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Research Paper

Therapeutic Effect of Exosomes Derived From Bone Marrow Mesenchymal Stem Cells on Lingual Papillae Mucositis Induced by 5-fluorouracil in Albino Rats

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ABSTRACT

Introduction: 5-fluorouracil (5-FU) is one of the prevalent anti-cancer drugs that is commonly used in chemotherapeutic modalities to treat head and neck solid cancers. However, various studies have reported that 5-FU has the ability to generate toxicity in different tissues, causing oral mucositis. Using exosomes derived from stem cells is gaining huge attention for therapies, as it may have certain advantages over adult stem cell-based therapies. This study aimed to evaluate the therapeutic effect of bone marrow-derived stem cells exosomes on the cytotoxicity induced by 5-FU on the lingual papillae of albino rats.

Materials & Methods: Thirty male albino rats weighing between 150-200 grams were equally and randomly divided into 3 groups as follows: Group I (control group): containing 10 rats, received saline daily via oral gavage for 14 days. Group II (5-FU group): containing 10 rats, received a single intraperitoneal (IP) injection of 5-FU® drug (50 mg/kg) each. Group III (5-FU + exosomes group): containing 10 rats; the rats was treated as group II, then received a single injection of exosomes through the tail vein day 2 (100 µg/kg/dose suspended in 0.2 mL PBS). Rats of each group were euthanized after 14 days, and tongue specimens were collected for histological, ultrastructural, and immunohistochemical evaluation.

Results: In the 5-FU treated group, there were marked degenerative changes of the filiform papillae, such as areas of keratin separation and hyperkeratinization and the fungiform papillae showed atrophy and deformed taste buds. The exosomes-treated group, however, showed marked improvement in histological, ultrastructural, and immunohistochemical findings.

Conclusion: Exosomes derived from bone marrow mesenchymal stem cells (MSCs) exerted an obvious therapeutic effect against the induced mucositis caused by the cytotoxic effect of 5-FU, as reflected in improved histological, ultrastructural, and immunohistochemical findings.

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1. Introduction

5-fluorouracil (5-FU) is an antimetabolite drug that is frequently utilized as an effective chemotherapeutic agent. It was discovered that this drug is effective against a widespread diversity of solid tumors and is considered by the World Health Organization (WHO) as one of the most effective drugs used in cancer treatment. To date, 5-FU continues to be a mainstay of treatment for cancers of the digestive tract, colorectal cancer, as well as cancers arising in other organs [1].

5-FU has a multifaceted cytotoxic activity that involves thymidylate synthase inhibition and the integration of its metabolites into RNA and DNA. Since thymidine is essential for both DNA replication and repair, DNA replication arrest is caused by a large increase in dUTP levels and unusually low dTTP levels when thymidylate synthase is inhibited. Additionally, 5-FU may be integrated into the structure of RNA, impairing its ability to function normally. Consequently, the DNA and RNA synthesis disruption caused by 5-FU results in the suppression of cell division, directing the cell towards apoptosis [2].

Oral mucositis (OM) is a common, distressing adverse effect of 5-FU. Several methods of intervention have been explored to overcome the OM induced by 5-FU chemotherapy, such as cryotherapy, low-level laser therapy, and keratinocyte growth factor. However, several limitations have been found concerning these previous modalities [3].

Mesenchymal stem cells (MSCs) have been vastly utilized in numerous inflammatory diseases, as they have several characteristics, such as directed differentiation, antioxidant activity, anti-apoptotic effects, and promotion of cell regeneration. MSCs are believed to exert their therapeutic effect through the release of various factors, such as cytokines, growth factors, and exosomes. Exosomes are nanosized (30–150 nm in diameter), circular, membrane-bound vesicles that are released by cells and transport several types of proteins, RNA, metabolites, and lipid membrane components to adjacent and distant cells. Exosomes surpass the benefits of MSCs by providing targeted administration, minor immunogenicity, and high repairability [4].

Exosomes derived from MSCs (MSCs-EXOs) main function is cell-to-cell communication, as they transport nucleic acids, such as mRNAs, miRNAs, and lncRNAs, which can modulate target genes. The promising role of MSC-exosomes was confirmed by a recent study in wound healing and the alleviation of scars through re-epithelization, angiogenesis, and regulation of collagen remodeling [5].

