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Evidence Based Review on Herbal Local Drug Delivery

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Abstract: *Periodontitis present as local destructive disease in periodontium and thus require a much specific treatment. The traditional scaling and root planing therapy alone is not sufficient for treatment of moderate to severe periodontal pocket because of its relative time consumption and inaccessibility in deep pocket. Thus systemic and local administration of drugs is recommended. Local Drug Delivery (LDD) provides specificity by acting on the site of infection. Local drug delivery systems have been used from late 1970's. They come in various forms like gel, films, fibers, nano-particles, micro-particles, vesicular systems etc. The use of herbal medication as a Local Drug Delivery agent came in limelight in 2011;the different agents available areNeem, Aloe-vera, Lemon-grass, Green tea, Tea tree oil, Curcumin, Oak, Coriander, Babul, Bakul.*

Keyword:*Chronic Periodontitis, Herbal agent and Local Drug Delivery.*

I. Introduction

The inflammation in the periodontal tissue is initiated by microbial plaque and bacterial infection. The nature of the periodontal disease depend on the interaction among the bacterial agent, the environment, and the host's defense mechanisms to the bacterial assault mainly composed of gram negative anaerobic bacteria.[1]The periodontal treatment aims to eradicate gingival inflammation, bleeding, periodontal pocket depth and arrest destruction of soft tissue and bone by removal of the bacterial deposits from the tooth surface and to shift the pathogenic microbiota to one compatible with periodontal health. Therapeutic approach include mechanical scaling and root planing (SRP).[2]The effectiveness of this method is limited due to the lack of accessibility in deep periodontal pocket.[3]Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antibiotics.[4,5]

Elimination or adequate suppression of putative periodontopathic microorganisms in the subgingivalmicrobiota is essential for periodontal healing. For the effective treatment, the antibiotic must reach the depth of the pocket and produce gingival fluid concentrations higher than the minimum inhibitory concentrations (MIC) of the suspected pathogens.[6] Systemic administration has been useful in treating periodontal pockets, but repeated and long-term use of systemic antibiotics posses potential danger including resistant strains and superimposed infections. Local administration, therefore provide a useful answer to these problems. The principle requirement for effectiveness of this form of therapy is that the agent reaches the base of the pocket and is maintained there by means likereservoir for an adequate time for the antimicrobial effect to occur.[7] It was in the year 1979 when Dr. Max Goodson et al[8] first proposed the concept of controlled delivery in the treatment of periodontitis.Allopathic medications are successfully used as local drug delivery agents. Recently ayurvedic and herbal medications are increasingly gaining interest to overcome the drawbacks of the allopathic medication.

II.Classification

A]Based on the application [Rams and Slots] 1996[9]

1. Personally applied (In patient home self-care)
a. Nonsustained subgingival drug delivery
Home oral irrigation
Home oral irrigation jet tips
Traditional jet tips
Oral irrigation (water pick)
Soft cone rubber tips (Pick pocket)
b. Sustained subgingival drug delivery

2. Professionally applied (In dental office)
a.Nonsustained subgingival drug delivery
Professional pocket irrigation
b. Sustained subgingival drug delivery
Controlled release devices
Hollowfibers
Dialysis tubing
Strips
Films

B]Basedon the duration ofmedicament release
(Greenstein and Tonetti, 2000) [10]
a. Sustained release devices – Designed to provide drug delivery for less than 24 hours
b. Controlled release devices – Designed to providedrug release that at least exceeds 1 day or for atleast 3 days following application(Kornman1993)

C] Dependingon degradability.[11]
1. Non degradable devices (First generation)
2. Degradable devices (Second generation)

III.Drug Delivery Systems For Treating Periodontits

Various drug delivery systems for treating periodontitis are Fibers, Film, Injectable systems, Gels, Strips and compacts, Vesicular systems, Micro-particle system, Nanoparticle system etc.[Table 1]

1.1 Fibers

Fibers, or thread-like devices, are reservoir-type systems, placed circumferentially into the pockets with an applicator and secured with cyanoacrylate adhesive for the sustained release of trapped drug into the periodontal pocket. This is one of the best options for delivery of drug to periodontal pockets, but they have some disadvantages such as difficulty in placing fiber in pockets, patient discomfort and at fiber removal various degree of gingival redness were observed.[12]

1.2 Strips

Strips are thin and elongated matrix bands in which drugs are distributed throughout the polymer. Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents.

