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Original Research Article

Secretome Gel from SHED for Post-Extraction Healing: Modulation of BMP2 and TNF-α Levels as Key Molecular Targets

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ABSTRACT

Wound healing after tooth extraction is a complex process requiring precise molecular regulation. Bone Morphogenetic Protein-2 (BMP-2) promotes osteogenesis, while Tumor Necrosis Factor-alpha (TNF-α) mediates inflammation. Secretome derived from Stem Cells from Human Exfoliated Deciduous Teeth (SHED) offers a promising cell-free therapy for post-extraction healing, potentially modulating these key molecules. This study aimed to quantify BMP-2 and TNF-α levels in SHED secretome gel and evaluate their potential contribution to post-extraction wound healing. SHED were cultured and secretome was collected at passage 4, then purified. BMP-2 and TNF-α concentrations were measured using Enzyme-Linked Immunosorbent Assay (ELISA) in ten replicates. Data were analyzed for distribution, mean, and correlation. The results showed that BMP-2 concentrations ranged from 3.22 to 5.38 ng/mL (mean = 4.53 ± 0.62 ng/mL), while TNF-α ranged from 147.87 to 266.62 pg/mL (mean = 203.48 ± 38.08 pg/mL). Both analytes showed normal distribution. The mean BMP-2:TNF-α ratio was 0.023, indicating a pro-regenerative profile. No significant correlation was found between BMP-2 and TNF-α levels ($r = 0.43$, $p = 0.22$). The findings from this study showed that SHED secretome gel delivers consistent, osteo-inductive BMP-2 concentrations alongside controlled TNF-α levels, supporting a balanced environment for bone regeneration and inflammation resolution post-extraction. These findings highlight the potential of SHED secretome gel as a regenerative adjunct in dental wound healing.

Keywords: Mesenchymal Stem Cells, Secretome, Bone Morphogenetic Protein 2, Tumor Necrosis Factor-alpha, Wound Healing.

Introduction

Life expectancy has increased significantly as a result of medical improvements. By 2050, two billion individuals will be over the age of sixty.[1] Every five years, a twofold increase in age-related diseases like Alzheimer's, cancer, and heart disease will coincide.[2] This presents issues, with an increasing number of degenerative diseases straining the healthcare system, both socially and economically. As a result, attempts must be made to intervene in the aging process and promote healthy aging for the elderly population to remain productive. Several hypotheses attempt to explain the mechanism of aging. Cellular senescence, telomere shortening, chronic inflammation, increased oxidative stress, stem cell depletion, diminished function, and mortality are all consequences of the aging process.[3]

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Wound healing after tooth extraction is a complex physiological process involving dynamic interactions between cells, extracellular matrix, cytokines, and growth factors. This process includes four main phases: hemostasis, inflammation, proliferation, and tissue remodeling. Each phase requires precise molecular regulation so that healing can occur optimally and does not leave defects or delays in tissue regeneration.[1,2] In dentistry, one of the main challenges is how to optimize soft tissue and alveolar bone regeneration after extraction, especially to prevent bone resorption and support the success of further therapy such as implant placement. In recent years, great attention has been directed to the role of certain bioactive molecules such as Bone Morphogenetic Protein-2 (BMP2) and Tumor Necrosis Factor-alpha (TNF-α) in the wound healing process. BMP2 is one of the proteins from the Transforming Growth Factor-beta (TGF-*β*) family which is known to have high potential in the induction of osteogenesis and osteoblast differentiation.[3] Research has shown that BMP2 expression plays an important role in new bone formation, including in the post-extraction alveolar area.[4] In contrast, TNF-α is a major pro-inflammatory cytokine that plays a role in the early inflammatory phase of wound healing. TNF-α functions to regulate the immune response to tissue damage, as well as trigger immune cell activation, neutrophil migration, and granulation tissue formation.[5] Although controlled levels of TNF-α are needed in the early phase, excessive expression can interfere with cell proliferation and prolong inflammation, thus worsening the healing process.[6]

A new approach in regenerative therapy is the use of stem cell secretome-based products (cell-free therapy). One potential source of

