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Perioceutics

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Abstract
Perioceutics, or the use of pharmacological drugs particularly formulated to control periodontitis, is a fascinating and rising approach in the treatment of periodontal disease, together with mechanical debridement. A perioceutic's purpose is to re-establish equilibrium between pro-inflammatory mediators and destructive enzymes on the one hand, and anti-inflammatory mediators and enzymes on the other. Host modulatory therapy (HMT) is a treatment approach aimed at reducing tissue degradation and stabilising or even regenerating the periodontium by altering or downregulating destructive components of the host response while enhancing protective or regenerative responses. This research examines Host Modulatory Therapy, which will be a beneficial tool for dentists in the future when used in conjunction with mechanical therapy to treat periodontal disorders.

Keywords: Host modulation, perioceutics, periodontal therapy, therapeutic agents

Introduction:

Periodontal disease is a chronic infectious disease of the oral cavity caused by gram negative associated pathogens organised as a biofilm, the presence of which elicits an inflammatory response in the host [1]. Pathogenic microorganisms can cause tissue destruction directly or indirectly by activating and modifying host responses. In general, the host response serves as a protective mechanism, preventing local infection from spreading further [2].

The host immunoinflammatory response to bacterial plaque can thus be viewed as a "double-edged sword," in that it is intended to protect the periodontium, but it is ultimately responsible for perpetuating the destruction of the periodontium in susceptible patients who have an exaggerated inflammatory response to plaque [3]. Host modulatory therapies (HMTs) have been developed as a result of this paradigm shift, which can improve therapeutic outcomes, slow disease progression, allow for more predictable patient management, and possibly even serve as periodontitis prophylactic agents. Williams and Golub were the first to introduce the Host Modulation concept to dentistry. "There are convincing results from animal and human trials indicating that pharmacologic drugs that control the host responses thought to be involved in the pathophysiology of periodontal damage may be useful in reducing the progression of periodontal disease," Williams stated in 1990 [4].

Along with mechanical debridement, "Perioceutics," or the use of pharmacological drugs particularly formulated to control periodontitis, is an intriguing and emerging approach in the management of periodontal diseases [5]. Heska Corporation first coined the term perioceutic (periodontal + therapeutic). This field of "perioceutics," which includes antimicrobial therapy and host modulatory therapy to produce beneficial changes in the microflora and host response, has emerged as a critical aid in the management of susceptible patients

who develop periodontal disease in conjunction with mechanical debridement [6].

For the treatment and management of periodontal diseases, there are a variety of host modulatory therapeutic agents that are an essential aspect of perioceutics and are employed as an adjuvant to standard periodontal therapies [7].

Aim of Host modulation therapy (HMT):

- To decrease tissue destruction and maintain or even regenerate the periodontium by modulating or down-regulating destructive features of the host response and up-regulating protective or regenerative responses.
- To rebalance the pro-inflammatory mediators and destructive enzymes on the one hand, and the anti-inflammatory mediators and enzyme inhibitors on the other.

Mechanism of Host Modulation Therapy:

Periodontal disease is caused by plaque bacteria such as Porphyromonas gingivalis, Prevotella intermedia, Aggregatibactar actinomycetemcomitans, Tannerela forsythia, and possibly others such as Campylobacter rectus, Fusobacterium nucleatum, and Spirochetes. Their presence as an exogenous infection, as well as their dominance in pathogenic flora, triggered a cascade of immune responses in the host. Bacteria and their metabolic products, as well as lipopolysaccharide (LPS), induce the host response when these bacteria colonise the tooth surface near the gingival margins [Figure 1]. Bacteria and their by-products directly harm junctional epithelial cells. The junctional epithelial cells respond by releasing cytokines, prostaglandin E2 (PGE2), matrix metalloproteinase (MMPs), and tumour necrosis factor-alpha (TNF-α). These mediators cause neutrophils to migrate to the periodontal infection site, activating the immune system. If these inflammatory cells can use intercellular killing mechanisms to keep bacteria and their products (such as LPS endotoxins) at bay, the disease is limited to the gingiva. If these mechanisms fail to control the bacterial challenge, and pathogens and their products penetrate host tissues, the inflammation worsens and progresses to periodontitis.

