SYNTHETIC THYMOSIN B-4 (TB-500): TRANSFORMING HEALING AND TISSUE REPAIR IN DENTISTRY

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ABSTRACT

Introduction: Wound healing and tissue repair remain constant challenges in dentistry, since several clinical procedures—such as tooth extractions, periodontal surgeries, implant placement, and management of oral mucosal lesions—depend directly on the patient's biological response. The search for therapeutic agents capable of accelerating and optimizing regeneration has driven research into biomolecules with regenerative properties, among which thymosin β-4 stands out, a natural peptide involved in cell migration, angiogenesis, extracellular matrix remodeling, and modulation of inflammation. Its synthetic version, known as TB-500, has attracted scientific interest due to its potential in different medical fields, although it still lacks validation in dental contexts. **Objective:** This study aimed to systematically review the scientific literature on thymosin β-4 (TB-500) and to discuss how its biological effects may be applied in regenerative dentistry, identifying current knowledge gaps and proposing future research perspectives. **Methodology:** An integrative search was carried out in PubMed, Scopus, PMC, and ClinicalTrials.gov databases, considering publications up to 2025, using descriptors such as "thymosin β4," "TB-500," "wound healing," "oral regeneration," and "dentistry." Included studies comprised in vitro assays, animal experimental research, and human clinical trials analyzing tissue repair, healing, collagen deposition, angiogenesis, or inflammatory modulation associated with the peptide. Non–peer-reviewed works and studies with insufficient data were excluded. **Results and Discussion:** The analysis demonstrated that thymosin β-4 promotes cell migration, stimulates angiogenesis, reduces apoptosis, modulates inflammatory responses, and accelerates re-epithelialization in different tissues, showing significant improvement in wound healing speed in cutaneous models and cytoprotective action under inflammatory conditions. In vitro studies further evidenced its role in inhibiting signaling pathways such as NF-κB and MAPK, thereby reducing inflammatory mediators and osteoclastic differentiation. Despite these positive findings, no studies were identified applying thymosin β-4 or TB-500 directly to oral tissues such as gingiva, alveolar bone, or oral mucosa, which represents a critical scientific gap. The available evidence suggests that TB-500 could potentially be used in post-extraction healing, periodontal regeneration, alveolar repair, and closure of oroantral communications, but standardized protocols regarding dosage, route of administration, and treatment duration are not yet established. **Conclusion:** It is concluded that synthetic thymosin β-4 (TB-500) presents relevant biological properties for tissue regeneration and holds potential for dental applications; however, the absence of specific clinical trials and methodological standardization highlights the urgent need for well-designed preclinical and clinical studies before its practical use in dentistry can be validated.

Keywords: Thymosin β-4; TB-500; oral tissue regeneration; wound healing; regenerative dentistry.

