Original Article

CLINICAL AND HISTOLOGICAL EVALUATION OF SERRATIOPEPTIDASE ON ORAL WOUND HEALING IN RABBITS: IN VIVO STUDY

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ABSTRACT

Serratiopeptidase, a proteolytic enzyme with anti-inflammatory and fibrinolytic properties, has shown potential in wound healing, though its specific effects on oral mucosal repair remain underexplored. This study employed an integrated approach combining histopathological analysis with biochemical and hematological assessment in a rabbit oral mucosal wound model. Fifteen rabbits were allocated into control and serratiopeptidase-treated groups, with samples collected on days 3 and 10 post-intervention. Histological evaluation, complete blood count analysis, and serum inflammatory markers (CRP, LDH) were performed. Histopathological examination revealed significantly accelerated healing in serratiopeptidase-treated animals. At day 3, treated lesions showed advanced granulation tissue formation, extensive angiogenesis, and early re-epithelialization, whereas controls showed persistent inflammation. By day 10, treated animals exhibited complete re-epithelialization with well-organized tissue architecture, while controls displayed incomplete healing. These findings correlated with hematological data showing significantly reduced neutrophil counts (1.66±0.59 versus 2.70±1.73×10⁹/L, p=0.009) and increased lymphocyte counts (3.01±1.33 versus 1.78±1.06×10⁹/L, p=0.006) in the treated versus control groups at day 10. Inflammatory biomarkers demonstrated a biphasic response with early elevation followed by rapid normalization in treated animals. Serratiopeptidase significantly enhances oral mucosal healing by coordinating modulation of the inflammatory response, promoting angiogenesis, and accelerating re-epithelialization. The enzyme demonstrates pro-resolution properties that optimize the entire healing cascade.

Key words: Serratiopeptidase, Oral mucosal healing, Histopathology, Angiogenesis, Re-epithelialization.

Introduction

Oral mucosal healing occurs faster and scarlessly than skin healing. Mucosal environment features include unique inflammatory responses, specific fibroblast subpopulations, and saliva growth factors that promote exceptional regenerative ability. Even with this natural advantage, surgical injury, periodontal disease, and systemic healing issues may hinder oral tissue repair, requiring therapeutic interventions [1-7].

Serratia marcescens' proteolytic enzyme, serratiopeptidase, is anti-inflammatory, fibrinolytic, anti-edematous, and promotes wound healing. The enzyme modulates inflammatory pathways by interacting with cyclooxygenase enzymes, hydrolyzing inflammatory mediators, degrading fibrin deposits, and disrupting bacterial biofilms. Serratiopeptidase is used in several medical specialties, although its histopathological effects on oral mucosal healing are unknown [8-14].

This rabbit model study will explore serratiopeptidase effects on oral tissue repair, utilizing histopathological, hematological, and biochemical approaches [15-19]. We believe serratiopeptidase will improve healing by regulating inflammatory responses and encouraging morphological and systemic tissue regeneration. The study investigates healing progression using histological assessment and systemic inflammatory and hematological markers [20-24].

Materials and Methods

Experimental design and animal model: This study used 15 adult New Zealand white rabbits (Oryctolagus cuniculus) weighing 2.5-3.0 kg, approved by the Institutional Animal Care and Use Committee. All operations complied with worldwide recommendations for laboratory animal welfare. Animals were housed in a controlled environment at 22±2°C, with 12-hour light/dark cycles, and received a regular feed and water ad libitum.

The animals were randomly allocated into two primary experimental groups: (1) Control group (n=7) receiving standard wound care without therapeutic intervention, and (2) Treatment group (n=8) administered serratiopeptidase at a therapeutic dosage of 10 mg/kg daily orally, and a 1% (w/w) serratiopeptidase gel was prepared. Serratiopeptidase powder (enteric-coated granules equivalent to 10,000 SPU/mg) was incorporated into a biocompatible, mucoadhesive oral gel base (e.g., hydroxypropyl methylcellulose or Carbopol base). The concentration was chosen based on preliminary studies and existing literature on topical enzyme applications.

Standardized oral mucosal wounds (6mm diameter) were created using aseptic surgical techniques under general anesthesia.

The first application of approximately 0.2 mL of the 1% SP gel was directly onto the wound site using a sterile syringe without a needle. The gel was gently spread to cover the entire wound. Applications were repeated three times daily (8:00 am, 4:00 pm, and 12:00 am)

Oral gavage: This is the most accurate way to ensure the animal receives the full intended dose. The SP powder would be suspended in a suitable vehicle (e.g., water, saline, or methylcellulose solution).

