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# Host Modulating Agents: A Short Review

Dr. Sumati Patel[1], Dr.Mohammad Aamir[2]
[1]*(Consultant, Realtooth dental clinic, Lucknow, Uttar Pradesh)*
[2]*(Assistant Professor, Department of Periodontology, BabuBanarasiDas College of Dental Sciences, Lucknow, Uttar Pradesh)*

***Abstract***
*Periodontal diseases are responsible for tissue destruction which leads to periodontal breakdown. Various destructive enzymes and inflammatory mediators are involved in destruction. Mechanical therapy along with various chemotherapeutic agents such as NSAIDS, Doxycycline, etc aids in managing periodontitis. Host Modulating agents aims to focus on the reduction of tissue destruction by modifying or decreasing the regulating destructive aspects of the host response and upregulating protective or regenerated responses.*

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## I. Introduction

Dental Plaque is the root cause of causing direct damage to the periodontal tissue. It releases $H_2S$, butyric acid, enzymes and mediators which cause direct inflammatory changes in the tissues that beginsdestructive processes and hence, affect the teeth in oral cavity[1].

The host response is basically protective by intent but can contrarily result in tissue damage that incorporates the collapse of connective tissue fibers in the PDL and breakdown of the alveolar bone.

Host modulating agentsdoes not shut off the normal defense mechanism of the inflammation instead, they improve excessive or pathologically elevated inflammatory responses to increase the chances of wound healing and periodontal firmness. Therapeuticagents are used to stop the developmentof periodontitis by arbitration of the infectiousmechanism. It is used as an adjunct with conventional periodontal treatmentmodalitieswhich includes scaling and rootplaning. It provides the chances for modulating or decreasing destruction by healing chronic inflammatory response. The concept was firstintroduced by William and Golub in 1990[2]. Initially supplemental therapies were solely anti-microbial such as use of antibiotics and antiseptics. New approaches include modulation of host response.

## II. Classification (Agents Used In Host Modulation)

**A) Based On Mechanism Of Action :-(3 Categories)**
1.Antiproteinases
2.Anti-Inflammatory
3.Bone Sparing
**B) Based On Route Of Drug Administration: -**
*I)Systemic*
A) NSAIDS
B) SDD
C)Bisphosponates
D)N.O. SDrugs (Nitric Oxide Sparing Drugs)
*II)Local*
A) Tetracycline Fibres
B) Emp (Enamel Matrix Protein)
C)GF (Growth Factors)

**Mechanism Of Action**
Many host modulating agents have been developed to prevent and manage the periodontal problems[3]. The most common mechanisms by which these acts are the following:

*A. Via Inhibition of Matrix metalloproteinases (MMPs) -Through chemically Modified Tetracyclines (CMTs)*

Tetracyclines have been used as an antibiotic since long time. Periodontal pathogens produce MMPs. However, it is noted that endogenous MMPs are not the bacterial proteinases that are mainly responsible for tissue destruction that states the importance of the role of host modulatory approaches in periodontal therapy. Chemically modified tetracyclines are tetracyclines which lacksdimethyl amino group on the 4th carbon atom.
It inhibits the calcium atoms that MMPs require for their action & decreases MMPs expression. They acts as scavengers for reactive oxygen species & modulates the osteoclast functions.

*B. Via Inhibition of Arachidonic Acid metabolites-through NASIDs*
Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibits the formation of prostaglandins, including PGE2, which is produced by neutrophils, macrophages, fibroblasts, and gingival epithelial cells in response to the presence of lipopolysaccharide (LPS). PGE2 has been observed to be increased in periodontal disease compared with the level in healthy patients. NSAIDs inhibit prostaglandins and thus reduces tissue inflammation. They are used to treat pain, acute inflammation, and a variety of chronic inflammatory conditions. Systemic NSAIDs include the following:
• Salicylates (e.g. aspirin)
• Indomethacin[4]
• Propionic acid derivatives (e.g. ibuprofen, flurbiprofen, naproxen)

*Locally administered NSAIDS*
It includeKetoprofen that inhibits both cyclooxygenase and lipoxygenase pathway. In addition, Ketorolac trimethamine rinse and S-ketoprofen dentifrices[5] can also be used.
It is possible as these drugs are lipophilic and are easily absorbed into gingival tissues.