Antigens, LPS, and other virulence factors stimulate host responses, resulting in gingivitis or the onset of periodontitis. The host response includes recruiting neutrophils, producing protective antibodies, and possibly releasing anti-inflammatory cytokines such as TGF-β, IL-4, IL-10, and IL-12. A persistent bacterial challenge disrupts homeostatic mechanisms, causing the release of mediators such as pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α), proteases (e.g., MMPs), and prostanoids (e.g., PGE2), which can promote extracellular matrix destruction and bone resorption in the gingiva [8].

Host-Modulating Agents:

Several HMT agents that have been developed to block or modify periodontitis pathways [9].

1. Inhibition of arachidonic acid (AA) metabolite: through nonsteroids anti-inflammatory drugs

    i. Cyclooxygenase (COX)-1 inhibitors: indomethacin, flurbiprofen, and naproxen

    ii. COX-2 inhibitors: rofecoxib

    iii. COX and lipoxygenase (LOX) inhibitors: triclosan and topical ketoprofen

    iv. LOX inhibitors: lipoxins.

2. Modulation of matrix metalloproteinases (MMPS)

    i. Recombinant tissue inhibitor of metalloproteinase

    ii. Sub-antimicrobial dose of doxycycline

    iii. Hydroxamic acid peptides such as galardin

    iv. Bisphosphonates

    v. Chemically modified tetracyclines (CMTs).

3. Modulation of bone remodelling: therapeutic approach to treat pathologic bone defect

    i. Conventional therapy

    ii. Tumor necrosis factor-alpha

    iii. Anticytokine drugs

    iv. Antiresorptive therapies

        a. Hormone replacement therapy

        b. Bisphosphonates

        c. Disruptive of the receptor activator of nuclear factor-κB ligand/receptor

Volume 5, Issue 3; May-June 2022; Page No 747-756

activator of nuclear factor-κB/osteoprotegerin interactions

d. Vitamin D

e. Statins.

4. Regulation of immune and inflammatory response:

i. Suppressing proinflammatory cytokines: interleukin 1 (IL1) and TNF-α receptor antagonist

ii. Modulation of nitric oxide (NO) activity

a. Inhibition with mercapto alkyl guanidines

b. Inhibition of nuclear poly (ADP-ribose) polymerase (PARP) enzyme.

iii. Generation of protective antibodies through vaccination (periodontal vaccines)

iv. Infusion/supplementary anti-inflammatory cytokines: IL-4 and IL-10

v. Antagonist for endothelial cell adhesion molecules

Inhibition of arachidonic acid metabolism [Figure 2]

Arachidonic acid can be metabolized by either the cyclooxgenase (COX) or the lipooxygenase (LOX) pathways. Prostaglandins, prostacyclin, and thromboxane are the end products of the COX pathway, whereas leukotrienes and hydroxyeicosatestraenoic acid are the end products of the LOX pathway. The basic rationale for using NSAIDs is to block arachidonic acid metabolites, which are proinflammatory mediators involved in a variety of bone resorptive and tissue degrading processes. By inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism, NSAIDs prevent the formation of prostaglandins. They are used to treat a variety of chronic inflammatory diseases by reducing tissue inflammation and pain (Philip and Preshaw, 2008).

Since NSAIDs are lipophilic and are absorbed into gingival tissues, they can also be applied topically in most cases. Topical NSAIDs that have been studied include ketorolac tromethamine rinse and Sketoprofen dentifrice [10].

In 1993, Bezzere et al. [11] discovered that COX2 inhibition by selective COX2 inhibitors offered the possibility of reducing periodontal inflammation without the side effects associated with long-term non-selective NSAID use. COX2 inhibited alveolar bone loss.

A compound which has received interest as both an antibacterial and anti-inflammatory agent is triclosan. Triclosan has the ability to inhibit both the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid metabolism (Gaffar et al., 1995) [12].

