there is substantial evidence that MTX induces cytotoxic effects (Saud et al., 2022), including oxidative stress, cell death, and organ damage, particularly of the salivary glands (Attarbashee et al., 2025; Heller et al., 2025). In 2023, Kızıl et al. found that the adverse effects of MTX result from its ability to generate free radicals and activate cell death pathways by increasing *caspase-3* gene expression and decreasing *Bcl-2* levels. Recently, there has been growing interest in substances known for their antioxidant and cell-protective qualities to reduce organ damage caused by medications (Attarbashee et al., 2023; Attarbashee, 2025; Mustafa et al., 2025). Ferulic acid (FA) is a compound that occurs naturally in the cell walls of plants like wheat, rice bran, and oats. It has potent anti-inflammatory and anti-apoptotic properties (Kumar et al., 2024).

Several studies have shown that FA protects against oxidative damage in liver, kidney, and brain tissues (Zhai et al., 2023; Khatun et al., 2024). However, the available evidence on its protective role for salivary glands, especially in MTX-induced toxicity, is scarce (Marin et al., 2022). Henceforth, this study aims to investigate the protective and therapeutic benefits of FA on the submandibular salivary glands in rats exposed to MTX. It will use histological analysis and evaluate interleukin (IL)-1β, IL-10, and caspase-3 in the inflammatory process and apoptosis.

Materials and Methods

Drugs and chemicals

MTX was obtained from Koçak Farma (Turkey), and FA was obtained from Talsen Chemicals Co. (New York). Both pharmaceuticals were administered to rats after preparation in normal saline solution.

Study animals

Twenty-four adult Albino Wistar rats (190- 210 g) aged 6 to 9 weeks were used in this experiment. Animals were kept in separate polypropylene cages that were free of contaminants. The cages had a large wire-mesh bottom that was kept clean to prevent the rats from licking or touching each other. Rats were housed at 22-25 ˚C and on a 12-hour light/dark cycle. They had a ventilation system that constantly changed the room's air, and they had access to fresh water and standard ad libitum food. Before we started our experiment, the animals were given 1 week to acclimate to the housing (Luty 2021; Salman et al., 2013).

The experiment was conducted under document number UoM from January 2025 until June 2025. The Institute Animal Ethical Committee (IAEC) of the College of Dentistry approved the study proposal on January 17, 2025. All activities followed pertinent rules and principles (Naji et al., 2022; Dawood & Abu-Raghif, 2023; Ridha-Salman et al., 2024).

Experimental groups

Twenty-four rats were randomly divided into 4 experimental groups, with 6 animals per group. Group I (control) spans 18 days of receiving a normal saline solution without treatments during the study. On the 15th day of the research, group II (MTX-treated) rats received a single intraperitoneal (IP) injection of MTX (40 mg/kg). They were left untreated for 3 subsequent days. Group III was the protective group (FA+MTX). They were pretreated with FA (60 mg/kg/d, orally) for 14 days, followed by a single IP injection of MTX (40 mg/kg) on day 15. Group IV was the therapeutic group (MTX+FA). They were received FA (60 mg/kg/day, orally) after MTX administration for 3 days (on days 15, 16, and 17). On day 18, the rats were euthanized using ketamine (80 mg/kg) and xylazine (10 mg/kg), followed by the excision of submandibular salivary gland tissue and subsequent preparation for histological and biochemical examination. Processing tissue samples produced a homogenate for bioindicator research, and the supernatants were collected and stored at 80 ˚C. The biochemical assay was conducted 3 times to ensure the reliability and consistency of the results. After the exams, practically all markers remained consistent with earlier results.

Histological examination

After extraction, rats' submandibular tissue specimens were promptly preserved in 10% buffered formalin, de-

hydrated in graded ethanol, and cleared with xylene (Al-Allaf et al., 2022; Attarbashee et al., 2023; Sultan & Taqa, 2024; Ali et al., 2025). The biopsy was subsequently immersed in paraffin and placed onto cool plates to form paraffin blocks. The submandibular salivary samples were subsequently sectioned into 4- to 5-µm slices using a microtome. A water soak was used to deposit the slide section, and a few mL of di-n-butyl phthalate in xylene were added to the tissue fragment before the coverslip was applied. An alight microscope was utilized for the execution of blind examinations and assessments» (Mammdoh et al., 2023; Ridha-Salman et al., 2025).