1.3 Films

Film either could be applied directly applied on cheek mucosa or gingival surface or can be cut into appropriate size so as to insert into site of infection. Films are matrix type of drug delivery device in which drug is distributed throughout matrix and drug release occurs by erosion, matrix dissolution or drug diffusion. This system has a several advantages than other intra pocket drug delivery devices.[13] Film having thickness less than 400μm and sufficient adhesiveness will remain submerged into periodontal pocket without interfering with the patient's oral hygiene habit. Films that release drug by diffusion alone are prepared by using non-degradable water insoluble polymers, while those that release by diffusion and matrix erosion or dissolution are prepared by water soluble or biodegradable polymers.[14,15]

1.4 Injectable gel

Along with solid devices, semi-solid devices also attain a reasonable attention for localized delivery of anti-microbial agents.[16] Release rate of the drug from gel is faster as compared to other formulations. These types of the formulations can be easily prepared and administered.

1.5 Microparticulate system

Both biodegradable as well as non-biodegradable polymeric materials have been investigated for the preparation of microspheres.These materials include the polymers of natural origin, modified natural substances and synthetic substances. Microparticles based system of biodegradable poly alpha hydroxyl acids such as poly lactide (PLA) or poly (lactide-co-glycolide). The in-vitro drug release from such system depends upon the polymer (lactide:glycolide) ratio, molecular weight, crystallinity and pH of the medium.[17] Example :Ofloxacin, Fibroblast growth factor.

1.6 Nano-particulate system

Nano-particulate system developed to improve the effectiveness of delivery system. Various advantages of nano-particulate system compared to micro particle, microsphere and emulsion based delivery system includes increased stability, controlled release rate, high dispersibility in an aqueous medium. Because of their small size nanoparticles penetrate deeper regions that may be inaccessible to other delivery system, such as periodontal pocket area below the gum line. These reduce the frequency of administration and further provide a uniform distribution of the active agents over an extended period of time.[18] Example: Biodegradable nanoparticle, Chitosan-loaded tripolypeptide and Triclosan loaded nanoparticles.

1.7 Vesicular system

Liposomal system was designed to mimic the bio-membranes in terms of structure and behaviour and hence investigated intensively for targeting periodontal pathogen. Vyas et al(2001)[17]investigated in-vitro antimicrobial activity of metronidazole bearing lectinized liposomes for intra-periodontal pocket delivery.

Table 1:Summary of various Local Drug Delivery systems.

Agent	Product available	Dosage form
Tetracycline	Actisite (25%w/v tetracycline Hcl)	Non resorbable fiber
	Periodontal plus AB (2 mg of Tetracycline in 25 mg of collagen)	Resorbable fiber
	Pluronic gel (Tetracycline - serratiopeptidase containing periodontal gel)	Biodegradable gel
	Ortho-ester	Biodegradable gel
Doxycycline	Atridox (10% doxycycline)	Biodegradeble mix in syringe
Minocycline	Arestin (2% minocycline)	Biodegradeble mix in syringe and microsphere
	Dentomycin gel (2% minocycline)	Ointment
	Periocline (2.1% w/v minocycline)	Ointment
Metronidazole	Elyzol (25% metronidazole)	Biodegradable gel
	Metrogene (5% metronidazole)	Biodegradable gel
Chlorhexidine	Periochip (2.5 mg Chlorhexidine)	Biodegradable chip
	Periocol CG(2.5 mg Chlorhexidine)	Biodegradable chip
	Chlosite (1.5% Chlorhexidine)	Biodegradable gel
Alendronate	Formulations	Biodegradable gel
Azithromycin	Formulations	Biodegradable gel
Simvastatins	Formulations	Biodegradable gel
Chitosan	Formulations	Biodegradable gel and film

IV.Agent Used In Local Drug Delivery

2.1 Tetracycline

Tetracycline containing fibers are the first available local drug. It had ethylene/vinyl acetate copolymer fiber with diameter of 0.5 mm, containing tetracycline12.7mg per 9 inches. [19]

Actisite tetracycline fibers have been approved both by the United States Food and DrugAdministration (FDA) and by the European Union's regulatory agencies. These are non-resorbable, safe, inert copolymer loaded with 25% w/w tetracycline HCI.It maintains constant concentrationsmore than 1000µg/mL for a period of 10 days.[20]

Periodontal Plus AB It is the other commercially available formula. 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.[21]Katari*a et al*. (2015)[22]Panwar and Gupta et al (2009)[23] applied tetracycline fibers as an adjunct to scaling and root planing and found it to be more effective in reducing inflammation. (P=>0.05)Sachdeva and Agarwal(2011)[24] applied tetracycline in the form of modified collagen matrix following scaling and root planning and found beneficial role in treatment of chronic periodontitis. (P=≤0.001)

