



ISSN: 0975-766X  
CODEN: IJPTFI  
Review Article

Available through Online  
www.ijptonline.com

## RECENT ADVANCES IN THE TREATMENT OF PERIODONTITIS

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Received on 09-10-2014

Accepted on 25-10-2014

### Abstract

Periodontitis is an inflammatory disorder which is characterized by microbial colonization of periodontal pockets which ultimately leads to the bacterial plaques and tooth loosening. Therefore it is a common infection which is to be taken care of in the present scenario as it can occur in individuals belonging to any gender or race. Various drug delivery systems containing both antibiotics as well as plant extracts are in use to improve the clinical symptoms of periodontitis. However the preferred one being the one which incorporates antibiotics in it. Moreover local drug delivery systems are more appropriate for use due to their site specificity and requirement of low therapeutic dose resulting in reduction in undesirable peripheral side effects. The present review elaborates the various treatment modalities employed to treat periodontitis.

**Keywords:** Antibiotics, Local drug delivery systems, Periodontitis, Periodontal pockets.

### Introduction

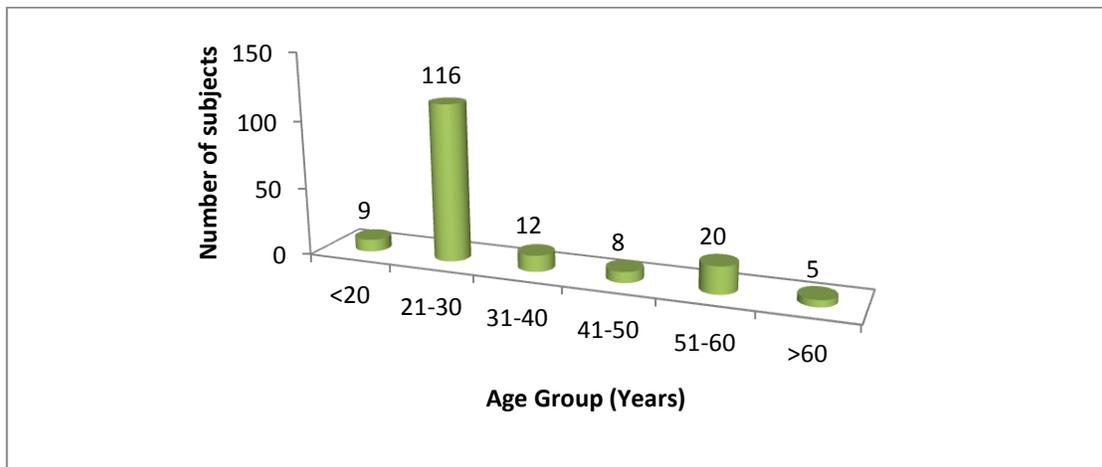
Periodontitis is often described as a multi-factorial Inflammatory disease leading to damage to the bone and soft tissue forming the tooth which consequently results in tooth loss<sup>[1-4]</sup>. It involves the overgrowth of anaerobic organism in the sub gingival<sup>[1,5]</sup>.

It is a general term which generally includes pathological conditions pertaining to tooth supporting structures<sup>[6]</sup>. These conditions causes changes in the morphology of gingival tissues and leads to the formation of periodontal pocket which in turn supports the growth and propagation of anaerobic pathogenic bacteria<sup>[4,7]</sup>. These bacteria act on host tissue causing damage to the alveolar bone, periodontal ligament and destroy the integrity of the tooth<sup>[4,8,9]</sup>.

After the onset of gingivitis, an inflammatory response follows which encompasses the release of antibodies as well as lymphocytes and neutrophil activation. This in turn is defensive. T-lymphocytes are associated with periodontal bone resorption while on the other hand T and B cells induce osteoclastic activity<sup>[10]</sup>.

The conventional treatment includes use of systemic administration of antibiotics which has the disadvantage that the drug is diluted several times before reaching the desired site of action. In addition there are associated side effects. To overcome the antibiotics are administered directly to the site in low therapeutic doses<sup>[1,5]</sup>.