Inhibition of matrix metalloproteinases

Chemically modified tetracyclines (CMTs)

CMTs are those which lack dimethylamino group on the 4th carbon atom [13]. Golub et al. (1987) [14], discovered that the carbon 4 position side-chain of tetracyclines was responsible for their antimicrobial activity. CMTs were created later in a series of experiments by removing the dimethylamino group from the carbon 4 position of the A ring of the four-ringed (A, B, C, D)

structure. The resulting compound, 4-de-dimethylaminotetracycline (CMT-1), lacked antimicrobial activity but retained anticollagenase activity in vitro and in vivo [Figure 3]. These agents are powerful inhibitors of proinflammatory mediators and can raise levels of anti-inflammatory mediators like IL-10. CMTs inhibit the production of epithelial-derived MMPs by inhibiting cellular expression and synthesis, as well as inhibiting or chelating the calcium ions required for MMP action [15]. It inhibits MMPs that are already active, scavenges reactive oxygen species, and modulates osteoclast functions. The primary advantage of CMTs over traditional tetracyclines is that long-term systemic administration does not cause gastrointestinal toxicity, and higher plasma concentrations can be obtained with less frequent administration regimens [14].

Subantimicrobial dose doxycycline

Burns et al. (1989) [16] discovered that doxycycline was the most effective tetracycline in inhibiting collagenolytic activities. According to Golub et al. [17], this property of doxycycline provided the pharmacological rationale for the use of a low or sub-

Volume 5, Issue 3; May-June 2022; Page No 747-756

antimicrobial dose of doxycycline, which was shown to be effective in inhibiting mammalian collagenase activity without developing antibiotic resistance. A low, sub-antimicrobial dose doxycycline (SDD) preparation containing 20 mg doxycycline was introduced, as opposed to the 50 or 100 mg dose available for antibiotic purposes. It is a 20-mg dose of doxycycline hyclate taken twice daily for 3–9 months as an adjunct to root surface instrumentation in the treatment of periodontitis. It is marketed as "Periostat".

A three-month prescription corresponds to a three-month maintenance recall. SDD therapy begins with the start of initial periodontal therapy and lasts three months until the first re-evaluation or maintenance appointment. Sites with persistent or progressing pockets may necessitate additional instrumentation, and SDD prescriptions may be extended for an additional three months.

Mechanism of action: [Figure 4]

Doxycycline, in addition to its antibiotic properties, has the ability to downregulate MMPs, a family of zinc-dependent enzymes capable of degrading extracellular matrix molecules such as collagen (Birkedal-Hansen, 1989) [18] causing connective tissue breakdown. [19].

Doxycycline downregulates MMPs by various mechanisms:

1. In junctional epithelium [20]

    • Inhibition of production of epithelial-derived MMPs by inhibiting cellular expression and synthesis

2. In connective tissue [20]

    • Direct inhibition of active MMPs by cation chelation

    • Inhibition of oxidative activation of latent MMPs

    • Downregulates the expression of key inflammatory cytokines including interleukin IL-1, IL-6, and TNF-α, as well as PGE2

    • Scavenges and inhibits production of reactive oxygen species (ROS) produced by PMNs

    • Inhibition of MMPs and ROS protects α1 proteinase inhibitor (α1-PI), thereby indirectly reducing tissue proteinase activity

    • Stimulates fibroblast collagen production

3. Alveolar bone [20]

    • Reduces osteoclast activity and bone resorption

    • Blocks osteoclast MMPs

    • Stimulates osteoblast activity and bone formation

Modulation of bone metabolism

Bisphosphonates

These are pyrophosphate analogues that are nonbiodegradable and have a high affinity for calcium phosphate crystals. According to El-Shinnawi et al. (2003) [21], bisphosphonates are bone seeking agents that inhibit bone resorption by disrupting osteoclast activity. They have been shown to bind to hydroxyapatite crystals and prevent their dissolution, as well as increase osteoblast differentiation and inhibit osteoclast activation [22]. They disrupt osteoblast metabolism and lysosomal enzyme secretion. These compounds also appear to inhibit MMP activity via a mechanism involving cation chelation. More recent evidence has suggested that bisphosphonates also possess anti-collagenase properties.

Classification

1. First-generation bisphosphonates include Alkyl side chains (e.g., etidronate)

2. Second-generation bisphosphonates include amino bisphosphonates with an amino-terminal group (e.g., alendronate and pamidronate).

3.Third-generation bisphosphonates have cyclic side chains (e.g., risedronate) [23]

The antiresorptive properties of bisphosphonates increase approximately 10-fold between

drug generations.

Mechanism of action of bisphosphonates as host modulation agent [24]

Bisphosphonates acts on osteoclast function at tissue, cellular and molecular levels.

