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MECHANICAL, CHEMICAL AND HERBAL ASPECTS OF PERIODONTITIS: A REVIEW

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ABSTRACT

Periodontitis is a common and widespread disease, which occurs due to the pathogenic bacterial infections (like *Porphyromonas gingivalis, Bacteroides* spp., *E. coli, Staphylococcus aureus, S. mutans* etc.) established within the gingival sulcus. This condition, when not arrested, will cause formation of periodontal pocket. In order to eliminate or control the disease and arrest further periodontal tissue destruction, periodontal pockets need repeated sub gingival mechanical cleansing. This scaling procedure is unpleasant and painful. Systemic antibiotics have their role to play, but are limited by the duration of treatment and also the availability of the antibiotic at the site of action in sufficient quantity. It is not possible to administer broad spectrum antibiotics at its optimum dosage levels, multiple times over large periods. The spread of drug resistant pathogens is one of the most serious threats to successful treatment of microbial diseases. Down the ages essential oils and other extracts of plants have evoked interest as alternates for bacterial infections. Dental plaque is the main etiological factor of periodontal diseases and this article is focused on its prevention through mechanical, chemical and herbal techniques.

INTRODUCTION: The word "periodontitis" comes from peri ("around"), odont ("tooth") and -itis ("redness"). Periodontitis is a set of diseases which usually attacks the peridontium. The periodontium is the specialized tissues that both surround and support the teeth, maintaining them in the maxillary and mandibular bones.

The periodontium includes the alveolar bone, the cementum (on the root surface of teeth), the gingiva (gums), and the periodontal ligament (between the tooth and bone). Periodontitis in comparison with Gingivitis is a more severe inflammation, because not only it affects the tissues, but also, it affects the bottom of the teeth. If it is not treated at all, it may lead to a loss of teeth [1, 2].

Periodontal disease is one of the most important concerns for dentists and patients. Morris *et al*., (2001) reported that in the United Kingdom 40-45% of adults have moderate destructive periodontal disease and 5-10% has a severe form of the disease. They also reported that 72% of adults have visible plaque; which is the main causative factor of periodontal disease. In the United States 50% of adults have gingivitis affecting at least 3-4 teeth; two-thirds of the population has sub gingival calculus, and about a one-third have periodontitis [3, 4.]

Albandar and Rams in (2002) reported that more than 82% of the United States adolescents have overt gingivitis and signs of gingival bleeding. They reported that the prevalence of gingivitis for children and adolescents in other parts of the world is almost the

same or possibly higher than that of the United States adolescents. These authors in their report further suggested that improving the oral hygiene of the population will have a great impact on the occurrence of periodontal disease. This suggestion had been expounded by Morris et al (2001) who also suggested that improved oral hygiene would result in the widespread improvement in management of the disease [5].

Dental Plaque: Dental plaque is a complex of several hundred species of bacteria living together, forming an adherent biofilm. It is the principal etiological factor in periodontal diseases and caries. If plaque is allowed to accumulate, with no intervention or oral hygiene methods, gingivitis is established after 2-3 weeks of plaque formation which further turns into periodontitis (**Figure 1**).