A survey was conducted by Silvia et al on 170 subjects in June 2013 and the prevalence of periodontal diseases was determined in different age groups of the patients. Subjects in the age group of 21-30 yrs suffered most due to periodontitis and gingival bleeding<sup>[11]</sup>.



**Fig1: Demographic pattern occurring in periodontal diseases<sup>[11]</sup>.**

### Causes of Infection

Dental infection can occur in several ways<sup>[12]</sup> like introduction of pathogens, by imbalance indigenous flora or entry of bacteria into the sterile pulp of the tooth. The increased level of cytokines and pro-inflammatory factors prove that the mechanism regulating these genes are dysfunctional in periodontitis<sup>[13]</sup>.

### Organisms Causing the Infection<sup>[14]</sup>

#### 1. Aerobic & facultative anaerobic bacteria

Pseudomonas sp  
Enterobacteriaceae sp.  
Gram +ve cocci  
Streptococcus mutans gp  
Gram +ve bacilli  
Lactobacillus sp.

#### 2. Anaerobic bacteria

Gram +ve cocci  
Peptostreptococcus sp.

Gram –ve bacilli	VeillonellaPrevotella sp.
Gram +ve bacilli	Actinomyces
Spirochetes	Treponemadenticola

So these organisms are the prime factors causing Periodontitis.

### **Systemic factors and periodontitis:**

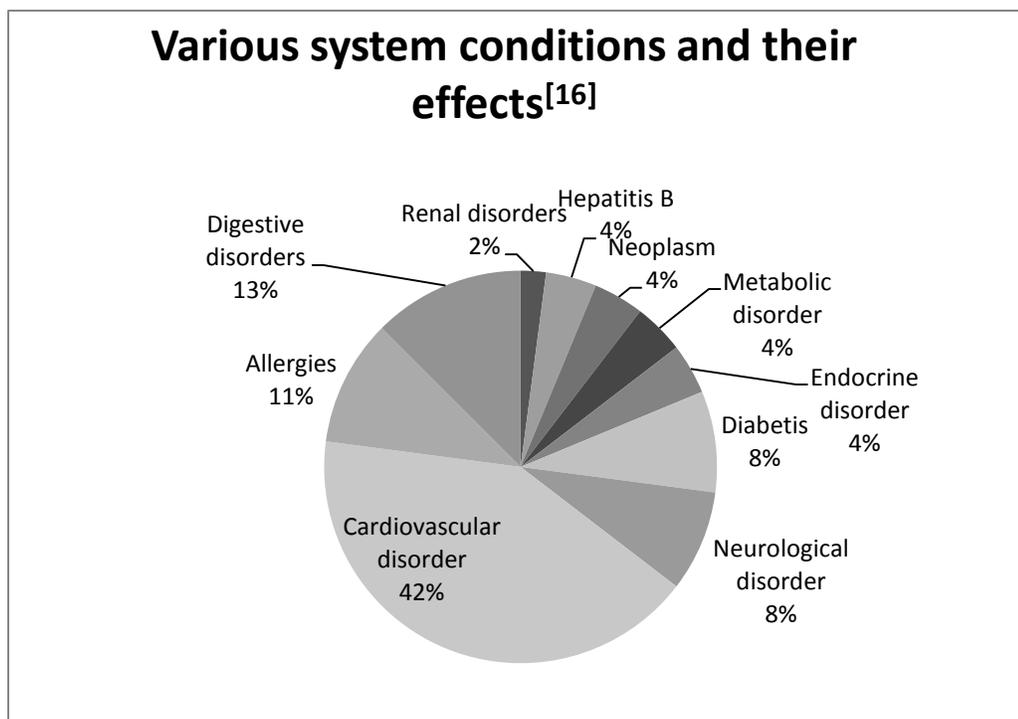
The prevalence of the disease varies with sex, ethnic background, geographic region and socioeconomic status. In addition, certain conditions may be predisposing or aggravating factors for periodontitis, including accumulation of subgingival plaque, smoking and conditions associated with an immune disorder (e.g., diabetes mellitus, AIDS)<sup>[15]</sup>. The environmental and genetic factors greatly hamper the host-microbe equilibrium<sup>[16-18]</sup>.