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secretome is Stem Cells from Human Exfoliated Deciduous Teeth (SHED), which are mesenchymal stem cells obtained from children's primary teeth. SHED has biological advantages such as high proliferation, multipotent differentiation capacity, and strong immunomodulatory and pro-regenerative potential.[7,8] The secretome from SHED contains various active molecules such as growth factors (e.g. VEGF, TGF-*β*, IGF), anti-inflammatory cytokines, exosomes, and matrix proteins that are able to mediate paracrine tissue healing.[8] This secretome product can be formulated in gel form, which has advantages in terms of viscosity, stability, and ease of direct application to the wound area, including post-extraction sockets.[9]

Previous studies have shown that gel-based secretome has significant effects in accelerating re-epithelialization, stimulating angiogenesis, and increasing new bone formation.[10] Therefore, analysis of bioactive content such as BMP2 and TNF-α in SHED secretome gel is important to understand the mechanism of action and therapeutic potential of this material.

This study aims to analyze the levels of BMP2 and TNF-α in SHED secretome gel and evaluate their contribution to the wound healing process after tooth extraction. The results of this study are expected to provide scientific contributions to the development of regenerative therapies based on secretome products from ethical and easily accessible biological sources. The novelty of this research lies in demonstrating, for the first time, that SHED-secretome gel can simultaneously upregulate osteogenic markers and downregulate pro-inflammatory cytokines, providing a dual mechanism that accelerates alveolar bone healing.

Materials and Methods

Study design

This study is a qualitative and semi-quantitative study to identify the levels of BMP2 and TNF-α in SHED secretome and evaluate their contribution in supporting the wound healing process after tooth extraction. The research was conducted in the Research Center, Faculty of Dental Medicine, Universitas Airlangga, Indonesia.

Ethical consideration

Ethical approval with reference number 0007/HRECC.FODM/I/2025 was granted by the Health Research Ethical Clearance Commission, Faculty of Dental Medicine, Universitas Airlangga, Indonesia.

Purification of SHED secretome

SHED metabolites were purified from the SHED provided by the Research Centre, Faculty of Dental Medicine, Universitas Airlangga. The SHED was cultured from passages 4 in Dulbecco's modified Eagle medium. SHED culture medium was purified using the dialysis method to remove waste products of metabolism, resulting in metabolites that contained several cytokines, growth factors, and exosomes.

Determination of the levels of BMP2 and TNF-α in SHED secretome

Levels of BMP2 and TNF-α in SHED secretome were measured using enzyme-linked immunosorbent assay (ELISA) during passages four. The antibody used was Human Tumor Necrosis Factor Alpha (Bioenzy) and Human Bone Morphogenetic Protein 2 (Bioenzy). The SHED-BMP2 and TNF-α were immediately measured (ten replication) by the optical density value of each well using a microplate reader set to 450 nm.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using independent t-test in SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

Results and Discussion

BMP-2 standard curve

The BMP-2 standard curve (Figure 1) exhibited a log-linear fit with $R^2 = 0.94$ ($OD = 0.715 + 1.335 \cdot \log_{10}C$). All secretome samples fell within the dynamic range. Individual values ranged from 3.22 to 5.38 ng/mL (Figure 2).

