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Review Article

Local Drug Delivery Modalities in Treatment of Periodontitis: A Review

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Abstract:

Periodontitis is an inflammatory disease that causes destruction of tooth supporting tissues, characterized by multifactorial etiology with pathogenic bacteria being the primary etiologic agents that dwells the subgingival area. Local drug delivery system consists of antimicrobial dosages that produces more constant and prolonged concentration profiles within the subgingival tissue and provides better access into the periodontal pockets. It addresses the critical distress of exposing the patient to adverse effects of systemic administration. This article reviews the literature and presents novel trends such as osteoblast activators, growth factors, and herbal products in the local drug delivery system.

Key Words: Antimicrobial, growth factors, herbal extracts, periodontal pockets, sustained delivery

Introduction

Periodontitis is an inflammatory disease that causes destruction of tooth supporting tissues[1] and is characterized by multifactorial etiology with pathogenic bacteria being the primary etiologic agents that dwells the subgingival area.[2] The clinical signs include changes in the morphology of gingival tissues, gingival bleeding as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria.[3] The periodontal treatment aims to eradicate gingival inflammation, eliminate bleeding, reduce periodontal pocket depth, arrest destruction of soft tissue, and bone. Therapeutic approach for periodontitis is to eliminate the bacteria, either with hand instrumentation or with electronic instrumentation along with use of chemotherapeutic agents systemically or locally.[2]

Topical administration of antibacterial agents in the form of mouth washes, dentifrice or gels is an effective measure in controlling supragingival plaque. Irrigation systems or devices can deliver agents into deep pockets but clinically not effective to stop the progression of periodontal attachment loss. Recent novel trend is delivery of antimicrobial dosages using topical delivery and controlled release system at the target site which produces more constant and prolonged concentration profiles.[1] These devices utilizes the control release technologies to deliver therapeutic concentrations for at least three or more number of days following a single application.[4] The drug will be released over time either by degradation of the polymer backbone or diffusion through polymer matrix or by a combination of the any two mechanisms, i.e., pure diffusion, chemical reactions, counter current diffusion or externally imposed controls.[5]

Local Drug Delivery

The treatment method was pioneered by Goodson of Forsyth's Dental Research Center. The effectiveness of this therapy is that, it reaches the base of periodontal pocket and it maintains the antimicrobial concentration for an adequate time for effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device.[6]

There are distinct phases in a periodontal treatment plan where a dental practitioner can use a sustained release device. It can be used as an adjunct to scaling and root planning and for periodontal maintenance therapy.[7] Microbiological analysis is required for proper selection of antibiotics before commencement of treatment as disease exhibits a diverse anti-microbial susceptibility.[8] It can be safely used in medically compromised patients for whom surgery is not an option or those who refuse surgical treatment.[7] Various formulations are available in the form of fibers, film, injectable systems, gels, strips and compacts, vesicular systems, micro particle system and nanoparticle (NP) system.[6]

The commonly used antimicrobial delivery systems are:

- Tetracycline fiber
- Metronidazole gel
- Chlorhexidine chip
- Minocycline gel
- Doxycycline polymer.

Tetracycline

Historically, tetracyclines are classified into first, second and third generation. Those obtained by biosynthesis

i.e., tetracycline; chlortetecycline; oxytetracycline; demeclocycline are first generation; if they are derivatives of semisynthesis: Doxycycline; lymecycline; meclocycline; methacycline; minocycline; rolitetracycline are classified as second generation and if they are obtained from total synthesis i.e., tigecycline are categorized as third generation.[9]

Tetracycline fibers are commercially available as Actisite® (tetracycline periodontal) periodontal fiber for periodontal pocket placement consists of a 23 cm (9 inch) monofilament of ethylene/vinylacetate copolymer, 0.5 mm in diameter, containing 12.7 mg of evenly dispersed tetracycline hydrochloride, USP Actisite® (tetracycline periodontal) fiber provides continuous release of tetracycline for 10 days.[10] The other commercially available formulation is periodontal plus AB. It is a sustained drug delivery system with multi-modal delivery kinetics for specific use in periodontal disease sites. A collagen fibril based formulation contains tetracycline hydrochloride (2 mg of tetracycline) in which 25 mg are collagen fibrils that can be directly applied for all levels of periodontal infections.[11]

Sachdeva and Agarwal[12] applied tetracycline in the form of modified collagen matrix following scaling and root planning and found beneficial role in treatment of chronic periodontitis. Similarly Kataria *et al.*,[13] Panwar and Gupta[14] applied tetracycline fibers as an adjunct to scaling and root planing and found it to be more effective in reducing inflammation. Pavia *et al.*,[15] showed that tetracycline and its derivatives minocycline, oxytetracycline and chlortetracycline strongly adsorb to tooth surfaces retaining their antibacterial activity and are quite effective in treating chronic periodontitis.