Inflammatory, anti-inflammatory, and apoptotic biomarkers measurement

Rat glandular tissue homogenates were examined for IL-1β, IL-10, and caspase-3 using a standardized sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Cloud-Clone Corp). The initial stage of the assay involves applying anti-biomarker antibodies to a 96-well plate. The extract samples and baseline standards were added to the wells, where the encapsulating antibodies bound to IL-1β, IL-10, and caspase-3 in the samples. The pore spaces (unbound sites) were subsequently rinsed with wash buffer before the application of a biotin-conjugated specific antibody. After removal of the detached biotin-conjugated antibody, streptavidin and horseradish peroxidase (HRP) were carefully added to the plate. The quantity of diverse bioindicators in each collection was assessed by comparing its optical density to standard curves. The results of the bioindicator quantity and optical density measurements obtained by spectrophotometry were compared. The plates were cleaned again, and TMB-substrate combinations were subsequently applied, indicating the levels of the associated markers by the resultant hue. The color magnitude is calculated at 450 nm as the hue transitions from blue to yellow with the stop solution.

Statistical analysis

The data have been entered into GraphPad Prism software, version 10.5.0. The descriptive statistical analysis incorporates the Mean±SD. The results were presented graphically and analyzed using appropriate statistical methods. A one-way analysis of variance (ANOVA) was employed to examine differences in the means of quantitative variables across groups, followed by the Tukey HSD post hoc test to determine which group means differed significantly. The significance threshold was set at $P<0.05$ for all statistical analyses.

Results

Effects of MTX and FA on inflammatory and anti-inflammatory biomarkers

The MTX group showed markedly elevated IL-1β levels and reduced IL-10 levels compared with the control group ($P<0.05$). Nonetheless, the FA+MTX and MTX+FA groups had significantly lower IL-1β levels and higher IL-10 levels than the MTX group ($P<0.05$). According to Table 1 and Figure 1, no significant differences were observed in any variables between the FA+MTX and MTX+FA groups ($P>0.05$).

Influences of MTX and FA on apoptotic biomarker

The apoptotic marker caspase-3 was significantly increased in the MTX group relative to the control group ($P<0.05$). However, the FA+MTX and MTX+FA groups showed a significant drop in caspase-3 levels compared to the MTX group ($P<0.05$). According to Table 1 and Figure 2, no significant differences were observed in any variables between the FA+MTX and MTX+FA groups ($P>0.05$).

Histological findings

Figure 3 illustrates the normal histological architecture of the submandibular salivary gland in the control group. Hematoxylin and eosin (H&E)-stained sections revealed well-organized mucous acini, granular convoluted tubules, and striated ducts without evidence of structural disruption or inflammatory changes. In contrast, Figure 4 shows the submandibular gland morphology in the MTX-treated group, characterized by extensive necrosis of mucous acinar cells and granular convoluted tubules, inflammatory cell infiltration, and marked vascular congestion, indicating severe tissue damage and inflammation resulting from MTX toxicity. Figure 5 represents histological sections from the FA + MTX protective group, in which the salivary glands exhibit largely preserved mucous acini, with only mild necrosis and degeneration in the granular convoluted tubules. Some vascular congestion remains evident, suggesting partial but significant protection against MTX-induced tissue injury by FA. Figure 6 shows the histological appearance of the MTX+FA therapeutic group, in which the glandular architecture is well preserved and closely resembles that of the control group. The mucous acini, granular convoluted tubules, and striated ducts show no evident necrosis, and there is no inflammatory infiltration, indicating effective post-exposure recovery facilitated by FA.