1. Smoking being one of the most important risk factor followed by diabetes<sup>[19,20]</sup>.

Campus et al reported a high risk for dental caries was associated with smoking tobacco<sup>[21]</sup>. Smokers generally have more plaque index and lesser number of bleeding sites than non-smokers thus have more chances of formation of periodontal pocket with increased bone loss<sup>[22,23]</sup>. However the condition can be reverted by quitting smoking<sup>[19]</sup>. Bergstrom et al. found that the intensity of vascular reaction after 28 days of plaque-induced gingivitis in smokers was only 50% of that observed in non-smokers<sup>[24]</sup>.

2. Diabetes patients have greater bleeding incidents, bone loss and gingival recession in comparison to non-diabetic individuals<sup>[19,25]</sup>. Chronic periodontitis play a role of metabolic stressor for diabetes control that increases insulin resistance or be a continuous source of inflammatory marker secretion<sup>[26]</sup>. The mechanism which explains the possible relationship between diabetes and periodontitis is the monocytychyperresponsiveness to bacterial antigens seen in diabetic patients which in turn causes an increased production of proinflammatory cytokines and mediators that result in tissue destruction, attachment loss, and bone loss<sup>[27-29]</sup>.
3. Stress conditions decreases the saliva flux providing a favourable condition for the bacterial growth. Emotional stress modifies the pH and composition of saliva<sup>[16,20]</sup>. Hormonal changes at puberty or during pregnancy add to periodontitis<sup>[19,30]</sup>.
4. Periodontitis can often be transformed into a more serious condition i.e Sjogren's syndrome which is an autoimmune systemic condition leading to xerostomia<sup>[19,31]</sup>.

5. Pneumonia : Periodontal pathogens in saliva or dental plaque were shown to be a risk factor for aspiration pneumonia<sup>[32]</sup>.