Sample collections were performed at two critical time points post-intervention (days 3 and 10) to capture both the inflammatory and early proliferative phases of healing.

Histopathological processing and analysis: Oral tissue specimens were processed using standardized histological techniques optimized for mucosal tissues. Tissues were immediately fixed in 10% neutral buffered formalin for 48-72 hours, dehydrated through a graded ethanol series (70%, 90%, 100%), cleared in xylene, and embedded in paraffin wax. Serial sections of 5µm thickness were prepared using a rotary microtome (Richert-Jung, 2030 Mot Biocut) and mounted on charged slides.

Protocol-based Hematoxylin and Eosin (H&E) staining was performed on tissue sections [10]. Using a semi-quantitative scoring system, two independent blinded investigators assessed histopathological parameters: inflammatory cell infiltration (0-3), re-epithelialization (0-3), granulation tissue maturity (0-3), angiogenesis (0-3), and tissue architecture restoration. Through consensus review, we resolved rating differences.

Hematological and biochemical analysis: Venipuncture was performed at set intervals. Complete blood count samples were obtained in EDTA tubes and analysed by an automated haematology analyzer (Sysmex XN-1000, Japan). White blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell count, haemoglobin, and platelet count were measured. After centrifugation, serum was stored at -80°C for biochemical analysis. LDH activity was measured spectrophotometrically using normal enzymatic techniques, whereas CRP levels were measured immunoturbidimetrically.

Statistical Analysis: R (4.3.0) and Python (3.11) with Pandas, SciPy, and StatsModels were used to analyze the data. The Shapiro-Wilk test determined distribution normality. Due to sample size and non-normal parameter distribution, non-parametric tests were used throughout. The Kruskal-Wallis H-test was the omnibus test for multiple group comparisons, and the Mann-Whitney U-test with Bonferroni correction was used for post-hoc pairwise comparisons. Statistical significance was determined at $p < 0.05$ for omnibus testing and $p < 0.0125$ for post-hoc comparisons. Data are shown as mean ± standard deviation unless otherwise stated.

Results and Discussion

Gross examination revealed that the gross shape and appearance showed that serratiopeptidase has greatly improved the wound, particularly at day 10 **(Figure 1)**.

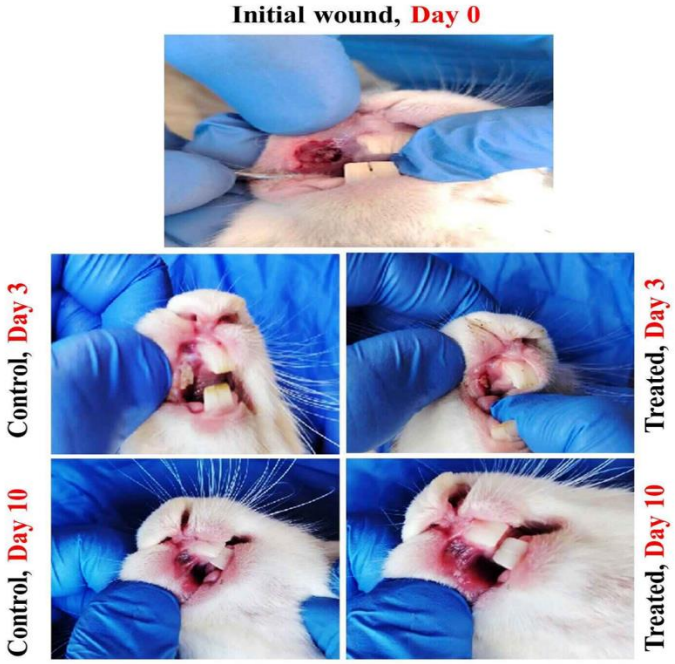


Figure 1. Gross appearance of the rabbit's mouth at wound site of the studied groups at two time points.

Histopathological assessment reveals enhanced healing morphology: Histopathological investigation showed qualitative and quantitative differences in the healing process between serratiopeptidase-treated and control mice at both time points compared with time zero before therapy **(Figure 2)**.

