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LITERATURE REVIEW

The Role of Hyaluronic Acid (Gengigel) in Periodontal Therapy: A Literature Review

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Abstract

Background: Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan widely distributed in connective tissues, where it plays a critical role in maintaining tissue hydration, cell proliferation, and wound healing. In periodontal therapy, the topical application of HA, particularly in its commercial form *Gengigel*, has attracted considerable attention for its potential to enhance clinical outcomes through anti-inflammatory, bacteriostatic, and regenerative mechanisms.
Objective: This narrative literature review aims to summarize and analyze the available evidence on the role of hyaluronic acid, particularly *Gengigel*, in non-surgical and surgical periodontal therapy, focusing on its biological properties, mechanisms of action, and clinical outcomes.
Methods: A narrative literature search was performed using PubMed, Scopus, and ScienceDirect (Elsevier) databases for publications between 2020 and 2025. Studies evaluating the adjunctive use of hyaluronic acid or *Gengigel* in periodontal treatment were identified. Around 20–30 relevant studies were reviewed and qualitatively analyzed to assess their findings regarding inflammation control, wound healing, and overall periodontal improvement.
Results: The reviewed studies consistently reported that topical *Gengigel* significantly reduces gingival inflammation, bleeding on probing, and post-treatment discomfort. Its anti-inflammatory effect is attributed to inhibition of prostaglandin and cytokine activity, while its regenerative capacity promotes fibroblast proliferation, angiogenesis, and epithelial migration. Clinical trials also indicate that HA enhances wound healing and accelerates soft-tissue repair when used as an adjunct to scaling and root planing. The hydrating properties of HA contribute to improved tissue elasticity and resilience, making it a valuable component in the non-surgical management of periodontal conditions. Furthermore, its biocompatibility and minimal adverse effects support its safe and repeated clinical use.
Conclusion: Hyaluronic acid, particularly in its commercial form *Gengigel*, is a promising adjunctive material in periodontal therapy due to its dual anti-inflammatory and regenerative actions. Its use leads to faster healing, reduced inflammation, and improved patient comfort. However, larger randomized clinical trials with standardized protocols are needed to confirm its long-term efficacy and establish optimal concentrations and delivery methods.

1. Introduction

Periodontal diseases are initiated by dental plaque, and it represents a widespread cause of tooth loss in adults, affecting nearly half of the adult population. Mechanical debridement, particularly using ultrasonic or laser instruments, is the most widely used treatment for periodontal diseases [1]. As an autoimmune and multifactorial disease, other enzymatic agents and natural immunomodulators have been added recently as an adjunctive therapy. In addition to enhanced thermoreceptors, agents that increase periodontal comfort are now widely sought.

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Absence of this type of research, whether considering only periodontal interdental space or more extensive matrix gels, also appears to be dedicated to a particular composition based on hyaluronic acid (HA). This review discusses the role of HA in the treatment of periodontal diseases [2].

2. Structure and Function of Hyaluronic Acid

Hyaluronic acid, a long-chain polymer, is a glycosaminoglycan (GAG) with a chemical formula: $C_{14}H_{20}NO_{11})_n$. It is naturally produced in the body and found in the connective, epithelial, and neural tissues. It is characterized by a high molecular weight, which can reach 1–3 million Daltons, and its capacity to bind greater amount of water and GAGs accounts for its slimy and gel-like consistency (see Figure 1) [4]. High molecular weight HA (HMW HA, >1.5 MDa) is endogenous and primarily provides space filling, hydrodynamic lubrication, and anti-inflammatory effects with limited tissue penetration. In contrast, low molecular weight HA (LMW HA, ~20–50 kDa) is often used in exogenous preparations, such as Gengigel, and exhibits greater bioavailability and tissue diffusion, enabling enhanced receptor interactions (e.g., CD44), angiogenesis, and pro-healing immunomodulatory action [5].

These and other proposed molecular structures foster its potential application in many biological systems. Its hydrating and lubricating properties result in the adjustment and maintenance of water courses in living bodies. It also preserves synovial fluid in joints and provides elasticity and lubrication in the skin [6].

