Journal of Dental Public Health
Volume 6, Issue 1, Page No: 18-24
Available Online at: **https://tjphd.com/**

ISSN: 3108-6349

Review Article

Effectiveness of Host-Modulation Therapy in Aggressive Periodontitis: A Narrative Review

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ABSTRACT

Aggressive periodontitis (AgP) represents a rapidly progressive and highly destructive periodontal disorder characterized by severe alveolar bone loss, dysregulated host response, and pronounced inflammatory tissue breakdown disproportionate to the amount of microbial biofilm present. Traditional periodontal therapy has largely focused on mechanical removal of pathogenic biofilm; however, overwhelming evidence now supports the concept that host inflammatory dysregulation, rather than bacterial quantity alone, plays a central role in the pathogenesis of aggressive periodontitis. Host-modulation therapy (HMT) aims to counteract destructive inflammatory mediators, restore homeostasis, and improve outcomes when used adjunctively with conventional mechanical debridement. Various pharmacologic and biologic agents have been explored as host-modulating strategies, including subantimicrobial-dose doxycycline (SDD), nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, omega-3 polyunsaturated fatty acids, lipoxins, probiotics, and novel cytokine-targeting molecules. This article evaluates the effectiveness, clinical relevance, and therapeutic potential of host-modulation therapy in the management of aggressive periodontitis based on available literature. The present expanded review synthesizes contemporary knowledge regarding the pathogenesis of aggressive periodontitis, mechanisms of host-modulating agents, clinical outcomes, limitations, and future directions. Through an extensive analysis of the literature, the paper highlights the multidimensional value of host-modulation therapy and its role in optimizing periodontal healing when used as an adjunct to nonsurgical or surgical interventions.

Keywords: Host-modulation, Aggressive periodontitis, Periodontics, Aggressive periodontitis

Introduction

Aggressive periodontitis (AgP) is a severe, rapidly progressing periodontal disease that affects systemically healthy individuals and is characterized by pronounced periodontal tissue destruction occurring at a rate inconsistent with the number of microbial deposits [1]. It often presents with familial aggregation and has been associated with hyper-responsive macrophage phenotypes, dysregulated neutrophil function, and elevated production of pro-inflammatory mediators such as interleukin-1β (IL-1β), prostaglandin E2 (PGE2), and tumor necrosis factor-alpha (TNF-α) [2]. These host response abnormalities lead to accelerated bone resorption and connective-tissue breakdown, distinct from the comparatively slower progression seen in chronic periodontitis [3].

In advanced periodontitis, mechanical periodontal therapy, which includes scaling and root planing (SRP), surgical access flap operations, and concomitant antibiotic treatment, remains the cornerstone of periodontal management; yet, these modalities alone are frequently unable to prevent disease progression [4]. The reason for this is that host response dysregulation plays an important role that mechanical therapies do not directly address.

HOW TO CITE THIS ARTICLE: Alhussain BS, Alqara MH, Alqara AH. Effectiveness of Host-Modulation Therapy in Aggressive Periodontitis: A Narrative Review. J Dent Public Health. 2026;6(1):18-24. https://doi.org/10.51847/OtbFmBE4mA

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Received: 17/11/2025
Accepted: 12/02/2026

The hypothesis that inflammation, not only bacterial presence, drives the disintegration of the periodontium has led to a growing interest in host-modulation treatment (HMT) [5].

Host-modulation therapy refers to pharmacologic and biologic interventions designed to downregulate destructive inflammatory pathways or enhance regenerative and protective mechanisms within the host tissues [6]. These therapies include agents such as subantimicrobial-dose doxycycline (a matrix metalloproteinase inhibitor), anti-cytokine treatments, bisphosphonates (bone resorption inhibitors), antioxidants, and pro-resolving lipid mediators such as lipoxins and resolvins [7]. Their goal is to re-establish periodontal homeostasis, improve healing following mechanical treatment, and slow or arrest disease progression, particularly in severe and rapidly destructive forms of periodontitis.