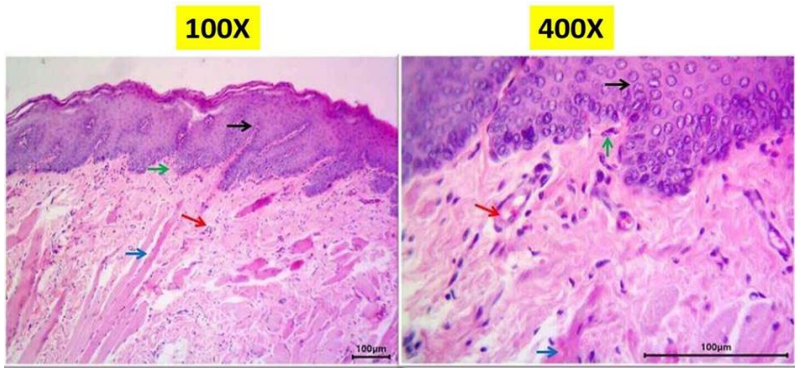
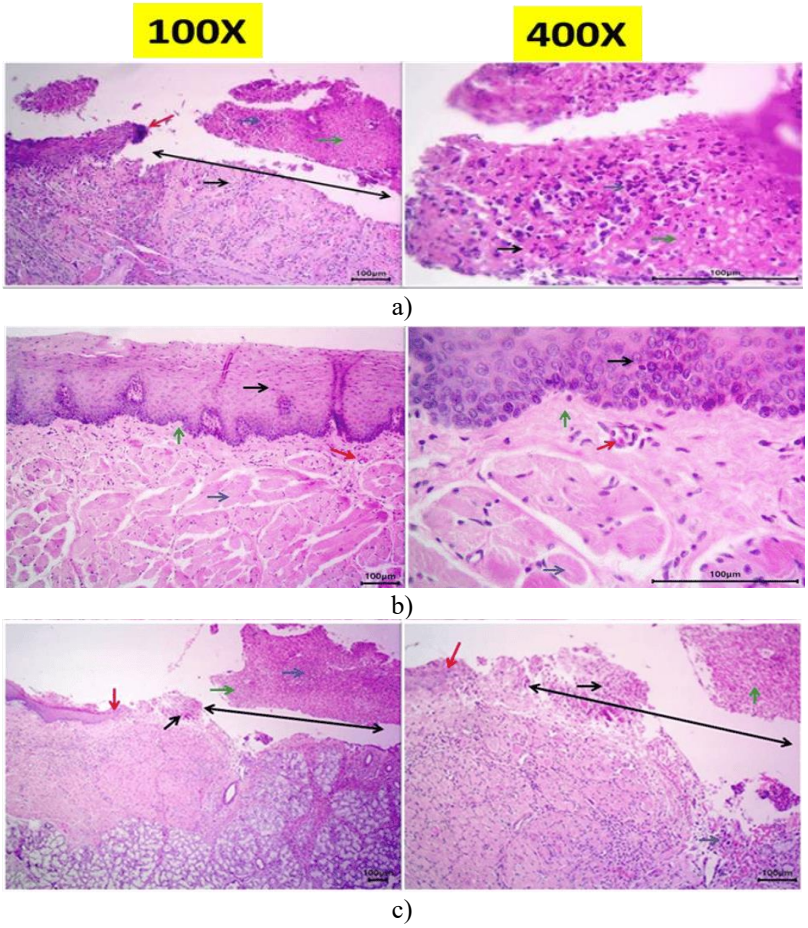


Figure 2. Histological sections of rabbit oral mucosa from the Control group (Zero) reveal an intact structure, with epithelial cells (e), submucosa (s), muscles (m), and blood vessels (bv). H&E stain, scale-bar=100µm.

Day 3 Post-Intervention: Control lesions (C3) had wide wound margins with extensive polymorphonuclear leukocyte infiltration, copious fibrinous exudate, and fully destroyed epithelial layers. The granulation tissue was immature and disorganized, with little angiogenesis. In contrast, serratiopeptidase-treated lesions (T3) showed rapid healing, with substantial angiogenesis, granulation tissue development, and wound margin re-epithelialization. In treated animals, inflammatory cell infiltration was significantly reduced despite comparable initial wound diameters, indicating faster inflammatory clearance **(Figure 3; Table 1)**.