Similar to other GAGs, after HA binds to a transmembrane receptor, it serves not only as a scaffold for molecules during tissue morphogenesis but also facilitates a range of other cellular processes, particularly migration, proliferation, differentiation, apoptosis, and cellular adhesion. Furthermore, it effects in stimulating angiogenesis, promoting certain immune responses, modulating the secretion of inflammatory mediators, and involvement in matrix remodeling [7]. Remodeling is centrally important in chronic inflammation as well as tissue repair and regeneration. Studies have also suggested that the intrinsic chemical structures help to compete with certain cytokines and form an insoluble hydrogel for the local, controlled release of drugs, thereby combating chronic inflammation and facilitating tissue formation. Given its biological roles, tissue compatibility, and relative lack of rejection response, HA and its derivatives have a wide range of potential applications, including those in both medical and dental fields [8].

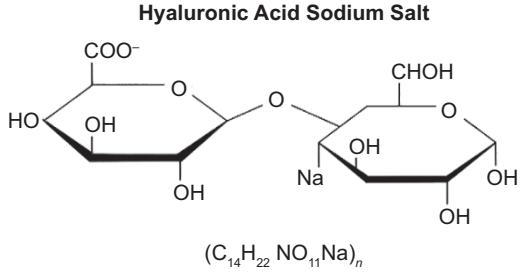


Figure (1): Chemical structure of hyaluronic acid.

Presence of several carboxyl groups, a long straight structure, and flexible molecules in HA helps to provide anti-inflammatory and healing effects. An *in vitro* assay, a water-based HA solution, which predominantly contains uncompressed and partially compressed linear molecules, can indeed coat human keratocytes and prevent cell damage from contact with pathogen-associated molecules. The same buffering characteristic of HA also causes the inflamed tissue to "decompress." At the same time, the long HA chain entangles and interacts with extracellular matrix molecules in dermal or submucosal connective tissue or wounds [9]. The cell excretes more HA under the guidance of cytokines or growth factors. One of the many growth factors active in the wound not only attracts bone marrow stem cells that home in for tissue repair but also stimulates dermal cells, fibroblasts, and epithelial cells to produce more HA. Furthermore, in the human body, CD44-producing T cells seem to form a more effective defense line to subdue potentially virulent bacteria in healing tissues. Only the linear or non-cross-linked HA of a sufficient dynamic molecular size, which promotes effective interaction with cell surface receptors and creates an entangled network on the tissue surface, exhibits the best anti-infective and pro-healing function profile [10].

3. Periodontal Diseases: Etiology and Pathogenesis

Periodontal diseases are infections of the periodontium that result from a complex interplay of bacteria, host immune response, and environmental and genetic factors. Molecular biological insights into the agents and mechanisms of periodontal invasion have revealed that the pathogenesis of periodontal diseases is a multifactorial process that can be initiated by both Gram-positive and Gram-negative bacteria, leading to a chronic inflammatory disease of periodontal soft tissue and loss of supporting bone, with the formation of periodontal pockets. It is a chronic disease, and an individual develops the disease because of an interaction of bacteria in the oral cavity, host immune and inflammatory responses, systemic conditions, and environmental factors such as smoking, certain food habits, and stress [11].

Periodontal infections originate from subgingival plaque biofilms, which consist of more than 50,000 species of bacteria in human oral cavity. There may be marked differences in oral flora even among healthy individuals, and the intact periodontium may have colonization by microorganisms. The disease develops when the immune system responds to the challenge of what it perceives as a harmful infection, and the commensal bacteria from the mouth have potential adhesive properties and can lead to the development of periodontal diseases [12].

The mechanical debridement results in the reduction of inflammation by controlling bacterial load in the oral cavity for a period of 3–9 months. However, if oral hygiene is not properly managed, the resolved inflammation may

recur. So, a variety of anti-collagenolytic agents, antibiotics, steroids, anti-inflammatories, and immunomodulatory agents are used in collaborative periodontal therapy to treat periodontal diseases topically and/or systemically. Pioneering strategies, such as tissue engineering, regenerative periodontal therapy, guided tissue regeneration, bone grafts, and resorbable and non-resorbable membranes, were aimed at reconstructing lost periodontal tissues [13].

4. Current Treatment Strategies in Periodontal Therapy

Current approaches to treat periodontal diseases have shifted from a surgical perspective to more conservative and less invasive methods. The classic modality for treating periodontitis is preferably nonsurgical, consisting of scaling and root planning (SRP) with either hand instruments or ultrasonic devices. The primary aim of SRP is to improve periodontal status by reducing microbial load on periodontally affected sites and smoothing the contaminated root surfaces [14]. As an adjunct to basic SRP, various treatment modalities such as systemic and local antimicrobial therapies, host modulation using tetracyclines, growth factors, bone replacement grafts, enamel matrix derivatives, membrane-guided bone regeneration, and more recently lasers are investigated. It is clear that adjunctive therapies usually provide only a small additional benefit over basic SRP [15].

