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Mechanism and Clinical Translation of Probiotic Preparations in the Prevention and Treatment of Periodontal Diseases

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Abstract: Periodontitis is a chronic infectious disease associated with oral microbial dysbiosis and characterized by excessive activation of host immune inflammation. It can lead to gingival inflammation, periodontal pocket formation, alveolar bone resorption, and even tooth loss, and is closely associated with systemic conditions such as diabetes and cardiovascular disease. Probiotics, as active microorganisms capable of regulating host microecology and immune function, demonstrate significant potential in the prevention and treatment of periodontal diseases. They exert protective effects by antagonizing pathogenic bacteria, restoring oral microbial homeostasis, inhibiting inflammatory responses, alleviating oxidative stress-induced damage, and promoting the repair of periodontal soft and hard tissues. The Nrf2-Keap1-ARE signaling pathway, a key regulator of antioxidant and anti-inflammatory responses in the body, is involved in the modulation of the periodontal microenvironment by probiotics and plays a crucial mediating role in inhibiting oxidative stress, resolving inflammation, and promoting osteogenic differentiation. Biomaterial carriers, represented by hydrogels, can enhance the retention and bioavailability of probiotics in the periodontal region, providing critical support for the clinical translation of probiotic preparations. This article systematically reviews the mechanisms of probiotics in periodontal diseases, elucidates the regulatory functions of the Nrf2-Keap1-ARE pathway, compares the application characteristics of different types of hydrogel carriers, and summarizes the current clinical applications, translational bottlenecks, and future directions of probiotic preparations, offering a theoretical basis for microecological regulation therapy and the development of novel formulations for periodontal diseases.

Keywords: Probiotics; Periodontitis; Oxidative stress; Nrf2-Keap1-ARE pathway; Hydrogel

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1. Introduction

Periodontal diseases are common conditions that endanger both oral and systemic health in humans. Their onset and progression are not solely caused by pathogenic bacterial infections but result from a combination of microbial community imbalance, host immune-inflammatory responses, oxidative stress damage, and tissue metabolic abnormalities [1,2]. During the pathological process of periodontitis, biofilms formed by pathogenic bacteria such as *Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans* continuously stimulate host tissues, triggering the accumulation of reactive oxygen species (ROS) and excessive release of inflammatory cytokines, further exacerbating tissue

destruction and bone resorption, and forming a vicious cycle of "infection—oxidative stress—inflammation—tissue damage." Systemic metabolic abnormalities such as diabetes significantly worsen periodontal lesions and reduce the effectiveness of conventional treatments, posing greater challenges for the prevention and treatment of periodontitis [3]. Traditional periodontal therapies can effectively remove plaque and calculus, but struggle to fundamentally restore oral microecological balance. Prolonged use of antimicrobial agents may also disrupt normal microbial flora structure and induce the emergence of drug-resistant strains. In recent years, microecological regulation therapy has gradually become a hot topic in periodontal disease research. Probiotics, due to their high safety, minimal side effects, and dual functions of ecological and immune regulation, have been widely applied in adjuvant treatment studies for periodontitis. With advancements in biomaterial technology, injectable, photocurable, and responsive hydrogels provide stable carriers for the local delivery of probiotics, effectively addressing issues such as probiotics being easily washed away by saliva, short survival times, and insufficient concentrations at lesion sites [4]. Meanwhile, the crucial roles of the Nrf2-Keap1-ARE signaling pathway in antioxidant, anti-inflammatory, and osteogenic processes have been gradually revealed, offering important theoretical support for elucidating the molecular mechanisms of probiotics in preventing and treating periodontitis.

2. Core mechanisms

The protective effects of probiotics on periodontal tissues are not achieved through a single pathway but are based on microecological regulation, synergistically acting at multiple levels, including pathogenic bacterial antagonism, immune-inflammatory regulation, oxidative stress alleviation, and tissue regeneration promotion, to form a systematic protective effect.

2.1. Oral microecological imbalance

In a healthy oral cavity, commensal and pathogenic bacteria coexist in a dynamic balance. When external stimuli or reduced host resistance occur, pathogenic bacteria overproliferate and form pathogenic biofilms, initiating subsequent tissue damage processes. Probiotics can inhibit the adhesion and proliferation of pathogenic bacteria through nutrient competition, spatial occupation, and antibacterial effects of metabolic products. Substances such as organic acids, hydrogen peroxide, and bacteriocins produced by probiotics can lower the local microenvironmental pH, disrupt the survival conditions of pathogenic bacteria, and simultaneously promote the proliferation of beneficial bacteria such as streptococci and actinomycetes, re-establishing a stable oral microbial flora structure and blocking the onset and progression of periodontitis at its source [5].