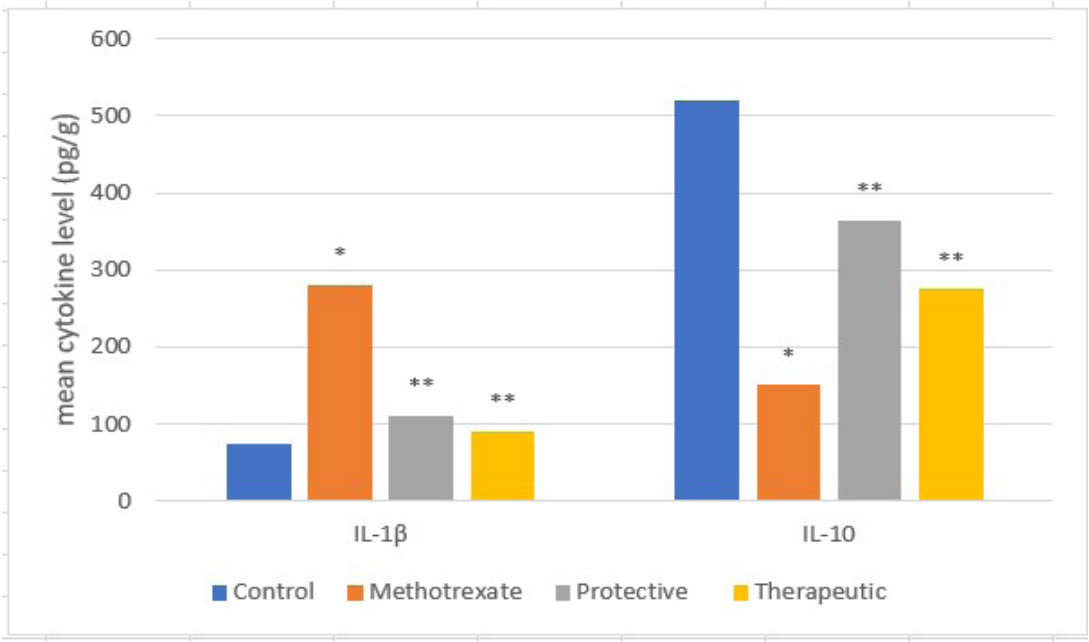

Figure 1. Impact of MTX and FA on inflammatory and anti-inflammatory biomarker levels IL-1β and IL-10

*Significant difference in contrast to the control group (P<0.05), **Significant difference in contrast to the MTX group (P<0.05).
Note: IL-1β and IL-10 were reported as pg/g tissue.

Discussion

The results of this work show that treatment with MTX causes substantial inflammatory and apoptotic alterations in rat submandibular salivary glands. This result is evidenced by significant elevations in IL-1β and caspase-3 levels, a reduction in IL-10, and severe histological damage, including necrosis, infiltration of inflammatory cells, and vascular congestion. These findings coincide with earlier studies showing that MTX induces

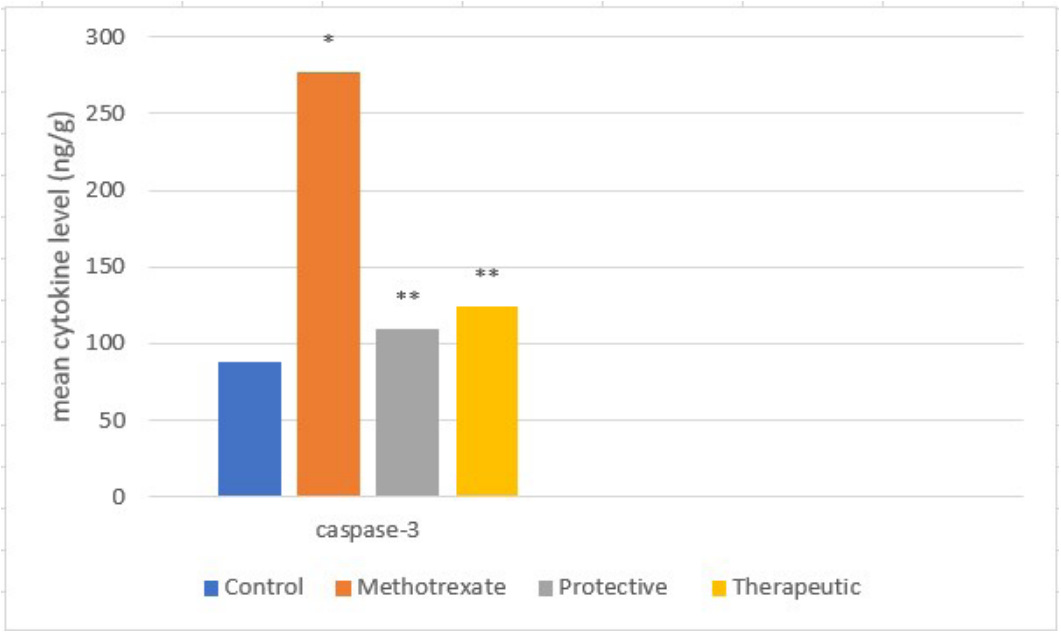

Figure 2. Impact of MTX and FA on apoptotic biomarker level caspase-3

*Significant differences in contrast to the control group (P<0.05); **Significant differences in contrast to the MTX group (P<0.05).
Note: Caspase-3 was expressed as ng/g tissue.