Overall, the results of SRP indicate a high inter-patient variability and reduction, but rarely complete elimination of bleeding upon probing and/or probing pocket depths. This, along with some additional positive treatment, effects only in small portions of the patients, suggests the need for personalized treatment plans that are tailored to individual patient variation in more detail. Again, in this light, some clear strategies on who might be a candidate for more intensive or surgical intervention still need to be formulated. The results of systematic reviews, combining information from a large pool of patients, thereby become diluted when trying to express the effect of therapy on most patients. In conclusion, both surgical and nonsurgical treatments have limitations, which can be viewed as an impetus to enhance our understanding of the local disease processes and demands for further research in the area [16].

5. Hyaluronic Acid in Periodontal Therapy: Mechanisms of Action

Hyaluronic acid, also known as Gengigel, is utilized in various modes in oral soft-tissue management. In the 1980s, HA acted through various mechanisms in periodontal therapy. Possible mechanisms of action are known. From the evidence-based aspect of these mechanisms, local application of Gengigel appears to be an effective method in conventional periodontal therapy, primarily in anti-homeostasis. This review aims to examine the potential mechanisms of Gengigel for periodontal treatments based on the existing literature [17].

Recent studies have reported that various mechanisms by which HA exerts its effects in periodontal therapy are part of healing strategies. The anti-inflammatory effect of HA is primarily related to its ability to modulate inflammatory signals in infected or inflamed periodontal tissue by modifying the immune response through receptor modulation. Although various doses have been tested, a 0.8% HA-enriched gel significantly reduces the high expression of pro-inflammatory mediators in the gingival crevicular fluid (GCF) [18].

Main studies indicate that the inflammatory healing process is significantly compromised and that cytokine and immunoglobulin A (IgA) levels drop in infected or inflamed tissues. The local use of Gengigel significantly reduces the value of plaque index in affected patients after the practice of nonsurgical periodontal treatment, compared to SRP only. Gengigel was also found to have a longer relapse rate between the two groups in the adjunctive therapy at months 3 and 6. In particular, the Gengigel base can play an important role in controlling hyperinflammation [19].

5.1. Anti-inflammatory properties

Hyaluronic acid plays a role in the battle against inflammation. Inflammation is a complex immunopathological response of the host to aggression, especially infection. In fact, a powerful inflammatory response may occur in cases of infections affecting the periodontium, characterized by consistently elevated levels of inflammatory cytokines. The knowledge of the bio-ceramic effect of HA and its role in tissue repair, alongside its robust anti-inflammatory action, allows us to classify HA in a new class of drugs that can be defined as immune restorative drugs. Interestingly, the addition of HA in Gengigel formulation appears to reduce the production of inflammatory vascular endothelial growth factor (VEGF), contrary to what happens with other preparations containing anti-inflammatory agents [20].

Hyaluronic acid is demonstrated to have an anti-inflammatory effect. It acts at different levels, either by modulating the cytokines released by immune cells or by directly affecting the immune cells. Lymphocytes and neutrophils are endowed with HA receptors and are targets of local HA, provided that, like fibroblasts, they contain primary amide groups. Among dedicated HA inhibitors, one reduces the synthesis of serotonin and prostaglandins in inflamed macrophages and is additionally endowed with anti-inflammatory, hypotensive, and pro-apoptotic activity. However, its role is still overlooked. HA operates at various interconnected levels to combat inflammation. It reduces the release of interleukin 1ß and tumor necrosis factor (TNF) by mononuclear cells collected from healthy donors and co-cultivated with Aggregatibacter actinomycetemcomitans. When HA is added to bacterial endotoxin-challenged macrophages in suspension, the macrophages release less TNF [21].