Volume 5, Issue 3; May-June 2022; Page No 747-756

1. Tissue level:
    - Decrease bone turnover due to decreased bone resorption
    - Decreased number of bone multicellular units
    - Net positive whole body bone balance
2. Cellular level:
    - Decreased osteoclast recruitment
    - Increased osteoclast apoptosis
    - Decreased osteoclast adhesion
    - Increased osteoblast differentiation and number
3. Molecular level:
    - Inhibit mevalonate pathway
    - Decreased post translational phenylation of GTP binding proteins

There are mainly two modes of action:

1. Indirect action
    - Indirect mode of action suggests that following exposure to bisphosphonates, an osteoclast inhibitory factor is secreted by osteoblasts that can inhibit the function of osteoclast.
2. Direct action
    - Bisphosphonate mediated inhibition of osteoclast development.
    - Induction of osteoclastic apoptosis.
    - Reduction of activity of osteoclasts.
    - Inhibiting the development of osteoclasts from hematopoietic precursors.
    - Downregulation of bone resorption by bisphosphonate that correlated with MMP inhibition [25].

Following systemic administration, BPs are selectively absorbed on bone surfaces and are found in all areas of high bone resorption activity. They are endocytosed in osteoclasts after being released during bone resorption activity, altering the normal intracellular biochemical processes. Bisphosphonates inhibit bone metabolism by suppressing interactions between the receptor activator of nuclear factor kappa B (RANK) and its ligand (RANKL), as well as osteoprotegerin.

Nonnitrogen-containing BPs (e.g. clodronate and etidronate) induce osteoclast apoptosis by activating the caspase pathway. It has the potential to inhibit the ATP-dependent intracellular enzyme osteoclast proton-pumping vacuolar ATPase (V-ATPase), which plays an important role in bone resorption by pumping protons into resorption lacunae.

Nitrogen-containing BPs (e.g. zoledronate and pamidronate) inhibit the mevalonate pathway's key enzyme farnesyl pyrophosphate synthase. This inhibits the biosynthesis of isoprenoid compounds, which modify GTP-binding proteins (prenylation). The inhibition of protein prenylation and the disruption of regulatory protein function eventually results in the loss of osteoclastic activity

Furthermore, by promoting osteoblast differentiation and maturation, BPs have an osteogenic action both in vitro and in vivo. This is accomplished by boosting matrix formation and collagen synthesis [26]

Metformin (MF)

MF is one of the most commonly used oral antihyperglycemic agent in the treatment of Type 2 diabetes mellitus. The bone sparing properties of MF have recently provided a new perspective in periodontal research. Many studies conducted by Pradeep et al. using MF gel at varying concentrations of 0.5 percent, 1 percent, and 1.5 percent MF gel as local drug delivery (LDD) in adjunct to SRP for the treatment of intrabony defects in patients with CP demonstrated significant improvement in clinical outcome [27]

Statins

Statins are a class of lipid-lowering drugs that are commonly used to treat hyperlipidemia and reduce the risk of cardiovascular disease. These medications have pleiotropic effects such as vasodilation, antithrombosis, antioxidant activity, antiproliferative activity, and anti-inflammatory activity. They also prevent the release of proinflammatory mediators such as cytokines and MMPs. Statins have been studied for their effects on periodontium in light of these plieotrophic effects. Pradeep et al. conducted several studies in which statins such as 1.2 percent atorvastatin gel, 1.2 percent simvastatin gel, and 1.2

Volume 5, Issue 3; May-June 2022; Page No 747-756

percent rosuvastatin gel were used as LDD in addition to SRP and showed greater improvement in clinical parameters than the placebo group [28].

Regulation of immune and inflammatory responses

Modulation of nitric oxide (NO) activity

Lietao et al. [29] reported that nitric oxide synthase (NOS) inhibitors protect against bone resorption and the inflammatory process in rats with ligature-induced periodontitis.

Inducible NOS (iNOS) is responsible for nitric oxide (NO) production by epithelial and inflammatory cells in response to proinflammatory cytokines in some inflammatory diseases such as rheumatoid arthritis and periodontal disease (Lappin et al. in 2000). Leitao et al. 2005, discovered that using a selective iNOS inhibitor – mercaptoethylguanidine – reduced alveolar bone loss and gingival inflammation, confirming that NO plays a negative role in the pathophysiology of periodontitis and that its modulation may prevent tissue destruction.