1 INTRODUCTION

Regenerative dentistry has progressively evolved in recent decades as the demand for biological solutions capable of restoring the structure and function of oral tissues has intensified. Clinical procedures such as tooth extractions, periodontal surgeries, bone grafts, and implant placement depend on the patient's capacity for tissue repair, which in many cases may be compromised by systemic conditions, local inflammation, infections, or reduced vascularization. Delayed or deficient healing may result in complications such as alveolitis, excessive bone resorption, implant failure, and prolonged patient discomfort. For this reason, the exploration of novel therapeutic agents that can accelerate healing and improve the quality of regeneration represents a growing priority in dental research. Thymosin β-4 (Tβ4) is a naturally occurring peptide originally identified as an intracellular actin-sequestering molecule, but later recognized for its multifactorial biological actions, including stimulation of angiogenesis, promotion of cell migration, modulation of inflammatory responses, reduction of apoptosis, and enhancement of extracellular matrix remodeling. These properties have attracted considerable attention in different medical specialties such as cardiology, dermatology, ophthalmology, and orthopedics, where Tβ4 has demonstrated promising effects on wound healing, tissue regeneration, and organ repair. In order to overcome the limitations of natural peptide extraction, a synthetic analogue known as TB-500 has been developed and has been investigated in preclinical models for its regenerative and cytoprotective effects. Although the majority of research on thymosin β-4 and TB-500 has focused on non-oral tissues, such as skin, myocardium, liver, and cornea, the mechanisms described are directly relevant to oral environments. Oral tissues are constantly exposed to mechanical forces, microbiota, and inflammatory challenges, making efficient and controlled healing processes essential for successful clinical outcomes. The ability of Tβ4 to stimulate re-epithelialization, vascular growth, and modulation of osteoclastic activity suggests a potential role in improving post-extraction socket healing, enhancing periodontal regeneration, supporting implant osseointegration, and accelerating mucosal repair after trauma or surgery. Despite this promising biological rationale, there is a notable gap in the scientific literature concerning the application of TB-500 in dentistry. To date, no randomized controlled trials or preclinical animal studies have specifically tested the peptide in oral tissues, and standardized protocols regarding dosage, route of administration, treatment duration, and long-term safety remain undefined. Moreover, ethical and regulatory barriers, combined with the experimental nature of TB-500, limit its immediate translation into clinical practice. Nevertheless, the strong evidence from extra-oral studies indicates that thymosin β-4 could represent a future paradigm shift in regenerative dentistry, provided that rigorous scientific validation is achieved. Given this background, the present study aims to review and synthesize the current evidence on thymosin β-4 (TB-500), to highlight its biological mechanisms of action, and to discuss its potential translational applications in dentistry. By identifying the strengths, limitations, and gaps in existing research, this work intends to contribute to the foundation for future

investigations that may establish TB-500 as a viable therapeutic tool in oral tissue repair and regeneration.

2 METHODOLOGY

This study was designed as an integrative, systematic literature review conducted in accordance with PRISMA guidance adapted to preclinical and clinical evidence relevant to regenerative dentistry. The research question was structured using the PICO framework where applicable, asking whether thymosin β-4 (and its synthetic analogue commonly referred to as TB-500), compared with placebo or standard care, shows biological or clinical benefits for wound healing and tissue repair that are translatable to oral tissues and dental procedures. We searched PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and ClinicalTrials.gov from database inception to September 2025 without year limits. To maximize sensitivity, we also screened gray literature (OpenGrey), reference lists of included studies and key reviews, and citation trails in Google Scholar. No language restrictions were applied during screening; full texts were included if available in English, Portuguese, or Spanish, or if an accurate translation could be obtained. Search strategies combined controlled vocabulary and free-text terms with Boolean operators and truncation adapted to each database. The core string used in PubMed was: ("thymosin beta 4" OR "thymosin β-4" OR "Tβ4" OR "TB-500" OR "TB500") AND ("wound healing" OR regeneration OR "tissue repair" OR angiogenesis OR re-epithel* OR fibroblast* OR osteoblast* OR "periodontal" OR "oral" OR "dentistry"). Equivalent mappings (e.g., EMTREE terms in Embase and MeSH in MEDLINE) were applied. All retrieved records were exported to a reference manager; duplicates were identified algorithmically and confirmed manually before screening. Eligibility criteria were prespecified. Inclusion criteria encompassed in vitro studies evaluating cellular processes relevant to repair (migration, proliferation, cytokine modulation, extracellular matrix dynamics) in cell types of interest to oral healing (e.g., fibroblasts, keratinocytes, endothelial cells, osteoblasts, periodontal ligament cells); animal studies assessing soft-tissue or bone healing outcomes with thymosin β-4 or TB-500 administered topically, locally, or systemically; human studies of any design (randomized, non-randomized, prospective, or case series) investigating wound healing, tissue repair, angiogenesis, or fibrosis modulation; and reviews with systematic methods that could contribute additional primary citations. Exclusion criteria were opinion pieces, editorials, non–peer-reviewed anecdotal reports, studies lacking primary data on healing or repair outcomes, unclear identification of the peptide or dosing, and irretrievable full texts after reasonable efforts. Because TB-500 is variably referred to in the literature, we required explicit identification of thymosin β-4 or a clearly described synthetic analogue; studies using unrelated "thymosin" preparations without peptide specification were excluded. Screening proceeded in two stages by two independent reviewers. First, titles and abstracts were screened against eligibility criteria; second, full texts of potentially relevant records were assessed. Disagreements were resolved by discussion and, if needed, a third reviewer. A PRISMA flow diagram was prepared to document identification, screening, eligibility, and inclusion counts. Data extraction was performed in duplicate using a pilot-tested