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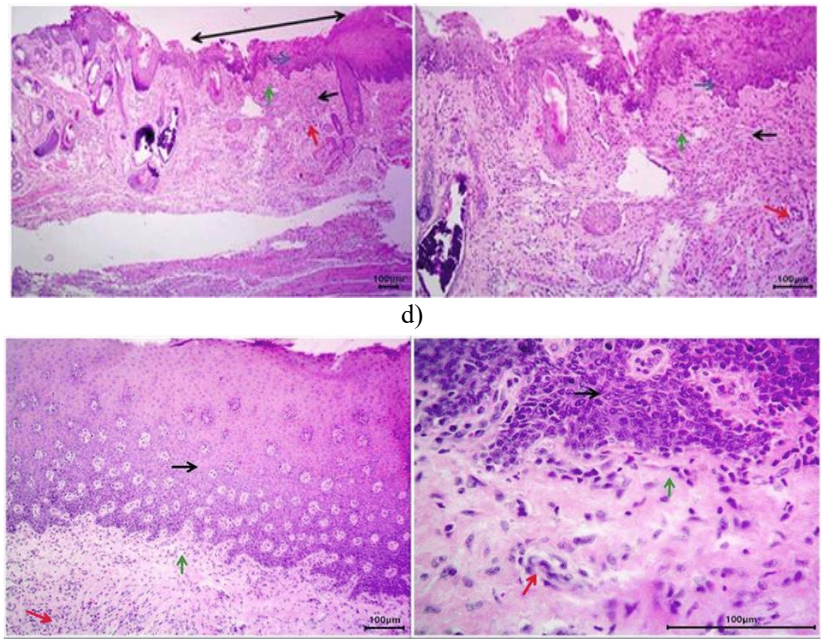

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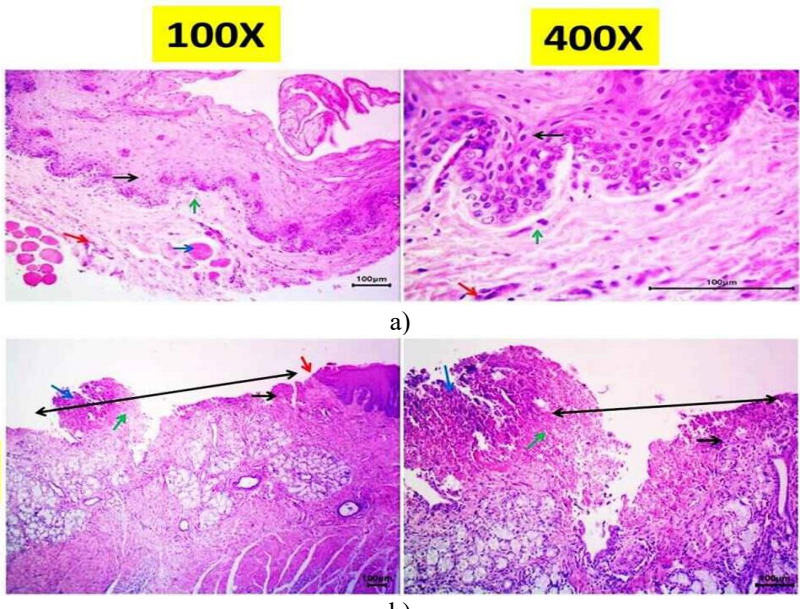
Figure 3. Histological sections of rabbit oral mucosa of the (a) **C3 lesion group** reveal the site of wound in the wide edges, granulation tissue (g), containing inflammatory fibrinous exudate (If), highly inflammatory cells infiltration (Ic), and a distracted mucosal epithelial layer (e). (b) **C3 normal group** reveals an intact structure, including mucosa with epithelial cells (e), submucosa (s), muscles (m), and blood vessels (bv). (c) **T3 lesion group** reveals the site of wound in wide edges (we), granulation tissue (g), inflammatory fibrinous exudate (→), inflammatory cells infiltration (Ic), and a distracted mucosal epithelial layer with re-epithelialization (re). (d) **T3 lesion group** reveals the site of wound, with highly granulated tissue (gt), with high blood vessels (angiogenesis) (→), few inflammatory cells infiltration (→), and complete re-epithelialization (re). (e) **T3 normal group** reveals intact structure as the mucosa with epithelial cells (e), submucosa (→), and blood vessels (bv). H&E stain, scale-bar=100µm

Day 10 post-intervention: The healing gap between experimental groups widened. Control animals (C10) had residual moderate inflammatory infiltration, partial re-epithelialization, and disorganized tissue architecture with immature granulation tissue. T10 animals demonstrated complete re-epithelialization with well-developed, organized granulation tissue, mature angiogenesis, and few remaining inflammatory cells, approaching normal mucosal shape **(Figure 4; Table 1)**.