Newer agents for host modulation

Enamel matrix proteins (EMD)

Emdogain, an enamel matrix derivative, is now commercially available for the treatment of periodontal defects after FDA approval. EMD initiate periodontal regeneration by recruiting cementoblasts to the root surface and stimulating them to form root-cementum, which then leads to regeneration of periodontal fibres and alveolar bone. EMD's above-mentioned actions support its role as a host modulating agent [30].

Bone morphogenetic protein (BMP)

BMPs. are a distinct class of differentiation factors that induce new bone formation at the site of implantation rather than altering the rate of pre-existing bone growth. Recombinant human bone morphogenetic protein-2 (rhBMP-2) has the potential to be a game changer in dental and periodontal reconstruction. BMP regulates the differentiation and modulation of mesenchymal cells into bone and bone marrow cells. Absorbable collagen sponge (ACS) containing rhBMP-2 has been approved for clinical use in certain oral surgery procedures, including localised alveolar ridge augmentation for extraction socket defects. These ACS gradually release the protein in the area where they are implanted, forming a scaffold on which new bone can grow. The ACS is absorbed and replaced by bone as the graft site heals [31].

Platelet derived growth factor

The FDA has approved GEM 21S, a growth-factor enhanced matrix that combines a bioactive highly purified rh platelet derived growth factor (PDGF)-BB with an osteoconductive bone matrix. As a host modulating agent, PDGF can increase neutrophil and monocyte chemotaxis, stimulate fibroblast proliferation and extracellular matrix synthesis, increase endothelial cell proliferation and differentiation, stimulate proliferation of mesenchymal progenitor cells, and stimulate fibroblast differentiation [32].

Recombinant human interleukin-11

Trepicchion et al. (1995) [33] discovered that IL-11 has anti-inflammatory effects by inhibiting TNF-α and other proinflammatory cytokines. Furthermore, Leng et al. (1995) discovered that it indirectly reduces tissue injury by stimulating tissue inhibitor of metalloproteinase-1 (TIMP-1). Martuscelli et al. (2000) investigated the ability of recombinant human IL-11 (rhIL-11) to reduce periodontal disease progression in dogs with ligature-induced periodontitis based on these previous studies. After an 8-week period of twice-weekly rhIL-11 administration, there was a significant reduction in the rate of clinical attachment and radiographic bone loss [34].

Tumor necrosis factor antagonist

TNF-α, an inflammatory cytokine released by activated monocytes, macrophages, and T lymphocytes, promotes inflammatory responses that play a role in the pathogenesis of rheumatoid arthritis and periodontal disease. TNF-α binds to two receptors expressed by a wide range of cells: the type 1 TNF receptor and the type 2 receptor. TNF-R1 activation appears to stimulate the inflammatory response, whereas TNF-R2 activation appears to suppress it. TNF pathway inhibition has the potential to significantly slow disease progression [35].

Anticytokine Drugs

Anticytokine therapy for periodontal diseases focuses on proinflammatory cytokines such as TNF- α, IL-1,

Volume 5, Issue 3; May-June 2022; Page No 747-756

and IL-6, which are required for the initiation of the inflammatory immune response and are produced for extended periods of time in periodontitis. The goal of this therapy is to bind cytokines to receptors on target cells such as fibroblasts. This new therapy has the potential to act as a host response modulator in the control of inflammatory gum diseases, and it may serve as the foundation for new molecular therapeutic approaches to the treatment of periodontitis (Yogesh Prakash Waykole et al. 2009). TNF antagonists (e.g., Infliximab, Etanercept) have been shown to be effective by targeting cytokines such as TNF- α.

Conclusion:

Host response modulation has emerged as a viable treatment concept for periodontal disease management, representing a significant step forward for clinicians and patients alike. In some cases, conventional therapy does not always result in the desired clinical outcome. In these cases, and for specific groups of periodontal disease-prone individuals, the use of HMT in conjunction with antibiofilm treatments may be beneficial. As methods for modulating the host response are available, they may be useful as adjunctive therapies in a wide range of clinical situations.