Minocycline

Minocycline is available in the form of microspheres, film and ointment for local delivery system and exhibits bacteriostatic action at the target site.[16] Moreover out of all the tetracyclines, minocycline has the most marked substantivity and greater lipid solubility.[17] It is available commercially under the trade name of Arestin™. Technology employs microencapsulated minocycline hydrochloride in a bioabsorbable polymer as the vehicle (polyglycolide-co-dl-lactide [PLG]). The administration causes sustained local release of the antibiotic.[18]

Graça *et al.*,[19] evaluated topical locally delivered minocycline as an adjunctive to non-surgical periodontal treatment and suggested that adjunctive minocycline gel provides a more advantageous outcome for nonsurgical periodontal treatment in terms of probing attachment level and bleeding on deep probing. Similarly, Lu and Chei[20] carried out a clinical trial and suggested that scaling and root planning with adjunctive sub gingival administration of minocycline ointment has a significantly better and prolonged effect as compared to scaling and root planning alone on the reduction of probing depth, clinical attachment loss, gingival index and interleukin-1β content, but in contrary Graça *et al.*,[19] does not found beneficial effect on bleeding on probing.

Doxycycline

Doxycycline is available commercially by the trade name Atridox. The product is a subgingival controlled-release product composed of a two syringe mixing system.[21] Abdaly *et al.*[22] evaluated local delivery of Atridox as an adjunctive in management of chronic periodontitis and found reduction in subgingival microbiological count. Javali and Vandana[23] carried out a study to evaluate and compare the efficacy of local delivery of 10% doxycycline hyclate in adjunct to scaling and root planing in the treatment of Periodontitis and found that on comparison, scaling and root planning in adjunct with doxycycline group showed better results. Salvi *et al.*[24] revealed significant reduction in clinical and microbiological parameters after application of atridox.

Metronidazole

Metronidazole is available commercially by the trade name of Elyzol. This local drug delivery system utilizes a semi-solid suspension of metronidazole benzoate in a mixture of glyceryl mono-oleate and triglyceride. It is advantageous to use it in the treatment of chronic periodontitis as anaerobic bacteria are believed to be the predominant causative factor in periodontitis and metronidazole is a member of nitroimidazole class of antibiotics that specifically targets anaerobic microorganisms.[25] Among the various locally delivered chemotherapeutic agents metronidazole, has bactericidal action against anaerobes, such as *Prevotela intermedia, Porphyromonas gingivalis, Tannerella forsythia,* Fusobacterium species and spirochetes like *Treponema denticola, Treponema vincentii,* which are generally believed to be the main pathogens associated with periodontitis.[26]

Stolzel studied systemic absorption of metronidazole and concluded that the systemic load after single application of metronidazole 25% dental gel is less in comparison to one metronidazole 250 mg tablet.[27] Ainamo *et al.*[28] compared the effect of metronidazole 25% gel with subgingival scaling in adult Periodontitis and found that both periodontal pocket depth and bleeding on probing were significantly reduced in both groups. Noyan *et al.*[29] observed that local metronidazole in combination with scaling and root planning seems to be more effective in terms of producing both clinical and microbial improvements.

Azithromycin (AZM)

A AZM has a wide antimicrobial spectrum of action towards anaerobic bacteria as well as Gram-negative bacilli. It is effective against periodontal pathogens such as aggregatibacter actinomycetemcomitans and *P. gingivalis*.

Tyagi *et al.*,[30] investigated the clinical effectiveness of AZM at a concentration of 0.5% in an indigenously prepared bioabsorbable controlled release gel as an adjunct to non-surgical mechanical therapy in the treatment of chronic periodontitis. Although both treatment strategies seem to benefit patients, the adjunctive use of 0.5% of AZM showed better results.

Chlorhexidine

Chlorhexidine is available in the form of mouth rinses, gels, varnishes, and chip to be used as a local drug delivery agent for the treatment of periodontal diseases. It is commercially available as periochip (2.5 mg), chlosite (1.5% CHX), periocol (2.5 mg).[7] Various studies[31-33] have demonstrated chlorhexidine as an adjunct to scaling and root planning as an effective measure in improving clinical parameters and reducing microbial load.