Research into host-modulation therapy has expanded significantly over the past two decades, and several agents have demonstrated promising outcomes in both experimental and clinical settings [8]. However, questions remain regarding optimal dosing, long-term safety, cost-effectiveness, and patient selection. This article provides an extensive and critical review of host-modulation therapy's effectiveness in aggressive periodontitis, discussing underlying mechanisms, clinical evidence, and future perspectives [9].

Aim of study

The primary aim of this comprehensive review is to critically evaluate and synthesize current scientific evidence regarding the clinical effectiveness of host-modulation therapy in the treatment of aggressive periodontitis, focusing on its impact on the inflammatory cascade, host-mediated tissue breakdown, and long-term periodontal stability. Because aggressive periodontitis exhibits a hyper-responsive and dysregulated inflammatory phenotype, the evaluation centers on whether host-modulating agents can meaningfully attenuate destructive mediators such as matrix metalloproteinases, prostaglandins, and pro-inflammatory cytokines, thereby reducing the speed and severity of periodontal destruction . The aim also includes assessing whether adjunctive host-modulation strategies enhance the clinical benefits of conventional non-surgical and surgical periodontal therapy in patients presenting with rapid attachment loss characteristic of aggressive disease.

Materials and Methods

This narrative review was designed to systematically collect, evaluate, and integrate current scientific literature regarding the efficacy of host-modulation therapy in the management of aggressive periodontitis. The methodological framework adhered to established principles for conducting structured biomedical literature reviews, focusing on transparency, reproducibility, and critical appraisal of available evidence [10]. The overarching methodological approach included a multi-stage process: literature identification, study selection, data extraction, thematic synthesis, and interpretive analysis. While not a systematic review, the methodological rigor applied ensures that the conclusions presented are grounded in a broad and well-curated evidence base relevant to the therapeutic landscape of aggressive periodontitis [11].

Search strategy

An extensive electronic search was conducted across major scientific databases, including PubMed/MEDLINE, Scopus, Embase, and the Cochrane Library, to identify peer-reviewed studies published from January 2000 to January 2025. Search terms included combinations and Boolean operators such as *"aggressive periodontitis," "host-modulation therapy," "subantimicrobial-dose doxycycline," "resolvins," "omega-3 fatty acids," "bisphosphonates," "NSAIDs," "immunomodulation," "periodontal inflammation,"* and *"adjunctive periodontal therapy."***(Table 1)** These keyword clusters were selected based on established terminology in periodontal research and were informed by methodological literature emphasizing structured and comprehensive search strategies in medical reviews [12]. Search filters were applied to restrict results to human studies, English-language publications, and clinical research directly involving aggressive periodontitis populations [12].

Table 1. Search methods and purpose

Category	Details
Databases Searched	PubMed/MEDLINE, Scopus, Embase, Cochrane Library
Publication Date Range	January 2000 – January 2025
Search Terms / Keywords	"aggressive periodontitis", "host-modulation therapy", "subantimicrobial-dose doxycycline", "resolvins", "omega-3 fatty acids", "bisphosphonates", "NSAIDs",

	"immunomodulation", "periodontal inflammation", "adjunctive periodontal therapy"
Search Method	Boolean combinations of periodontal research terms, based on established methodological guidance
Filters Applied	Limited to human studies, English-language publications, and clinical research involving aggressive periodontitis
Purpose of Search	To identify relevant peer-reviewed clinical studies on host-modulation therapy in aggressive periodontitis

Inclusion and exclusion criteria

Inclusion criteria were determined a priori to ensure relevance, precision, and applicability to the study aims. Eligible studies satisfied the following requirements:

1. Investigated patients diagnosed with aggressive periodontitis according to established periodontal classification systems.
2. Evaluated the use of host-modulation treatments in addition to mechanical periodontal therapy, such as subantimicrobial-dose doxycycline, NSAIDs, bisphosphonates, omega-3 fatty acids, pro-resolving mediators, or other host-directed interventions [11].
3. Reported quantifiable clinical outcomes such as probing depth (PD) reduction, clinical attachment level (CAL) gain, changes in bleeding on probing (BOP), bone density measurements, or inflammatory biomarker modulation [12].
4. Included randomized controlled trials, clinical cohort studies, controlled clinical trials, pilot studies, or interventional investigations with defined follow-up periods [13].