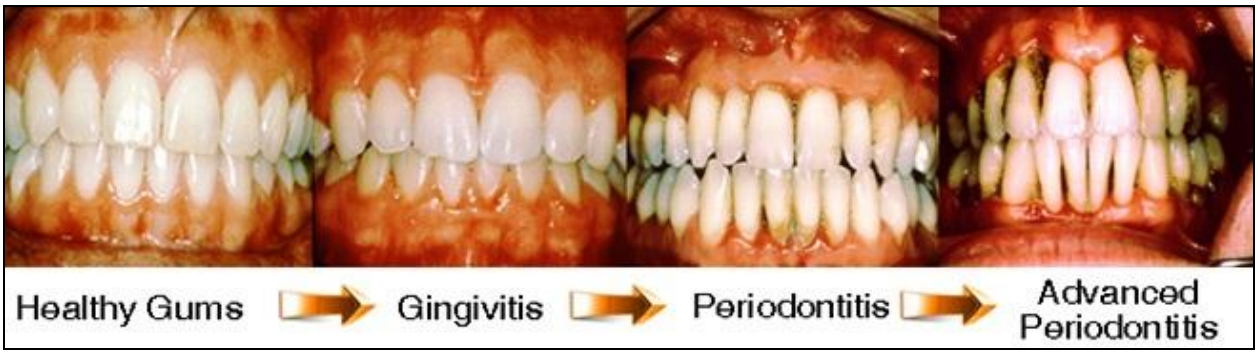

FIGURE 1: FLOW DIAGRAM OF PROGRESSION OF PERIODONTITIS

Steps involved in Supragingival plaque formation:

Step 1- The acquired pellicle is formed as an acellular coating composed of salivary proteins, on clean tooth surfaces. This layer enhances the adhesion of bacteria to the teeth.

Step 2- Within a few hours, gram positive aerobic bacteria, mainly like *streptococci, lactobacilli and actinomycetes* (the initial colonizers) adhere to the pellicle. Following this initial colonization, bacterial growth and multiplication increases rapidly. After 2-4 days more gram negative like *Porphyromonas gingivalis, Actinobacillus, Prevotella* , anaerobics (filamentous and cocci) organisms and fusiform bacteria with higher pathogenicity begin to colonize.

Step 3- Plaque maturation occurs after 4th day. The predominant organisms are filamentous with some spiral and spirochete species [6].

Sub gingival calculus formation: Bacterial products that pass through the junctional epithilium cause the inflammatory changes in the teeth supporting tissues. This initiates gingivitis. These changes facilitate bacterial colonization in the sub-gingival tissues. Sub-gingival plaque is composed of predominantly gram negative anaerobic organisms.

Tannerella forsythis, Porphyromonas gingivalis and Treponema denticola are considered to be the most predominant organisms in sub gingival plaque and these bacteria are causative in the establishment of periodontitis. If plaque is allowed to accumulate it will become mineralized and form calculus. The establishment of calculus results in further bacterial accumulation as a result of its porous nature and rough surface. Consequent to the formation of calculus periodontal disease is established and progressive loss of attachment may follow [7].

Periodontal Disease Pathogenesis: Periodontal disease varies by age of onset, severity, whether the disease is localized or generalized, the bacteria, and the host response. Current classifications include chronic, aggressive, localized aggressive and refractory periodontal disease. The host response has been identified as the primary factor determining periodontal disease progression, and is influenced by systemic diseases, risk factors, hormones and local factors. Following the onset of gingivitis, an active and progressive inflammatory process occurs. The host response to antigens and irritants released by bacteria includes the local release of antibodies, lymphocyte and neutrophil activation and their infiltration into the gingival tissue.

The activation of lymphocytes and neutrophils is defensive and involves bacterial as well as possible tissue destruction. T-lymphocytes are implicated in periodontal bone resorption as T and B cells derived from patients with periodontal disease induce osteoclastic activity. It has been found that differentiating factors from T cells act as receptors and increase osteoclastic activity. The cytokines and chemokines produced by leucocytes lead to inflammation and bone loss. Interleukin 1 (IL-1) and tumor necrosis factor (TNF) are both cytokines, and their presence results in the stimulation of matrixmetalloproteinase (MMP) which is followed by attachment loss and bone resorption [8].

The host response described indicates the importance of the genetic make-up of individual patients in periodontal disease. An example is Down's syndrome patients who have been found to have an altered immune response, with increased production of prostaglandins and MMP, supporting the importance of the genetic component in periodontal disease progression [9].

Mechanical control of Periodontal Disease: One of the goals of periodontal treatment is to eliminate pathogenic bacterial activity, thus halt-ing disease progression and enabling host recovery and gains in clinical attachment levels. Mechanical scaling and root planing are considered the basic standard treatment for periodontal disease, with the objectives of eliminating periodontal pathogens, plaque, calculus and bacterial debris, and leaving smooth surfaces.

