

# Managing Periodontitis with Host Modulation Therapy: Current Concept and Future Perspective

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## ABSTRACT

As our basic knowledge of the etiopathogenesis of periodontitis has improved over the past years, it has become evident that the periodontal disease is multifactorial disease caused by the bacteria which establishes the immune reaction in the host. This initiation of the host response leads to destruction of the surrounding periodontium which ultimately results in tooth loss. An ever-increasing research in the field of pathogenesis of periodontitis has revealed that the initial breakdown in chronic inflammatory periodontal disease often involves a failure of resolution pathways in order to restore host's homeostasis. The practice of modulating the host response to control periodontal disease has been employed for many years not only for the periodontal disease but also for various medical conditions. As a result, the goal of this review is to provide an overview of existing findings on host modulation therapies (HMTs). In addition, to describe some of the recent advances made over the years in the field of HMTs and to determine some pertinent conclusions about its involvement in disease development and its use in clinical therapy. This will provide a chance for more detailed investigation in this particular field. As a result, the goal of this review is to describe the current findings available in the literature on HMT.

**Keywords:** Host modulating agents, Host modulation, Pathogenesis of periodontitis, Periodontology.

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## INTRODUCTION

Although periodontal disease is described as a persistent microbial infection of the periodontium, the host's immunological and inflammatory response to the microbial onslaught also plays an important part in tissue damage. The two-way interaction between the host and the microbes largely influence the extent and severity of tissue destruction.<sup>1,2</sup> The conventional treatment modalities available including mechanical and surgical therapies, prove to be inadequate to inhibit or prevent the host-initiated tissue damage of the periodontium. Hence, emphasis now is shifting on mechanisms of modulating these interactions by use of host modulating agents as an adjunctive therapy to the conventional treatment.<sup>3,4</sup>

Since last few decades physicians has utilized the concept of modulating host response for the treatment of certain autoimmune diseases.<sup>5</sup> In 1970s Paul Goldhaber and Max Goodson associated arachidonic acid (AA) metabolites as a crucial inflammatory mediators for the bone loss in periodontitis,<sup>6</sup> but William and Golub proposed the notion of host modulation in dentistry in the year 1990.<sup>7</sup> The host modulation aims to regulate the host response causing destruction in the periodontal tissue without compromising the host immunity.<sup>8</sup>

Theories and concepts in the field of initiation and progression of periodontitis have evolved over time. In the recent times, substantial role of the host's response against the bacteria is given utmost importance for the pathogenesis of periodontitis, though earlier periodontal disease was considered to be solely a plaque-dependent disease.<sup>4</sup> The aforementioned paradigm evolution is considered as the basis for the development of host modulating therapies (HMTs) to enhance the conventional treatment outcomes, diminishes disease progression, and provide better forecasting treatment for patients with periodontitis. Therapeutic

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agents modulating host response focuses on inhibiting proteolytic enzymes, proinflammatory mediators, and osteoclastic activities.<sup>2</sup>

Therefore, the present article aims to summarize as well as to assess the present literature in relation to the utilization of host modulatory agents to regulate periodontitis and related tissue damage, and to extract some valuable findings to further elaborate its involvement in the management of periodontal disease and its application in the clinical practice.

## SEARCH STRATEGY

A literature search for published publications was conducted using both electronic and manual methods. A thorough search of electronic databases, including PUBMED, MEDLINE, and Google Scholar up to February 2023 was made. Key terms used in the search included host modulation in periodontics, Host response in periodontal disease, host modulating agents in periodontics, and pathogenesis of periodontal diseases (Fig. 1).