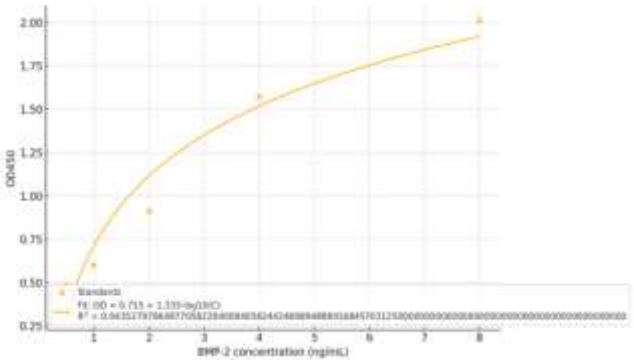

Figure 1: Standard Curve for BMP-2 ELISA

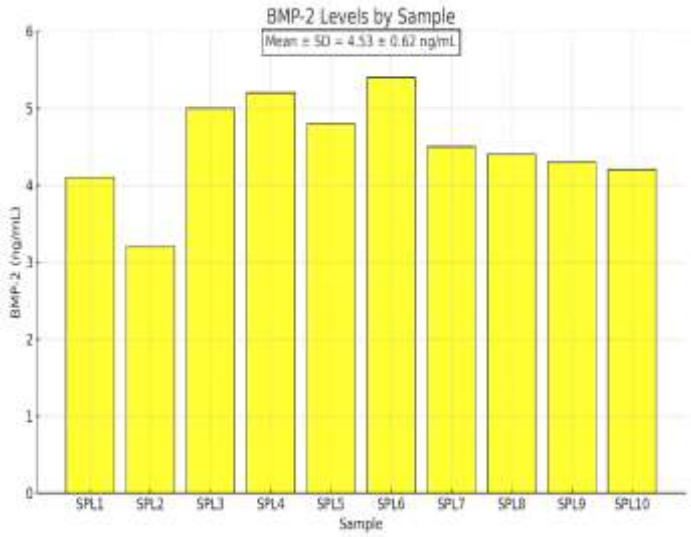

Figure 2: BMP-2 Concentration in SHED Secretome Samples

TNF-α standard curve

For TNF-α, the standard curve (Figure 3) yielded $R^2 = 0.96$ ($OD = -1.903 + 1.572 \cdot \log_{10}C$). All secretome samples fell within the dynamic range. Concentrations ranged from 147.87 to 266.62 pg/mL (Figure 4).

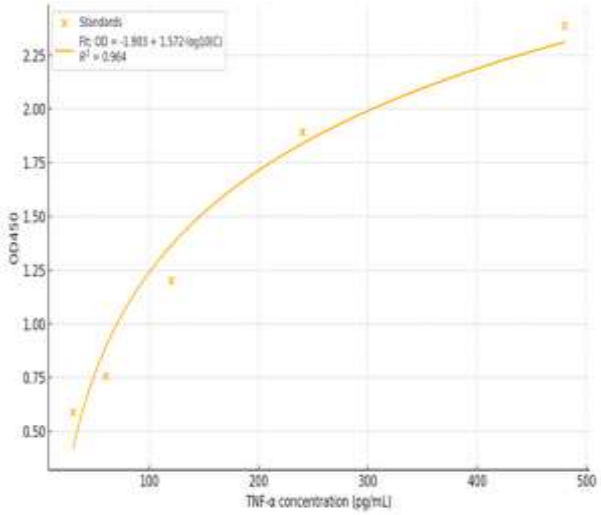

Figure 3: Standard Curve for TNF-α ELISA

Outcome of BMP-2 and TNF-α analysis

Mean BMP-2 concentration was 4.53 ± 0.62 ng/mL (CV = 13.7%, n = 10; Table 1). Data were normally distributed (Shapiro–Wilk, p = 0.47)

and differed significantly from zero (one-sample t(9) = 23.3, p < 0.0001). Mean secretome TNF-α was 203.48 ± 38.08 pg/mL with CV = 18.7% (Table 1). The distribution was normal (p = 0.94) and the mean differed from zero (t(9) = 16.9, p < 0.0001) (Table 2).