Table 1. Effects of MTX and FA on inflammatory, anti-inflammatory, and apoptotic biomarkers

Marker	Mean±SD			
	Study Groups			
	Control (n=6)	MTX (n=6)	FA+MTX (n=6)	MTX+FA (n=6)
IL-1β	75.01±1.47	280.05±5.93*	110.03±11.43**	89.99±11.46**
IL-10	520±8.09	150.01±6.51*	365.01±5.09**	275.04±5.44**
Caspase-3	88±4.56	283.71±17.51*	110±4.24**	124±4.93**

*Significant differences in contrast to the control group (P<0.05), **Significant differences in contrast to the MTX group (P<0.05).

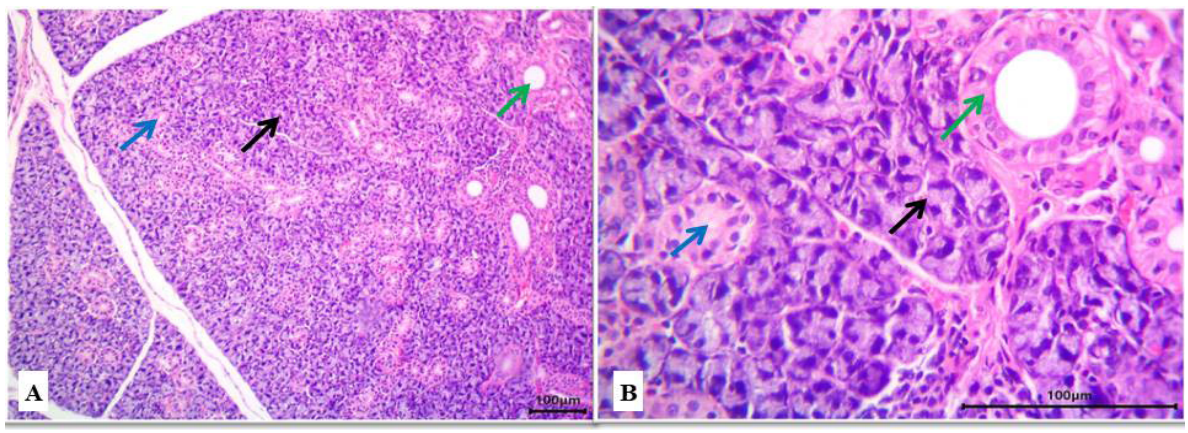

Figure 3. The submandibular salivary gland sections of a control rat showing the entire histological architecture of the mucous acini (black arrow), granular convoluted tubules (blue arrow), and striated ducts (green arrow)

H&E staining; scale bar=100 µm; A: ×100, B: ×400.

oxidative stress and supports a pro-inflammatory milieu in several tissues, including oral glands (Bayramowicz et al., 2022; Moubarak, 2024). A feature of MTX-induced cytotoxicity, the rise in pro-inflammatory cytokines, including IL-1β, has been linked to the activation of nuclear factor kappa B (NF-κB), which plays a vital role in organizing inflammatory responses and supporting apoptotic pathways (Al-Saffar et al., 2020).

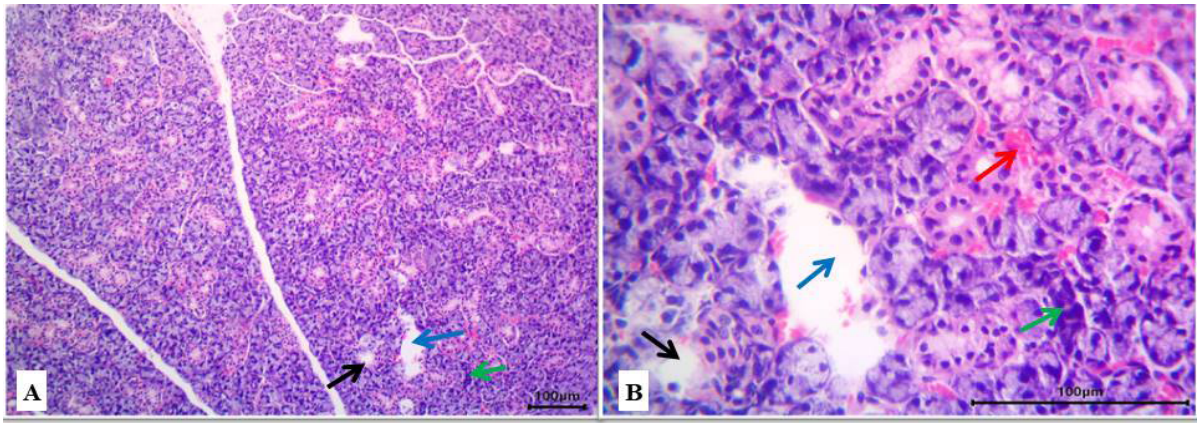

Figure 4. The submandibular salivary gland sections of the rat in the treated group showing necrosis of the mucous acini cells (black arrow), and granular convoluted tubule cells (blue arrow), infiltration of inflammatory cells (green arrow), and blood vessel congestion (red arrow)