Non-surgical scaling and root planing results in the clinician working blind in a closed environ-ment to disrupt and remove the subgingival biofilm, bacteria, debris and calculus from the root surfaces and adjacent soft tissue. In non-surgical cases, instruments may fail to reach the base of deep pockets adequately (75% of root surfaces), primarily due to the physical difficulties imposed by pocket morphology, yet it is in these deeper pockets that higher levels of periodontal pathogens exist [10].

Limitations in Mechanical Treatment:

- It is highly inconvenient and painful technique with least patient compliance.
- Plaque and microbial retention in grooves and pockets as well as within the dentinal tubules, and the presence of bacteria diffused in the soft tissue.
- Dental biofilm consists of bacteria that are tightly bound to each other.
- The presence of periodontal pathogens threatens the periodontal stability and health of treated sites due to bacterial migration from other periodontal sites or sites such as the dorsum of the tongue.
- Treatment failure is associated with the continued presence of, in particular, *A. actinomycetemcomitans* and *P. gingivalis.* The elimination of specific periodontal pathogens is of great importance in periodontal treatment and complete absence of these pathogens is the ideal.
- Tooth brushing and flossing are difficult methods of plaque control for young patients and for persons who have manual dexterity limitations.
- Several studies indicate that only between 2-10% of the population perform interdental hygiene (floss or toothpicks) on a daily basis [11, 12].

Patient Compliance: Continuous motivation and patient compliance is essential to establish a good plaque control programmes. Patient compliance for regular mechanical oral hygiene diminished with time. Compliance for daily flossing ranges from 10-40%. As a result of poor patient compliance with mechanical methods of plaque control, it is important to find adjunctive methods which need less effort but have proven antimicrobial activity. Several reports indicate that chemical control of plaque may be an effective and useful mean to overcome these shortfalls [13, 14].

Chemical Treatment: Chemotherapeutic products used to prevent and treat periodontal disease include mouthrinses, dentifrices, systemic antimicrobials, locally delivered antimicrobials and other therapeutics. Active ingredients used in mouthrinses and dentifrices include chlorhexidine gluconate, essential oils,

fluoride, cetylpyridinium chloride, zinc citrate and triclosan [15].

Systemic antibiotics used in the treatment of periodontal disease started with penicillin. Other antibiotics used include the tetracycline class (tetracycline, doxycycline and minocycline), erythromycin, clindamycin, and metronidazole.

Tetracycline was introduced as a treatment for periodontal disease after penicillin, and its adjunctive use in addition to scaling and root planing has been found to be more effective in reducing periodontal bacteria and inflammation than either scaling and root planing or systemic antibiotic therapy alone.

The choice of antibiotic (or combination of antibiotics) influences which bacteria are affected, for instance, metronidazole is highly effective against *P.gingivalis* but less effective for *A. actinomycetemcomitans*. Though effective, the use of systemic antibiotics means that all body tissues are exposed to the antibiotic, while relatively low levels are available locally where they are needed. Each of these drugs has its own advantages and disadvantages for its utility as an active ingredient and has a broad spectrum action against most periodontal pathogens [16].

Chlorhexidine has been shown to be a very effective anti plaque agent. It has a dual mode of action when used intra orally. It binds to receptor sides on plaque and the acquired pellicle thereby preventing further consolidation of plaque and at the same time has a bacteriostatic effect on the pathogens. Its ability to bind also generates substantivity for an extended duration. However, the important property of substantivity is not as critical in its role as a local drug since it would be placed with a reservoir which would keep on providing the chemical continuously over a period of days. Since it is not such a powerful bacteriocidal agent, it may not be as effective as the other agents in local therapy to combat periodontal pathogens[17].

Locally-delivered Antimicrobials:

1. **Atridox:** This is a gel based system manufactured by Atrix Laboratories and marketed by Collagenex. It is applied with a syringe, and forms a solid biodegradable implant. The doxycycline is released for 7 days. 10% doxycycline hyclate has been found to be an effective adjunct together with scaling and root planing. In one study stand-alone use of doxycycline hyclate was as effective as scaling and root planing in reducing probing depths and in increasing clinical attachment level gain [18].