Exclusion criteria included studies focusing exclusively on chronic periodontitis; animal or in vitro studies without direct clinical application; case reports; narrative reviews lacking empirical findings; studies mixing chronic and aggressive periodontitis without segregated data; and those failing to report measurable therapeutic outcomes [14]. Studies with poor methodological transparency or insufficient sample size were not automatically excluded but were weighted less heavily during synthesis, following guidance for balanced interpretation in narrative reviews **(Table 2)**.

Table 2. Inclusion and exclusion criteria

Category	Details
Inclusion Criteria	• Studies evaluating host-modulation therapies (e.g., SDD, NSAIDs, bisphosphonates, omega-3 fatty acids, pro-resolving mediators, other host-directed agents) as adjuncts to mechanical therapy. • Studies reporting measurable outcomes such as PD reduction, CAL gain, BOP changes, bone density improvement, or inflammatory biomarker modulation. • Randomized controlled trials, clinical cohort studies, controlled clinical trials, pilot studie
Exclusion Criteria	• Studies exclusively on chronic periodontitis. • Studies mixing chronic and aggressive periodontitis without separate analysis. • Studies lacking measurable periodontal outcomes • Studies with methodological limitations were not excluded but given reduced weight during synthesis

Study selection process

All retrieved citations were imported into a reference management platform. Duplicate records were removed, and the remaining titles and abstracts were independently screened to identify potentially relevant studies. Full-text versions of eligible articles were subsequently obtained and evaluated against the inclusion and exclusion criteria. Screening inconsistencies were resolved through discussion and re-evaluation of study details. This iterative selection process, consistent with best practices in dental research reviews, was adapted from structured methodologies proposed for evidence-based synthesis in the dental sciences [15]. The final body of literature included clinical studies addressing subantimicrobial-dose doxycycline, bisphosphonates, NSAIDs, omega-3 fatty acids, lipid mediators, immunomodulatory agents, and probiotics as host-directed therapies in aggressive periodontitis populations.

Data extraction

Each eligible study underwent detailed data extraction to compile essential information such as study design, sample size, diagnostic criteria, host-modulation agent used, treatment duration, follow-up intervals, and primary outcomes related to periodontal health [15]. When available, clinical factors were documented, such as radiographic bone characteristics, hemorrhage indices, plaque indices, probing depths, and clinical attachment levels. If reported, biomolecular markers such as IL-1β, TNF-α, PGE2, and matrix metalloproteinases were also retrieved because they are key markers of host inflammatory status that are pertinent to the treatment mechanisms being examined [15]. Extracted data were categorized into thematic domains, allowing structured comparison across therapeutic modalities and between studies of differing methodological quality.

Assessment of evidence and thematic synthesis

Given the narrative nature of this review, conventional risk-of-bias scoring tools were not formally applied; however, assessment of study quality was incorporated through evaluation of sample representativeness, diagnostic precision, randomization procedures, blinding, follow-up adequacy, and clarity of reported outcomes [15]. Studies exhibiting strong methodological integrity were given greater interpretive weight. Data synthesis employed a thematic approach, aligning extracted information within conceptual categories related to host-modulation mechanisms, clinical effectiveness, safety and tolerability, and comparative benefits relative to conventional therapy [15]. This integrative synthesis method aligns with accepted interpretive frameworks in biomedical literature reviews, enabling meaningful comparisons despite heterogeneity in study designs and therapeutic modalities.