Exosomes' therapeutic potential is gaining increased attention based on several studies within the orofacial discipline, as they have a promising potential in various contexts, such as the acceleration of wound healing in tongue defects, as well as enhancing wound healing with minimal scar formation [5, 6]. Therefore, the current study sought to assess the efficacy of bone marrow MSC-derived exosomes in alleviating the adverse effects of 5-FU on the lingual papillae of albino rats. The null hypothesis of the current research was that exosomes would not have a significant therapeutic effect on the 5-FU-induced lingual papillae mucositis.

2. Materials and Methods

2.1. Study setting and sample selection

The experiment was performed following the ethical guidelines of animal experimentation and was evaluated by the Faculty of Dentistry's Research Ethics Committee (REC), Suez Canal University, Ismailia, Egypt.

The sample size for this study was calculated using the Equation 1:

1. Total sample size N=29.903≈30 samples

2.2 Study procedures

2.2.1 Exosomes preparation

A. Bone marrow mesenchymal stem cells (BMMSCs) isolation and culture: Bone marrow cells were obtained from the tibia of albino male rats. Phosphate-buffered saline (PBS) was used to wash the cells. The flushed cells were put on 15 mL of Ficoll-Paque (Gibco Invitrogen, Grand Island, NY) and centrifuged at 400×g for 35 minutes. Cells at the interface were aspirated, washed twice in sterile PBS, and centrifuged for 10 min at 200×g, 5° C. The isolated BMMSCs were cultured in DMEM medium supplemented with 10% FBS and penicillin. Cells of the third passage (P3) were used in the study.

B. Identification of BMMSCs: morphology of BMMSCs under TEM and flow cytometric analysis for cluster of differentiation (CD) positivity 73, 90, and 105, and negativity for CD34 and CD45 were assessed.

C. Exosomes derived from BM-MSCs preparation: The exosomes were obtained using a cell supernatant exosome isolation kit (Thermo Fisher Scientific). They were then suspended in PBS and stored at -20 ˚C for future use. Exosomes were identified using transmission electron microscopy (TEM) and flow cytometry to detect CD63 and CD81 positivity, as well as fluorescent dye labelling.

2.3. Animals grouping and treatment protocol

Thirty male albino rats, each weighing between 150-200 grams, were housed in cages in the animal house of the Faculty of Dentistry, Suez Canal University. Rats were kept in a 12 h/12 h dark/light cycle with free food and water ad libitum. Rats were equally and randomly divided into three groups, each consisting of 10 albino rats, as follows:

Group I (control group): Rats received saline daily via oral gavage for 14 days.

Group II (5-FU group): Rats were injected with a single intraperitoneal (IP) injection of 5-FU® (50 mg/kg) each [7]. 5-FU® Utoral 250 mg/5 mL solution vial for intravenous (IV) infusion was purchased from Hikma Specialized Pharmaceuticals, Second Industrial Zone, 6th of October, Giza, Egypt.

Group III (exosomes group): Rats were treated as group II; then on day 2, a single injection of exosomes was administered through the tail vein (100 µg/kg/dose suspended in 0.2 mL PBS) [8].

After the experiment period, the animals were sacrificed with an extra dose of anesthesia, and the tongues from each rat were excised. The tissues were prepared for histological, ultrastructural, and immunohistochemical evaluations.

2.4. Methods of evaluation

2.4.1 Histological evaluation

After fixation of the gland specimens in 10% neutral buffered formalin, the specimens were dehydrated by immersion in successive ascending concentrations of ethanol (60%, 70%, and 95%). They were infiltrated with molten paraffin wax (55%) and embedded in paraffin wax blocks. The blocks were cut with a microtome to obtain 4-5 µm thick sections, which were mounted to glass slides and then stained with hematoxylin and eosin. After staining, the slides were examined under a light microscope.

2.4.2 Ultrastructural evaluation

Tongue specimens were fixed in 4% phosphate-buffered glutaraldehyde (0.1 mol/L, pH 7.4), and then post-fixed in 1% phosphate-buffered osmium tetroxide. Dehydration of the specimens was performed by placing them in successive dilutions of ethanol, followed by immersion in amyl acetate. Samples were then dried with liquid CO_2 and sputter-coated with a thin layer of gold particles. The dorsal surfaces of the tongues were examined using a Thermo Fisher USA Quattro S field emission gun, connected with EDAX, at the Nanotechnology Research Center (N.T.R.C) at the British University in Egypt.