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Volume 5, Issue 3; May-June 2022; Page No 747-756

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Volume 5, Issue 3; May-June 2022; Page No 747-756

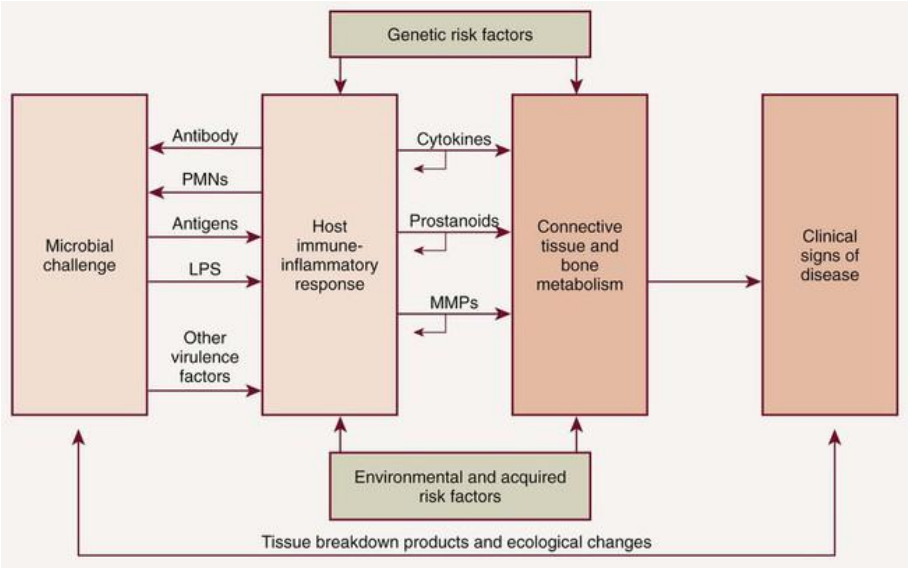

Figure 1. Host Modulation of the Pathogenesis of Periodontal Disease

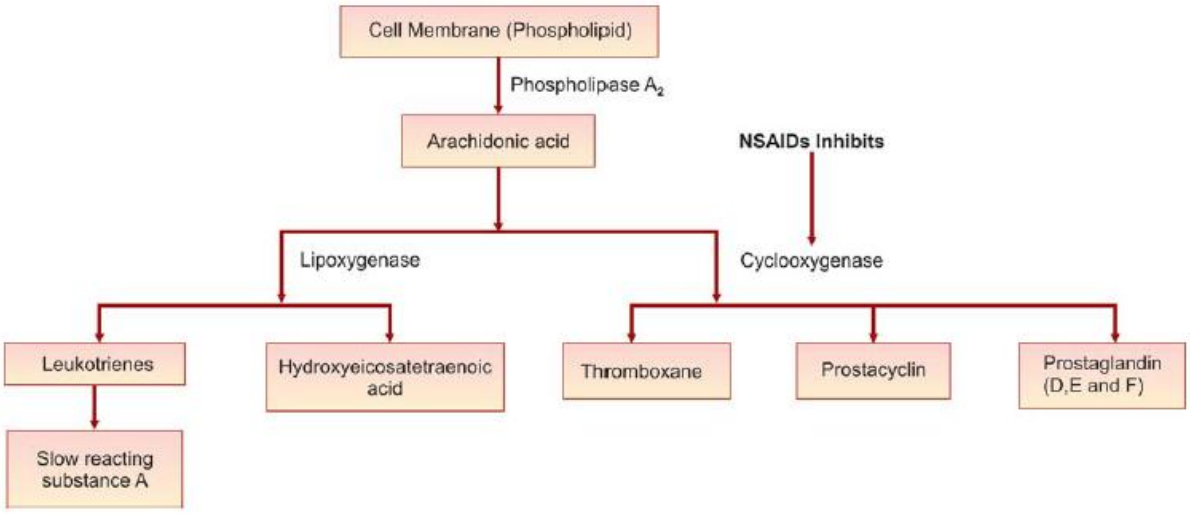