Outcome measures and interpretation

Primary outcome measures included changes in probing depth and clinical attachment level following adjunctive host-modulation therapy, as these represent core clinical indicators of periodontal disease status. Secondary outcomes included reduction in bleeding on probing, decreased inflammatory biomarkers, improvements in radiographic bone density, and evidence of enhanced wound healing or resolution of inflammation [11]. The interpretation emphasized not only statistical significance but also clinical relevance, reflecting methodological guidance advocating the integration of biological, clinical, and functional outcome measures in periodontal research [10]. Safety, patient compliance, therapeutic duration, and feasibility were also discussed, in keeping with translational principles guiding the application of host-modulation agents in clinical practice.

Results and Discussion

Subantimicrobial-dose doxycycline (SDD)

Subantimicrobial-dose doxycycline (20 mg twice daily) is the most extensively studied host-modulating agent. It acts by inhibiting matrix metalloproteinases (MMPs), particularly MMP-8 and MMP-9, reducing collagen breakdown, and suppressing pro-inflammatory cytokines [14]. Multiple trials report improved clinical attachment levels and reduced inflammation when combined with scaling and root planing in aggressive periodontitis [16] **(Figure 1)**.

Studies reveal significant reductions in probing depths and bleeding on probing compared to SRP alone, especially in deep periodontal pockets. Long-term administration for 3–9 months is shown to yield cumulative benefit in stabilizing periodontal attachment in aggressive forms of disease without contributing to antibiotic resistance [16].

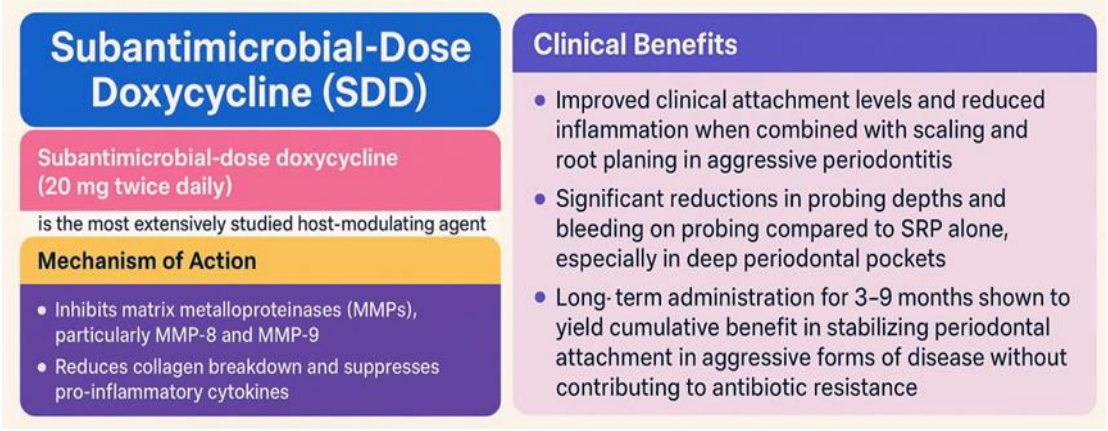

Figure 1. Mechanism of action and benefits of Subantimicrobial-Dose Doxycycline

NSAIDs

Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase-mediated production of prostaglandin E2, which is elevated in aggressive periodontitis and drives bone resorption [6]. While NSAIDs show reduction in inflammation and bone loss in short-term studies, concerns about gastrointestinal and renal toxicity limit long-term use [7].

Bisphosphonates

Bisphosphonates inhibit osteoclast-mediated bone resorption and have been explored as adjunctive periodontal therapy [2]. Clinical studies in aggressive periodontitis demonstrate improvement in radiographic bone density and reduced bone turnover markers when used locally or systemically [2]. However, concerns about osteonecrosis of the jaw limit their routine periodontal use.