5.2. Wound-healing effects

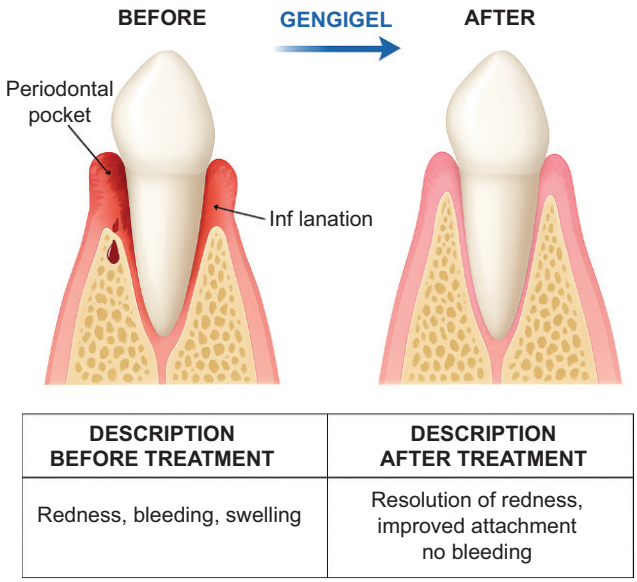
Promotion of wound healing is probably the most extensively studied feature of HA, with several mechanisms that explain its effects. Indeed, HA could promote tissue repair, spanning

from the biological stages of inflammation and re-epithelialization to the formation of granulation tissue and scar, the last two being particularly important in periodontal therapy. Specifically, re-epithelialization, the fundamental of periodontal healing process, could be supported by HA, as studies performed *in vivo* and *in vitro* showed a beneficial role of HA in promoting fibroblast migration, proliferation, and collagen synthesis, leading to optimal tissue repair [22].

In case a tissue is damaged, the homeostatic balance is interrupted, and both cells and intercellular substances are affected negatively. Healing starts when the repair system starts to work. HA plays a significant role in healing due to its presence in intercellular substances and its intimate association with cell walls. Inside the cells, it plays a specific role in hormonal chain. The requirements of healing tissues are obtained more rapidly, as HA contributes to scar tissue repair. Post-accelerated healing is observed following HA application, and it also promotes re-epithelialization by facilitating faster and more effective functioning [23].

More evidence about the healing power of HA was attained from some clinical studies on periodontal therapy, in which the effectiveness of different surgical techniques was tested by comparing both clinical and microbiological outcomes obtained with or without the adjunct of HA. Laser-assisted therapy showed a lower gingival index score, probing pocket depth, and bleeding on probing when HA was applied. Periodontal regeneration following the periosteal releasing incision, sinus graft, and palatal-free gingival graft was accelerated and, therefore, suggested for 3-, 4-, and 6-week follow-up phases instead of the standard 6-, 9-, and 12-week follow-up period without HA. A better clinical healing after use of palatal-free gingival graft was reported using HA in an open control study. In a study of 10 patients assigned to control and test sites, a faster and better result was accomplished with bioabsorbable-modified combination of hydroxyapatite and HA, corresponding to 21 days for soft-tissue healing. The combination of bioabsorbable-modified hydroxyapatite and HA resulted in an early reduction of postoperative complaints and a pleasant acceleration of re-epithelialization [24].

Non-steroidal anti-inflammatory drug (NSAID)-induced inhibition of prostaglandin delayed re-epithelialization of chronic wounds in animal studies, whereas the addition of HA solution led to rapid and regular tissue repair. Indeed, a moist environment around the wound is recommended to enhance healing process. As a result, HA is a mucous-regenerating agent that must be used in oral and dental surgery (see Figure 2). During wound-healing, HA fosters both cell migration and attachment. Lastly, some anti-inflammatory and bacteriostatic characteristics of HA must be mentioned, properties that contribute to proper healing of inflamed and possibly infected tissues [25].



DESCRIPTION BEFORE TREATMENT	DESCRIPTION AFTER TREATMENT
Redness, bleeding, swelling	Resolution of redness, improved attachment no bleeding

Figure (2): Effect of hyaluronic acid on inflamed periodontal tissues.

5.3. Antimicrobial activity

Several studies have shown the antimicrobial properties of HA. Moreover, in recent years, several *in vitro* studies have demonstrated that HA can inhibit the growth of some pathogenic strains of bacteria associated with periodontal diseases. The use of HA is shown to be an advantage in maintaining the oral health of people, preventing the formation of a conjunctival layer of bacteria, and their subsequent colonization and biofilm formation [26]. HA helps to maintain oral health by forming a protective barrier on mucosal surfaces by preventing bacterial adhesion and biofilm formation. Its strong moisture-retaining ability keeps tissues hydrated and resilient, reducing susceptibility to microbial invasion. Additionally, HA interferes with bacterial attachment mechanism and modulates immune response by reducing pro-inflammatory cytokines and enhancing early immune defenses. These combined effects contribute to its role in preventing infection and supporting tissue-healing [6].