2. **Actisite:** This system has tetracycline preloaded in hollow ethylene/vinyl acetate fibers. It is manufactured by Proctor & Gamble, USA and dispensed in 23 cm long fibres, 0.5 mm in diameter containing 12.7 mg of tetracycline. The entire length is usually inserted in a single lesion all around the tooth. In case the lesion is isolated to specific areas, the fiber can be cut to size and then placed into the lesion. The tetracycline is released from the fiber over a period of 7 to 10 days. The concentrations of tetracycline achieved in the gingival crevicular fluid (GCF) are more than enough to be able to disinfect the lesion totally. The crucial issue is to remove the fiber after the specified period as it will not dissolve or resorb. Another important consideration is the relative chance of the fiber slipping out of the pocket during the 7 to 10 day period. One can optionally seal the pocket with a cynoacrylate dressing to safeguard against this eventuality. The biggest disadvantage of this product is its non-resorbable nature of the drug delivery matrix [19].

3. **Periochip:** PerioChip is a biodegradable chip made of hydrolyzed gelatin impregnated with 2.5 mg of the antibiotic chlorhexidine gluconate. Chlorhexidine is released from the PerioChip in a biphasic manner with 40% being released in the first 24 hours following placement and the remaining 60% released over the following seven to 10 days. The PerioChip, a 4 mm x 5 mm x 350 µm chip about the size of a baby's fingernail, with a weight of 7.5 mg is inserted directly into the infected periodontal pocket. The GCF concentrations achieved is 1000 mcg/ml over a period of about 7 days. The chip itself will biodegrade and dissolve in about 8 to 10 days time. The negative point in this product is the non-biocompatibility of the matrix probably due to the additives and the crosslinking chemicals used [20].

4. **Arestin:** This is an antibiotic delivered in a unique delivery system manufactured by OraPharma Inc.USA. These are microspheres of Minocycline HCL (each micosphere containing 1 mg of the minocycline) which are to be injected into the pocket. These mircosphere adhere to the soft tissue and then start dissolving slowly thereby releasing the Minocycline in a sustained manner. The spheres are bioadhesive, bioresorbable polymer in powder form produced by a microencapsulation process [21].

5. **Elyzol:** This is a metronidazole based gel/strip which can be placed in the periodontal pocket. The vehicle biodegrades after the active drug has been released over a period of short time. The gel is a 25% metronidazole gel which has been suggested for topical application. The substantiviy of any topical gel in the oral cavity is very doubtfull to start with. The second issue is the ability of the gel to penetrate to any substantial depth in the pocket. This is basically not a product that could be compared to a longer term sustained local drug delivery product. There is also a strip which is pre-impregnated with Metronidazole for placement in pockets [22].

Mechanism of action: One study found that chlorhexidine, tetracycline, doxycycline and other antibiotics all anti-oxidant activity and suggested that anti-oxidative activity may be part of the mechanism of action of chemotherapeutics used in the treatment of periodontal disease. Chlorhexidine inhibits plaque formation by binding to bacteria and preventing their adhesion to the teeth [23, 24].

Limitations:

- Chemotherapeutic mouthrinses have up to 12 hour's substantivity, therefore unless rinsing is regularly performed there is no long-lasting effect from their use.

- Chemotherapeutic rinses will penetrate the outer layers of mature biofilm, while the innermost area of the biofilm where the most bacterial vitality is seen will be unaffected.

- Additionally, it is in deeper periodontal pockets that the more virulent gram-negative anaerobic periodontal pathogens are most prevalent and it is known that mouthrinses may not reach deep into periodontal pockets. The use of irrigators with blunt-ended cannulae, or syringes, may improve the ability of the chemotherapeutic agent to reach deeper into the site in shallow to moderately deep periodontal pockets.

- Some chemotherapeutic rinses are subject to physical and biochemical constraints that limit their application in periodontal treatment. Like Chlorhexidine can cause staining of the tongue, teeth and restorations and also supragingival calculus.

- The crevicular flow volume is exchanged approximately 40 times in one hour, presenting a limitation for locally directed medications. This rate increases in the presence of infection, resulting in further dilution and displacement of locally delivered chemotherapeutics.

- One of the outcomes of this is an increasing number of resistant bacteria strains [25, 26, 27].