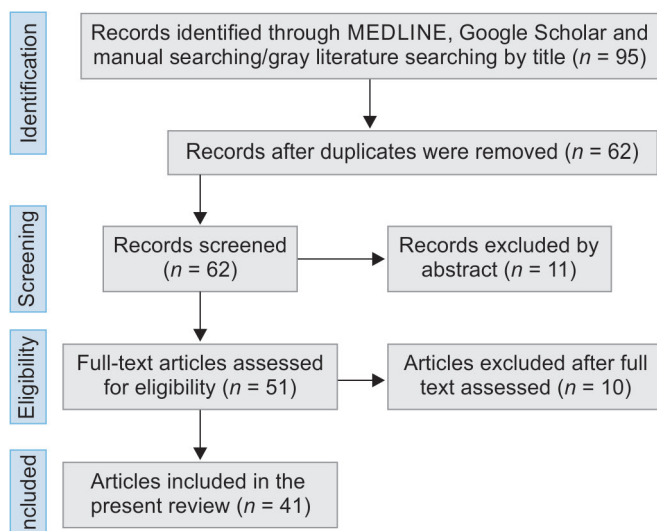


Fig. 1: Search and selection process of articles for the review

## PATHOGENESIS OF PERIODONTITIS AND MECHANISM OF MODULATING HOST RESPONSE

Periodontal diseases is a multifactorial condition, which is thought to be initiated in the presence of bacteria, but are not considered sufficient for the progression of the disease. A wide range of microbial compounds, such as chemotactic factors, such as lipopolysaccharide (LPS), microbial peptides, and other bacterial antigens are produced by subgingival plaque bacteria.<sup>9</sup> These chemotactic factors then diffuse across the junctional epithelium (JE) into the gingival connective tissues stimulating the host epithelial as well as connective tissue cells. These triggered host cells then cause inflammatory response in the tissues by producing inflammatory mediators. Defense cells which travel in response to the chemotactic stimulus, enter the gingival crevice.<sup>3</sup> There is also significant vasodilation and an increase in vascular permeability, which leads to fluid collection within the gingival tissues. Plasma cells transformed from B lymphocytes, start synthesizing antibodies against specific bacterial antigens. Antibodies from the host immune cells are released in the gingival tissue in response to the bacterial products entering the circulation, hence leading to enhanced PMN phagocytosis and bacterial killing.<sup>10</sup>

In response to the bacterial challenge there is an increase in the levels of anti-inflammatory or protective mediators, which in turn balances the elevated levels of the proinflammatory or destructive mediators.<sup>2</sup> Host modulatory treatment (HMT) can be utilized to break the positive feedback cycles, therefore, eventually diminishing the high amounts of proinflammatory mediators that cause tissue damage. An elevated levels of anti-inflammatory mediators are present in disease resistant individuals which are necessary to maintain the equilibrium between the host response and the associated bacterial challenge.<sup>11</sup> Tissue deterioration will occur in the susceptible host if an imbalance exists, with high quantities of inflammatory mediators found in the host tissues.

## TARGETS FOR HOST MODULATORY AGENTS

1. Arachidonic acid metabolites modulation: Prostaglandins (PGs) are one of the most crucial mediator in periodontitis for bone loss.<sup>12</sup> PGs are metabolized via the cyclooxygenase (COX) route,

and leukotrienes via the lipoxygenase (LOX) pathway, resulting in unbound AA.<sup>12,13</sup>

2. Lipid-inflammatory mediators: Resolution of acute inflammation occurs via endogenous chemical mediators, such as resolvins, protections, and recently identified maresins. Various steps which are involved in the LOX and COX pathways produces certain mediators and its precursors like Omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid, and docosahexaenoic acid.<sup>14</sup>
3. Matrix metalloproteinases (MMP) modulation: The destruction of extracellular matrix is mediated via certain mediators, such as MMP, zinc and calcium-dependent. MMPs proteolytic inactivation is self-controlled, and is also blocked by mediators like  $\alpha 2$  macroglobulin and tissue inhibitors of MMPs (TIMPs).<sup>11</sup>
4. Agents modulating actions against cytokines: Proinflammatory mediators, such as IL1, IL6, TNF, interferon, etc. and various anti-inflammatory cytokines (e.g., IL4, IL10, etc.) have enormous potential for altering the undesirable impact of the host-inflammatory response; thus, HMT antagonizing cytokines can be argued as a viable course of treatment for periodontitis.<sup>10</sup> Various mechanisms which are involved in the antagonizing action include:

- Antagonizing the receptor for cytokine. For example, Kineret (Anakinra, Amgen) is one of the commercially available IL1 receptor antagonist (IL1ra).
  - Antibodies like anticytokine: This includes certolizumab, pegol, adalimumab, golimumab, tocilizumab, ustekinumab have been studied for their efficacy as host modulating agent.
  - Soluble cytokine receptors: Methylxanthine derivative Pentoxifylline modifies TNF-production, which further affects the TNF-accumulation. Toll-like receptor downregulation has been associated with the anticipated expression of cytokine signaling in diseased periodontal tissues.
5. Nitric oxide activity modulation: Nitric oxide (NO) is exploited in various biological procedures vacillating from immune homeostasis to cancer.<sup>15</sup> It is produced by three isoenzymes known as NOSs from the substrate L-arginine. Inducible forms of NOS (iNOS) is produced in response to inflammatory stimuli like bacterial LPS.<sup>16</sup> It is proposed that oral microbiome produces iNOS overexpression in patients with periodontitis as nearly zero NO activity was detected in the experimental animal setup.<sup>16,17</sup>
  6. Targeting RANK-RANKL pathway: Osteoprotegerin (OPG) act as a decoy receptor blocking the activation of nuclear factor-kappa B (N-kB) ligand (RANKL) and RANK interaction which inhibits the differentiation of osteoclasts.<sup>18</sup> Anti-inflammatory drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) downregulates the preosteoclast conversion from hematopoietic cells. Antagonists of RANKL can also inhibit this interaction. Matrix metalloproteinases antagonists hinder protease degradation of the extracellular organic matrix, whereas the anti-integrins impedes the osteoclastic adhesion to the matrix.<sup>19</sup>

## CHEMOTHERAPEUTIC AGENTS CURRENTLY AVAILABLE FOR MODULATING HOST RESPONSE

1. Nonsteroidal anti-inflammatory drugs: It downregulates the PGs synthesis, which also includes PGE2 which is synthesized in response to LPS via various autologous cells, such as neutrophils, macrophages, fibroblasts, and gingival epithelial cells. Prostaglandins upregulates bone resorption by osteoclasts.<sup>20</sup>

PGE2 has proven to downregulate fibroblastic activity and in addition has modulatory action on the immune response.<sup>6</sup> Short-term administration of NSAIDs reduced gingival crevicular fluid (GCF) and MMP-8 levels.<sup>21</sup> Studies also suggested that low-dose aspirin as an adjunct periodontal therapy was beneficial in reducing periodontal attachment loss.<sup>6</sup>

Routine administration for a longer duration is crucial for the periodontal benefits to become apparent, but prolonged dosing of NSAIDs can be associated with substantial adverse effects which include gastrointestinal complications, bleeding tendencies, and renal and hepatic impairment. Also a concept of “rebound effect” is associated with discontinuing the long-term usage of NSAIDs in which an accelerated bone loss and periodontal destruction becomes evident even more than what was seen before the NSAID therapy.<sup>22</sup> Hence, NSAIDs are not used as adjunctive treatment modality in the periodontitis patients.

