Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Review
Volume 15, Issue 3, 2025, 35
https://doi.org/10.33263/BRIAC153.035

Silk Sericin – Chitosan: The Promising Suitable Combination Polymers for Preventing Orthodontic Relapse, A Review

Iga Putri Imansari [1], Sri Suparwitri [1], Francisco José Vázquez-Santos [2], Ananto Ali Alhasyimi [1,*]

[1] Department of Orthodontics, Universitas Gadjah Mada, Yogyakarta 55281, Indonesia; igaputriimansari@mail.ugm.ac.id (I.P.I.); suparwitri_fkg@ugm.ac.id (S.S.); anantoali@ugm.ac.id (A.A.A.);
[2] Department of Orthodontics, University of Santiago de Compostela, Spain; fvazquezsantos@gmail.com;
* Correspondence: anantoali@ugm.ac.id;

Received: 9.03.2025; Accepted: 10.05.2025; Published: 8.06.2025

Abstract: Pursuing further orthodontic treatment for functional and cosmetic purposes is increasingly captivating. Clinicians must thoroughly understand tissue reactions during orthodontic relapse to prevent post-orthodontic relapse, such as managing inflammation and bone remodeling. Biological therapies, including biomaterials, can promote bone growth and prevent bone resorption, which can significantly accomplish bone remodeling and reduce relapse. As an anti-inflammatory substance, silk sericin from natural composite Bombyx mori can potentially reduce pro-inflammatory cytokines in the bone remodeling process and directly reduce osteoclast formation and activation. Chitosan acts as an osteoclast inhibitor and enhances bone regeneration by increasing osteoblast maturation. This condition can reduce the risk of orthodontic relapse. Both of these biomaterials have the ability to regulate the synthesis of inflammatory mediators, including decreasing pro-inflammatory cytokines, increasing bone regeneration, regulating the immune response, and preventing the production of oxidative stress species. These findings can serve as crucial strategies for preventing orthodontic relapse by regulating alveolar bone remodeling. Despite all the benefits of sericin and chitosan, further studies are needed to focus on understanding their formulation and *in vitro* and *in vivo* testing to ensure effectiveness on a global scale.

Keywords: orthodontic relapse; silk sericin; chitosan; medicine; bone remodeling.

1. Introduction

Orthodontic treatment involves adjusting the position of teeth to attain optimal bite function and cosmetic appeal by applying mechanical force [1]. Following successful orthodontic treatment, teeth are prone to relapse to their initial position without a retention period [2]. The prolonged and unstable nature of bone remodeling is a common source of orthodontic relapse, frequently occurring throughout orthodontic therapy [3]. Following orthodontic treatment, retention stages are crucial for maintaining long-term stability, preserving the correct alignment of dental components, and preventing recurrence [4]. Relapse is the phenomenon wherein, following treatment, the tooth arrangement that was corrected reverts to its pre-treatment situation [5]. After orthodontic treatment, the relapse rate ranges

from roughly 70% to 90%, and this problem still exists [4]. Soft tissue pressure, the limit of dentition, the effect of the occlusion, periodontal and gingival forces that impact periodontal fiber rebound, and alveolar bone remodeling are other possible factors that could contribute to post-orthodontic relapse [6].

In animal investigation, Franzen *et al*. [7] observed that the process of alveolar bone remodeling significantly contributed to the occurrence of orthodontic relapse. The most important contribution is as a type of turnover of bone remodeling, where older bone is replaced by newly formed bone. The bone remodeling process includes osteoblasts, which create new bone, and osteoclasts, which break down existing bone [2]. To accomplish bone remodeling, the aforementioned cells cooperate and communicate with one another. Biological therapies that promote bone growth and prevent bone resorption can significantly reduce relapse. These findings can be important strategies for avoiding recurrence by regulating alveolar bone remodeling [8]. Biological materials or biomaterials should be able to regulate the synthesis of inflammatory mediators, including suppressing the production of pro-inflammatory cytokines in order to regulate the immune response or inflammatory process [9].