form capturing study design; model or population; peptide identity, purity when reported, dose, route, frequency, and timing; comparators; follow-up duration; primary and secondary outcomes; analytical methods; and adverse events or safety signals. For preclinical studies, we preferentially extracted quantitative endpoints such as re-epithelialization rate, neovascularization metrics, collagen content, histomorphometry, micro-CT bone volume fraction, and standardized inflammation scores; for clinical studies, we extracted healing time, complication rates, pain or functional outcomes, and any imaging or histological corroboration. Risk of bias and study quality were appraised with tools appropriate to design: SYRCLE's Risk of Bias tool for animal experiments; Cochrane RoB 2 for randomized clinical trials; ROBINS-I for non-randomized human studies; and OHAT or adapted in vitro quality checklists for cell-based experiments (evaluating blinding of outcome assessment, replication, concentration–response testing, and assay validity). Certainty of the body of evidence for each outcome domain (e.g., re-epithelialization, angiogenesis, collagen deposition, bone formation, inflammation modulation) was graded using a GRADE-informed approach adapted to preclinical evidence, explicitly considering risk of bias, inconsistency, indirectness (especially for translation to oral tissues), imprecision, and potential publication bias. Given the expected heterogeneity in models, dosing regimens, routes of administration, and outcome metrics, we prespecified a narrative synthesis as the primary analytic approach. When three or more sufficiently homogeneous studies reported compatible quantitative outcomes, we planned exploratory random-effects meta-analyses with Hartung–Knapp adjustments, standardized mean differences for continuous outcomes, and risk ratios for dichotomous outcomes, alongside I^2 to quantify heterogeneity and leave-one-out sensitivity analyses. Subgroup and sensitivity analyses—if data permitted—included peptide form (native thymosin β-4 versus TB-500 analogue), route (topical/local versus systemic), tissue type (soft tissue versus bone), and healing context (acute wound versus chronic defect). Because dentistry-specific evidence was anticipated to be scarce, we prospectively defined an "applicability assessment" step rating each finding for translatability to oral environments (mucosa, periodontal tissues, alveolar bone) considering saliva exposure, microbiota, and mechanical loading. To enhance transparency and reproducibility, all search strings, screening decisions, and extracted datasets were archived in a version-controlled repository and cross-checked by a second reviewer. Ethics committee approval was not required because the study utilized publicly available data without human participant contact or identifiable information. If protocol registration became necessary for journal submission, we planned prospective registration of the review protocol in PROSPERO with the finalized research question, methods, and planned analyses.

3 RESULTS AND DISCUSSION

Across the screened literature, the body of evidence on thymosin β-4 (and synthetic analogues commonly referred to as TB-500) comprised in vitro assays, preclinical animal studies in non-oral tissues, and a small number of early-phase human investigations outside dentistry. No study was identified that directly evaluated TB-500 in oral tissues (gingiva, alveolar bone, periodontal ligament, or oral mucosa) in humans, and only indirect signals exist for oral

relevance. Consequently, results are presented by biological domains that are mechanistically pertinent to dental healing (re-epithelialization, angiogenesis, extracellular matrix dynamics and collagen deposition, inflammation and cell survival, and bone-related outcomes), followed by an appraisal of translational applicability to oral environments, dose/route considerations, and safety.

Re-epithelialization and soft-tissue closure. In multiple cutaneous wound models, thymosin β-4 consistently accelerated epithelial gap closure relative to controls, often accompanied by improved wound edge cellularity and keratinocyte migration. In vitro, epithelial and stromal cells exposed to the peptide demonstrated enhanced motility and cytoskeletal remodeling compatible with faster wound coverage. The magnitude of improvement varied across models, timing, and routes (topical vs. systemic), but directionality favored intervention. For dentistry, this domain maps onto post-extraction socket mucosal closure, donor-site healing in periodontal surgery, and post-incision soft-tissue repair, where faster re-epithelialization could reduce discomfort, infection risk, and time to re-intervention (e.g., implant placement).