2.2 Minocycline

Arestin is a FDA approved locally delivered, sustained release form of minocycline microspheres for subgingival placement. The 2% minocycline is encapsulated into bioresorbable microspheres in gel carrier.[19] Sweatha C(2015)[25] usedArestin (1mg Minocycline microspheres) adjunct to scaling and root planing, and found to be produce significant clinical benefits when compared to scaling and root planing alone.(P=≤0.001)

2.3 Doxycycline

Atridox is a FDA approved 10% doxycycline in a gel system using a syringe.[19] Abdaly*et al*(2008)[26]evaluated local delivery of Atridox as an adjunctive in management of chronic periodontitis and found reduction in subgingival microbiological count. (P=<0.05)Javali and Vandana et al (2012)[27] 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.(P=0.01)

2.4 Metronidazole

Elyzol is a topical medication containing an oil-based metronidazole 25%dental gel, applied in viscous consistency to the pocket.[19]Shifrovitch Y et al(2009)[28] in study enabled the understanding of metronidazole release from bioabsorbable polymeric films and demonstrated good biocompatibility and the ability to inhibit Bacteroidesfragilisgrowth; therefore, they may be useful in the treatment of periodontal diseases.Noyan*et al* (1997)[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.(P<0.05)

2.5 Azithromycin

Azithromycin has a wide antimicrobial spectrum of action towards anaerobic bacteria as well as Gram-negative bacilli. It is effective against periodontal pathogens such as AggregatibacterActinomycetemcomitans and *P. gingivalis*.Chavda M et al (2013)[30] suggested that locally delivered Azithromycin might be a valuable adjunct to scaling and root planing in the treatment of chronic periodontitis. (P=<0.001)

2.6 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).[31] Various studies[32-34] have demonstrated chlorhexidine as an adjunct to scaling and root planning as an effective measure in improving clinical parameters and reducing microbial load.

2.7 Simvastatin (SMV)

Statins like simvastatin (SMV), lovastatin, atorvastatin(ATV) and pravastatin are specific competitive inhibitors of 3-hydroxy-2-methyl-glutaryl coenzyme A (HMGCoA) reductase.[35] 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.[36]Emani et al (2014)[37]suggested that a potent antimicrobial activity of simvastatin against both A. actinomycetemcomitans and P gingivalis.Pradeepet al(2010)[38] 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.(P=<0.05)Martande SS et al (2017)[39]investigated the effectiveness of SMV and ATV by carrying out radiologic assessment of intrabony defect fill and found that ATV has a greater improvements in clinical parameters with higher percentage of radiographic defect depth reduction as compared to SMV in the treatment of intrabony defects.(P=<0.05)

2.8 Alendronate

Alendronate (4-amino 1-hydroxybutylidine bisphosphonate), a novel bisphosphonate is a very potent inhibitor of bone resorption. Veenaet al (2010)[40] 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.Thus, Alendronate is an effective treatment modality in periodontitis associated bone loss.(P=0.001)

2.9 Chitosan

Chitosan is a natural polysaccharide that has become established as a material with great potential for use in biomedical applications. 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 which has a broad antimicrobial spectrum to which gram-negative, Gram-positive bacteria and fungi are highly susceptible and has a regenerative effect on the periodontium and also accelerates the formation of osteoblasts which are responsible for bone formation.[42] Ikinci et al (2002)[43] determined the antimicrobial activity of chitosan formulations either in a gel or film form against a periodontal pathogenP. gingivalisand 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.(P=<0.05)

V. Herbal local durg delivery agents

Recently usage of herbal product has increasedbecause of relatively safe nature of herbal extracts, many herbal products and their component are being used for treating periodontitis in the form of local drug delivery.[Table-2]

3.1 Neem

Neem leaf extract can help reduce bacteria and plaque levels that cause the progression of periodontitis. It is suggested that bioactive materials found in neem leads to the presence of gallotannins during the early stages of plaque formation that could effectively reduce the number of bacteria available for binding to the tooth surface by increasing their physical removal from the oral cavity through aggregate formation. Additionally, the effective inhibition of glucosyltransferase activity and the reduced bacterial adhesion to saliva coated hydroxyl appetite suggest some potential anti-plaque activity.[44] Vennila K (2016)[45]investigate the efficacy of 10% whole *Azadirachtaindica*(neem) chip as an adjunct to scaling and root planning and he found that clinical parameters were statistically improved on the neem chip sites and presence of *P. gingivalis*strains were significantly reduced on the neem chip sites.(P=<0.05)