Because of their possible uses in many spheres of biomedical engineering, perfect characteristics, cytocompatibility, bioactivity, and antibacterial qualities, polymeric materials have become the most popular field of research and always have an advantage over other classes of materials [10]. Several research has shown that polymeric materials could be used in tissue engineering to replace heart valves, bone, and cartilage, as well as skin, hip, and dental implants [11]. Polymers have attracted a lot of attention recently from scholars because of their possible uses in the rapidly developing field of orthodontics [12]. Natural polymers have emerged as a major source for producing matrices that accurately replicate biological environments due to their resemblance to the components of the body's original extracellular matrix. A platform of sophisticated supporting materials can be created by their controlled construction, producing scaffolds or hydrogel-based systems with adaptable fibrous and/or porous architecture [13]. For instance, in a 7-day *in vivo* experiment that investigated the relapse phase, the application of synthetic carbonated hydroxyapatite–chitosan hydrogel derived from blood cockle shells was discovered to effectively mitigate relapse following orthodontic tooth movement by significantly increasing the number of fibroblasts and osteoblasts and concurrently reducing the number of osteoclasts [4]. The topical application of bisphosphonate risedronate with gelatin hydrogel diminishes relapse seven days post-tooth stabilization, while the local injection of epigallocatechin gallate-modified gelatin inhibits osteoclastogenesis, presenting a potential novel therapeutic strategy to modify tooth movement and prevent orthodontic relapse [8]. Hence, to address the knowledge gap, this review aims to explore the association between sericin and chitosan as suitable biomaterials and elucidate the potential of this biomaterials modality to reduce orthodontic relapse

2. The Biological Background During Orthodontic Relapse

Oral hygiene, orthodontic pressures, and periodontal health all have a major impact on the outcome of orthodontic therapy. The response of the surrounding periodontal tissue and bone remodeling is influenced by orthodontic treatments' frequency, length, and force level[14]. All types of orthodontic appliances apply a variety of differential stresses to the periodontal tissues [15]. Pro-inflammatory and anti-inflammatory cytokines are considered critical mediators of tissue remodeling [16]. The tissue and biological response patterns that occur immediately after the termination of orthodontic force are comparable to those seen

during active orthodontic tooth movement (OTM) [17]. In the course of relapse, the previously stressed side of OTM now endures increased strain. This leads to enhanced osteoclast differentiation, resulting in bone resorption [18]. Conversely, the area of the bone that was before subjected to pressure transforms into the region experiencing tension, facilitating the proliferation of osteoblasts and commencing new bone formation [19]. As a result, the periodontal ligament (PDL), cementum, and alveolar bone experience a change in signaling and cellular response. This suggests that the opposite side of the tooth will experience the same mechanisms as those observed during active tooth displacement [7].

In recent rat investigations for 10 days, the rat's maxillary teeth were pushed mesially using closed coil springs. The removal of the appliance resulted in rapid relapse. On the initial day, molars exhibited a relapse exceeding 60% of their active mobility. Relapses diminished after the third day and stabilized within three weeks. The relapse rate was analogous to physiological tooth drift throughout this interval, with recurrence being 80% to 90% of the attained movement. The studies on recurrence following tipping movement suggest a rapid relapse that slows down after a few days. After 10-20 days, relapse rates range from 40-90% of the initial movement [17]. This relapse will always occur due to the instability of many types of fibers in PDL [2]. The collagen fibers no longer secure the tooth to the alveolar bone. The periodontal ligament is now comprised of loose connective tissue, predominantly including collagen type III fibers with indeterminate orientation. Blood vessels and fibroblasts are prevalent in loose connective tissue. The majority of cases demonstrate direct resorption of cancellous bone generated during relapse. This causes the PDL's stress and strain distribution to alter, which alters the production and release of chemicals that control the PDL, the alveolar bone's, and the cementum's cell differentiation, proliferation, and activation, such as pro-inflammatory cytokines [20].

Two types of local regulatory proteins are identified in the relapse process, such as growth factors and cytokines, shown clearly in Figure 1. Growth factors affect cellular development, proliferation, differentiation, and maturation, whereas cytokines are primarily involved in hematopoietic and immunological functions. The latter can function as pro-inflammatory and anti-inflammatory mediators, augmenting immunological and antibody responses. The difference between growth factors and cytokines is ambiguous, as certain cytokines can promote or inhibit cellular growth and differentiation [17]. The principal growth factors implicated in bone remodeling and relapse are derived from the epidermal growth factors (EGF) such as EGF and transforming growth factor-α (TGFα), fibroblast growth factors (FGFs), insulin-like growth factors (IGFs), vascular endothelial growth factors (VEGFs), and colony-stimulating factors (CSFs) and transforming growth factor-β (TGFβ) superfamily, which encompasses TGFβs and bone morphogenetic proteins (BMPs) [21]. The relapse movement correlates with elevated levels of many cytokines, including receptor activator of nuclear factor-k B (RANK), receptor activator of nuclear factor-k B ligand (RANKL), and osteoprotegerin (OPG) [19]. These cytokines interact with different target cells and engage in various immunological processes. It is generally acknowledged that IL-1 is thought to be the primary trigger that starts the inflammatory response [17].