Bacterial resistance: Bacterial resistance continues to emerge, and the widespread use of systemic antibiotics is associated with increased antibiotic resistance that represents a major health threat worldwide. Studies have found that locally-applied antimicrobials substantially reduce bacterial resistance compared to use of systemic antibiotics. In a study to determine the most effective method for reducing plaque formation and the level of bacteria on tooth surface, it was found that micro-organisms in inflamed gums are resistant to penicillin (44%) and tetracycline (30%) but were not resistant to antibacterial plant extracts like the Neem [28].

Herbal control on Periodontitis: Medicinal plants have been used as traditional treatments for numerous human diseases for thousands of years and in many parts of the world. In rural areas of the developing countries, they continue to be used as the primary source of medicine. About 80% of the people in developing countries use traditional medicines for their health care. The natural products derived from medicinal plants have proven to be an abundant source of biologically active compounds, many of

which have been the basis for the development of new lead chemicals for pharmaceuticals. With respect to diseases caused by microorganisms, the increasing resistance in many common pathogens to currently used therapeutic agents, such as antibiotics and antiviral agents, has led to renewed interest in the discovery of novel anti-infective compounds. As there are approximately 500,000 plant species occurring worldwide, of which only 1% has been phytochemically investigated, there is great potential for discovering novel bioactive compounds [29].

Benefits of herbal drugs:

- Herbal drugs have long era of use and better patient tolerance as well as public acceptance.
- Herbal drugs acts as a renewable source, which is our only hope for sustainable supplies of cheaper medicines for the worlds growing population.
- Availability of medicinal plants is not a problem especially in developing countries like India having rich agro-climatic, cultural and ethnic biodiversity.
- The cultivation and processing of medicinal herbs and herbal products is environment-friendly.
- Throughout the world, herbal medicine has provided many of the most useful and vast variety of drugs to the modern medical science [30].

Various botanicals have been reported to inhibit the growth of several oral microrganisms particularly *Streptococcus mutans* and thus prevent caries. The need for affordable, effective, and non toxic alternatives has led to the search for compounds from natural sources such as plants, which may overcome the high incidence of oral diseases. Natural products have been used for thousands of years in folk medicine and they are believed to be the new source of antimicrobial agents [31]. There have been numerous reports of the use of traditional plants and natural products for the treatment of oral diseases.

Many plant-derived medicines used in traditional medicinal systems have been recorded in pharmacopeias as agents used to treat infections and a number of these have been recently investigated for their efficacy against oral microbial pathogens [32].

Botanicals like *Acacia Catechu, Cinnamomum zeylanicum, Allium sativum, Propolis, Mikania laevigata, Mikania glomerate, Drosera peltata, Helichrysum italicum, Coptidis rhizome, Piper cubeba, Azadirachta indica, Syzygium Aromaticum* and Tea tree oil (*Melaleuca Alternifolia*) are some potential anti- microbial deriving agents used in the management of dental infections caused by *Streptococcus mutans* [33].

Mode of action: Those botanical which contain phenolic compounds have anti-inflammatory and prostaglandin synthetase-inhibiting activity. In a neutrophil chemotaxis assay, Azuma et al. demonstrated that phenolic compounds act as scavengers of free oxygen radicals and, hence, affect leukocyte activity. Further, in an in vitro study, Firatli et al showed that the antioxidative effect of essential oil moutwash expressed as the percentage inhibition of spontaneous oxidation was greater than that of chlorhexidine [34, 35].

Advantages of Essential Oil Derived Mouthwash:

- This essential oil has been recommended for use after periodontal surgery since it reduces plaque formation without interfering with the healing process.
- Essential oil mouthrinses are also effective against Streptococcus mutans which is one of the most important causative bacteria for dental caries.
- Essential oil mouthrinses also reduces plaque and inflammation around dental implants.
- They can be used effectively in the management of halitosis with no side effects even if used for a long period.
- Essential oil mouthrinses can also be used as a pre-procedural mouthrinse. This will reduce the

numbers of bacteria in the aerosols produced by ultrasonic scaling.