2.4.3. Immunohistochemical evaluation

Other sections, 5 µm thick, were processed and stained using rabbit polyclonal anti-mouse antibody against Bcl-2-associated X protein (BAX) (Santa Cruz Biotechnology, Cat. No. sc- 526), which was used for apoptotic assessment. BAX protein activation results in increased permeability of the mitochondrial outer membrane, release of cytochrome c, and activation of caspases, indicated by brown cytoplasmic and membranous expression. Slides were examined with ZEISS Primo Star light microscopy and photographed using a Tucsen IS1000 10.0 MP camera. The mean area percentage expression of the markers was measured using Image Ja ll platform [9].

2.4.4. Statistical analysis

The statistical analysis was performed using GraphPad Prism software, version 6.0. The results are reported as the Mean±SD. Statistical analysis was performed using One-way ANOVA, followed by a post-hoc Tukey's test. A significance level of $P<0.05$ was employed to determine the significance of all results. The experiments were replicated in triplicate, each with 3-6 repetitions.

3. Results

3.1. Isolation, identification, and characterization of BMMSCs

BMMSCs were isolated and identified by their spindle-fusiform shape and formation of colonies (Figure 1A). Characterization by flow cytometry analysis revealed that BMMSCs were positive for CD73, CD90, and CD105 surface markers and negative for CD34 and CD45 (Figure 1B).

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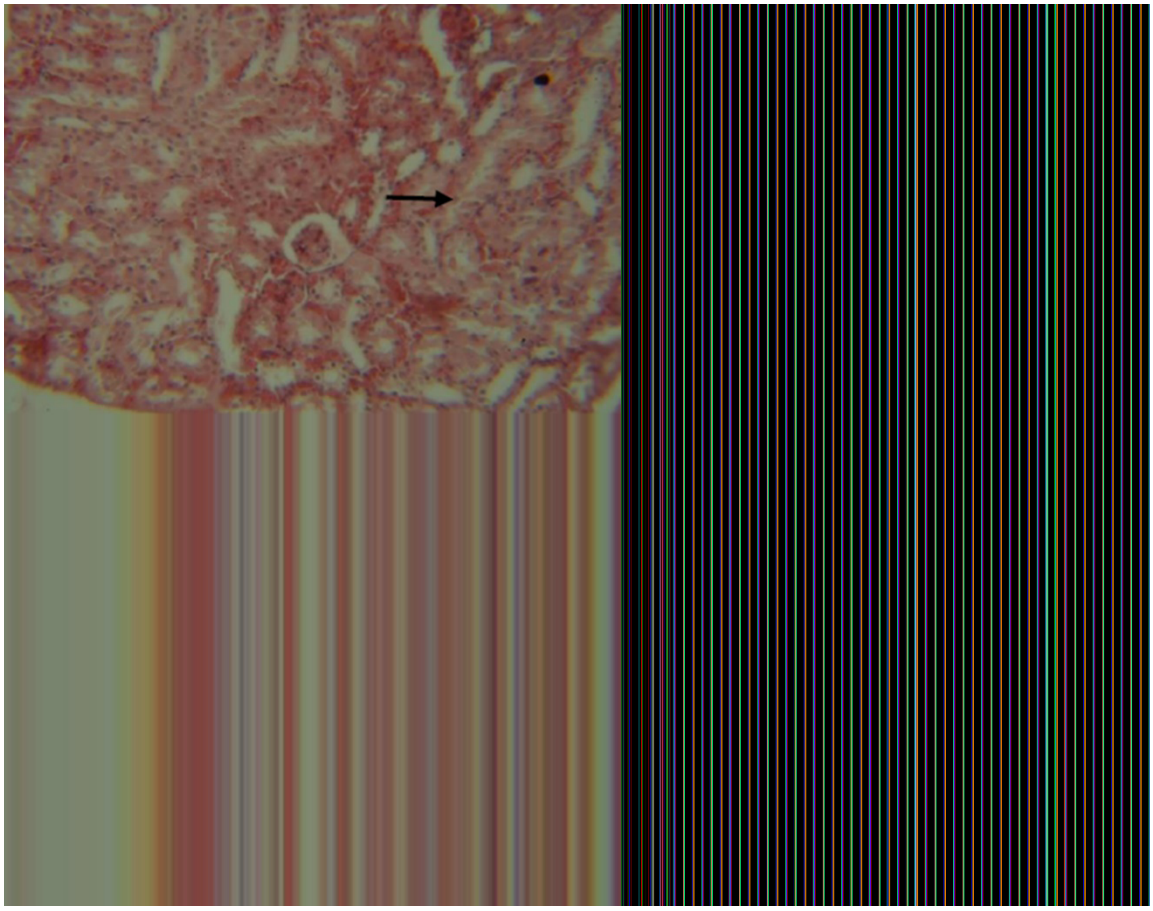