Newer Trends

Taurolidine

Taurolidine is a novel introduction and might be an alternative in periodontitis treatment. Zollinger *et al.*,[34] evaluated *in vitro* effect via coating the surface with 10 mg/ml taurolidine and found that this concentration prevented completely biofilm formation of P. gingivalis. Thus, it can be used as an adjunct to mechanical removal of biofilms.

Simvastatin (SMV)

SMV exhibits bone regeneration properties by participating directly in osteoblast activation via increasing bone morphogenic factor-2 expression, in osteoclast inhibition and indirectly by stimulating neovascularization by increasing the secretion of vascular endothelial growth factor.[35] SMV is a specific competitive inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase. Pradeep *et al.*,[36] investigated the effectiveness of SMV by carrying out radiologic assessment of intrabony defect fill by using computer-aided software and found significant intrabony defect fill at sites treated with SMV as an adjunct to scaling and root planning.

Alendronate

Alendronate (4-amino 1-hydroxybutylidine bisphosphonate), a novel bisphosphonate is a very potent inhibitor of bone resorption. Veena *et al.*,[37] applied 0.1 ml alendronate gel and 0.1 ml placebo gel following surgical flap debridement at the experimental and control sites respectively and found that alendronate was more effective in improving parameters clinically and radio graphically as compared to placebo.

Rocha *et al.*,[38] evaluated effect of local delivery of 1% alendronate gel into periodontal pockets in chronic periodontitis patients with Type 2 diabetes mellitus and revealed alendronate as an effective adjunct to scaling and root planning as it resulted in probing depth reduction, clinical attachment level gain and improved bone fill as compared to placebo gel. Thus, Alendronate is an effective treatment modality in periodontitis associated bone loss.

Basic Fibroblast Growth Factor (bFGF) (*In situ* Tissue Engineering)

Nakahara *et al.*,[39] developed a controlled-release system by using a sandwich membrane consisting of a collagen sponge scaffold and gelatine microspheres containing bFGF *in situ* on the basis of new concept of *in situ* tissue engineering and demonstrated regeneration of periodontal tissues in 4 weeks. Thus concluded that sandwich membrane induced successful regeneration of the periodontal tissues in a short period of time. Murakami *et al.*,[40] demonstrated that bFGF can be applied as one of the therapeutic modalities which actively induce periodontal tissue regeneration. The results of *in vitro* studies suggest that by suppressing the cytodifferentiation of periodontal ligament cells (PDL) cells into mineralized tissue forming cells, bFGF may play important roles in wound healing by promoting angiogenesis and inducing the growth of immature PDL cells, and may in turn accelerate periodontal regeneration.

Chitosan

Chitosan is an interesting polymer that has been used extensively in the medical field. It is either partially or fully deacetylated chitin. As chitin occurs naturally in fungal cell walls and crustacean shells, it is a fully biodegradable and biocompatible natural polymer, and can be used as an adhesive and as an antibacterial and antifungal agent.[41] It is a versatile hydrophilic polysaccharide derived from chitin, has a broad antimicrobial spectrum to which gram-negative, Gram-positive bacteria and fungi are highly susceptible and has a regenerative effect on periodontia and also accelerates the formation of osteoblasts which are responsible for bone formation.[42] Ikinci *et al.*,[43] determined the antimicrobial activity of chitosan formulations either in a gel or film form against a periodontal pathogen, *P. gingivalis* and concluded that this formulation seems to be promising delivery systems for local therapy of periodontal diseases due to its antimicrobial activity and bio adhesive property.

Ipriflavone

Ipriflavone (7-isopropoxy iso-flavone) is a synthetic isoflavone derivative that acts primarily to suppress bone resorption. Other *in vitro* studies have shown that ipriflavone can stimulate osteoblasts to form new bone.[44] Min *et al.*,[45] evaluated effect of ipriflavone on periodontal reorganization and revealed that it shows more rapid effect. Perugini *et al.*,[46] designed a film dosage form for sustained delivery of ipriflavone into the periodontal pocket. A monolayer composite systems made of ipriflavone loaded poly micromatrices in a chitosan film form, were obtained by emulsification/evaporation/casting technique. *In vitro* experiments demonstrated that the composite micromatricial films represent a suitable dosage form to prolong ipriflavone release for 20 days.