2. Bisphosphonates: Bisphosphonates which affect the osteoclastic activity are bone-seeking agents. They in addition to inhibiting bone resorption, also possess anticollagenase activity.<sup>18</sup> This potential of modulating bone resorption has proved to be beneficial in managing periodontitis. Bisphosphonates inhibited alveolar bone resorption in experimentally generated periodontitis animal models. In several animal studies, treatment with the alendronate has resulted in evident increase in bone density.<sup>18</sup> Similarly, in various human studies, bisphosphonates have resulted in superior alveolar bone status and density.<sup>23</sup> Etidronate is the first-generation bisphosphonates which has alkyl side chains. Alendronate and Pamidronate are the second-generation bisphosphonates and have amino-terminal group. Risedronate, for example, is a third-generation bisphosphonate with cyclic side chains. There is almost 10-fold antiresorptive properties among these generation of bisphosphonates.<sup>23</sup> Bisphosphonates possess a number of side effects, including preventing bone calcification and modifying white blood cell counts. Additionally, avascular necrosis of the jaws following bisphosphonate therapy highlights the danger of bone necrosis after tooth extraction.<sup>18</sup> Although only the intravenous administration of bisphosphonates is associated with bisphosphonate-related osteonecrosis of the jaw (BRON/ONJ), yet the oral use of bisphosphonate for the management of periodontitis as an HMT agent is discouraged.
3. Subantimicrobial dose doxycycline (SDD): Tetracyclines show anticollagenolytic action, according to Golub et al., and therefore was put forward as a host modulating drug in the management of periodontitis in 1985.<sup>7</sup> In accordance with the research results of Burns et al.,<sup>24</sup> doxycycline has been proved to be one of the most effective tetracycline which can inhibit the host’s collagenolytic activities while preventing antibiotic resistance. This doxycycline characteristic provided the pharmacological ground for using a SDD as an HMT agent. Subantimicrobial dose doxycycline is one of the only the U.S. Food and Drug Administration (FDA) approved HMT agent. A 20-mg dose of doxycycline is described as an SDD, which acts as HMT agent and adjunct to conventional SRP.<sup>25</sup> The 20-mg dosage works through inhibiting enzymes, cytokines, and osteoclasts rather than by acting as an antibiotic.
4. Enamel matrix derivatives, growth factors, and bone morphogenetic proteins (BMPs): The FDA has certified certain agents like enamel matrix proteins (Emdogain), recombinant human platelet-derived growth factor-BB (GEM 21S), and BMP-2

(rhBMP-2 [Infuse]) as HMTs for supplementary use during surgery. However, adverse events associated with the administration of BMPs have been reported, including osteolysis, seroma or hematoma, infection, arachnoiditis, dysphagia, increased neurologic deficits, and cancer.<sup>26</sup>

## CHEMOTHERAPEUTIC AGENTS AVAILABLE FOR MODULATING HOST RESPONSE—FUTURE PERSPECTIVE

1. Anticytokine therapy: It utilizes deactivating monoclonal antibodies or receptor blockers in order to inhibit the action of proinflammatory cytokines which include TNF, IL-1, or IL-17.<sup>27</sup> In addition, drugs like infliximab which is a monoclonal antibody to TNF and etanercept, a agonist of TNF receptor, and anakinra which inhibits IL-1 receptor, are being tested for their clinical safety and effectiveness. Anticytokine therapy may have some potential adverse effects on immunity.<sup>23</sup> Therefore, a locally administered route is preferred to systemic route.
2. Specialized proresolution mediators: Various clinical trials have utilized dietary intake of omega-3 PUFAs and have resulted in better treatment outcome in patients with periodontal disease when compared with conventional SRP. But, these intervention studies failed to involve a larger sample sizes.<sup>28</sup> Therefore, clinical studies with larger sample size needs to be conducted to substantiate the preliminary favorable outcomes. A recently discovered proresolving pathway has the capacity to upregulate endogenous neutrophil transmigration inhibitors.<sup>29</sup> In a similar manner, resolvin D1 has been demonstrated to inhibit the integrin beta-2 antagonist’s downregulation caused by interleukin-17.<sup>13</sup>
3. Probiotics: The complete mechanisms of action of probiotics is certainly difficult to understand but they seem to regulate both the microbial as well as the host response in periodontal disease.<sup>30</sup> Several probiotic compositions have shown to achieve a stable composition which is harmonious with health, but the results obtained are short-lived and terminates once the intake is stopped. In addition, probiotics also enhance barrier activity, modulating T-regulatory cells, and inhibit proinflammatory responses. *Lactobacillus reuteri* is used in a number of clinical studies and a noteworthy improvement in clinical indicators of periodontal disease has been observed as a result from these investigations. Therefore, probiotics proved to be effective and can be utilized as an adjunctive therapy to conventional SRP.<sup>31–33</sup>
  - Complement: A recent preclinical mouse model study, has proved a cause-and-effect association between complement system and periodontal disease.<sup>34</sup> This has encouraged research into the extent to which inhibition of C3 by inhibitor Cp40 could benefit the patients with periodontitis.<sup>35</sup> Cp40 has the ability to inhibit inflammation and bone loss when administered locally via intragingival injection in young adult nonhuman primates.<sup>33</sup> A potential drug named AMY-101 has been proposed for therapeutic involvement in complement-mediated diseases. The Cp40 forms the basis for development of AMY-101.<sup>36</sup> Locally administered AMY-101 appears to be a favorable approach as a HMT in treating patients with periodontal disease.
4. Vaccination: The initial need for immunization against any microbially produced illness is the identification of the causal agent. Thus, the notion of periodontitis vaccination emerged only when particular red complex bacteria were acknowledged.