Figure 1. Spindle-shaped cells characterizing by various method

A) Spindle-shaped cells identifying the BMMSCs by inverted microscope; B) Characterization of BMMSCs by flow cytometry analysis revealing positive expression of CD73, CD90, and CD105, as well as negative expression of CD34 and CD45; C) Characterization of BMMSCs-derived exosomes by TEM; D) Characterization of exosomes by flow cytometry analysis showing positive expression of CD63 and CD81

3.2. Characterization of exosomes

1. TEM was used to characterize exosomes derived from BMMSCs. These exosomes were characterized by their consistent size range of 30-100 nm and spherical shape (Figure 1C).

2. Furthermore, the positive expression of specific markers CD63 and CD81 was confirmed using flow cytometry analysis (Figure 1D).

3.2. Histological results

I. Group I (control group): Histological examination of the dorsal surfaces group I rats revealed normal histological picture. The dorsal surface of the tongue was lined by keratinized stratified squamous epithelium. Filiform papillae were the most numerous, with a conical shape and tapering tips (Figure 2A). Fungiform papillae were few, short, and scattered among the filiform ones. The apices of the fungiform papillae were broad, with a taste bud on their top and a distinctive taste pore. (Figure 2B).

II. Group II (5-FU group): Histological examination of the dorsal surfaces of rats treated with 5-FU showed severe atrophic and degenerative changes. The filiform papillae exhibited areas of keratin separation and hyperkeratinization, with lining epithelial cells displaying vacuolated cytoplasm and pyknotic nuclei across several layers (Figure 2C). The fungiform papillae were deformed in their epithelium and taste buds (Figure 2D).

III. Group III (exosomes group): The examined tongues of rats that received exosomes derived from BMMSCs showed marked improvement in the histological structure. Filiform papillae exhibited partial improvement, showing tapering ends with few short, blunt-ended papillae (Figure 2E). The fungiform papillae appeared

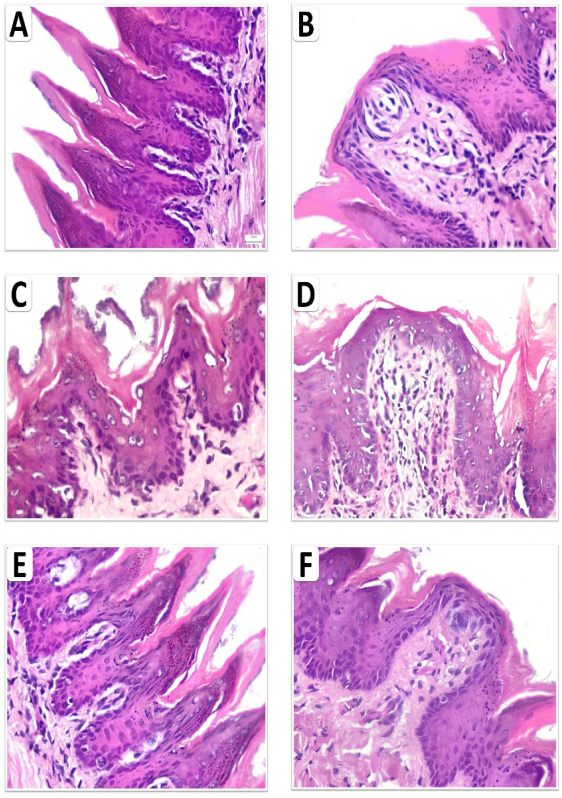

Figure 2. Microscopic evaluation of lingual papilla in control and treatment groups

A) Dorsal surface of control group showing the filiform papillae; B) Fungiform papillae of the control group with a taste bud with a well-defined taste pore (arrow); C) Dorsal surface of the 5-FU group showing deformed filiform papillae with areas of keratin separation (red arrow): Apoptotic cell in the epithelium were observed (black arrows); D) Fungiform papilla of 5-FU group showed atrophied and deformed shapes with obliteration of taste bud (arrow); E) Filiform papilla of the exosomes group showing almost normal shape with blunt ends; F) Fungiform papillae of the exosomes group showing an almost normal shape with a taste bud (arrow) (H&E; magnification ×400)

nearly normal, with well-defined taste buds and minimal signs of deformation (Figure 2F).