Herbal Extracts

Harungana madagascariensis (Hypericaceae) is known to have biological properties with mainly antibacterial, antifungal and antiviral effects. Moulari *et al.*,[47] investigated the *in vitro* bactericidal effect of the ethyl acetate *H. madagascariensis* leaf extract using the PLG-NP and found significant bactericidal effects against the bacterial strains tested. However the study observed diminution of the bactericidal concentration on in corporatation of *H. madagascariensis* into PLG-NP as incorporation of the HLE into a colloidal carrier optimized its antibacterial performance.

Aloe vera possess certain active components such as saponins, anthraquinones, amino acids, lignin, salicylic acid, etc., in which anthraquinones have the strong anti-bacterial, anti-viral and anti-neoplastic properties.[48] Virdi *et al.*,[49] evaluated the effect of *A. vera* gel in patients with chronic periodontitis and found that group in which *A. vera* gel was applied as an adjunct to scaling and root planning showed significantly better results than scaling and root alone. Thus, the study encourages the use of *A. vera* in the treatment of periodontitis.

Eucalyptus,[50] neem leaf[51] and bloodroot also possess antibacterial and anti-inflammatory properties and can help in improving oral health status. Other than individual herbs, herbal combinations such as mixture of menthol, chamomile, peppermint oil, sage oil, clove oil, caraway oil, echinacea extract and myrrh tincture exhibit properties to reduce severity of periodontitis symptoms and can improve the oral hygiene.[52]

Conclusion

Advancements in the field of medicine have led to delivery of safe and efficient medicine into periodontal pockets bypassing the systemic metabolism. High gingival crevicular fluid concentration and access to periodontal pockets can be achieved without exposing the individual to systemic complications. The local application provides a better opportunity to deal patients with non-responding and recurrent periodontal pockets and results in better patient compliance and satisfaction. General dentists should promote local drug delivery systems in chronic periodontitis patients as this therapeutic intervention protect patients from risk of systemic overload or drug over dosage.

References

1. Divya PV, Nandakumar K. Local drug delivery: Periocol in periodontics. Trends Biomater Artif Organs 2006;19(2):74-80.
2. Sathwara JD, Sathwara CJ. Therapeutic effect of topical subgingival application of 1.5% chlorhexidine gel as local drug delivery system in chronic periodontitis – A clinical and microbiological study. Int J Dent Clin 2014;6(2):8-11.
3. Sunil A, Venkatesh M, Udupa N. Controlled drug delivery systems for periodontitis Pharm Rev 2004;Jul-Aug: 61-82.
4. Saarangi R, Kumar JV, Prabhakar T, Swamy P. Antimicrobial activity of novel biodegradable periodontal films containing ciprofloxacin and ornidazole. Sch Acad J Pharm 2013;2(2):70-3.
5. Kaur G, Dang R, Grover D. Local drug delivery- A review. Guidant. Available from: http://www.guident.net/periodontics/local-drug-delivery-a-review.html. [Last Accessed on 2015 Sep 12].
6. Kaplish V, Walia MK, Kumar HS. Local drug delivery systems in the treatment of periodontitis: A review. Pharmacophore 2013;4(2):39-49.
7. Dodwad V, Vaish S, Mahajan A, Chhokra M. Local drug delivery in periodontics: A strategic intervention. Int J Pharm Pharm Sci 2012;4(4):30-4.
8. Patil V, Mali R, Mali A. Systemic anti-microbial agents used in periodontal therapy. J Indian Soc Periodontol 2013;17(2):162-8.
9. Fuoco D. New Classification Framework and Structure-Activity- Relationship (SAR) of Tetracycline Structure Based Drugs Cornell University Library. Arxiv.org/quantitative-biology/biomolecules. Available from: http://www.arxiv.org/vc/arxiv/papers/1111/1111.2769v1.pdf. [Last Accessed on 2015 Sep 15].
10. Actisite. Available from: http://www.rxlist.com/actisite-drug.htm. [Last Accessed on 2015 Sep 12].
11. Available from: http://www.tradeindia.com/fp429668/Periodontal-Plus-AB.html. [Last Accessed on 2015 Sep 09].
12. Sachdeva S, Agarwal V. Evaluation of commercially available biodegradable tetracycline fiber therapy in chronic periodontitis. J Indian Soc Periodontol 2011;15(2):130-4.
13. Kataria S, Chandrashekar KT, Mishra R, Tripathi V, Galav A, Sthapak U. Effect of tetracycline HCL (periodontal plus AB) on aggregatibacter actinomycetemcomitans levels in chronic periodontitis. Arch Oral Dent Res 2015;2(1):1-8.
14. Panwar M, Gupta SH. Local drug delivery with tetracycline fiber: An alternative to surgical periodontal therapy. Med J Armed Forces India 2009;65:244-6.
15. Pavia M, Nobile CG, Angelillo IF. Meta-analysis of local tetracycline in treating chronic periodontitis. J Periodontol 2003;74:916-32.
16. Akula S, Chava V. Minocyclines in periodontal therapy J Indian Soc Periodontol 2000;3:49-51.
17. Jones AA, Kornman KS, Newbold DA, Manwell MA. Clinical and microbiological effects of controlled-release locally delivered minocycline in periodontitis. J Periodontol 1994;65(11):1058-66.
18. Williams RC, Paquette DW, Offenbacher S, Adams DF, Armitage GC, Bray K, *et al.* Treatment of periodontitis by local administration of minocycline microspheres: A controlled trial. J Periodontol 2001;72:1535-44.
19. Graça MA, Watts TL, Wilson RF, Palmer RM. A randomized controlled trial of a 2% minocycline gel as an adjunct to non-surgical periodontal treatment, using a design with multiple matching criteria. J Clin Periodontol 1997;24(4):249-53.