The combination of HA with other therapeutic strategies, such as the implementation of regenerative materials, has shown synergistic effects with promising results. Some *in vitro* studies have proposed the potential use of HA as a valid prophylactic strategy to reduce the incidence and severity of the inflammatory phase caused by periodontal biofilm. All these findings indicate a fundamental role of HA in the management of periodontal diseases as well as in accomplishing periodontal treatment to optimize the results of conventional therapy [27].

Therefore, HA has proved to have antimicrobial and anti-inflammatory properties, which appear to reduce tissue damage that results from the progression of chronic periodontitis and the acute phase of forced inflammatory response of periodontal tissues. The antimicrobial activity of HA promotes the treatment of periodontal diseases to mitigate conditions of chronic injury and acute exacerbation of inflammation and tissue damage [28].

Hyaluronic acid modulates the action of certain pro-inflammatory cytokines, depending on its molecular mass, thereby controlling the amount of these mediators in periodontal inflammation. The results showed a higher

percentage of greater minimal inhibitory concentrations observed in the presence of HA in its low molecular forms. In 2019, Monasterio *et al.* evaluated the antimicrobial behavior of Staphylococcus strains when challenged by different molecular forms of HA [29]. Antibacterial tests against this biofilm-producing capability revealed a lower susceptibility in all Staphylococcus strains evaluated when compared in a planktonic state. The reduced antimicrobial susceptibility of Staphylococcus strains emphasizes a greater activity of HA in its medium and higher molecular forms [29].

6. Clinical Studies on the Efficacy of Gengigel in Periodontal Treatment

Several clinical studies confirmed the efficacy of Gengigel, a specific formulation of HA, in periodontal treatment. These studies examined different patient populations by using different methodologies. In most of the selected studies, Gengigel was able to improve significantly the clinical periodontal parameters regarding plaque accumulation, gingival inflammation, and pocket depth reduction as well as attachment level gain [30].

The clinical data revisions clearly demonstrate the potential efficacy of Gengigel as an adjunctive treatment in improving the results of periodontal treatment. Some of the studies also confirmed patient's well-being and satisfaction with Gengigel therapy. However, more long-term follow-up research is recommended to support these results and test Gengigel's potential as adjuvant therapy in helping to control progression of chronic systemic diseases that also affect the periodontium, for instance, diabetes from type 2 onwards, cardiovascular diseases, and pregnancy [31].

7. Conclusion and Future Directions

Gengigel, a hydrogel containing 250 mcg/g of LMW HA, has shown promising results as an adjunct in nonsurgical periodontal therapy. Clinical evidence suggests that exogenously applied LMW HA mimics its endogenous counterpart in promoting tissue regeneration and reducing healing period. Its application in oral mucosa therapy may prevent further tissue damage and enhance spontaneous healing due to the mucosa's high regenerative capacity. Although more studies are needed to establish dosage guidelines and clinical protocols, current findings support the integration of HA in dental and surgical practices, encouraging multidisciplinary collaboration for optimal patient outcomes.

7.2. Recommendations for Future Work

Future studies should focus on large-scale, randomized clinical trials to evaluate the efficacy of HA in various stages of periodontal diseases. Comparative studies between different formulations and concentrations of HA may provide more insight into optimal clinical protocols. Additionally, long-term follow-up studies are recommended to assess the sustained effects of HA on periodontal healing and patient comfort.

Conflict of Interest

The authors declared that there was no conflict of interest regarding the publication of this paper.

Authors' Contributions

Contributor's role	Degree of contribution		
	Lead	Equal	Supporting
Conceptualization		HAA,LAS	
Data curation		HAA,LAS	
Formal analysis		HAA,LAS	
Funding acquisition		HAA,LAS	
Investigation		HAA,LAS	
Project administration		HAA,LAS	
Resources		HAA,LAS	
Supervision		HAA,LAS	
Validation		HAA,LAS	
Visualization		HAA,LAS	
Writing—original draft		HAA,LAS	
Writing—review & editing		HAA,LAS	

Data Availability

No new data were generated or analyzed in this study. All information was based on previously published literature, which was appropriately cited in the manuscript.

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