Omega-3 fatty acids and resolvin-based therapy

Pro-resolving lipid mediators, including resolvins derived from omega-3 fatty acids, actively terminate inflammation and promote tissue regeneration [17]. Clinical trials show that omega-3 supplementation combined with low-dose aspirin yields significant improvements in CAL, PD, and gingival inflammation in aggressive periodontitis [18]. Similar studies suggest beneficial effects on alveolar bone regeneration.

Probiotics

Probiotics such as *Lactobacillus reuteri* have demonstrated immunomodulatory potential by suppressing pathogenic bacteria and regulating cytokine expression [11]. Some trials show improvements in PD and inflammatory markers when combined with mechanical therapy in aggressive periodontitis [3], though results remain inconsistent.

Cytokine-targeting therapies

Experimental therapies include monoclonal antibodies targeting IL-1β, TNF-α, and RANKL, which show significant lesion size reduction and improved bone turnover in pilot studies [6]. However, high cost and risk of systemic immunosuppression limit widespread use.

Aggressive periodontitis is a multifactorial disease characterized by bacterial infection in the context of an exaggerated host inflammatory response. Standard mechanical debridement only partially addresses the destructive cascade; therefore, host-modulation therapy becomes essential for comprehensive management [18].

SDD remains the most validated host-modulating therapy due to its strong clinical evidence, safety, and established mechanism of inhibiting tissue-destructive enzymes. Its benefits appear particularly pronounced in deep pockets, which are highly susceptible to inflammatory breakdown in aggressive periodontitis.

Because they actively encourage the resolution of inflammation rather than just its suppression, omega-3 fatty acids and resolvins represent a promising new frontier [19]. They show positive effects on bone regeneration and appear highly relevant given the rapid alveolar bone destruction characteristic of aggressive periodontitis.

Bisphosphonates offer potential benefits for bone metabolism but require caution due to the risk of osteonecrosis, particularly with systemic use [19]. Probiotics and herbal anti-inflammatory agents, while attractive due to safety profiles, require more robust evidence.

Cytokine-targeting biologics demonstrate remarkable mechanistic specificity but are limited by cost, availability, and systemic risks [20].

In general, host-modulation therapy should be considered an addition to mechanical periodontal therapy rather than its replacement. Combination therapy that addresses both host-mediated and microbial mechanisms yields the best results [20].

Conclusion

Host-modulation therapy emerges as a rational and biologically grounded adjunctive strategy designed to complement conventional periodontal treatments by targeting the molecular and cellular pathways responsible for tissue destruction. Among the wide range of therapeutic agents evaluated, subantimicrobial-dose doxycycline (SDD) stands out as the most extensively studied and clinically validated host-modulating agent for aggressive periodontitis. Its ability to inhibit matrix metalloproteinases, downregulate inflammatory cytokines, and stabilize connective tissue architecture makes it a valuable adjunct to scaling and root planing, with strong evidence demonstrating improvements in probing depth reduction, clinical attachment gain, and inflammatory control.

Similarly, omega-3 polyunsaturated fatty acids and pro-resolving lipid mediators, particularly resolvins, offer a compelling alternative approach by promoting active resolution of inflammation rather than simply suppressing inflammatory pathways. These agents show promise in enhancing periodontal healing, reducing inflammatory burden, and potentially contributing to alveolar bone regeneration. Their favorable safety profile and mechanistic alignment with the pathobiology of aggressive periodontitis position them as important emerging therapies requiring further large-scale clinical evaluation.

Overall, the collective evidence strongly supports the integration of host-modulation therapy into the comprehensive management of aggressive periodontitis. Such an approach aligns with current understanding of the disease as a biologically complex inflammatory disorder requiring multifaceted intervention strategies. Incorporating host-modulating agents alongside mechanical debridement allows clinicians to address both microbial and host-mediated pathogenic components, thereby offering a more complete therapeutic framework and improving patient outcomes.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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