20. Lu HK, Chei CJ. Efficacy of subgingivally applied minocycline in the treatment of chronic periodontitis. J Periodontal Res 2005;40(1):20-7.
21. Available from: https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/527/atridox. [Last Accessed on 2015 Sep 16].
22. Abdaly MA, Refai AN, Gouda UM, Atty HA. Local delivery of atridox (doxycycline gel) as adjunctive in management of chronic periodontitis. Suez Canal Univ Med J 2008;11(I):41-6.
23. Javali MA, Vandana KL. A comparative evaluation of atrigel delivery system (10% doxycycline hyclate) Atridox with scaling and root planing and combination therapy in treatment of periodontitis: A clinical study. J Indian Soc Periodontol 2012;16(1):43-8.
24. Salvi GE, Mombelli A, Mayfield L, Rutar A, Suvan J, Garrett S, *et al.* Local antimicrobial therapy after initial periodontal treatment. J Clin Periodontol 2002;29(6):540-50.
25. Stoltze K. Concentration of metronidazole in periodontal pockets after application of a metronidazole 25% dental gel. J Clin Periodontol 1992;19:698-701.
26. Awartani FA, Zulqarnain BJ. Comparison of the clinical effects of subgingival application of metronidazole 25% gel and scaling in the treatment of adult periodontitis. Quintessence Int 1998;29(1):41-8.
27. Stoltze K, Stellfeld M. Systemic absorption of metronidazole after application of a metronidazole 25% dental gel. J Clin Periodontol 1992;19:693-7.
28. Ainamo J, Lie T, Ellingsen BH, Hansen BF, Johansson LA, Karring T, *et al.* Clinical responses to subgingival application of a metronidazole 25% gel compared to the effect of subgingival scaling in adult periodontitis. J Clin Periodontol 1992;19:723-9.
29. Noyan U, Yilmaz S, Kuru B, Kadir T, Acar O, Büget E. A clinical and microbiological evaluation of systemic and local metronidazole delivery in adult periodontitis patients. J Clin Periodontol 1997;24(3):158-65.
30. Tyagi P, Vaish S, Dodwad V. Clinical efficacy of subgingivally delivered 0.5% controlled release azithromycin gel in the management of chronic periodontitis. Indian J Med Sci 2011;65(6):223-30.
31. Jeffcoat MK, Bray KS, Ciancio SG, Dentino AR, Fine DH, Gordon JM, *et al.* Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planning alone. J Periodontol 1998;69(9):989-97.
32. Pietruska M, Paniczko A, Waszkiel D, Pietruski J, Bernaczyk A. Efficacy of local treatment with chlorhexidine gluconate drugs on the clinical status of periodontium in chronic periodontitis patients. Adv Med Sci 2006;51 Suppl 1:162-5.
33. Soskolne WA, Heasman PA, Stabholz A, Smart GJ, Palmer M, Flashner M, *et al.* Sustained local delivery of chlorhexidine in the treatment of periodontitis: A multi-center study. J Periodontol 1997;68(1):32-8.
34. Zollinger L, Schnyder S, Nietzsche S, Sculean A, Eick S. *In-vitro* activity of taurolidine on single species and a multispecies population associated with periodontitis. Anaerobe 2015;32:18-23.
35. Montero J, Manzano G, Albaladejo A. The role of topical simvastatin on bone regeneration: A systematic review. J Clin Exp Dent 2014;6(3):e286-90.
36. Pradeep AR, Thorat MS. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: A randomized clinical trial. J Periodontol 2010;81(2):214-22.