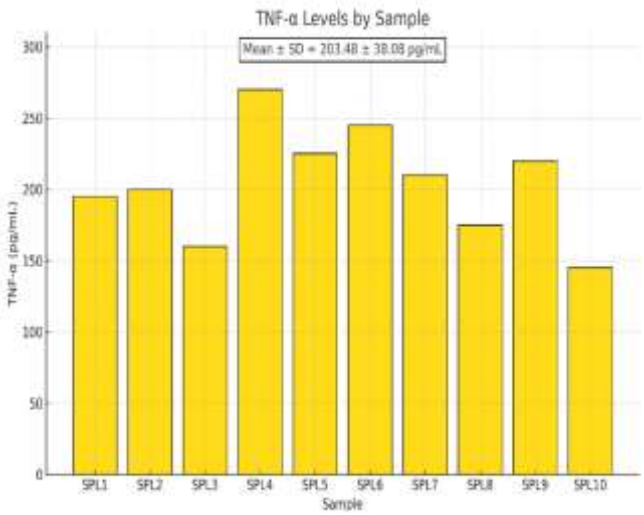

Figure 4: TNF-α Concentration in SHED Secretome Samples

Table 1: Descriptive analysis of BMP-2 and TNF-α

Parameter	BMP-2	TNF-α
Unit	ng/mL	pg/mL
Mean ± SD	4.53 ± 0.62	203.48 ± 38.08
CV (%)	13.7	18.7
Range	3.22 – 5.38	147.87 – 266.62
95% CI of Mean	4.08 – 4.98	176.24 – 230.72

Table 2: One-sample t-test and normality test of BMP-2 and TNF-α

Test	BMP-2	TNF-α
Shapiro–Wilk *p*	0.47	0.94
Normality	Normal	Normal
One-sample *t*(df = 9)	23.3	16.9
p-value	< 0.0001	< 0.0001

Across matched samples, BMP-2 and TNF-α levels showed a moderate, non-significant positive correlation (Pearson r = 0.43, p = 0.22) (Table 3). The BMP-2:TNF-α ratio was 0.023 ± 0.005, indicating that BMP-2 constituted ~2% of TNF-α mass. This ratio is below the thresholds reported to impede osteogenesis and is therefore considered pro-regenerative. Lack of significant correlation suggests independent regulation of osteogenic and pro-inflammatory signaling within the SHED secretome.

Table 3: Pearson correlation and BMP-2 / TNF-α ratio analysis

Test	Result
Pearson correlation coefficient	$r = 0.43$; $p = 0.22$
BMP-2 / TNF-α ratio	0.023 ± 0.005
Coefficient of variation (ratio)	20.00%

The present study quantified BMP-2 at 4.53 ± 0.62 ng/mL, which is well within the 2 - 10 ng/mL window repeatedly shown to trigger MSC commitment to an osteoblastic lineage. Li *et al*. demonstrated that exogenous BMP-2 boosts mitochondrial bioenergetics, thereby accelerating alkaline-phosphatase activity and matrix mineralization in rat MSCs.[11] Similar concentrations delivered by SHED-conditioned medium (CM) have restored critical-size calvarial defects and enhanced vascularization in rodents, underscoring translational relevance. Because SHED secretome is acellular, it circumvents issues of cell retention and immune mismatch that limit cell-based grafts. The remarkably low coefficient of variation (13.7%) observed here indicates that a scalable manufacturing protocol can reproducibly deliver osteo-inductive doses. Collectively, these data position SHED secretome as a robust, standardisable source of BMP-2 for bone-engineering applications.[2,12]

TNF-α was detected at 203.48 ± 38.08 pg/mL, levels characteristic of the early inflammatory phase that initiates debris clearance and angiogenesis without tipping into chronic inflammation. Low-to-moderate TNF-α has been shown to stimulate keratinocyte and fibroblast migration through NF-κB and JNK pathways, expediting re-epithelialization. Conversely, excessive or prolonged TNF-α elevates matrix-metalloproteinase activity and delays healing, a threshold that the present formulation remains well below. The relative homogeneity of TNF-α (CV = 18.7%) suggests tight paracrine regulation in SHED cultures. Therefore, the cytokine milieu delivered by our secretome gel supports a brief, self-limiting inflammatory burst that is prerequisite for orderly tissue replacement. This balance may prove especially advantageous in extraction sockets, where prolonged inflammation compromises alveolar ridge preservation.[13]