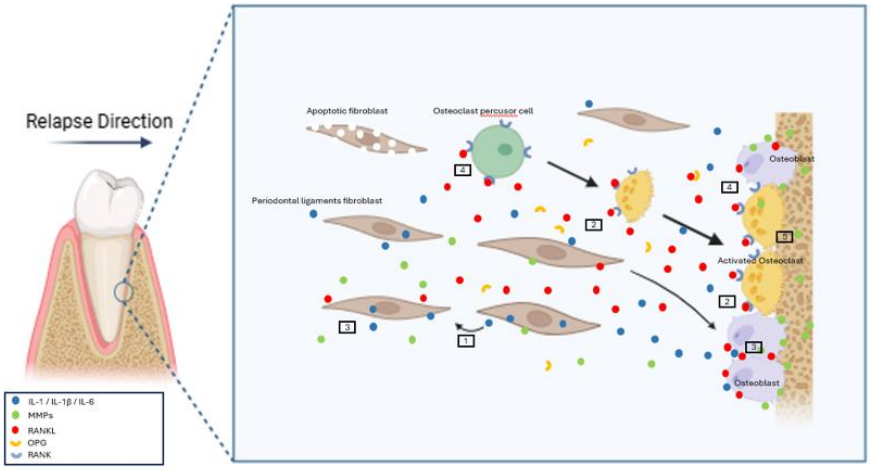

Figure 1. A summary of the remodeling activities on the leading side of relapse direction. Under compressive strain in relapse condition (without force), fibroblasts (1) produce IL-1 and IL-6, which increase the expression of RANKL ligand (2) MMPs (3). MMPs destroy osteoid and ECM of PDL (4), while RANKL promotes osteoclast activation and development (5). (an original image generated with the BioRender online platform for scientific illustration).

Immediately following the cessation of force, mononuclear phagocytes, fibroblasts, and endothelial cells within the periodontal ligament (PDL) secrete the pro-inflammatory cytokines IL-1β and pentraxin-related protein (PTX3) on the pressure side. In sterile settings, PTX3 plays a role in tissue remodeling and healing. The differentiation of precursors into osteoblasts and osteoclasts is mediated by these molecules, which include FGF, IGF-1, IL-1α, IL-1β, IL-6, and TNFα [17]. IL-1β is the most powerful and effective pro-inflammatory cytokine [22]. TNF-α is primarily synthesized by activated monocytes and macrophages. However, it can also be generated by osteoblasts, epithelial cells, and endothelial cells [23]. TNF-α can cause osteoclastogenesis in bones by binding to the p55 receptor on osteoclast precursors [24]. IL-1β and TNF-α stimulate osteoclast differentiation and raise RANKL and M-CSF levels in osteoblasts [25]. The RANKL triggers osteoclast development as an osteoclastogenesis process which activates osteoclast transcription factors [2]. Osteoclasts are also directly impacted by IL-1β, which encourages bone resorption on the tooth's leading side and causes relapse movement [25]. In conjunction with TNF-α, it induces apoptosis in osteocytes, leading to osteoclast recruitment and bone resorption on the PDL pressure side while suppressing osteoblasts [24]. The necrotizing tissues initiated an inflammatory response by pulling leukocytes and nearby phagocytes, such as macrophages and foreign body giant cells, from inflammatory mediators, including IL-1β, TNF-α, and PGE2, in the surrounding tissue. By phagocytosing the dead cells and debris, these cells get rid of them.

Additionally, protein denaturation alters the extracellular matrix (ECM). This condition made the straightened teeth move opposite orthodontic tooth movement direction [17]. Osteoclasts also underwent M-CSF differentiation into monocytes and then osteoclast precursors. The RANKL, which is released by fibroblasts and osteoblasts, is necessary for their further differentiation [8].

3. The Potential of Chitosan as an Osteoclastogenesis Inhibitor, Enhance Bone Regeneration and Reduce Risk of Orthodontic Relapse

The second most prevalent polymerized carbon in nature, chitin, is the biocompatible polymerized carbon chitosan source. Its antibacterial, antimicrobial, rapid tissue development,

biodegradability, capacity to transport medications with small molecular weights, emulsifying, high bioactivity, chelating, and biocompatible qualities make it useful in a number of biological fields [26]. Chitosan is utilized in medicine and dentistry as an antacid, antioxidant, antibacterial, plaque inhibitor, osteogenesis promoter, hemostatic agent, fat absorbent, ulcer and wound healer, and more [27]. Chitosan has been widely employed in research, including in medicine as a wound dressing, tissue engineering material, and artificial skin. The chitosan scaffold can be combined with collagen, gelatin, or fibroin to enhance its biocompatible qualities [26]. It has been demonstrated that chitosan increases osteogenic cell differentiation and stimulates the production of new bone *in vitro* experiments assessing its impact on cell-level bone formation [27].