- Rinsing and sub-gingival irrigation with essential oil mouthrinses before dental procedures will reduce chances of bacteraemia that might result from dental procedure [14, 36, 37].

CONCLUSION: The global need for alternative prevention, treatment options and products for oral diseases that are safe, effective and economical arises due to the rise in disease incidence (particularly in developing countries), increased resistance by pathogenic bacteria to currently used antibiotics and chemotherapeutics, opportunistic infections in immuno-compromized individuals and financial considerations in developing countries.

Despite several agents being commercially available, these chemicals can alter oral micro-biota and have undesirable side-effects such as vomiting, diarrhea and tooth staining. For example, bacterial resistance to most (if not all) of the antibiotics commonly used to treat oral infections (penicillins and cephalosporins, erythromycin, tetracycline and derivatives and metronidazole) has been documented. Other antibacterial agents used in the prevention and treatment of oral diseases, including cetylpyridinium chloride, chlorhexidine, amine fluorides or products containing such agents, are reported to exhibit toxicity, cause staining of teeth or in the case of ethanol (commonly found in mouthwashes) have been linked to oral cancer.

Hence, the search for alternative products continues and natural phytochemicals isolated from plants used in traditional medicine are considered as good alternatives to synthetic chemicals.

REFERENCES:

1. Reddy PD, Satyanarayana T, Purushothaman M: Local Drug Delivery of Herbs for Treatment of Periodontitis. Journal of Innovative trends in Pharmaceutical Sciences 2010; 1:245-251.
2. Kornman KS: Controlled release local delivery- Antimicrobials in Periodontics. Prospects for the future. Journal of Periodontology 1993; 64:782-791.
3. Oliver RC, Brown LJ, and Loe H: Periodontal diseases in the United States population. Journal of Periodontics 1998; 69: 269-278.
4. Morris AJ, Steele J, and White DA: The oral cleanliness and periodontal health of UK adults in 1998. British Dental Journal 2001; 191: 186-192.
5. Albandar JM, and Rams TE: Global epidemiology of periodontal diseases: an overview. Periodontology 2002; 29:7-10.
6. Fine DH, Furgang D, and Barnett ML: Comparative antimicrobial activities of antiseptic mouthrinses against isogenic planktonic and biofilm forms of actinobacillus actinomycetemcomitans. Journal of Clinical Periodontology 2001; 28:697-700.
7. Bernimoulin JP: Recent concepts in plaque formation. Journal of clinical Periodontology 2003; 30 (5): 7-9.
8. Taubman MA, Valverde P, Han X, Kawai T: Immune response: the key to bone resorption in periodontal disease. Journal of Periodontology 2005; 76:2033-41.
9. Graves DT, Cochran D: The contribution of interleukin-1and tumor necrosis factor to periodontal tissue destruction. Journal of Periodontology 2003; 74:391-401.
10. Santos A: Evidence-based control of plaque and gingivitis. Journal of Clinical Periodontology 2003; 30:13-16.
11. Quirynen M, Soete M, Van Steenberghe D. Infectious risks for oral implants: a review of the literature. Clin Oral Impl Res 2002; 13:1–19.
12. Kalsbeek H, Truin GJ, Poorterman JH, Rossum GM, Rijkom HM, and Verrips GH: Trends in periodontal status and oral hygiene habits in Dutch adults between 1983 and 1995. Community Dentistry Oral Epidemiology 2000; 28:112-118.
13. Bakdash B: Current patterns of oral hygiene product use and practices. Periodontology 1995; 8: 11-14
14. Yengopal V: Preventive Dentistry: Essential oils and oral malodour. South African Dental Journal 2004; 59:204-207.
15. Mombelli A, Samaranayake LP: Topical and systemic antibiotics in the management of periodontal diseases Int Dent J. 2004; 54:3-14.
16. Loesche WJ, Syed SA, Morrison EC, Kerry GA: Metronidazole in Periodontitis. Clinical and Bacteriological Results after 15 to 30 Weeks. Journal of Periodontology 1984; 55:325-335.
17. Zaura-Arite E, Marle J, Cate JM. Confocal microscopy study of undisturbed and chlorhexidine-treated dental biofilm. J Dent Res. 2001; 80(5):1436-1440.
18. Garrett S, Johnson L, Drisko CH: Two multi-center studies evaluating locally delivered doxycycline hyclate, placebo control, oral hygiene, and scaling and root planing in the treatment of periodontitis. Journal of Periodontology 1999; 70(5):490-503.
19. Aimetti M, Romano F, Torta I: Debridement and local application of tetracycline-loaded fibres in the management of persistent periodontitis: results after 12 months. J Clin Periodontol 2004; 31(3):166-172.
20. Radvar M, Pourtaghi N, Kinane DF: Comparison of 3 periodontal local antibiotic therapies in persistent periodontal pockets. J Periodontol. 1996; 67(9):860-865.
21. Williams RC, Paquette DN: Treatment of periodontitis by local administration of minocycline microspheres: a controlled trial. J Periodontol. 2001; 72:1535-1544.
22. Kinane DF, Radvar M: A six-month comparison of three periodontal local antimicrobial therapies in persistent periodontal pockets. Journal of Periodontology 1999; 70(1):1-7.
23. Firatli E, Unal T, Onan U, Sandalli P: Antioxidative activities of some chemo-therapeutics. A possible mechanism in reducing gingival inflammation. J Clin Periodontol. 1994; 21(10):680-683.
24. Wolff LF: Chemotheraputic agents in the prevention and treatment of periodontal disease. Northwest Dentistry 1985; 64:15-24.
25. Zaura-Arite E, Van Marle: Confocal microscopy study of undisturbed and chlorhexidine-treated dental biofilm. J Dent Res. 2001; 80(5):1436-1440.

