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# Host Modulation

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## Abstract

Host modulation is considered to be new research area in dentistry. In medicine, host modulation was introduced way before dentistry in treating arthritis and osteoporosis. It is mainly focusing on the host part during host-bacteria interaction. Although there are many agents introduced for this purpose, the most well-studied host modulation therapy in dentistry is doxycycline. It shows less tissue destruction when used for few months along with periodontal therapy. It has anticollagenase properties which shows a promising effect when used to treat chronic inflammation.

**Keywords:** host modulation, doxycycline, anticollagenase, matrix metalloproteinases enzymes

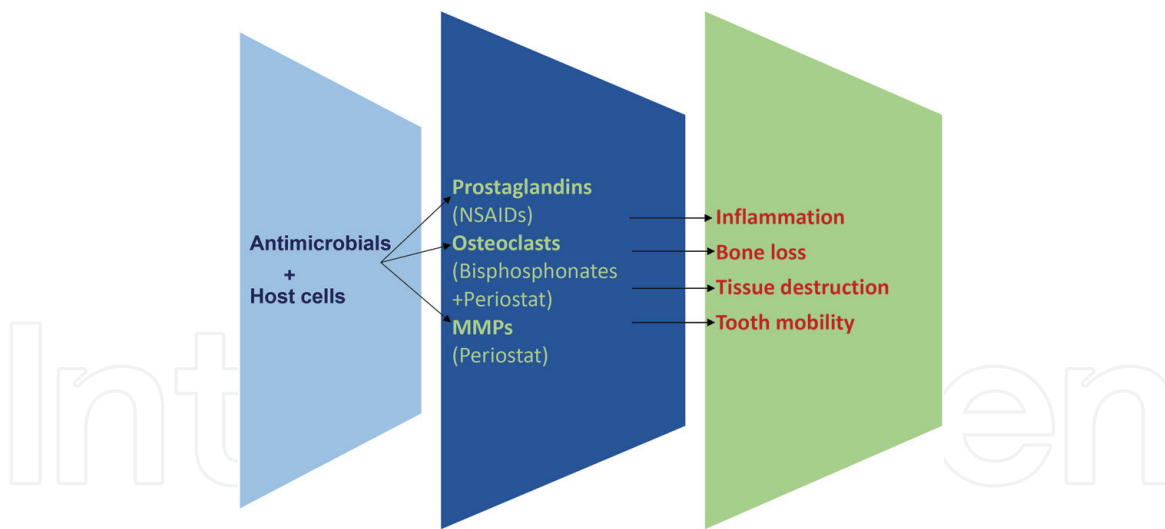
## 1. Introduction

Host modulation therapy is a newly introduced term to the field of dentistry. Host refers to the body hosting the disease while modulation refers to changing the status of something in response to external modifier.

In periodontal diseases, bacteria/microbes are the main pathogen in initiating the disease while the host is the body hosting the bacteria. Host modulation therapy is the chemical agent that can be used as an adjunct to the systematized periodontal therapy to improve the diseased state and inhibit the tissue destruction. As proved in many studies, bacteria cause direct tissue destruction by releasing enzymes and other virulent factors and indirectly by letting the host tissue to release collagenases which in turn destruct the tissue. Host modulation is working on the indirect arm of this process.

Host modulation was introduced in dentistry by William [1] and Golub et al. [2] in the 1990s. Both discussed the idea of having a chemical agent that modulate the host response and improve the periodontal health. The response to the periodontal disease as well as the progression of the periodontal disease varies considerably among individuals. Some patients are susceptible to a disease more than others which make, the host modulation therapy preferable in such cases.

Host modulation can be used to reduce levels of enzymes, collagenases, and proinflammatory cytokines. Moreover, it can modify osteoclast and osteoblast activities (**Figure 1**). It has a role in modifiable risk factors (e.g., smoking, diabetes) and unmodifiable risk factors (e.g., genetic susceptibility) as it help the body to overcome those risk factors. In systemic host modulation, it has the effect on multiple sites on the oral cavity with 'sub-antimicrobial-dose doxycycline' (SDD) and locally with agents such as bone morphogenic proteins (BMP) to improve wound healing at the surgical site.