Figure 2. Mechanism of action of nonsteroidal anti-inflammatory (NSAIDs) drugs

Volume 5, Issue 3; May-June 2022; Page No 747-756

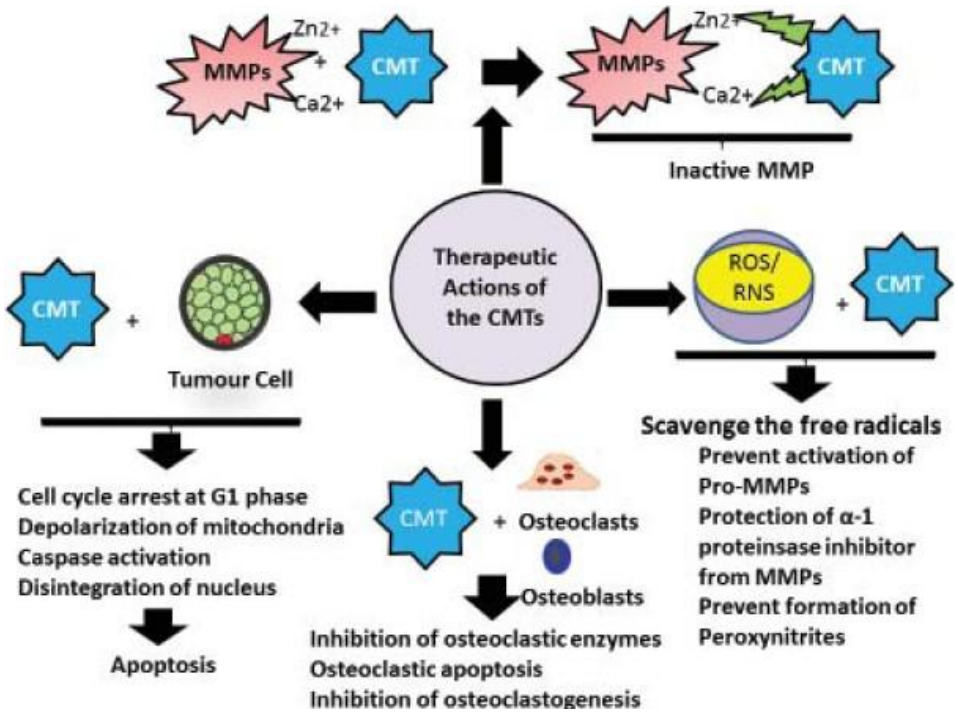

Figure 3. Therapeutic actions of chemically modified tetracyclines

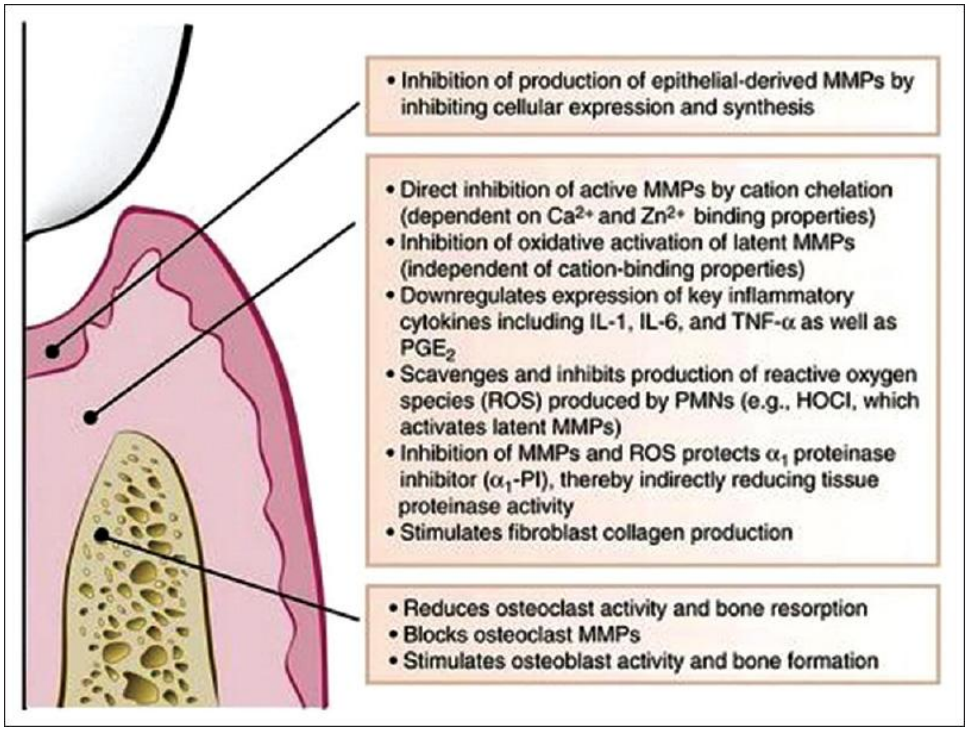

Figure 4. Mechanism action of SDD

Volume 5, Issue 3; May-June 2022; Page No 747-756