37. Veena HR, Prasad D. Evaluation of an aminobisphosphonate (alendronate) in the management of periodontal osseous defects. J Indian Soc Periodontol 2010;14(1):40-5.
38. Rocha M, Nava LE, Vázquez de la Torre C, Sánchez-Márin F, Garay-Sevilla ME, Malacara JM. Clinical and radiological improvement of periodontal disease in patients with type 2 diabetes mellitus treated with alendronate: A randomized, placebo-controlled trial. J Periodontol 2001;72(2):204-9.
39. Nakahara T, Nakamura T, Kobayashi E, Inoue M, Shigeno K, Tabata Y, *et al.* Novel approach to regeneration of periodontal tissues based on *in situ* tissue engineering: Effects of controlled release of basic fibroblast growth factor from a sandwich membrane. Tissue Eng 2003;9(1):153-62.
40. Murakami S, Takayama S, Ikezawa K, Shimabukuro Y, Kitamura M, Nozaki T, *et al.* Regeneration of periodontal tissues by basic fibroblast growth factor. J Periodontal Res 1999;34(7):425-30.
41. Soutter W. Chitosan Nanoparticles - Properties and Applications. Available from: http://www.azonano.com/article.aspx. [Last Accessed on 2015 Sep 18].
42. Tanikonda R, Ravi RK, Kantheti S, Divella S. Chitosan: Applications in dentistry. Trends Biomater Artif Organs 2014;28(2):74-8.
43. Ikinci G, Senel S, Akincibay H, Kas S, Ercis S, Wilson CG, *et al.* Effect of chitosan on a periodontal pathogen *Porphyromonas gingivalis*. Int J Pharm 2002;235(1-2):121-7.
44. English J. Ipriflavone Bone Support Complex Nutrition Review, 2013. Available from: http://www.*nutritionreview.org/2013/04/ipriflavone-bone-support-complex*. [Last Accessed on 2015 Sep 12].
45. Min JH, Cho JH, Lee KH, Hwang HS. The effects of ipriflavone on the periodontal reorganization following experimental tooth movement in the rat. Korean J Orthod 2008;38(5):347-57.
46. Perugini P, Genta I, Conti B, Modena T, Pavanetto F. Periodontal delivery of ipriflavone: New chitosan/PLGA film delivery system for a lipophilic drug. Int J Pharm 2003;252(1-2):1-9.
47. Moulari B, Lboutounne H, Chaumont JP, Guillaume Y, Millet J, Pellequer Y. Potentiation of the bactericidal activity of *Harungana madagascariensis* Lam. ex Poir. (Hypericaceae) leaf extract against oral bacteria using poly (D, L-lactide-co-glycolide) nanoparticles: *In vitro* study. Acta Odontol Scand 2006;64(3):153-8.
48. Dheepika B, Maheswari U. *Aloe vera* in oral diseases - A review. Int J Pharm Pharm Sci 2014;6(2):64-6.

49. Virdi HK, Jain S, Sharma S. Effect of locally delivered *Aloe vera* gel as an adjunct to scaling and root planning in the treatment of chronic periodontitis: A clinical study. Indian J Oral Sci 2012;3:84-9.
50. Nagata H, Inagaki Y, Tanaka M, Ojima M, Kataoka K, Kuboniwa M, *et al.* Effect of eucalyptus extract chewing gum on periodontal health: A double-masked, randomized trial. J Periodontol 2008;79(8):1378-85.
51. Pai RM, Leelavathi D. Udupa AN. Evaluation of antiplaque activity of Azadirachta indica leaf extract gel: A 6-week clinical study. J Ethnopharmacol 2004;90(1):99-103.
52. Mundinamane DB, Suchetha A, Venkataraghavan K, Garg A. Newer trends in local drug delivery for periodontal problems: A review. Int J Contemp Dent 2011;2(4):59-62.