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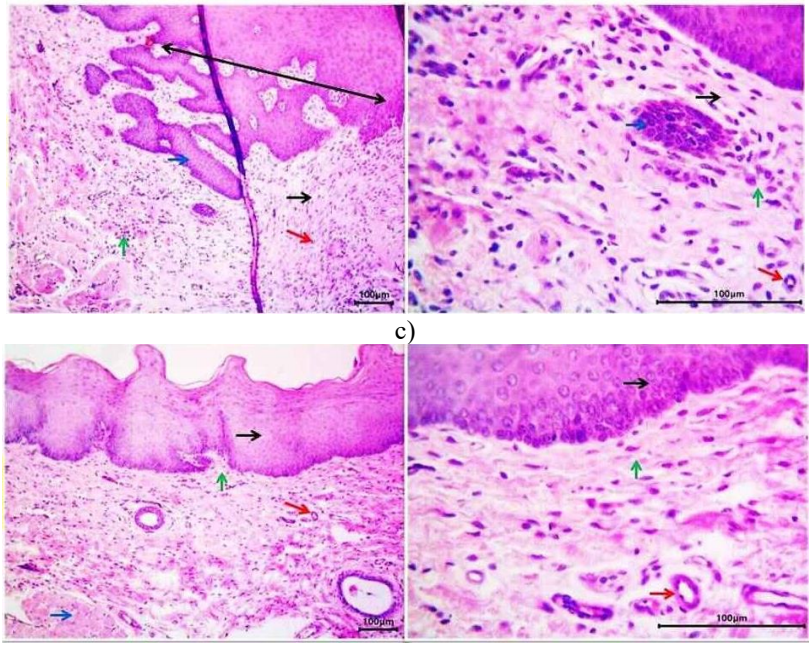

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Figure 4. Histological sections of rabbit oral mucosa from the (a) C10 normal group reveal intact structure, with epithelial cells (e), submucosa (s), muscles (m), and blood vessels (bv). (b) **C10 lesion group** reveals the site of wound in wide edges, granulation tissue (g), containing inflammatory fibrinous exudate (→), inflammatory cells infiltration (Ic), and a distracted mucosal epithelial layer with slight re-epithelialization (re). (c) **T10 lesion group** reveals the site of wound (w), with well-developed granulation tissue (g), with blood vessels (angiogenesis) (bv), few inflammatory cells infiltration (Ic), and complete re-epithelialization (re). (d) **T10 normal group** reveals intact structure as the mucosa with epithelial cells (e), submucosa (s), muscles (m), and blood vessels (bv). H&E stain, scale-bar=100µm.

Table 1. Semi-quantitative histopathological assessment of healing parameters

Healing Parameters	Control, Day 3	Treated, Day 3	Control, Day 10	Treated, Day 10
Inflammatory Cell Infiltration	3.0±0.0*	1.8±0.5	2.2±0.4*	0.8±0.4
Re-epithelialization	0.0±0.0	1.8±0.4*	1.2±0.4	2.8±0.4*
Granulation Tissue Maturity	0.8±0.4	2.2±0.4*	1.4±0.5	2.8±0.4*
Angiogenesis	1.0±0.0	2.6±0.5*	1.6±0.5	2.8±0.4*
Tissue Architecture	0.8±0.4	2.0±0.0*	1.4±0.5	2.8±0.4*

Score range: 0-3, with 3 indicating the most favorable outcome. Data expressed as mean±SD, n=7, * indicates p value less than 0.05 considered as significant using two-sample t-test when comparing treated versus control.

Hematological parameters correlate with histological findings: **Table 2** shows temporal fluctuations in leukocyte profiles that match the histological findings. On day 10, treated animals had significantly lower neutrophil counts (1.66±0.59×10⁹/L) than controls (2.70±1.73×10⁹/L; p=0.009), indicating mild histological inflammatory infiltration. Lymphocyte counts in treated animals were considerably greater (3.01±1.33×10⁹/L) than controls (1.78±1.06×10⁹/L; p=0.006), indicating increased tissue segment proliferation and complete re-epithelialization.

Table 2. Hematological parameters in control and serratiopeptidase-treated groups

Parameter (×10⁹/L)	Groups	Day 3	Day 10
White blood cells	Control	4.11±2.28	**5.53±3.44**
	Treated	2.62±1.66	**5.47±1.72**
	p value	0.19	**0.97**
Neutrophils	Control	1.12±0.54	**2.70±1.73**
	Treated	0.84±0.44	**1.66±0.59**

	p value	0.31	**0.009**
Lymphocytes	Control	2.43±1.28	**1.78±1.06**
	Treated	1.31±0.82	**3.01±1.33**
	p value	0.08	**0.006**
Monocytes	Control	0.43±0.37	**0.64±0.50**
	Treated	0.40±0.29	**0.90±0.40**
	p value	0.87	**0.31**
Data expressed as mean±SD, n=7, p value less than 0.05 considered as significant using a two-sample t-test.			