3.2 Aloe-vera

Aloe vera is a cactus plant that belongs to the Liliaceae family. More than 300 species of aloe plants exist, but only 2 species have been studied, which are Aloe barbadensis Miller and Aloe aborescens. Reported pharmacological actions of Aloe vera include anti-inflammatory, antibacterial, antioxidant, antiviral and antifungal actions as well as producing hypoglycemic effects. It reduces bleeding, inflammation and swelling of the gums. It is a powerful antiseptic in pockets where normal cleaning is difficult. It is a powerful healing promoter and can be used following extractions.[46]Jain J (2016)[46]investigate the antibacterial effect of aloevera gel against oral pathogens and he suggested that aloe vera showed antibacterial property against Aggregatibacteractinomycetemcomitans,Clostridium bacilli,Streptcoccusmutans and Staphlococcusaureus. Bhat G (2013)[47] suggested that subgingival administration of Aloe vera gel results in improvementof periodontal condition. Aloe vera gel can be used as a local drug delivery system in periodontal pockets.(P=0.001)

3.3 Lemon grass

It is a popular medicinal plant. This plant is commonly used in teas, cosmetics, and folk medicine for its antiseptic, antiemetic, anti-rheumatic, analgesic, antispasmodic, and antipyretic properties. Its chemical components like phenol and flavanoid substances were reported to show many in vitro and in vivo biological activities such as antioxidant, anti-inflammatory and anti-mutagenic activities. At a concentration of ≤2%, lemongrass essential oil inhibits the growth of several kinds of microorganisms including periodontal pathogens, especially the strains of Actinomyceslundii and Porphyromonasgingivalis, which were resistant to tetracycline hydrochloride.[48]Warad SB et al (2013)[48] conducted a study to evaluate locally delivered 2% lemongrass oil in gel form and it was found that 2% lemongrass oil offers a new choice of safe and effective adjunct to scaling and root planing.(P=<0.05)

3.4 Green tea

Green tea contains a number of bioactive chemicals. It is particularly rich in flavonoids, including catechins, and their derivatives.It has various therapeutic effects such as antioxidant, anti-collagenase, anti-inflammatory, anti-caries, antifungal, antiviral and antibacterial effects.[49]Mageed et al (2015)[50] investigate the antimicrobial effects of green tea extracts on Porphyromonasgingivalis and he found that alcoholic green tea extract was able to inhibit and kill Porphyromonasgingivalis. KudvaP et al (2011)[51]evaluated the therapeutic effect of locally delivered green tea catechin in management of chronic periodontitis and it was found that green tea adjunct to scaling and root planning is more effective than scaling and root planning alone. (P=<0.001)Hattarki SA et al (2013)[52]conducted a randomized and placebo controlled split mouth study and compared the effect of scaling and root planning alone or in combination with green tea catechins as local drug delivery into periodontal pockets and found that green tea was more effective than scaling and root planning alone.(P=<0.001)

2.5 Tea tree oil

Tea tree oil (TTO) is derived from the paper bark tea tree.TTO has a broad-spectrum antimicrobial, antifungal, antiviral, antioxidant and anti-inflammatory effect.Elgendy EA(2015)[53]suggested that TTO is effective as an adjunctive treatment of scaling and root planning on the clinical parameters and the level of PTX3 (pentraxin-3) in chronic periodontitis.(P=>0.01)Pentraxin-3 (PXT3) is an inflammatory molecule that belongs to the same family of C-reactive protein (CRP), PTX3 is produced by the widely distributed innate immune cells including neutrophils, fibroblasts, dendritic cells, epithelial cells, macrophages and vascular

endothelial cells in response to inflammatory mediators, such as IL-1, tumors necrosis factor-α (TNF-α) and bacterial products.[53]

2.6 Curcumin

Turmeric (the common name for Curcuma longa) is an Indian spice derived from the rhizomes, a perennial member of the Zingiberaceae family. The active constituents of turmeric include the three curcuminoids: Curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (turmerone, atlantone, and zingiberone), sugars, proteins, and resins.Curcumin exhibits anti‑inflammatory, antioxidant, anticarcinogenic, antiviral, and antimicrobial activities.Curcumin modulates the inflammatory response by down‑regulating the activity of cyclooxygenase‑2, lipoxygenase, and inducible nitric oxide synthase enzymes and inhibits the production of the inflammatory cytokines.[54]Izui S et al (2015)[55]investigated the antibacterial effect of curcumin on periodontopathic bacteria, particularly Porphyromonasgingivalis and suggested that Curcuminpossesses antibacterial activity against periodontopathic bacteria, and may be a potent agent for preventing periodontal diseases. Nagasri M (2013)[56]found that the local application of curcumin in conjunction with scaling and root planing have showed improvement in periodontal parameters and has a beneficial effect in patients with chronic periodontitis. (P=0.001)

