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Mini Review Article

Beyond Probiotics: Postbiotics as Emerging Microbiome-Modulating Agents in Periodontal Therapy

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Abstract

Periodontitis is no longer regarded as a simple infection caused by a limited group of pathogens, but rather as a dysbiosis-driven inflammatory disease shaped by complex interactions between the subgingival microbiota and host immune response. Conventional non-surgical periodontal therapy remains the cornerstone of disease control; however, recurrent inflammation, microbial recolonization, and inter-individual variability in treatment response have encouraged interest in adjunctive microbiome-modulating strategies. Probiotics have been investigated for this purpose, particularly *Lactobacillus reuteri*, but concerns related to viability, colonization, strain specificity, and clinical reproducibility have limited their broader translation. Postbiotics, defined as preparations of inanimate microorganisms and/or their components that confer a health benefit on the host, represent a biologically plausible next step in periodontal therapeutics. Unlike live probiotics, postbiotics may offer improved safety, stability, standardization, and compatibility with local delivery systems. Their potential periodontal effects may involve interference with pathogenic biofilm formation, modulation of epithelial barrier function, attenuation of excessive inflammatory signalling, and support of microbial ecological balance. Current evidence remains largely preclinical or extrapolated from probiotic research, and well-designed clinical trials are still needed. Nevertheless, postbiotics provide a promising framework for adjunctive periodontal care, particularly as part of personalized, host-microbiome-oriented treatment strategies.

Keywords: Postbiotics, Periodontitis, Oral Microbiome, Dysbiosis, Probiotics, Host Modulation, Periodontal Therapy, Biofilm

Introduction

Periodontal disease is a chronic inflammatory condition initiated and sustained by a dysbiotic microbial community within the subgingival biofilm. The current classification system emphasizes periodontitis as a complex disease characterized by progressive attachment loss, radiographic bone loss, and variable rates of progression influenced by microbial, immunological, behavioral, and systemic factors [1]. Although mechanical disruption of biofilm through scaling and root planing remains the foundation of periodontal therapy, complete and durable ecological restoration is not always achieved, especially in deep pockets, high-risk patients, smokers, individuals with metabolic disorders, or patients with recurrent inflammation [2].

This therapeutic limitation has shifted attention from purely antimicrobial strategies toward approaches that can reshape the host-microbiome interface. The classical concept of eliminating periodontal pathogens has been progressively replaced by models emphasizing polymicrobial synergy, keystone pathogens, inflammatory amplification, and ecological imbalance [3-5]. In this context, probiotics were introduced as adjunctive agents capable of competing with pathogens, producing antimicrobial substances, and modulating host immunity. Several clinical studies and systematic reviews have suggested that probiotic supplementation may provide short-term improvements in clinical periodontal parameters when used alongside non-surgical therapy [6-9].

However, the probiotic concept also has practical limitations. Live microorganisms require viability, appropriate storage, strain-specific validation, and the ability to exert effects in the highly competitive oral environment. These constraints have led to increasing interest in postbiotics, which may preserve beneficial microbial-derived functions without requiring live bacterial administration. The aim of this mini review is to discuss the rationale, mechanisms, potential applications, and current limitations of postbiotics as emerging microbiome-modulating adjuncts in periodontal therapy.

From Probiotics to Postbiotics: A Conceptual Shift

The International Scientific Association for Probiotics and Prebiotics defined postbiotics as a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host [10]. This definition is important because it distinguishes postbiotics from purified metabolites, vaccines, and conventional antimicrobial agents. A postbiotic is not simply a bacterial by-product; rather, it is a deliberately prepared non-viable microbial entity, with or without associated cellular components or metabolites, that produces a measurable biological benefit.

In periodontology, this concept is particularly attractive. The oral cavity is an open ecosystem exposed to continuous salivary flow, dietary changes, mechanical forces, hygiene practices, and interspecies microbial interactions. Under such conditions, stable colonization by administered live probiotics may be unpredictable. Postbiotics, in contrast, do not need to survive, replicate, or colonize periodontal niches to exert biological effects. Their activity may depend on cell-wall fragments, surface proteins, lipoteichoic acids, peptidoglycans, extracellular vesicles, bacteriocin-like substances, organic acids, enzymes, or other heat-stable microbial components [11,12] Wegh, et al., (2019).

The transition from probiotics to postbiotics should not be interpreted as a rejection of probiotic therapy. Rather, probiotic evidence provides a biological and clinical foundation for postbiotic development. For example, L. reuteri-containing lozenges have demonstrated adjunctive clinical and microbiological effects in chronic periodontitis, including reduced probing depth and delayed recolonization by periodontal pathogens in selected studies [6,7,13]. These findings suggest that microbial-derived interventions can influence periodontal outcomes. Postbiotics attempt to preserve this therapeutic logic while reducing the dependence on bacterial viability.