The potential application of chitosan in medicine as a carrier for therapies aimed at bone and periodontal regeneration [27]. Chitosan transiently opens the tight junctions between epithelial cells, adheres to the mucosal surface, and enhances membrane permeability [28]. In particular, *in vitro* and *in vivo*, chitosan has been utilized to promote bone growth [4]. Chen *et al*. [27] revealed that implanting a chitosan scaffold on a 5 mm bone defect of rats considerably improves bone repair. At 3 weeks, the chitosan wound demonstrated centripetal bone growth around the defect in contrast to the control without any treatment, which showed poorly structured connective tissue infiltrated the control wounds. At 4 weeks post-surgery, the chitosan-treated group had considerably more regenerated bone compared to the control. The group that received cross-linked chitosan biomaterials had the highest level of osteogenesis [27]. Osteoinduction is recruiting immature mesenchymal stem cells and stimulating them to become preosteoblasts [17]. Osteoconduction involves the growth of bone on a surface, similar to bone grafting. Chitosan may promote differentiation into osteoblasts, fostering an environment favorable for osteoinduction until bone development, facilitating osteoblastogenesis during orthodontic relapse [27].

Chitosan nanofibers can stimulate the expression of genes associated with osteoblast differentiation and enhance osteoblast maturation. Alkaline phosphatase (ALP), osteopontin (OPN), and osteocalcin (OCN) are early markers of osteoblast activity that facilitate the maturation of osteoblast function and the mineralization of ECM [17]. These osteoblast-associated genes are normally regulated at the transcriptional level. Runt-related transcription factor 2 (RUNX2), an osteogenic master transcription factor, has been shown to govern osteoblast development and maturation. Ho *et al*. revealed that in chitosan nanofiber scaffolds, after being cultured, the number of osteoblasts with positive signals significantly increased by upregulated ALP, OPN, and OCN gene expression [29]. The upregulation of OPN, ALP, and OCN is directly connected to osteoblast differentiation [17]. The studies investigated RUNX2's involvement in chitosan nanofiber-induced osteoblast mineralization. Human osteoblasts exposed to chitosan nanofibers had significantly higher RUNX2 messenger ribonucleic acid ((m)RNA) expression. Similarly, treatment with chitosan nanofibers increased RUNX2 protein production. Previous research has shown that activating RUNX2 increases ALP, OCN, and OPN (m)RNA expression while promoting osteoblast development, enhancing osteogenesis and bone repair. Thus, RUNX2-mediated control of osteoblast-associated gene expression plays a significant role in regulating osteoblast proliferation and maturation on bone remodeling before orthodontic relapse occurs [30]. Furthermore, chitosan was determined to be appropriate for producing extremely porous scaffolds with interconnected pores that are permissive to bone ingrowth into the graft and have good bone ECM-mimicking capacity [13]. Because of their special properties, chitosan nanofibers have good stability, permeability,

porosity, and resemblance to the ECM and are noticeably better than those of other morphologies; hence, it has the ability to reduce orthodontic relapse.

4. Silk Sericin, an Anti-inflammatory Substance, Potential in Reducing Relapse Following Orthodontic Tooth Movement

Natural silk fiber produced by the silkworm *Bombyx mor*i (*B. mori*) has two main components: hydrophobic fibroin and hydrophilic sericin. Sericin assembles the cocoon that provides the ideal conditions metamorphose environment for the larvae into adults [31]. Sericin is the second largest component of raw silk after fibroin and has a molecular weight distribution of 10,000–300,000 g/mol. Sericin can bind and coat two fibroin filaments found in raw silk, which binds and coats the two fibroin filaments in the raw silk [26]. Silk sericin has biological qualities, including biocompatibility, biodegradability, enhancing cell adhesion, immunocompatibility, anti-inflammatory, antimicrobial activity, antioxidant, and photoprotective. Silk sericin has been identified as a potential sustainable biomaterial for a variety of biomedical and pharmaceutical applications [32].

Noosak *et al*.[33] revealed that sericin extracts at concentrations of 40, 80, 160, and 320 μg/ml increased cell viability by approximately 135%, 115%, 116%, and 90%, respectively. This shows that the extract had no cytotoxic effects on osteoblast cells (MC3T3-E1 cell). Sericin extract at 40 μg/mL significantly enhances osteoblast cell proliferation by up to 135% compared to the untreated control. Improving proliferation and maturation of osteoblast condition is crucial to enhancing tooth stability during orthodontic tooth movement. The gelatin hydrogel method in orthodontics allows for accurate administration of risedronate to achieve localized effects. These data suggest that sericin risedronate hydrogel plays a significant role in bone remodeling and can prevent relapse [32].