3.3. Ultrastructural results

I. Group I (Control group): The dorsal surface of the control group demonstrated numerous filiform papillae, which were simple conical structures found particularly on the tip and lateral edges of the dorsal surface of the tongue (Figure 3A). Interspersed among these were fungiform papillae, characterized by their dome- or mushroom-like shape and a central depression known as the taste pore (Figure 3B).

II. Group II (5-FU group): The dorsal surface of the 5-FU group revealed filiform papillae with blunted tips and an apparent decrease in thickness and number. They were arranged in an irregular pattern with a random distribution and showed surface desquamation (Figure 3C). The fungiform papillae lost the characteristic mushroom-like shape, exhibited ill-defined taste pores, or sometimes absence of the taste pore, and desquamation of superficial cells was observed (Figure 3D).

III. Group III (exosomes group): The dorsal surface of group III animals treated with exosomes showed marked improvement. Almost normal filiform papillae were observed, with some papillae showing signs of disorientation and rough keratinized bases (Figure 3E). Fungiform papillae were almost normal, with a well-defined taste pore (Figure 3F).

3.4. Immunohistochemical results

BAX immunostaining was used to the evaluate apoptosis through the assessment of its staining in tissues examined from the three groups. Group I (control group), BAX cytoplasmic staining showed a mild reaction restricted to the superficial layers of the lingual epithelium (Figure 4A). In group II (5-FU), BAX expression increased and expanded through the entire epithelial thickness of the tongues (Figure 4B). In group III (exosomes),

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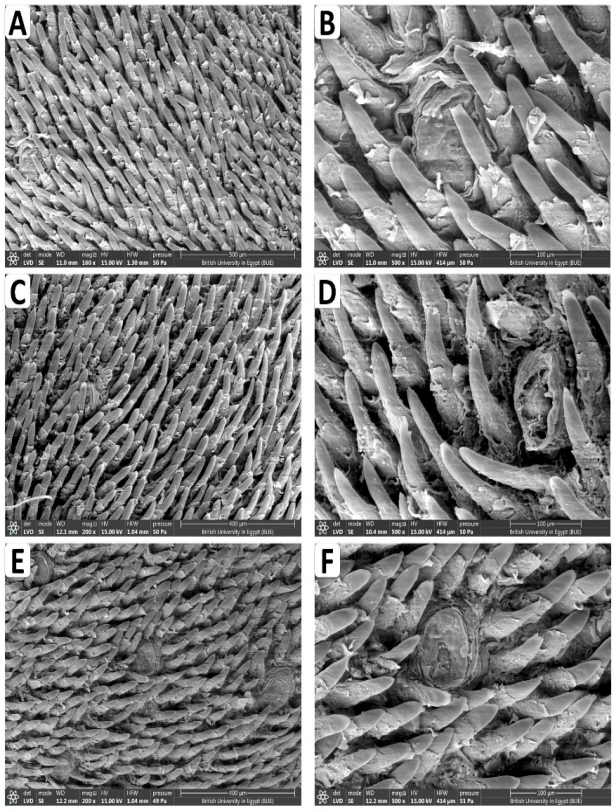

Figure 3. Electron microscopic evaluation of the lingual papilla in control and treatment groups

A) Scanning electron micrograph of the control rat's dorsal surface showing sharp and parallel rows of conical filiform papillae, with a fungiform papilla in between (arrow); B) Higher magnification of the previous figure showing fungiform papillae of the control group with a taste bud and a well-defined taste pore (arrow); C) 5-FU group showing randomly distributed and irregularly arranged filiform papillae with more or less blunt apices, apparent surface desquamation, and marked aggregation of keratin (arrows); D) Dorsal surface of the 5-FU group showing deformed fungiform papillae with ill-defined taste pores(arrow); E) Scanning electron micrograph of the group III rat tongue showing almost normal filiform papillae, with few disoriented papillae: Numerous almost normal fungiform papillae were seen in between the filiform ones (arrows); F) Fungiform papillae of exosomes group showing an almost normal shape with a taste bud and a well-defined taste pore (arrow)

BAX expression showed a mild-to-moderate cytoplasmic staining reaction throughout the lingual epithelium (Figure 4C).