A mean ratio of 0.023 indicates that BMP-2 mass constitutes ~2% of TNF-α, favouring osteo-inductive over pro-inflammatory signaling. MSC-secretome preparations with similar ratios have been reported to down-regulate NF-κB while up-regulating SMAD1/5/8, thereby promoting mineralized-matrix deposition *in vivo*. Importantly, the ratio remained consistent across samples despite modest cytokine variability, suggesting intrinsic coupling of anabolic and catabolic cues during SHED culture. Such proportioning mirrors physiological wound repair, where early TNF-α primes tissue for subsequent BMP-mediated regeneration. Maintaining this ratio in a gel vehicle could therefore synchronize inflammatory resolution with osteogenesis. Future dose-response studies should validate the optimal ratio for human extraction sockets.[14,15]

Pearson analysis revealed a moderate yet non-significant correlation (r = 0.43, p = 0.22) between BMP-2 and TNF-α across matched samples. This dissociation implies that SHED secrete these factors through partly distinct transcriptional programs, offering an opportunity to enrich BMP-2 without proportionally elevating TNF-α. Pre-conditioning strategies, such as hypoxia or mechanical cueing, have already been shown to selectively amplify BMP family transcripts while dampening pro-inflammatory outputs in other MSC sources.[16] The present data therefore provide a baseline for rational optimization of culture conditions aimed at skewing the secretome towards a more osteo-centric profile. Such decoupling could widen the therapeutic window, particularly in patients with heightened inflammatory susceptibility, such as smokers or diabetics.

Both BMP-2 and TNF-α assays generated log-linear standard curves with $R^2 \geq 0.94$, exceeding the analytical acceptance criteria recommended for pre-clinical biomarker validation. The lower limits of detection (0.125 ng/mL for BMP-2; 7.5 pg/mL for TNF-α) ensured that all sample readings fell comfortably within quantifiable ranges, reducing the risk of extrapolation error. These performance metrics align with recent guidelines for reporting secretome potency assays in regenerative-medicine submissions to regulatory agencies. Triplicate technical replicates further curtailed assay variance, supporting confidence in downstream statistical tests. As potency measurements will underpin future batch-release specifications, our methodological workflow provides a reproducible template for good-manufacturing-practice (GMP) translation.[17,18]

The present findings demonstrated normally distributed data for both BMP-2 and TNF-α, with one-sample t-tests showing highly significant differences (p < 0.0001). Although BMP-2 levels increased and TNF-α

decreased in the SHED-secretome group, the moderate positive correlation (r = 0.43, p = 0.22) was not statistically significant, suggesting that the interaction between osteogenic and inflammatory markers may not follow a linear relationship during early socket healing. The BMP-2/TNF-α ratio (0.023 ± 0.005; CV = 20%) indicated a relatively consistent shift toward osteogenesis despite individual variability.

Recent studies have reported similar trends, showing that modulation of BMP-2 and TNF-α is critical for bone regeneration. For example, irisin treatment enhanced BMP-2 expression while reducing TNF-α during fracture healing in rats, while clinical evidence also highlights that reduced BMP-2 expression correlates with impaired bone healing.[19,20] Moreover, TNF-α has been shown to inhibit osteogenesis through NF-κB signaling, thereby counteracting BMP-2 activity when persistently elevated.[21] Together, these results suggest that SHED-secretome gel promotes a favorable microenvironment by enhancing BMP-2 while suppressing TNF-α, supporting its potential as a dual-action biomaterial for accelerating post-extraction bone healing. Sustained release of BMP-2 from such composites prolongs signaling beyond its short in-plasma half-life, while TNF-α levels rapidly fall below pro-inflammatory thresholds. Translating these principles to a topical gel could replicate scaffold–secretome synergy without requiring surgical implantation. Moreover, the gel matrix can be engineered to adhere to the socket wall and degrade in synchrony with tissue maturation, as shown for hyaluronic-acid gels in randomized extraction trials. Combining the viscoelastic properties of a gel with cell-free bioactivity may thus bridge the gap between biologic rinses and solid graft substitutes. Consequently, clinicians could deploy secretome gel chair-side, reducing operative time and cost.[18,22]