Silk sericin is non-toxic to fibroblast cells and promotes wound healing compared to normal saline [33]. After adding silk sericin to culture media, monocytes and macrophages release minimal levels of IL-1β and TNF-α, indicating that it is not harmful to the cells. In rat tissues 7 days after injury, silk sericin-treated wounds have considerably suppressed inflammatory mediators (IL-1β and TNF-α) levels during healing. Low levels of IL-1β and TNF-α decrease RANKL expression, an osteoclast differentiation and maturation factor, which can directly reduce osteoclast formation and activation [2]. The findings support that sericin has the potential to minimize the osteoclastogenesis process on the trailing side of orthodontic relapse by decreasing IL-1β and TNF-α.

5. Utilization of Chitosan Scaffold Combined with Noncovalent Silk Sericin Nanohydrogel

Cell growth compatibility is necessary foriomedical applications, such as scaffolds for tissue engineering or bone biomaterial [34]. It ought to be sufficiently permeable to allow for the growth of cells. The pore diameter needs to be appropriate for the cell type being cultivated [13]. The scaffold must also be non-cytotoxic, biocompatible, and biodegradable [35]. Noncovalent interactions are essential in materials, facilitating molecular identification, directionality, addressability, and programmability of supramolecular properties. Nowadays, a lot of ongoing biomaterial research is on nanohydrogels based on sericin and chitosan scaffolds in order to create wound material for vascular tissue, joints, bones, and artificial cartilage [26].

Evidence suggests that sericin-chitosan scaffolds, such as silk sericin and chitosan films with different volume ratios, could be useful for wound dressing [36]. Sericin and chitosan are highly compatible, and combining them can enhance their individual beneficial properties when used as a polymer or scaffold. While both are biocompatible and have antibacterial properties, their combination can improve structural configuration, enhance biocompatibility, and increase bioactivity. Recent research has shown that a nanofibrous matrix incorporating sericin and chitosan exhibits biocompatibility and bioactivity, making it a useful wound dressing material for expedited healing and prevention of infection at the wound site. The enhanced cell viability seen with sericin and chitosan is attributable to their non-toxic characteristics toward L929 cells [37]. The biocompatibility of sericin-chitosan porous scaffolds with human cells may benefit future applications in tissue engineering. Reduced chitosan molecular weights (15,000 and 100,000 g/mol) led to a more uniform distribution of sericin and decreased viscosity in the scaffold [26]. An overview of the main role of sericin and chitosan will be shown in Table 1. This study indicates that sericin derived from silk waste can be integrated with chitosan to form a self-assembled scaffold that enhances porosity and cell adhesion while remaining non-toxic and potentially applicable in orthodontics, particularly for improving post-orthodontic tooth stability.

Table 1. Overview of the main role of sericin and chitosan.

Polymer	Origin	Advantage	Role	References
Sericin	The silk of different animals (e.g., Silkworms from *Bombyx mori*, *Antheraea pernyi*, and *Samia Cynrhia Ricini)*	- Biocompatible - Biodegradable - Slow degradation - Excellent mechanical properties - Bioactive - Thermo-reversible behavior/ easy gelling - High mechanical strength	Inhibit IL-1β and inhibit TNF-α	[10,13]
Chitosan	Deacetylation of chitin found in the shells of crustaceans, insects, and fungus cell walls	- Biocompatible - Biodegradable - Non-Toxic - Non-Allergenic - Bioactive - Inexpensive	Enhance RUNX2, ALP, OPN, OCN	[10]

6. Conclusions

Preventing undesired post-treatment alterations in orthodontics is crucial, and understanding the biological relapse process is needed. This paper examines and suggests the potential use of polymeric materials in orthodontics, focusing on silk sericin and chitosan as new approaches to relapse prevention materials to improve patient quality of life. Therefore, the combination of both of the materials combines the properties of silk sericin in increasing osteoblast cell proliferation and decreasing osteoclastic activity by suppressing pro-inflammatory cytokines such as IL-1β and TNF-α, while chitosan stimulates RUNX2, ALP, OPN, and OCN can help regulate the maturation of osteoblast function and bone ECM mineralization as well as enhance post-orthodontic treatment stability. Although the evidence is not clear enough to provide recommendations for human trials, this study suggests a direction for further research. Future animal research should adhere to established protocols. Protocols should replicate human clinical settings, including drug scheduling, dose equivalency, and mode of administration. They should also consider the unique mechanisms that induce tooth movement and relapse evaluation procedures.