as apparent etiologic microbes in the initiation of periodontitis.<sup>37</sup> So far, subunit vaccination approaches have mostly focused on *P. gingivalis* virulence factors, including the cysteine proteinases (RgpA, RgpB, and Kgp gingipains), fimbriae and hemagglutinin B. Subcutaneous immunization of rats with the *P. gingivalis* gingipain hemoglobin-binding domain might produce specific IgG and provide modest defense against alveolar bone loss. Another study used a blend of gingipains in Freund's lacking adjuvant to immunize rats, which resulted in increased-titer serum IgG2a activity and defense against periodontal bone destruction.<sup>38</sup> Additional study is necessary to determine the immunization regimens and immune response mechanisms that are most effective in reducing periodontal disease in primates. Much more work is required to establish the most advantageous adjuvant formulations and immunization methods (mucosal routes have been considered to be better than systemic routes), in order to generate vaccine candidates that are efficient not only in inducing immune responses to the pathogens but also in suppressing the disease. Thus, in addition to boosting specific immunity against periodontal microbes, vaccinations should induce adequate non-inflammatory immune responses that avoid tissue destruction and promoting inflammation resolution and healing.<sup>37</sup>

5. Sclerostin regulation with sclerostin antibody (Scl-Ab): Sclerostin is primarily released by mature osteocytes and is expressed by the SOST genes. Considering it to be an inhibitor of the canonical Wnt pathway, it inhibits bone formation. Sclerostin, according to current research, plays a substantial part in the disease progression. Sclerostin regulation with sclerostin antibody is also being hailed as a possible HMT agent which can be used for the management of periodontal disease.<sup>39</sup> Some investigations discovered that eliminating sclerostin slowed bone deterioration and partially protected alveolar bone from resorption, hence delaying periodontitis development. Therefore, the administering of Scl-Ab can be a viable therapeutic option for bone modulation initiated by periodontal disease.
6. Targeting inflammasomes: Inflammasomes function as an internal homeostatic barrier, modulating the level of inflammation in both health and disease. Inflammasomes are multiprotein complexes that convert pro-IL-1 $\beta$  into its physiologically active form. They play a crucial role in regulating host defense systems and inflammatory disorders.<sup>39</sup> Inflammasomes are governed by a variety of proteins and processes, including COPs (pyrin domain CARD-only proteins), TRIMs (tripartite motif family proteins), POPs (PYD-only proteins), autophagy, and interferons. Periodontal disease has been associated with an increase in inflammasomes and a subsequent decrease in inflammasome regulator proteins, such as POPs, TRIMs, and COPs.<sup>40</sup> Resolvins and lipoxins, which target TNF and IL-1 and alter inflammasome priming, are now used as periodontal treatment drugs. Targeting the problem at the molecular and cellular levels may limit cytokine production and keep the disease from advancing into an inflammatory state. Directly targeting inflammasomes may provide an interesting potential treatment strategy for the management of inflammasome-related periodontal and periimplant disease.

## CONCLUSION AND FUTURE OUTLOOK

The evolution of HMT is based on an improved understanding of the host's immunoinflammatory response and host-bacterial

interactions that contribute to periodontal tissue loss. Many clinical studies have indicated the role and effectiveness of host modifying medications in the treatment of several periodontal diseases. The HMT can be effectively employed as an additional therapy, especially in susceptible and high-risk individuals when a long-term and upregulated host response to bacteria enhances MMP and osteoclast activity.

Though the understanding of periodontal disease pathophysiology remains impoverished, existing knowledge has led to promising outcomes in preclinical investigations on host modulation. More research is required in the future to create immunotherapy techniques and to comprehend the risks and long-term success of these therapies.

## Ethical Approval

This review used only publicly available and published data, hence an official ethical clearance and consent was not required.

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