26. Eakle W: Depth of penetration in periodontal pockets with oral irrigation. J Clin Periodontol. 1986; 13:39-44.
27. Ciancio SG: Antiseptics and antibiotics as chemotherapeutic agents for periodontitis management. Compendium of Continuing Education in Dentistry 2000; 21:59-78.
28. Subramaniam K: The effect of different concentrations of Neem (*Azadiractha indica*) leaves extract on the inhibition of *Streptococcus mutans* (*In vitro*). Dent. J. 2005; 38(4):125-133.
29. Chitme HR, Chandra R, and Kaushik S: Studies on anti-diarrhoeal activity of *calotropis gigantea* in experimental animals. Journal of Pharmacy & Pharmaceutical Sciences 2003; 7:70-75.
30. Sakarkar DM, Kosalge SB, Sheikh S. Formulation Development and Evaluation of Unit Moulded Herbal Semisolid Jelly useful in treatment of Mouth Ulcer. International Journal of PharmTech Research 2011; 3(3):1705-1713.
31. Prabu GR, Gnanamani A, Sadulla S: Guaijaverin-a plant flavonoid as potential antiplaque agent against Streptococcus mutans. J. Appl. Microbiol. 2006; 101:487-495.
32. Cowan MM: Plant products as antimicrobial agents. Clinical Microbiology Reviews. 1999; 12(4):564–582.
33. Dhinahar S, Lakshmi T: Role of botanicals as antimicrobial agents in management of dental infections- a review. International Journal of Pharma and Bio Sciences. 2011; 2(4):B690-B704
34. Azuma Y, Ozasa N, Ueda Y, Takagi N. Pharmacological studies on the anti-inflammatory action of phenolic compounds. J Dent Res. 1986; 65:53-56.
35. Firatli E, Unal T: Antioxidative activities of some chemotherapeutics. A possible mechanism in reducing gingival inflammation. Journal of Clinical Periodontology. 1994; 21(10):680-683.
36. Fine DH, Furgang D, Barnett ML, Drew C, Steinberg L, Charles CH, and Vincent JW: Effect of an essential oil-containing antiseptic mouthrinse on plaque and salivary *Streptococcus mutans* levels. Journal of Clinical Periodontology 2000;27:157-161.
37. Ciancio SG, Lauciello F, Shiby O, Vitello M, and Mather M: The effect of an antiseptic mouthrinse on implant maintenance: plaque and periimplant gingival tissues. Journal of Periodontology 1995; 66: 962-965.

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