Author Contributions

Conceptualization and design, I.P.I. and A.A.A.; Literature review, I.P.I., S.S., F.J.V. and A.A.A.; Formal analysis, I.P.I and A.A.A.; Writing-original draft preparation, I.P.I., S.S., F.J.V. and A.A.A.; Writing-review & editing, A.A.A.; Supervision, S.S. and A.A.A. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

Funding

This research received no external funding.

Acknowledgments

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Hariadi, A.; Karunia, D.; Christnawati, C.; Farmasyanti, C.A.; Alhasyimi, A.A. Effect of Blue-Light-Emitting Diode Exposure on Collagen Density of Periodontal Ligament During Orthodontic Tooth Movement in Rats. *Biointerface Res. Appl. Chem.* **2022**, 12, 8231-8240, https://doi.org/10.33263/BRIAC126.82318240.
2. Alhasyimi, A.A.; Rosyida, N.F.; Ana, I.D. Effect of nanoemulsion carbonated hydroxyapatite-statin administration on Acp 5 and Runx-2 expression during orthodontic relapse in rats. *J. Oral Biol. Craniofacial Res.* **2025**, *15*, 129-135, https://doi.org/10.1016/j.jobcr.2024.12.013.
3. Alhasyimi, A.A.; Rosyida, N.F.; Rihadini, M.S. Postorthodontic Relapse Prevention by Administration of Grape Seed (*Vitis vinifera*) Extract Containing Cyanidine in Rats. *Eur. J. Dent.* **2019**, *13*, 629-634, https://doi.org/10.1055/s-0039-3401440.
4. Hadi, A.F.N.; Aghniya, S.N.; Haidar, G.A.; Sihombing, W.S.M.; Sutedjo, A.; Alhasyimi, A.A. Post-Orthodontic Relapse Prevention through Administration of a Novel Synthetic Carbonated Hydroxyapatite–Chitosan Hydrogel Derived from Blood Cockle Shell (*Anadara granosa* L.). *Dent. J.* **2024**, *12*, 18, https://doi.org/10.3390/dj12010018.
5. Alhasyimi, A.A.; Pudyani, P.P.; Asmara, W.; Ana, I.D. Enhancement of post-orthodontic tooth stability by carbonated hydroxyapatite-incorporated advanced platelet-rich fibrin in rabbits. *Orthod. Craniofacial Res.* **2018**, *21*, 112-118, https://doi.org/10.1111/ocr.12224.
6. Littlewood, S.J. Responsibilities and Retention. *APOS Trends Orthod*. **2017**, *7*, 211-214, https://doi.org/10.4103/apos.apos_82_17.
7. Franzen, T.J.; Monjo, M.; Rubert, M.; Vandevska-Radunovic, V. Expression of bone markers and micro-CT analysis of alveolar bone during orthodontic relapse. *Orthod. Craniofacial Res.* **2014**, *17*, 249-258, https://doi.org/10.1111/ocr.12050.