2.2. Overactivation of the immune-inflammatory

Responses Pathogen-associated molecular patterns can activate host signaling pathways such as TLR4/NF-κB, leading to the massive release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which trigger the degradation of gingival connective tissue and alveolar bone resorption [6]. Probiotics can bidirectionally regulate host immune responses, inhibiting the excessive activation of pro-inflammatory signaling pathways and reducing the synthesis and release of inflammatory cytokines on the one hand, and promoting the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, guiding macrophage polarization toward the M2 phenotype, facilitating inflammation resolution and tissue repair, while enhancing the barrier function of the periodontal epithelium and reducing the risk of pathogenic bacterial invasion and dissemination on the other hand [7,8].

2.3. Oxidative stress

Under infectious and inflammatory conditions, host cells produce large amounts of ROS, exceeding the body's antioxidant system's clearance capacity, causing cellular lipid peroxidation, protein damage, and DNA destruction, further amplifying

inflammatory signals and inhibiting osteogenic differentiation [9]. Probiotics can alleviate oxidative stress damage by enhancing the body's antioxidant capacity, scavenging ROS, and increasing antioxidant enzyme activity, with their regulatory effects largely dependent on the mediation of the Nrf2-Keap1-ARE signaling pathway. Under normal physiological conditions, Nrf2 binds to Keap1 and remains in the cytoplasm, where it is easily ubiquitinated and degraded [10]; when oxidative stress occurs, Nrf2 dissociates from Keap1 and translocates into the nucleus, binding to antioxidant response elements (ARE) to initiate the expression of antioxidant proteins such as HO-1, NQO1, and SOD, thereby inhibiting oxidative stress, reducing inflammation levels, promoting the expression of osteogenic-related genes, and achieving the protection and repair of periodontal tissues.

2.4. Periodontal tissue regeneration and alveolar bone reconstruction

Probiotics can positively regulate bone metabolism by inhibiting RANKL expression, increasing OPG levels, reducing osteoclast differentiation and bone resorption, while promoting the expression of osteogenic marker genes such as Runx2 and OCN, enhancing osteoblast activity. They can also promote the proliferation of periodontal ligament cells and collagen synthesis, accelerating soft tissue repair and providing support for the structural and functional recovery of periodontal tissues [11].

2.5. Schematic diagram of the regulatory mechanism of the Nrf2-Keap1-ARE pathway

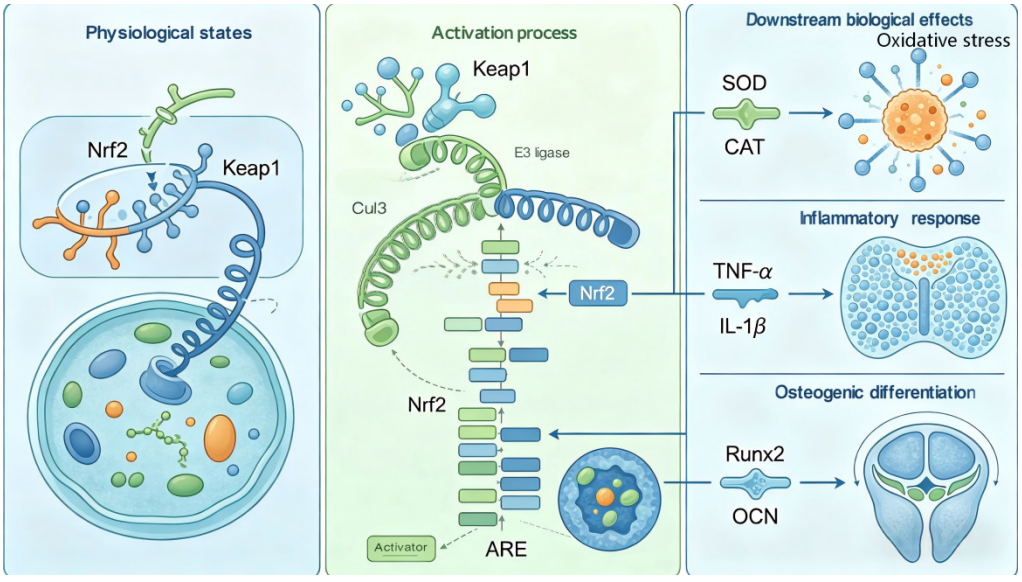

Figure 1. Mechanism of the Nrf2-Keap1-ARE pathway in regulating oxidative stress, inflammatory responses, and osteogenic differentiation.