Inflammatory biomarkers: CRP and LDH levels followed histological development **(Table 3)**. On day 3, treated rats showed increased CRP (7.6±1.0 mg/L) and LDH (887±25 U/L), indicating active tissue remodeling and angiogenesis. Serratiopeptidase administration led to normalization of indicators (CRP: 4.6±4.1 mg/L; LDH: 500±176 U/L) in treated mice by day 10, whereas controls remained elevated, indicating progression of healing **(Table 3)**.

Table 3. Inflammatory biomarker profile in the studied group.

Biomarkers		**Day 3**	**Day 10**
CRP	Control	1±0.001	7.3±0.2
	Treated	7.6±1	4.6±4.1
	p value	0.0001	0.11
LDH	Control	499±200	470±269
	Treated	887±25	500±176
	p value	0.0003	0.81
CRP=c-reactive protein, LDH=lactate dehydrogenase, Data expressed as mean±SD, n=7, p value less than 0.05 considered as significant using two-sample t-test			

Integrated analysis reveals coordinated healing enhancement: Histopathological, hematological, and biochemical parameters indicate that serratiopeptidase accelerates tissue remodeling, inflammatory resolution, and proliferative activities such as angiogenesis and re-epithelialization. The strong inverse relationship between neutrophil reduction and tissue organization improvement ($r = -0.89$, $p = 0.018$) indicates that inflammatory resolution and morphological recovery are linked.

Serratiopeptidase modulates morphological, cellular, and systemic repair to promote oral [25-27] mucosal healing, according to this comprehensive study. Histopathology shows that the enzyme accelerates wound closure and promotes tissue regeneration, with increased angiogenesis, complete re-epithelialization, and optimal extracellular matrix organization [28-31].

Day 3 histopathological changes in treated animals are significant [32-36]. Strong granulation tissue formation, extensive angiogenesis, and enhanced inflammatory markers suggest serratiopeptidase improves initial healing [37-41]. Early activation accelerates inflammation, improving healing by day 10. This pro-resolution mechanism supports the growing belief that healing depends on properly executed and rapidly eliminated inflammation rather than repression. The enzyme's fibrinolytic function may repair tissue and remove matrix damage [20].

The significant hematological changes in treated mice correlate with histological improvements in the tissues. Reduced neutrophils and expanded lymphocytes imply a coordinated immunological switch from innate inflammatory to adaptive reparative responses [21, 42, 43].

Neutrophil persistence is a marker of poor healing, while lymphocyte predominance promotes tissue regeneration through growth factor synthesis, immunological coordination, and angiogenesis. The connection between systemic immune measures and histological healing scores supports our findings. It implies that serrati peptidase regulates the immune system beyond local tissue modification [44, 45].

The biphasic biomarker response pattern illuminates serrati peptidase's mechanism. The histologically observed granulation tissue development and angiogenesis suggest that the initial rise of CRP and LDH in treated mice is due to tissue remodeling rather than destructive inflammation. Fast marker normalization implies rapid completion of the inflammatory phase and regeneration. Serratiopeptidase may accelerate healing rather than reduce inflammation, as this biphasic pattern contrasts with the chronically higher inflammatory markers in controls [46].

These data support serratiopeptidase use of serratiopeptidase in oral surgery, periodontal therapy, and healing-impaired diseases. Histopathological evidence of

accelerated angiogenesis and re-epithelialization indicates its use in periodontal flap surgeries, pre-prosthetic procedures, and oral mucosal lesion care, where rapid mucosal coverage is crucial for success. Safety boosts the enzyme's clinical [47-51] translation potential [52].

Conclusion

This comprehensive study indicates that serratiopeptidase coordinates inflammation, angiogenesis, and tissue regeneration to promote the healing of oral mucosa. Histological evidence of rapid wound closure with superior tissue architecture, along with hematological and biochemical correlations, supports the enzyme's therapeutic potential. Serratiopeptidase, a promising oral tissue regeneration drug, optimizes the healing cascade rather than targeting single components.

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Conflict of interest: None

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Ethics statement: The research approved and registered at Alnoor University by Ethical Approval Committee (Approval Number Alnoor Dent. 0001.bas on 29 April 2025).

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