Angiogenesis and perfusion. Preclinical studies repeatedly showed increased microvessel density, endothelial cell migration, and pro-angiogenic signaling following exposure to thymosin β-4. Enhanced perfusion is a cornerstone for stable healing in the oral cavity, which is frequently challenged by microbial load and mechanical stress. Translationally, improved angiogenesis could benefit guided tissue regeneration, soft-tissue graft take, and early phases of osseointegration by supporting nutrient and oxygen delivery; however, the balance between physiological neovascularization and unwanted hypervascularity in inflamed or dysplastic oral sites remains to be established.

Extracellular matrix organization and collagen deposition. Histological and biochemical analyses indicated more organized granulation tissue and increased, better-aligned collagen fibers in peptide-treated wounds. These findings suggest a shift toward a regenerative remodeling pattern with potentially less scarring. In oral contexts, matrix quality influences flap stability, peri-implant soft-tissue seal integrity, and periodontal connective tissue maturation. Nevertheless, without oral-tissue–specific data, it is uncertain whether similar collagen architecture and biomechanical gains would occur under saliva exposure and mastication forces.

Inflammation, apoptosis, and cytoprotection. In vitro and in vivo models reported down-modulation of pro-inflammatory mediators and signaling (e.g., reductions in canonical pathways associated with cytokine release), alongside decreased apoptosis and improved cell survival under oxidative stress. These immunomodulatory effects could translate into reduced postoperative edema, pain, and secondary complications in dental surgery. They may also be pertinent to periodontitis-like environments, where hyperinflammation and oxidative stress drive connective tissue and bone loss. Still, the complex interplay between oral biofilms, host immunity, and peptide signaling requires targeted experimentation before clinical extrapolation.

Bone-related outcomes. Direct evidence on alveolar or craniofacial bone is lacking. Some animal studies in non-oral settings suggested downstream effects compatible with osteogenic support—through vascularization, matrix organization, and local inflammation control—which are prerequisites for bone regeneration. For dentistry, hypotheses include improved socket preservation, defect fill in periodontal intrabony lesions, and peri-implant bone quality. Definitive conclusions cannot be drawn in the absence of micro-CT, histomorphometry, and biomechanical endpoints from jaw-bone models.

Dose, route, and delivery systems. Reported dosing regimens varied widely across studies and were seldom harmonized by body weight, exposure time, or peptide purity, hindering cross-study comparison. Topical formulations, local injections, and systemic administration were all explored in non-oral contexts. For dental translation, local delivery is conceptually attractive—e.g., incorporation into collagen membranes, hydrogels, PRF-based carriers, or scaffold coatings—because it may achieve higher tissue concentrations with limited systemic exposure, while aligning with existing regenerative workflows. Rational dose-finding in oral tissues, release-kinetics characterization, and stability testing in saliva and enzymatic milieu are necessary prerequisites.

Safety and tolerability. The available data suggest acceptable short-term tolerability in preclinical models and limited early-phase human use outside the mouth, with few acute adverse signals reported. Nonetheless, robust long-term safety profiles, immunogenicity assessments, and off-target effects remain insufficiently characterized—especially regarding the potential to influence dysregulated angiogenesis or fibroproliferative responses, and theoretical concerns in premalignant oral lesions. In dentistry, routine use would require standardized manufacturing, quality control, contaminant testing, and adherence to regulatory frameworks governing experimental biologics.

Heterogeneity, bias, and certainty of evidence. Considerable heterogeneity was observed in model systems, endpoints, timing, and analytical methods. Many studies lacked blinding of outcome assessors or did not report randomization and sample-size justification, elevating risk of bias. Publication bias cannot be excluded given the preponderance of small, positive studies. Applying a GRADE-informed lens, certainty of evidence is moderate for enhancement of re-epithelialization and pro-angiogenic effects in non-oral tissues, low to very low for bone-specific endpoints, and very low for dental clinical outcomes due to indirectness and absence of oral studies.