This schematic diagram (**Figure 1**) systematically illustrates the physiological state, activation process, and downstream biological effects of this pathway. Under physiological resting conditions (left column), the transcription factor Nrf2 binds to the negative regulatory protein Keap1 in the cytoplasm, maintaining low levels of Nrf2 through ubiquitination-mediated degradation, with the pathway in an inhibited state [12]. When cells are stimulated by oxidative stress or other factors, the conformation of Keap1 changes, leading to the dissociation of Nrf2, which then translocates into the nucleus and binds to antioxidant response elements (ARE), initiating the transcription of downstream target genes [13].

Upon activation of Nrf2-ARE, it regulates cellular functions through multiple pathways:

(1) It upregulates the expression of antioxidant enzymes such as SOD and CAT, scavenging reactive oxygen species (ROS) and exerting antioxidant effects [14];

(2) It inhibits the release of pro-inflammatory cytokines such as TNF-α and IL-1β, regulating inflammatory responses;

(3) It participates in the regulation of bone differentiation and metabolism through molecules such as Runx2 and OCN [15].

This pathway serves as a core mechanism for cellular defense against oxidative stress, regulation of inflammation, and maintenance of tissue homeostasis, holding significant research value in fields such as tumors, bone metabolic diseases, and inflammatory diseases.

3. Comparison of hydrogel material properties for probiotic delivery

In local periodontal applications, hydrogels represent one of the most ideal carriers for probiotics, enhancing retention time, maintaining activity, and enabling controlled-release delivery [16]. Different types of hydrogels exhibit significant differences in origin, properties, drug-loading methods, and response characteristics. This directly affects the delivery efficacy of probiotics and their clinical applicability.

Table 1. Comparison of properties of different types of hydrogels in local probiotic delivery

Material Type	Typical Materials	Drug Loading Type	Responsive Mechanism	Advantages	Disadvantages
Natural Hydrogel	Chitosan, sodium alginate, gelatin, hyaluronic acid, collagen	Live probiotics, anti-inflammatory proteins, growth factors	Passive release, pH-responsive, ion-responsive [17]	Excellent biocompatibility, biodegradable, good adhesion, high oral environment compatibility, easy to mold	Low mechanical strength, fast degradation rate, moderate stability, batch-to-batch variability
Synthetic Hydrogel	PEG, PLGA, PVA, photocurable acrylate hydrogels	Probiotics, small molecule drugs, antimicrobial peptides, and enzyme preparations	Light-responsive, pH-responsive, temperature-responsive, enzyme-responsive	High mechanical strength, stable structure, controllable degradation rate, injectable/ photocurable, and precise drug release	Slightly lower biocompatibility than natural materials, relatively complex preparation process, degradation products of some materials require attention [18]

4. Clinical application and translation status of probiotic preparations

The clinical application of probiotics in periodontal diseases has gradually transitioned from basic research to clinical practice, with application methods primarily including local delivery and systemic intake. Both methods have demonstrated favorable outcomes in the adjunctive treatment of diseases, such as gingivitis, chronic periodontitis, and diabetic periodontitis.

4.1. Local delivery

Local application is the preferred method for periodontal probiotic therapy, as it enables direct action on the lesion site, increases local drug concentration, and reduces the risk of systemic exposure [19]. Common clinical dosage forms include probiotic gels, solutions, films, periodontal packs, and injectable hydrogel preparations, which are typically used after periodontal basic treatment. These formulations significantly reduce periodontal probing depth, decrease probing bleeding, and improve clinical attachment levels. Long-term use helps maintain microbial stability and reduce disease recurrence rates [20]. For patients with diabetes complicated by periodontitis, local probiotic preparations can alleviate oxidative stress and inflammatory responses exacerbated by hyperglycemia, enhancing the efficacy of conventional periodontal treatment.