**Figure 1.**  
The effect of different systemic host modulation therapy agents and their target during gingivitis and periodontitis.

## 2. Systemic host modulation

Various medications which are used for host modulation therapy are administered orally.

### 2.1 Bisphosphonates

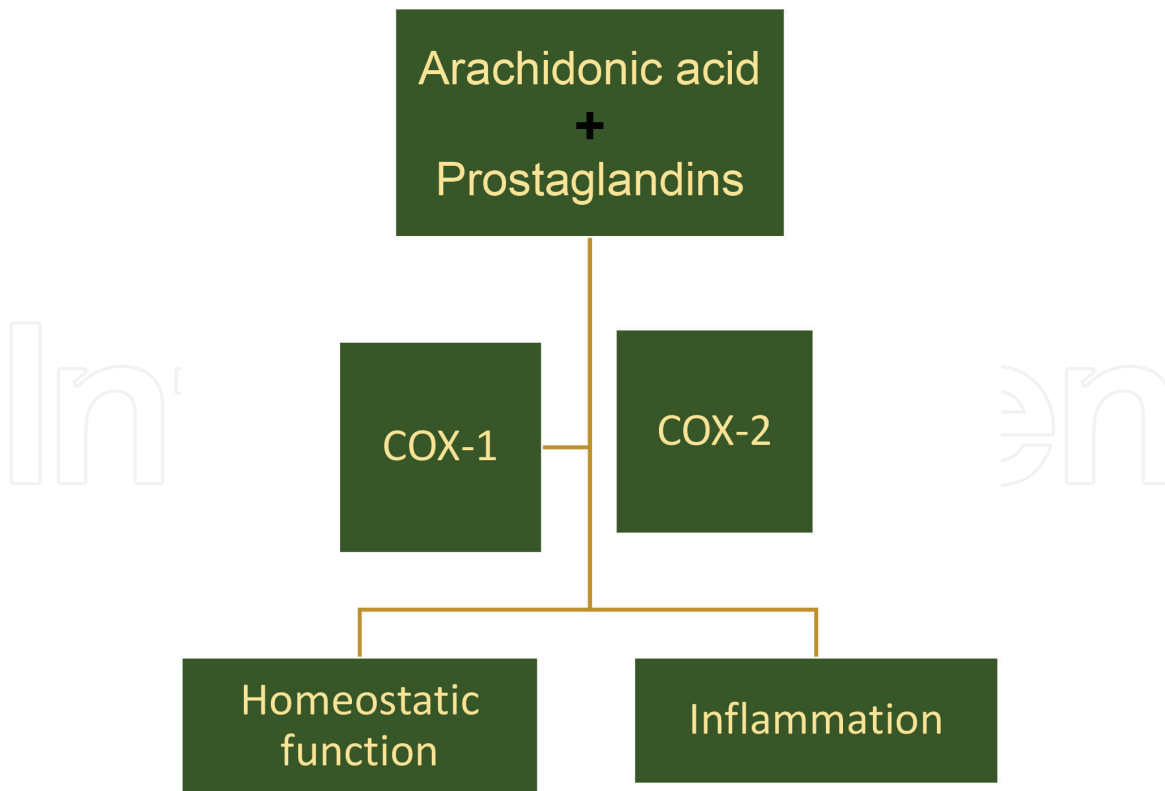
Bisphosphonate is an agent that is used to inhibit bone resorption by interfering with osteoclasts. The actual mechanism of action is yet unclear. Some researches show that bisphosphonate interfere with osteoclast cellular adenosine triphosphate (ATPs) [3]. Bisphosphonate possesses anticollagenase properties [4]. Bisphosphonates is helpful in periodontal disease associated with bone loss.

In an animal study, bisphosphonate shows more bone density in beagle dogs using alendronate [5]. Complications associated with using bisphosphonate are mainly bisphosphonate-related osteonecrosis of the jaw (BRONJ). It is mainly associated with intravenous administration of bisphosphonate [6]. Bisphosphonate is not yet been approved as host modulation therapy for periodontitis.