8. Rosyida, N.F.; Ana, I.D.; Alhasyimi, A.A. The Use of Polymers to Enhance Post-Orthodontic Tooth Stability. *Polymers* **2023**, *15*, 103, https://doi.org/10.3390/polym15010103.
9. Fasolino, I.; Raucci, M.G.; Soriente, A.; Demitri, C.; Madaghiele, M.; Sannino, A.; Ambrosio, L. Osteoinductive and anti-inflammatory properties of chitosan-based scaffolds for bone regeneration. *Mater. Sci. Eng. C* **2019**, *105*, 110046, https://doi.org/10.1016/j.msec.2019.110046.
10. Silva, A.S.; Costa, E.C.; Reis, S.; Spencer, C.; Calhelha, R.C.; Miguel, S.P.; Ribeiro, M.P.; Barros, L.; Vaz, J.A.; Coutinho, P. Silk Sericin: A Promising Sustainable Biomaterial for Biomedical and Pharmaceutical Applications. *Polymers* **2022**, *14*, 4931, https://doi.org/10.3390/polym14224931.
11. Mawazi, S.M.; Kumar, M.; Ahmad, N.; Ge, Y.; Mahmood, S. Recent Applications of Chitosan and Its Derivatives in Antibacterial, Anticancer, Wound Healing, and Tissue Engineering Fields. *Polymers* **2024**, *16*, 1351, https://doi.org/10.3390/polym16101351.
12. Hassan, R.; Aslam Khan, M.U.; Abdullah, A.M.; Abd Razak, S.I. A Review on Current Trends of Polymers in Orthodontics: BPA-Free and Smart Materials. *Polymers* **2021**, *13*, 1409, https://doi.org/10.3390/polym13091409.
13. Filippi, M.; Born, G.; Chaaban, M.; Scherberich, A. Natural Polymeric Scaffolds in Bone Regeneration. *Front. Bioeng. Biotechnol.* **2020**, *8*, 474, https://doi.org/10.3389/fbioe.2020.00474.
14. Antonarakis, G.S.; Zekeridou, A.; Kiliaridis, S.; Giannopoulou, C. Periodontal considerations during orthodontic intrusion and extrusion in healthy and reduced periodontium. *Periodontology 2000* **2024**, *0*, 1-25, https://doi.org/10.1111/prd.12578.
15. Motyl, S.; Manfredini, D.; Oruba, Z.; Bugajska, J.; Sztefko, K.; Stós, W.; Osiewicz, M.; Loster, B.W.; Lobbezoo, F. Evaluation of interleukin-1 beta and the ratio of interleukin-1 beta to interleukin-1 receptor antagonist in gingival crevicular fluid during orthodontic canine retraction. *Dent. Med. Probl.* **2021**, *58*, 47-54, https://doi.org/10.17219/DMP/132954.
16. Maltha, J.C.; Kuijpers-Jagtman, A.M. Mechanobiology of orthodontic tooth movement: An update. *J. World Fed. Orthod.* **2023**, *12*, 156-160, https://doi.org/10.1016/j.ejwf.2023.05.001.
17. Maltha, J.C.; Krishnan, V.; Kuijpers-Jagtman, A.M. Cellular and Molecular Biology of Orthodontic Tooth Movement. In Biological Mechanisms of Tooth Movement; Krishnan, V., Kuijpers-Jagtman, A.M., Davidovitch, Z., Eds.; John Wiley & Sons: **2021**; pp. 33-48, https://doi.org/10.1002/9781119608912.ch3.
18. Alhasyimi, A.A.; Suparwitri, S.; Christnawati, C. Effect of carbonate apatite hydrogel-advanced platelet-rich fibrin injection on osteoblastogenesis during orthodontic relapse in rabbits. *Eur. J. Dent.* **2021,** *15*, 412-419. https://doi.org/10.1055/s-0040-1721234.
19. Sharma, S.; Pamnani, M. Evaluation of salivary cytokines in patients with fixed orthodontic treatment. *Int. J. Health Sci.* **2022**, *6*, 2250–2256, https://doi.org/10.53730/ijhs.v6ns3.5996.
20. Narmada, I.B.; Rubianto, M.; Putra, S.T. The Role of Low-Intensity Biostimulation Laser Therapy in Transforming Growth Factor β1, Bone Alkaline Phosphatase and Osteocalcin Expression during Orthodontic Tooth Movement in Cavia porcellus. *Eur. J. Dent.* **2019**, *13*, 102-107, https://doi.org/10.1055/s-0039-1688655.
21. Vélez, E.L.P.; Rivera, D.A.; Amaya, A.M.S.; Hernandez, J.C.; Toro, D.A.; Trujillo, N.V. Clinical and molecular factors associated with external apical root resorption by orthodontics: Umbrella review. *APOS Trends Orthod.* **2024**, *14*, 214-224, https://doi.org/10.25259/APOS_176_2022.
22. Kim, S.S.; Seo, S.R. Caspase-3 targets pro-interleukin-1β (IL-1β) to restrict inflammation. *FEBS Lett.* **2024**, *598*, 1366-1374, https://doi.org/10.1002/1873-3468.14864.
23. Chen, S.; Saeed, A.F.U.H.; Liu, Q.; Jiang, Q.; Xu, H.; Xiao, G.G.; Rao, L.; Duo, Y. Macrophages in immunoregulation and therapeutics. *Signal Transduct. Target. Ther.* **2023**, *8*, 207, https://doi.org/10.1038/s41392-023-01452-1.
24. Suparwitri, S.; Hidayat, W.; Hendrawati, H.; Alhasyimi, A.A. Levels of Tumor Necrosis Factor-α (TNF-α) and Transforming Growth Factor-β1 (TGF-β1) in Gingival Crevicular Fluid during Canine Retraction Using Elastic Chain and Closed Coil Spring. *Dent. Hypotheses* **2018**, *9*, 31-35, https://doi.org/10.4103/denthyp.denthyp_5_18.
25. Otsuka, Y.; Kondo, T.; Aoki, H.; Goto, Y.; Kawaguchi, Y.; Waguri-Nagaya, Y.; Miyazawa, K.; Goto, S.; Aoyama, M. IL-1β promotes osteoclastogenesis by increasing the expression of IGF2 and chemokines in non-osteoclastic cells. *J. Pharmacol. Sci.* **2023**, *151*, 1-8, https://doi.org/10.1016/j.jphs.2022.10.007.
26. Chollakup, R.; Uttayarat, P.; Chworos, A.; Smitthipong, W. Noncovalent Sericin-Chitosan Scaffold: Physical Properties and Low Cytotoxicity Effect. *Int. J. Mol. Sci.* **2020**, *21*, 775, https://doi.org/10.3390/ijms21030775.