4.2. Systemic intake

Systemic application primarily involves oral probiotic powders, capsules, and emulsions, which indirectly influence oral microbiota and host immune function by regulating intestinal microecology. This approach is suitable for patients with poor systemic conditions, recurrent disease, or those unable to undergo frequent local treatments. Multiple clinical studies have shown that continuous administration of preparations containing *Lactobacillus reuteri* and *Lactobacillus rhamnosus* effectively improves gingivitis symptoms, reduces the pathogenic bacterial load in the oral cavity of periodontitis patients, and positively regulates systemic inflammatory markers [21,22].

In clinical treatment protocols, probiotics are often used as adjunctive agents in combination with periodontal basic therapy, forming a comprehensive treatment model of "debridement + antibacterial + anti-inflammatory + repair." Compared to monotherapy, this approach more effectively controls infection, alleviates inflammation, and promotes tissue repair, particularly in patients with moderate-to-severe periodontitis or periodontitis complicated by systemic conditions [23].

Despite the promising clinical application prospects of probiotic preparations, their clinical translation faces several bottlenecks. Probiotic strains exhibit high specificity, with significant variations in efficacy among different strains, and there is currently a lack of unified screening and evaluation criteria. The complex oral environment, including salivary flushing, chewing movements, and microbial competition, makes it difficult for probiotics to colonize and survive long-term, affecting treatment durability [24]. Live probiotic preparations have stringent storage and transportation requirements, making them prone to inactivation and limiting clinical adoption. Additionally, large-scale, long-term, multicenter clinical studies remain relatively insufficient, and standardized protocols for dosing, treatment duration, and patient eligibility have yet to be established.

5. Development directions for clinical translation of probiotic preparations

With advancements in microecological medicine, biomaterials, and molecular biology technologies, the clinical translation of probiotic preparations for periodontal diseases will progress toward precision, intelligence, and efficiency. Precision strain screening and engineering modification represent a critical future direction. By selecting probiotic strains with strong targeting and high stability based on oral microecological characteristics and host disease types, and enhancing their antibacterial, colonization, and tolerance capabilities through gene editing technologies, treatment efficacy can be significantly improved [25].

Optimization of biomaterial carriers will drive upgrades in probiotic delivery systems. Photocurable, injectable, and multi-responsive hydrogels enable stable retention and controlled release of probiotics in periodontal tissues. Combined delivery with Nrf2 pathway activators, anti-inflammatory drugs, or osteogenic factors can produce synergistic therapeutic effects, particularly in complex cases such as diabetic periodontitis.

Clinical research and standardized system construction are key supports for clinical translation. Conducting more large-sample, long-term follow-up, multicenter randomized controlled trials to clarify the scope of application, optimal protocols, and safety of probiotic preparations, and establishing full-process standards for strain selection, preparation, clinical application, and efficacy evaluation, will accelerate their transition from laboratory to clinical practice.

Individualized microecological regulation represents an important future trend in precision periodontal therapy. By customizing personalized probiotic formulations and treatment plans based on oral microbiota sequencing results, targeted interventions can maximize treatment efficacy and drive the transition of periodontal disease treatment from traditional symptomatic models to precision microecological regulation models.

6. Conclusion

Probiotic preparations hold significant application value in the prevention and treatment of periodontal diseases, exerting protective effects through multiple mechanisms, including regulating oral microecological balance, antagonizing pathogens, inhibiting excessive immune inflammation, alleviating oxidative stress damage, and promoting periodontal

tissue regeneration. The Nrf2-Keap1-ARE signaling pathway plays a key regulatory role in their antioxidant, anti-inflammatory, and osteogenic processes. Hydrogel carrier materials effectively enhance the delivery efficiency and bioactivity of probiotics in periodontal tissues, with natural and synthetic hydrogels offering distinct advantages that can be selected based on clinical needs. Currently, probiotic preparations have been preliminarily applied in clinical practice, demonstrating significant efficacy in the adjunctive treatment of periodontitis. However, challenges remain in strain standardization, colonization survival, preparation stability, and insufficient clinical evidence. Future efforts should focus on precision strain development, intelligent delivery system construction, clinical standard refinement, and individualized treatment exploration to promote the safe, efficient, and standardized clinical application of probiotic preparations for periodontal diseases, providing new therapeutic strategies for chronic periodontitis, diabetic periodontitis, and other conditions.

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Disclosure statement

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