*Triclosan*
It is a non-ionic antibacterial agent that inhibits both cyclooxygenase and lipoxygenase pathway and thus interferes in arachidonic acid pathway[6]. Dentifrice containing sodium fluoride and triclosan have shown positive results in the treatment of Periodontitis.

*C. Via Modulation of Bone metabolism*
Bisphosphonates are bone seeking agents which inhibits bone resorption by disrupting osteoclast activity. They interfere with osteoblast metabolism and secretion of lysosomal enzymes. Recent evidence has suggested that bisphosphonates also possess anticollagenase properties.They are classified into:-
1) 1st generation bisphosphates: eg. Etidronic acid and Clodronic acid
2) 2ndgeneration bisphosphates: eg. Alendronate and Pamidronate.
3) 3rd generation Bisphosphonates: eg: risedronate[7].

Bisphosphonates inhibits the development of osteoclasts & induces apoptosis of osteoclasts which leads to reduction of osteoclastic activity. It prevents the development of osteoclasts from hematopoieticcells. It also stimulates production of osteoclast inhibitory factor&Decreases bone reportion by inhibiting MMPs.

D. Via Regulation of immune and inflammatory responses
1. **Modulating Nitric Oxide activity:** Nitric oxide (NO) is a highly reactive free radical which reacts with metal and thiol residues resulting in lipid peroxidation, protein damage, DNA damage and stimulation of cytokine release. Nuclear Poly ADP-ribose polymerase enzyme decreases Nitric oxide toxicity[8].
2**. Suppression of proinflammatory cytokines:** Cytokines are regulatory proteins which controls the survival, growth, differentiation, and function of cells. They function as a network and share overlapping features. Cytokines antagonists such as IL-1receptor antagonist or soluble TNF receptors competitively inhibit receptor mediated signal transduction[9] to avoid tissue damage and maintain homeostasis.
3. **Other Locally administered agents:**They include agents such as enamel matrix proteins, growth factors, and bone morphogenic proteins which have been investigated for potential use as adjuncts to surgical procedures. They improve wound healing as well as stimulate regeneration of lost bone, periodontal ligament, and cementum thus, restoring the complete periodontal attachment apparatus. The only local host modulatory agent currently approved by the FDA for adjunctive use during surgery is Emdogain[10]. It is believed to regulate the initiation, propagation, cessation, and maturation of enamel hydroxyapatite crystals. They also take part in cementogenesis.

E. Via Miscellaneous Host Modulatory agents
1.Probiotics

Probiotics have demonstrated meaningful potential as therapeutic options for a variety of diseases as they have been known to modulate cytokine secretion profiles, influence T-lymphocyte populations, protect against physiologic stress, and enhance intestinal epithelial cell function and antibody secretion[11]. They are also used in periodontal dressings[12].

2. Hypochlorous acid and taurine-N-monochloramine

Hypochlorous acid (HOCl) and taurine-N-monochloramine (TauCl) end-products of the neutrophilic respiratory burst, modulate the host inflammatory response by inhibiting the production of interleukin-6, prostaglandins, and other proinflammatory substances. They play a crucial role in the periodontal inflammatory process by offering opportunities for the development of novel host-modulating therapies for the treatment of periodontitis[13].

3. Cimetidine

Cimetidine is a powerful H2-(Histamine) receptor antagonist, which eliminates histamine's inhibitory effects on immune response, thus acting as a modulator of inflammation and immunity by inhibiting neutrophil chemotaxis and superoxide production, thereby increasing cyclic adenosine monophosphate (cAMP) levels and down-regulating cytokines.

4.Periodontal vaccines

Toll like receptors (TLRs) offer novel targets for host-modulation therapy in periodontitis since manipulation of TLR signalling would contribute to control of infection or regulation of inflammation and, furthermore, synthetic or natural TLR agonists could serve as novel periodontal vaccine adjuvants[14].

## III. Conclusion

The improved understanding of the host-bacterial interactions and the host immuno-inflammatory response leading to periodontal tissue destruction has led to the development of Host modulatory therapy which is considered as a bench mark in the treatment of patients with periodontal diseases. They have been beneficial in immunocompromised patients and in peri-implant disease where local and systemic efficiency of host modulatory therapy are used as an adjunct to conventional local disinfection treatment. Although the efficacy and usefulness of host modulating agents have improved the treatment in several cases, still more research& trialsare required for making faster treatment responses and to increase periodontal stability.

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