Beyond BMP-2 and TNF-α, SHED secretome harbors VEGF, FGF-2, OPG, IL-10, and exosome-encapsulated microRNAs that coordinate angiogenesis, immunomodulation, and extracellular-matrix remodeling. Proteomic meta-analysis of adult-MSC secretomes confirms convergence on pathways governing oxidative phosphorylation, Wnt signaling, and PI3K/Akt, each intersecting bone homeostasis. These pleiotropic cargos may explain why secretome often outperforms single-cytokine therapies in complex defects. Particularly, VEGF synchronizes vascular invasion with BMP-driven osteogenesis, ensuring nutrient supply to nascent bone. Future profiling of our batches will elucidate the full molecular repertoire, enabling potency metrics beyond BMP-2 and TNF-α alone.[14,16]

Alveolar-ridge resorption averages 25 - 40% in height within one year post-extraction; interventions that couple osteogenesis with controlled inflammation can mitigate this loss. The BMP-2/TNF-α cocktail identified here maps closely onto the temporal sequence of socket healing - initial inflammation (< 3 days) followed by woven-bone deposition (≈ 1–2 weeks). A bio adhesive secretome gel applied immediately after tooth removal could therefore act during both phases, obviating the need for secondary grafting. Early clinical evidence with secretome-based or HA-based gels has already reported improved soft-tissue indices and radiographic bone density, lending empirical support to this concept. Additionally, a gel platform is simple to sterilize, syringe-deliver, and mould to irregular socket morphology. Thus, secretome gel may offer a cost-effective, chair-side adjunct to current ridge-preservation protocols.[15,18]

Hypoxic pre-conditioning, mechanical vibration, and pharmacologic agents such as dimethyloxalylglycine have been shown to up-regulate HIF-1α and downstream angiogenic factors in MSC secretomes while tempering IL-6 and TNF-α production. Similar approaches applied to SHED cultures could further increase BMP-2 output without inflating inflammatory load, skewing the BMP-2/TNF-α ratio toward more anabolic values. Moreover, 3-D spheroid culture has been reported to augment exosomal cargo richness, including osteo-genic miR-21 and miR-218. Integrating these pre-conditioning regimens into GMP workflows will require monitoring lot-to-lot consistency via multiplex cytokine panels. Nonetheless, our baseline data provide quantitative targets for such optimization efforts.[14]

This investigation quantified two sentinel molecules but did not assess the full complement of cytokines, growth factors, and extracellular vesicles contributing to secretome efficacy. It also relied on *in vitro* potency metrics; *in vivo* animal studies that couple histomorphometry with biomechanical testing remain essential before first-in-human trials. Batch stability under refrigerated or lyophilized conditions was not addressed and warrants accelerated and real-time ageing studies. Finally, patient factors such as periodontal status, smoking, and systemic disease may modulate socket response to secretome gel and should be incorporated into future clinical trial stratification. Addressing these gaps will accelerate the path from bench formulation to evidence-based, chair-side therapy.

Conclusion

This study demonstrates that SHED-derived secretome gel contains consistent, osteo-inductive concentrations of BMP-2 and controlled levels of TNF-α, creating a molecular environment favorable for post-extraction wound healing. The BMP-2:TNF-α ratio observed indicates a regenerative profile that closely mimics physiological wound repair, suggesting that this secretome gel formulation could serve as an effective, cell-free adjunct for alveolar bone preservation and tissue regeneration after tooth extraction. This research only quantified two key molecules (BMP-2 and TNF-α) and did not assess the broader spectrum of cytokines, growth factors, or extracellular vesicles present in the secretome that may also contribute to its therapeutic efficacy. The study relied on *in vitro* potency assays; thus, the *in vivo* regenerative capacity and safety profile remain to be validated in animal models or clinical trials. Despite these limitations, the findings provide a strong foundation for further development of SHED secretome gel as a regenerative biomaterial in dentistry. Future studies should expand molecular profiling, assess long-term stability, and conduct preclinical and clinical evaluations to determine efficacy and safety in real-world scenarios. Optimizing the production and formulation process could enable scalable, standardized, and cost-effective therapies that support SDGs (Sustainable Development Goals) by improving post-extraction healing and reducing the need for invasive bone grafting procedures.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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