3.5. Statistical results

3.5.1. Mean area percent of Bax immunoexpression

The highest mean area percent of BAX immunoexpression was recorded in the 5- FU group, followed by exosomes group, while the lowest mean area percent was observed in group I (control). ANOVA results showed a statistically significant difference between groups ($P<0.0001$) (Figure 4D).

4. Discussion

Emerging research has pointed to the therapeutic potential of MSCs-EXOs in mitigating tissue damage caused by inflammation and cytotoxic agents. Given their immunomodulatory and regenerative properties, bone marrow MSC-derived exosomes hold promise as a novel treatment for 5-FU-induced toxicity [10]. Accordingly, this study sought to evaluate the efficacy of bone marrow MSC-derived exosomes in alleviating the adverse effects of 5-FU on the lingual papillae of albino rats. The tongue was selected as the focus of this study due to its critical functions in mastication, speech, and general health monitoring. The cytotoxic impacts of 5-FU on the tongue serve as a reliable model for studying OM, as the tongue is highly vascularized and metabolically active, making it susceptible to chemotherapeutic damage [11].

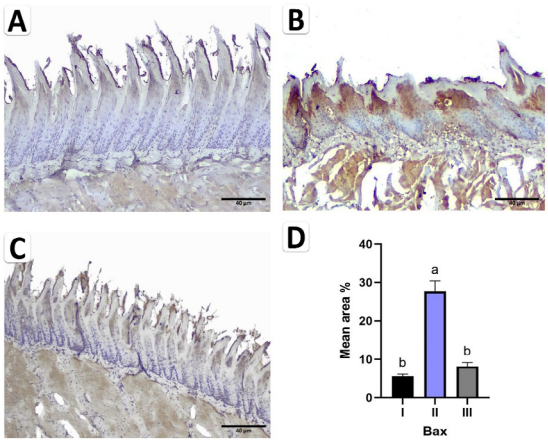

Figure 4. Immunohisthochemical evaluation of lingual papilla in control and treatment groups

A) Photomicrograph of the dorsal surface of the tongue of the control group showing BAX immunostaining a mild cytoplasmic reaction in the superficial layers of the lingual epithelium; B) 5-FU group showing strong cytoplasmic staining reaction; C) Exosomes group showing moderate cytoplasmic staining reaction throughout the lingual epithelium; D) Graph showing Mean±SD, and multiple comparison test of BAX mean area % immunoexpression

Note: Different letters indicate statistically significance differences.

The exosomes dose (100 µg/kg/dose suspended in 0.2 mL PBS) administered through the tail vein was chosen in accordance with Ebrahim et al. (2018) [8], who administered the same single dose to rats to examine the potential role of MSC-derived exosomes in enhancing autophagy activity and their effect on diabetic nephropathy. Moreover, exosomes derived from MSCs have been proven to promote OM healing, as reported by Gao et al. (2022) [12].

In this study, the tongues of 5-FU–treated rats (group II) showed marked degenerative histopathology in the filiform and fungiform papillae. These results were consistent with Elmansy et al. (2020) [13], who reported similar 5-FU–induced changes in rat tongue mucosa. They noted that filiform papillae, due to their high metabolic activity, reflect overall health; thus, drug toxicity can lead to papillary atrophy. They further attributed chemotherapy-related alterations to disrupted protein synthesis and increased apoptosis.

Moreover, the degenerative histopathological effects of 5-FU on the fungiform papillae in the current study were similar to those found by Arafat et al. (2021) [14], who studied the effect of Irinotecan, another chemotherapeutic drug similar to 5-FU, on the tongue mucosa and observed atrophy of the fungiform papillae with ill-defined taste buds. In the same instance, a significant thickening of the keratin layer was detected, which was explained as being due to the high sensitivity of the taste buds to chemotherapy.

The ultrastructural results of the current study of the tongues of group II rats showed that the filiform papillae had blunted tips, were irregularly arranged, and showed surface desquamation. The fungiform papillae also lost their characteristic mushroom shape and exhibited ill-defined taste pores, which were similar to those reported by Shalaby et Al. (2021) [15], who investigated the possible adverse effects of 5-FU on the mucosa of the tongue. The injury to the oral mucosal tissues due to the use 5 -FU was believed to result from oxidative stress and the release of reactive oxygen species (ROS), which stimulates numerous cellular signals that initiates mucosal damage, as stated by Chen et al. (2007) [16].