H&E staining; Scale bar=100 µm; A: ×100, B: ×400.

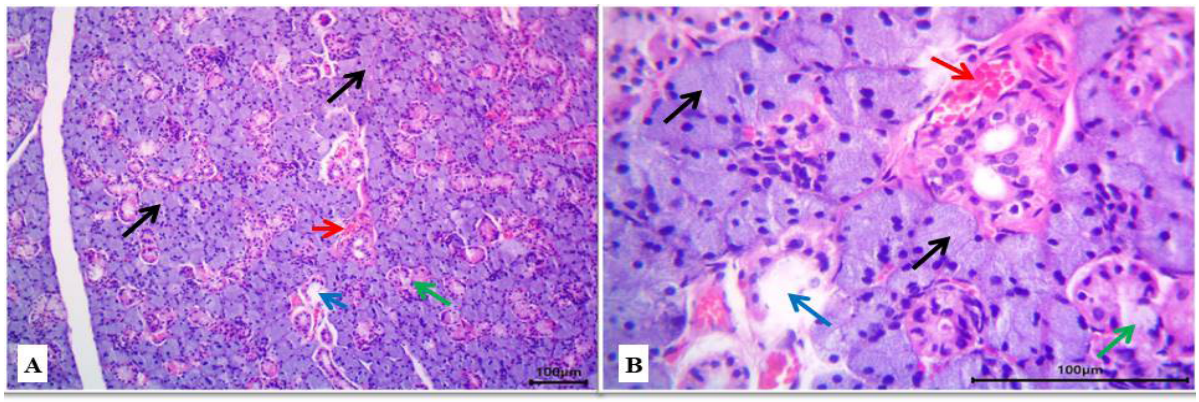

Figure 5. The submandibular salivary gland sections of the rat, dealing with the FA + MTX protective group, showing intact mucous acini cells (black arrow), mild necrosis (blue arrow), and degeneration (green arrow) of granular convoluted tubule cells, and blood vessel congestion (red arrow)

H&E staining; scale bar=100 µm; A: ×100, B: ×400.

The effectiveness of natural substances in treating oral tissue destruction is supported by a previous study (Hamzah et al., 2023). Studies on rats revealed preventive and healing benefits against MTX-induced damage. FA is a natural phenolic compound well known for its antioxidant properties. Rats in groups 3 and 4, with FA before and after MTX, showed declines in IL-1β and caspase-3 levels compared to the group that received MTX (group 2). This finding implies a decrease in both inflammatory processes and cell death. Research has consistently demonstrated that FA has anti-inflammatory properties by blocking NF-κB activation and reducing the production of inflammatory cytokines, such as IL-1β, tumor necrosis factor alpha (TNF-α), and IL-6 (Liu et al., 2022; Park & Han, 2024).

FA is recognized for its capacity to alleviate stress by eliminating reactive oxygen species (ROS) and enhancing natural antioxidant systems, such as superoxide dismutase (SOD) and catalase (CAT), thereby effectively maintaining cellular equilibrium. Furthermore, the application of FA after MTX exposure (groups 3 and 4) resulted in notable improvements in both biochemical and histological parameters, indicating a healing effect. The drop in caspase-3 levels and the improvement in structure in this group suggest that FA may affect mitochondrial pathways regulating cell death. It could function by increasing cell death proteins, such as Bcl-2, and by blocking cytochrome. The cytochrome complex leakage from mitochondria (Ferro et al., 2021; Joshi et al., 2021). The molecular mechanisms highlighted the role of FA in preventing and treating chemotherapy-induced organ damage effectively. Moreover, the study's emphasis on IL-10 regulation is noteworthy. Though IL-10 is usually regarded as an anti-inflammatory cytokine, the lower