Translational applicability to dentistry. Collectively, the biological signals—faster soft-tissue closure, better vascularization, organized matrix, and tempered inflammation—compose a plausible mechanistic framework for benefit in oral wound healing and regenerative procedures. However, dentistry presents unique constraints: constant microbial challenge, saliva-mediated dilution and enzymatic degradation, mechanical micro-trauma, and aesthetic-functional demands. Therefore, before clinical adoption, a staged research pathway is warranted: (i) jaw-specific animal models assessing soft- and hard-tissue endpoints with standardized dosing and local delivery; (ii) ex vivo and organotypic oral models probing peptide stability and host–microbiome interactions; and (iii) rigorously controlled early-phase

human trials in well-defined indications (e.g., post-extraction socket healing or periodontal defect regeneration), with safety and dose-finding as primary aims.

Overall interpretation. Thymosin β-4/TB-500 demonstrates a coherent, multi-modal pro-healing profile in non-oral settings that is highly relevant to the aims of regenerative dentistry. The promise is tempered by indirectness, methodological limitations, and unresolved questions of dosage, delivery, and long-term safety in the oral cavity. On balance, the results justify targeted preclinical and early clinical research within dentistry, rather than immediate clinical use. If subsequent studies confirm efficacy and safety with dental-appropriate delivery systems, the peptide could become a valuable adjunct to established regenerative protocols, potentially shortening healing timelines, improving tissue quality, and enhancing patient outcomes.

4 CONCLUSION

Synthetic thymosin β-4 (commonly referred to as TB-500) demonstrates a convergent, multi-modal pro-healing profile across non-oral models: it accelerates re-epithelialization, enhances angiogenesis and tissue perfusion, improves extracellular matrix organization with more orderly collagen deposition, and modulates inflammatory and apoptotic pathways under oxidative stress. Taken together, these domains map directly onto high-value targets in regenerative dentistry—post-extraction soft-tissue closure, periodontal and peri-implant soft-tissue stability, and, potentially, hard-tissue regeneration—thereby offering a biologically plausible rationale for dental translation. The peptide's putative benefits align with contemporary goals to shorten healing timelines, reduce complications, and improve the quality and predictability of oral tissue repair. At the same time, the current evidence base is indirect for dentistry. We found no preclinical studies explicitly conducted in oral tissues of the maxillofacial complex and no clinical dental trials testing TB-500. Methodological heterogeneity (peptide identity and purity, dosing, route and frequency, timing of administration, and outcome measures), small sample sizes, incomplete reporting, and frequent absence of randomization or blinded assessment limit internal validity and external generalizability. These gaps preclude firm estimates of effect size for oral indications and prevent defining optimal dose, delivery system, and duration of therapy suitable for the saliva-rich, microbially challenged, and mechanically loaded oral environment. Accordingly, TB-500 should be regarded as an **experimental adjunct**, not a ready-to-adopt therapy in dentistry. A staged research pathway is essential: (i) maxillofacial animal studies using standardized local delivery (e.g., membrane, hydrogel, scaffold coating, PRF-based carriers) with histomorphometry, micro-CT, and biomechanical endpoints for both soft and hard tissues; (ii) organotypic/ex vivo oral models interrogating peptide stability in saliva, enzymatic degradation, host–microbiome interactions, and release kinetics; and (iii) early-phase, rigorously controlled human trials in focused indications (e.g., post-extraction socket healing or intrabony periodontal defects) with safety and dose-finding as primary aims, and validated clinical and patient-reported outcomes as secondaries. In parallel, manufacturing standardization, analytical quality control, impurity profiling, and immunogenicity monitoring

are non-negotiable to ensure reproducibility and patient safety. If subsequent investigations confirm efficacy and safety with dental-appropriate carriers, doses, and regimens—and demonstrate durability of benefit without dysregulated angiogenesis or fibroproliferative responses—TB-500 may become a valuable addition to established regenerative protocols, potentially improving tissue quality, reducing postoperative morbidity, and optimizing timelines to definitive rehabilitation (including implant therapy). Until such criteria are met, its use should remain confined to ethically approved research settings under robust regulatory oversight, with transparent reporting and data sharing to accelerate collective progress.

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