These results were further confirmed by a previous study, which declared that 5-FU injection induces oxidative stress leading to cell death. When ROS are released, pro-inflammatory cytokines are subsequently produced,causing tissue damage and apoptosis. NF-κB is a crucial component of this process and is involved in the mucositis apoptotic pathway [17].

The immunohistochemical results using Bcl-2 associated X protein (BAX), which was used as a pro-apoptotic marker to assess the apoptotic reaction in the tongue mucosa of group II rats, confirmed the previously mentioned results, showing an increased BAX expression that extended throughout the lingual epithelial thickness.

BAX increase with 5-FU exposure was also observed by Mahran et al. (2024) [18] as a marker of hepatotoxicity, and across cancers, higher BAX generally correlates with a stronger chemotherapy response, while BAX silencing confers 5-FU resistance. Mechanistically, an increased BAX/Bcl-2 ratio stimulates mitochondrial outer-membrane permeability, cytochrome-c release, loss of mitochondrial potential, caspase activation, and eventually apoptosis [13].

In the current study, the tongues of rats that received exosomes derived from bone marrow stem cells (group III) showed noticeable improvement in the number and overall features of the filiform and fungiform papillae, with minimal signs of deformation in the taste buds. Li et al. (2025) [19] supported these results, reporting that the adipose mesenchymal stem cell-derived exosomes (ADMSCs-Exos) alleviated inflammation of the oral mucosal epithelium of irradiated mice and promoted the proliferation of oral mucosal epithelial cells, thereby reducing oral mucosal inflammation in mice with radiation-induced OM.

The mechanisms of OM induced by either radiotherapy or chemotherapy were explained by a review study, where the authors concluded that the NF-κB signal transduction pathway and pro-inflammatory cytokines contribute to the pathogenesis of OM [20]. Consequently, targeting the inhibition of NF-κB and its related pro-inflammatory cytokines has emerged as a primary focus for the treatment of OM.

Considering the similarity in the mechanisms of OM induced by cancer therapy as 5-FU, the results of the current study were consistent with the previously mentioned studies, as it has been reported that the re-epithelialization is accelerated in MSCs-Exos-treated mice. Exosomes likely act by attenuating NF-κB signaling and downstream cytokines (TNF-α, IL-1β, IL-6), aligning with MSC-exosome studies in OM and mucositis biology [21].

Immunohistochemistry showed a significant reduction in BAX expression in the exosome-treated group (group III) versus 5-FU alone (group II; $P<0.05$), indicating less apoptosis in the tongue mucosa. This aligns with Zhang et al. (2022) [22], who found that adipose-derived MSC exosomes lower ROS and inflammation, accelerating wound healing.

The results of this study underscore the potential of bone marrow MSC-derived exosomes as a therapeutic intervention for 5-FU-induced OM. By reducing inflammation, oxidative stress, and apoptosis, exosomes address the multifactorial pathogenesis of OM and facilitate tissue repair. These findings pave the way for further exploration of MSC-derived exosomes in clinical applications, particularly for managing the adverse effects caused by chemotherapy.

The current investigation demonstrated that exosomes derived from BMMSCs exerted an obvious therapeutic effect against mucositis induced by the cytotoxic effect of 5-FU.

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Compliance with ethical guidelines

The experiment was performed following the ethical guidelines of animal experimentation and was evaluated by the Faculty of Dentistry'S Research Ethics Committee (REC), Suez Canal University, Ismailia, Egypt (475/2022).

Data availability

The data used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' contributions

Conceptualization study and design: Sara Mostafa Shogaa and Elham Fathy Mahmoud; Analysis and data interpretation: Enas Mahmoud Hegazy; Investigation: Sara Mostafa Shogaa,Rania Abdelazeim Galho; Writing the original draft: Sara Mostafa Shogaa; Review and editing: Elham Fathy Mahmoud and Enas Mahmoud Hegazy; Supervision: Enas Mahmoud Hegazy, Enas Mahmoud Hegazy, Rania Abdelazeim Galhom, and Elham Fathy Mahmoud.

Conflict of interest

The authors declared no conflict of interest.

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