Biological Rationale in Periodontal Disease

The pathogenesis of periodontitis involves a self-reinforcing cycle between dysbiosis and inflammation. Keystone pathogens such as Porphyromonas gingivalis can subvert host immunity and promote a microbial community that sustains inflammation, even when present at relatively low abundance [3]. The inflammatory environment then provides tissue breakdown products that further support proteolytic and inflammophilic organisms, reinforcing disease progression [14].

Postbiotics may interfere with this cycle at several levels. First, they may reduce the ecological fitness of pathogenic species by inhibiting adhesion, co-aggregation, or biofilm maturation. Second, they may modulate epithelial and immune responses, attenuating excessive production of pro-inflammatory mediators. Third, they may enhance mucosal barrier function and antimicrobial peptide expression, thereby improving host resilience against dysbiotic shifts. Fourth, they may provide more predictable formulation properties than live probiotics, allowing incorporation into lozenges, gels, mouthrinses, periodontal chips, or slow-release local delivery systems.

This multi-targeted profile is especially relevant because periodontitis is not adequately addressed by antibacterial activity alone. Broad antimicrobial approaches may temporarily reduce bacterial load but can also disturb commensal communities. A postbiotic strategy, if properly designed, may aim not merely to suppress bacteria but to recalibrate the host-microbial interface.

Potential Mechanisms of Action

Biofilm Modulation

Subgingival biofilms are structurally complex and functionally resistant microbial communities. Their extracellular matrix limits antimicrobial penetration and facilitates persistence after therapy. In vitro studies have reported that both viable and heat-killed probiotic strains can inhibit oral pathogens, including P. gingivalis, Fusobacterium nucleatum, Streptococcus mutans, and Aggregatibacter actinomycetemcomitans [15]. Although viable organisms may exert broader effects through active metabolite production, heat-killed strains have also shown inhibitory activity against selected oral pathogens, supporting the plausibility of non-viable microbial preparations in oral health.

Heat-killed L. reuteri and cell-free culture supernatants have also been investigated during interaction with P. gingivalis, with findings suggesting antimicrobial and anti-virulence potential [16]. These data are relevant because they imply that some beneficial effects associated with probiotics may be mediated by microbial

components or secreted factors rather than by colonization alone. For periodontal therapy, such effects could be valuable during the early recolonization phase after scaling and root planing.

Host Immune Modulation

Periodontitis-associated tissue destruction is largely mediated by an exaggerated or unresolved host inflammatory response. Therefore, adjunctive agents that modulate inflammation without suppressing protective immunity are of particular interest. Postbiotic components may interact with pattern-recognition receptors, including Toll-like receptors, and influence downstream cytokine signaling. Depending on the strain and preparation method, these interactions may reduce excessive inflammatory mediator release, promote epithelial defense mechanisms, or support immune tolerance [11] Nataraj, et al., (2020).

This immunomodulatory potential is clinically relevant because persistent bleeding on probing, residual pocket inflammation, and recurrent disease activity often reflect more than bacterial load alone. A postbiotic that attenuates destructive inflammation while supporting antimicrobial defense could theoretically complement mechanical debridement and improve periodontal stability.

Barrier Support and Epithelial Defense

The junctional and sulcular epithelium represents a critical interface between the biofilm and connective tissue. Barrier disruption facilitates microbial invasion, inflammatory activation, and tissue breakdown. Postbiotic preparations may enhance epithelial resilience by supporting tight junction integrity, stimulating antimicrobial peptide production, and reducing pathogen-induced epithelial stress. Although direct periodontal clinical evidence remains limited, this mechanism is consistent with broader postbiotic research and may be particularly relevant for gingivitis, peri-implant mucositis, and early inflammatory lesions.

Reduction of Probiotic-Related Practical Barriers

Compared with live probiotics, postbiotics may offer important translational advantages. They are generally more stable during storage, less sensitive to temperature and pH changes, easier to standardize, and less likely to raise concerns in medically compromised individuals. In periodontal practice, where adjuncts may be applied locally or recommended for home use, these characteristics are important. A non-viable microbial preparation could potentially be incorporated into lozenges, gels, dentifrices, mouthrinses, biodegradable films, or periodontal pocket delivery systems without requiring maintenance of bacterial viability.

Possible Clinical Applications in Periodontology

Adjunct to Non-Surgical Periodontal Therapy

The most realistic near-term use of postbiotics is as an adjunct to scaling and root planing. Mechanical therapy reduces biofilm burden and inflammation, but recolonization occurs rapidly. Postbiotic agents applied after debridement could theoretically delay recolonization by pathobionts, reduce inflammatory rebound, and support a more health-compatible microbiome. This concept is supported indirectly by probiotic studies showing clinical improvements when L. reuteri lozenges were used with periodontal therapy [6,7,13].