27. Chen, C.-K.; Chang, N.-J.; Wu, Y.-T.; Fu, E.; Shen, E.C.; Feng, C.-W.; Wen, Z.-H. Bone Formation Using Cross-Linked Chitosan Scaffolds in Rat Calvarial Defects. *Implant Dent.* **2018**, *27*, 15-21, https://doi.org/10.1097/ID.0000000000000670.
28. Mura, P.; Maestrelli, F.; Cirri, M.; Mennini, N. Multiple Roles of Chitosan in Mucosal Drug Delivery: An Updated Review. *Mar. Drugs* **2022**, *20*, 335, https://doi.org/10.3390/md20050335.
29. Ho, M.; Liao, M.; Lin, Y.; Lai, C.; Lin, P.; Chen, R. Improving effects of chitosan nanofiber scaffolds on osteoblast proliferation and maturation. *Int. J. Nanomed.* **2014**, *9*, 4293-4304, https://doi.org/10.2147/IJN.S68012.
30. Ho, M.; Yao, C.; Liao, M.; Lin, P.; Liu, S.; Chen, R. Chitosan nanofiber scaffold improves bone healing via stimulating trabecular bone production due to upregulation of the Runx2/osteocalcin/alkaline phosphatase signaling pathway. *Int J Nanomed.* **2015**, *10*, 5941-5954, https://doi.org/10.2147/IJN.S90669.
31. Suzuki, S.; Sakiragaoglu, O.; Chirila, T.V. Study of the Antioxidative Effects of *Bombyx mori* Silk Sericin in Cultures of Murine Retinal Photoreceptor Cells. *Molecules* **2022**, *27*, 4635, https://doi.org/10.3390/molecules27144635.
32. Zhang, M.; Wang, D.; Ji, N.; Lee, S.; Wang, G.; Zheng, Y.; Zhang, X.; Yang, L.; Qin, Z.; Yang, Y. Bioinspired Design of Sericin/Chitosan/Ag@MOF/GO Hydrogels for Efficiently Combating Resistant Bacteria, Rapid Hemostasis, and Wound Healing. *Polymers* **2021**, *13*, 2812, https://doi.org/10.3390/polym13162812.
33. Noosak, C.; Jantorn, P.; Meesane, J.; Voravuthikunchai, S.; Saeloh, D. Dual-functional bioactive silk sericin for osteoblast responses and osteomyelitis treatment. *PLOS ONE* **2022**, *17*, e0264795, https://doi.org/10.1371/journal.pone.0264795.
34. Obulareddy, V.T.; Porwal, A.; Noor, T.; Catalano, F.; Minervini, G.; D'Amico, C.; Mancini, M.; Gorassini, F.; Fiorillo, L.; Cervino, G. Tooth as a Bone Graft Material: A Narrative Review. *Eur. J. Gen. Dent.* **2023**, *12*, 072-081, https://doi.org/10.1055/s-0043-1771533.
35. Fatahian, R.; Hosseini, E.; Fatahian, A.; Fatahian, E.; Fatahian, H. A Review on Potential Applications of Sericin, and its Biological, Mechanical, and Thermal Stability Characteristics. *Int. J. Eng. Sci. Technol*. **2022**, *9*, 1-9, https://doi.org/10.15282/ijets.9.1.2022.1001.
36. Mondal, I.H.; Chowdhury, T.; Islam, M.; Nuruzzaman, M. Development of nano ZnO loaded chitosan-sericin nano-biocomposite- a rapid homeostasis and effective wound healing agent. *Mater. Today Chem.* **2024**, *42*, 102446, https://doi.org/10.1016/j.mtchem.2024.102446.
37. Karthick, S.A.; Manjari, K.; Devi, M.G. Biocompatible and bioactive PVA/Sericin/Chitosan nanofibrous wound dressing matrix. *Appl. Surf. Sci. Adv*. **2023**, *13*, 100362, https://doi.org/10.1016/j.apsadv.2022.100362.

Publisher's Note & Disclaimer