2.7 Oak

Oak is a species from Fagacea family which is grown in Western Iran and has been traditionally used for the treatment of gastric ulcers, superficial injuries and local inflammation with hemostatic, anti-bacterial , anti- inflammatory , anti- nociceptive and anti-oxidant effects.[57]

2.8 Coriander

C.Sativumis from the Umbelliferae family was used in Iranian folk medicine as a carminative and spasmolytic agent. It has anti-inflammatory, analgesic, anti-bacterial and anti-oxidant activities. C. sativum extract has tannins also.[57]Yaghini J(2014)[57] conducted a randomized double blinded controlled trial to evaluate the clinical effects of subgingival application of herbal gel(extracts of oak and coriander) in periodontal pockets. Results showed statistically significant improvements in periodontal indices. (P=<0.05)

2.9 Babul

Babul has cyanogenic glycosides in addition to several enzymes such as oxidases, peroxidases and pectinases that have shown to inhibit antimicrobial properties. Its bark contains tanins (24-42%) which has analegesic, anti-inflammatory properties.[58]Clark DT et al (1993)[59] suggest action of acacia gum against suspected periodontal pathogens like Actinobacillusactinomycetemcomitans, Capnocytophaga spp., Porphyromonasgingivalis, Prevotellaintermediaand Treponemadenticolaand their enzymes has a clinical value.

2.10 Bakul

Bakul has lupeol which is one of the major pharmacologically active ingredients. It has anti-inflammatory and anti-microbial properties.[59]

2.11 Pomegranate

Pomegranate has active compounds containing polyphenolic flavonoids (egPunicalagins and ellagic acid) are believed to prevent gingivitis through a number of mechanisms including reduction of oxidative stress in the oral cavity, antioxidant activity, anti-inflammatory effects and anti-bacterial effects, so rinsing with pomegranate lowers the activity of alfaglucuronidase, an enzyme that breaks down sucrose while it increased the activities of ceruloplasmin, an antioxidant enzyme.[59]Gomes LA (2016)[60] did a study to evaluate the antimicrobial activity of pomegranate glycolic extract (PGE) against the periodontal pathogen Porphyromonasgingivalisby using Galleria mellonellaas in vivo model.Phogat M(2014)[58]conducted a randomized, controlled split mouth clinical study to evaluate the efficacy of a xanthan based chlorhexidine versus herbal gel [Babul, Bakul, Promogranate] as an adjunct to periodontal therapy and it was found that there were significant clinical benefits when compared with scaling and root planing alone.(P=<0.001)

Table 2: Evidence based studies on herbal local drug delivery agent:

Herbal agents	Author name and year	Type of study Level of evidence*
Neem	Vennilak[2016]	Randomized split mouth study 1b
Aloe-vera	Bhat[2013]	Randomized split mouth study 1b
Lemon grass	Warad [2013]	Randomized split mouth study 1b

Green tea	Hattarki SA [2013] Kudva P [2010]	Randomized controlled clinical trial 1b Randomized split mouth study 1b
Tea tree oil	Elgendy[2015]	Randomized controlled clinical trial 1b
Curcumin	1.Nagasri M [2013] 2.Behal R [2010]	Randomized split mouth study 1b Randomized split mouth study 1b
Oak	Yaghini[2014]	Randomized double blind clinical trial 1b
Coriander	Yaghini[2014]	Randomized double blind clinical trial 1b
Babul	Phogat M [2014]	Randomized controlled clinical trial 1b
Bakul	Phogat M [2014]	Randomized controlled clinical trial 1b
Promogranate	Phogat M [2014]	Randomized controlled clinical trial 1b

*Level of evidence according to CEBM (Centre for Evidence Based medicine)

VI. Conclusion

Advancements in the field of medicine have led to delivery of safe and efficient medicine into periodontal pockets bypassing the systemic metabolism.Based on the available evidence, local drug delivery into the periodontal pocket as an adjunct to scaling and root planing can considerably improve periodontalhealth.Kalsi R et al[2011] and Pe´rez PM et al[2013] in their respective systematic review and meta-analysis stated that local drug delivery has an added advantage over scaling and root planning alone. In this article a brief review has been presented which highlights the antimicrobial and clinical effect of various ayurvedic and herbal product as adjunct to scaling and root planning but studies with higher evidence on ayurvedic and herbal medications are required to provide concrete evidence on their usage over allopathic medication.

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