### 2.2 Nonsteroidal anti-inflammatory drugs

NSAIDs decrease the production of prostaglandins (PGE). PGE<sub>2</sub> is produced by different cells such as neutrophils and fibroblast in response to lipo-poly saccharide. It has been shown that PGE<sub>2</sub> is elevated in periodontitis in response to bacteria compared to non-periodontitis cases [7]. By reducing PGE<sub>2</sub> production, inflammation also subsides in periodontal disease. One study showed lower levels of matrix metalloproteinase enzymes (MMP-8) at the gingival crevicular fluid (GCF) after administration of NSAIDs [8]. Some studies showed that NSAIDs such as indomethacin [9], flurbiprofen [10], and naproxen [11] show reduced bone loss when used for a period up to 3 years. These are the non-selective NSAIDs that have been investigated in research as host modulation therapy. The main side effect when NSAIDs are used for prolonged period as host modulation therapy includes gastrointestinal pain and ulcer, bleeding, and renal and hepatic impairment.

Using selective cyclooxygenase-2 (COX-2) inhibitor could be a promising solution to the side effects of non-selective NSAIDs (**Figure 2**).



**Figure 2.**  
*Cyclooxygenase enzyme converts arachidonic acid to prostaglandins. COX-1 maintains the homeostatic functions at the body while COX-2 contributes more with the inflammation.*

Some studies administering selective NSAIDs showed less PGE<sub>2</sub> in human periodontal tissues [12]. On the other hand, selective NSAIDs reported side effects such as myocardial infarction. NSAIDs also show some rebound effects when the usage stopped which resulted in more tissue destruction afterward [13]. NSAIDs are not yet been approved as host modulation therapy for periodontitis.

### 2.3 Sub-antimicrobial-dose doxycycline

Sub-antimicrobial-dose doxycycline (SDD) is the only host modulation therapy approved by the U.S. Food and Drug Administration (FDA) and accepted by the American Dental Association (ADA). SDD (Periostat) is usually administered as 20 mg twice daily for a period of 3 months. Less than 3 months period was showing rebound effect of collagenase levels as the benefit of SDD is not yet been applied at the tissue [14]. In many cases, physicians are prescribing the medication for a period up to 9 months and regular follow up every 3 months to evaluate the effect of the medication.

SDD has an anticollagenase effect and inhibit osteoclast and proinflammatory cytokines. The effect of SDD is below the detection of bacteria which will not cause any resistance in the future. Moreover, there is no rebound effect registered after discontinuing the medication. The significant clinical effect of SDD compared to placebo in 266 patients when used as an adjunct to scaling and root planing (SRP) in periodontitis patients has been reported in a study [15]. Another study was showing the effect of SDD as an adjunct to SRP with smokers having periodontitis [16].

Large number of MMPs is released to the periodontal tissues during inflammation by different cells. MMP-8 and MMP-9 are major enzymes released from neutrophils during inflammation which cause tissue destruction through degrading type I collagen [17, 18]. The release of MMPs leads to progressive destruction of periodontal tissues which is related to the large number of neutrophils during inflammation.

### 3. Local host modulation

#### 3.1 Enamel matrix proteins, growth factors, and bone morphogenetic proteins

The locally administered host modulation therapy is used mainly to improve wound healing, increase bone formation, and to produce new periodontal tissue including periodontal ligament and cementum. They have been applied locally along with periodontal surgery. The FDA approved local host modulatory agents includes enamel matrix proteins (Emdogain), recombinant human platelet-derived growth factor-BB (GEM 21S), and BMP-2 (rhBMP-2 [Infuse]). These materials have been proved to provide some clinical benefits when used during periodontal surgical procedures. The focus of this chapter is on the non-surgical therapy of gingivitis and periodontitis.

### 4. Conclusions

To summarize, patient selection and motivation to do periodontal therapy is the key to start host modulation therapy. Moreover, medical status of the patient would affect the outcome of the treatment.

### Conflict of interest

None.

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