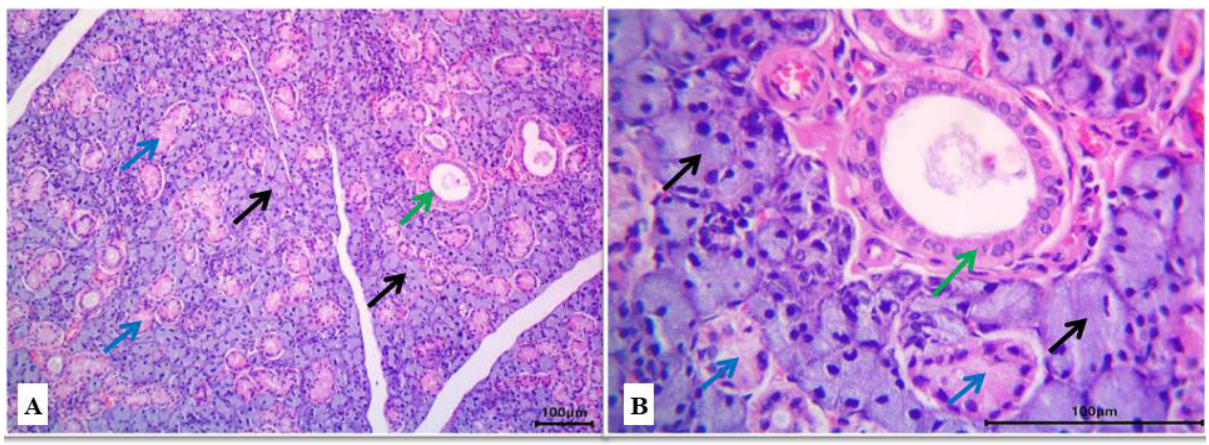

Figure 6. The submandibular salivary gland sections of the rat of the MTX + FA therapeutic group showing intact histological architecture of the mucous acini (black arrow), granular convoluted tubules (blue arrow), and striated ducts (green arrow)

H&E staining; Scale bar=100 µm; A: ×100, B: ×400.

levels observed in the MTX group and the increase in IL-10 levels in the FA + MTX protective and MTX + FA therapeutic groups could indicate modulation of the inflammatory response. The anti-inflammatory activities of FA are believed to be mediated by pathways such as MAPK, NF-κB, and SIRT1/AMPK/PGC-1α (DiNicolantonio et al., 2022). This finding suggests that FA affects the immunological response (AL-Saffar & Taqa, 2019) and acts as an antioxidant, anti-inflammatory, and anti-apoptotic agent.

Microscopic examination of tissues, in conjunction with analytical data, revealed that rats administered MTX exhibited significant damage to their glandular structures, including necrosis in mucous acini and granular convoluted tubules, inflammation, and increased blood flow in the affected region. These findings show that MTX affects cells and induces inflammation, most likely through increased ROS and mitochondrial dysfunction, as previously reported in studies of tissue damage in salivary glands and the liver (Mostafa et al., 2023; Mohammed & Al-Gareeb, 2021). Conversely, rats in the FA-treated group showed intact histological structures with low necrosis and limited inflammation, suggesting that FA is essential for preserving tissue integrity.

Moreover, the group exposed to FA after MTX demonstrated complete restoration of the normal glandular structure, suggesting that FA may also promote tissue healing and regeneration beyond its role in preventing cellular injury. FA's actions could help explain its characteristics, as it can increase survival pathways, promote blood vessel development, and regulate proteins like caspase-3. These results align with studies on liver and renal damage models (Shi et al., 2023; Bao et al., 2023).

Conclusion

The research demonstrated that MTX induces inflammation and cellular apoptosis in the submandibular salivary glands of rats, as indicated by increased levels of IL-1β and caspase 3, and decreased levels of IL-10, thereby disrupting tissue architecture. FA, administered either preventively or therapeutically, dramatically mitigated inflammation and apoptosis. These findings indicate that FA warrants further investigation in clinical settings, as they reveal its potential to preserve glandular function after chemotherapy.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Animal Ethical Committee (IAEC) of the College of Dentistry, University of Mosul, Mosul, Iraq (Code: UoM. Dent 25/1049).

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Authors' contributions

Methodology and writing the original draft: Maha Talal Fattah; Validation and supervision: Rana Khairi Attarbashee; Data assessment and final approval: Faehaa Azher Al-Mashhadane; Review and editing: Maha Talal Fattah and Faehaa Azher Al-Mashhadane; Resources: All authors.

Conflict of interest

The authors declared no conflict of interest.

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