However, postbiotics should not be positioned as substitutes for mechanical therapy. The EFP S3 guideline emphasizes a structured treatment pathway including oral hygiene instruction, risk factor control, subgingival instrumentation, and supportive periodontal care [2]. Postbiotics would fit best as adjunctive agents within this evidence-based framework.

Supportive Periodontal Therapy

Patients in maintenance often present with residual pockets or recurrent bleeding despite previous treatment. A postbiotic formulation could be used periodically during supportive periodontal therapy to help stabilize the microbiome and reduce low-grade inflammation. This approach may be particularly relevant in patients with repeated recolonization or those who are not ideal candidates for frequent antimicrobial use.

Gingivitis and Early Dysbiosis

Because gingivitis is reversible and largely driven by plaque-induced inflammation, postbiotics may have preventive potential before irreversible attachment loss occurs. A mouthrinse, lozenge, or toothpaste containing validated postbiotic components could be explored for patients with plaque-induced gingivitis, orthodontic appliances, reduced manual dexterity, or increased inflammatory susceptibility.

Peri-Implant Mucositis and Peri-Implantitis

The peri-implant environment shares several features with periodontal tissues, including biofilm-driven inflammation and host-mediated tissue breakdown. Postbiotics may be relevant in peri-implant mucositis, where non-surgical control and inflammation reduction are central. Nevertheless, direct evidence in peri-implant disease is still insufficient, and clinical extrapolation from periodontitis should be made cautiously.

Current Limitations and Research Gaps

Despite strong biological plausibility, postbiotic periodontal therapy remains an emerging field. Several limitations must be addressed before clinical recommendations can be made.

First, terminology remains inconsistent. Some studies use terms such as paraprobiotics, heat-killed probiotics, cell-free supernatants, microbial lysates, or postbiotics interchangeably, although they are not identical. This complicates evidence synthesis and regulatory interpretation.

Second, postbiotic activity is likely strain-specific and preparation-dependent. Heat inactivation, sonication, filtration, fermentation conditions, drying methods, and formulation

excipients can alter biological effects. Therefore, evidence obtained from one strain or preparation cannot be generalized to all postbiotics.

Third, clinical periodontal trials specifically evaluating postbiotics are scarce. Much of the current rationale is extrapolated from probiotic trials, in vitro antibacterial studies, or general postbiotic literature. Future trials should include standardized periodontal outcomes such as probing depth, clinical attachment level, bleeding on probing, plaque index, inflammatory biomarkers, and microbiome sequencing.

Fourth, dose, frequency, delivery vehicle, and duration remain undefined. Periodontal pockets, gingival margins, saliva, tongue dorsum, and mucosal surfaces represent distinct ecological niches. A formulation effective as a lozenge may not perform similarly as a gel or mouthrinse.

Finally, safety and long-term ecological consequences require evaluation. Although postbiotics may be safer than live probiotics in many settings, their immunological activity means they should not be assumed to be biologically inert. The goal should be balanced modulation rather than indiscriminate immune stimulation.

Future Perspectives

Future postbiotic research in periodontology should move beyond simple pathogen inhibition assays. More sophisticated models are needed, including multispecies biofilms, organotypic gingival epithelial models, inflammatory co-culture systems, and animal models of periodontal bone loss. Clinical studies should be randomized, placebo-controlled, adequately powered, and designed to evaluate both short-term clinical improvement and long-term stability.

Personalized periodontal care may also benefit from postbiotic strategies. Patients differ in microbiome composition, immune phenotype, systemic risk factors, and response to therapy. It is plausible that specific postbiotic formulations may be more effective in certain microbial or inflammatory profiles. Integration of microbiome analysis, salivary biomarkers, and clinical risk assessment may eventually allow selection of targeted adjuncts.

Another promising direction is combination therapy. Postbiotics could be combined with prebiotics, phytochemicals, hyaluronic acid, antioxidants, or locally delivered anti-inflammatory agents. Such combinations may provide complementary effects on biofilm ecology and host response. However, each combination would require rigorous validation rather than assumption of additive benefit [17-20].

Conclusion

Postbiotics represent a promising evolution in microbiome-based periodontal therapy. By offering microbial-derived bioactivity without requiring live bacterial administration, they may overcome several limitations associated with probiotics, including viability, storage, colonization, and safety concerns. Their potential mechanisms include inhibition of pathogenic biofilm development, modulation of inflammatory signaling, enhancement of epithelial defense, and support of microbial ecological balance. At present, the periodontal evidence base remains preliminary, and clinical translation requires well-designed human trials using standardized preparations and clinically meaningful outcomes. Nevertheless, postbiotics provide a compelling framework for the next generation of adjunctive periodontal therapies, particularly within personalized and host-microbiome-oriented treatment models.

Conflict of Interest

None.

Acknowledgment

None.

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