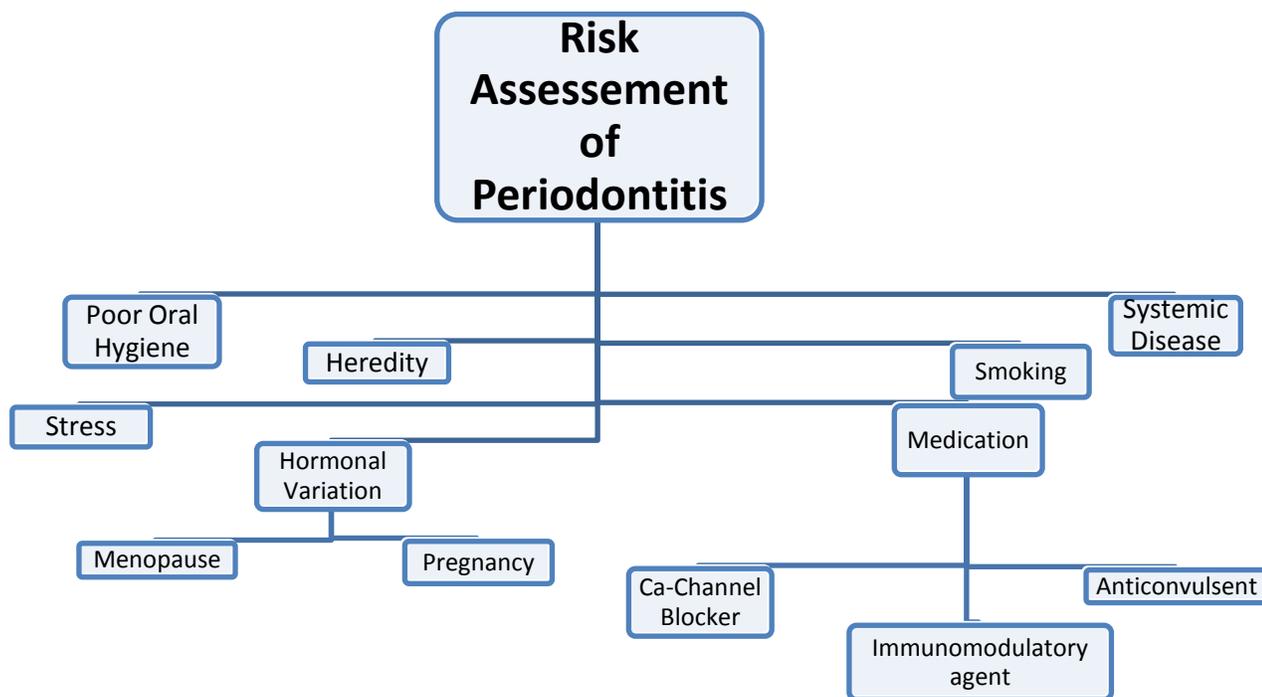


**Fig2: Graph shows the contribution of various systemic conditions which effects the periodontal diseases condition.**

### Genetic factors and periodontitis:

Genetic polymorphism play a role in the predisposition to and progression of periodontal diseases. Variations in any number or combination of genes that control the development of the periodontal tissues or the competency of the cellular and humoral immune systems could affect an individual's risk for disease<sup>[33]</sup>. Karimbux et al (2012), in the study concluded that IL1A and IL1B genotypes are significant contributors to chronic periodontitis in Caucasians<sup>[34]</sup>. Another study conducted by Li et al. gave the evidence that *Fok I* polymorph of Vitamin D receptor could be related to aggressive periodontitis in Chinese population. Moreover F allele also increases the risk of generalized aggressive periodontitis<sup>[35]</sup>. Gingival enlargement is a form of periodontal disease which is an inheritance condition in which gingival tissue progressively enlarges. It is considered as an autosomal dominant disease. Males and females are equally affected at a phenotype frequency of 1:175,000<sup>[36]</sup>. An increased vulnerability to severe periodontitis can be seen in Down syndrome, Chediak-Higashi syndrome and Papillon-Lefèvre syndrome. Alterations in the humoral immune system generates periodontal disease which in turn affects other systems such as cellular immunity or the

metabolic system<sup>[37]</sup>. The periodontal condition in Chediak-Higiashi syndrome manifests as early onset periodontitis<sup>[38]</sup>. Down syndrome is characterized by aggressive and generalized periodontitis<sup>[39]</sup>. In Papillon- Lefevre, periodontitis manifests as premature loss of teeth <sup>[40]</sup>.Hart et al. identified a gene on chromosome11 containing the cathepsin C gene, responsible for prepubertal periodontitis as well as Papillon – Lefevre syndrome (PLS)<sup>[41]</sup>.



**Fig 3: Flowchart of risk assesement of periodontitis<sup>[42]</sup>.**

### Treatment:

Therapeutic approaches are categorized as<sup>[43,44]</sup>

- Anti-infective, which is designed to prevent the progression of periodontal attachment loss by removing etiologic factors
- Regenerative, which includes treatment to restore structures destroyed by disease.

Root planning, scaling & surgical procedures were generally adapted to treat periodontitis but mechanical limitations of these procedures brought forward the use of antibiotics <sup>[5]</sup>.Scaling is done to clean the infected tooth of the bacterial plaques, pus and debris which accumulate in the periodontal pockets whereas root planning is undertaken to smoothen the tooth after scaling so that the gingival tissue can heal close to the root,shrinking the tissue and reducing the depth of the pocketthat had formed<sup>[45,47]</sup>. The FDA has approved the use of an ethylene vinyl acetate fiber that contains

tetracycline, a gelatin chip that contains chlorhexidine and a minocycline polymer formulation as adjuncts to scaling and root planning<sup>[48]</sup>.

### 1. Conventional Local Therapy:

It is aimed at removal of supra & mechanical plaques & degenerated & necrotic tissue lining the gingival wall of periodontal pocket<sup>[14]</sup>. Mechanical plaque controlling methods are effective however its inaccessibility to areas such as furcation, distal most teeth poses a problem for its use<sup>[9]</sup>. Recolonization of pathogens can occur after scaling & root planning<sup>[49]</sup>.

### 2. Antibiotic Therapy:

Both narrow and broad spectrum are used to treat periodontal infections<sup>[50]</sup>. The rationale for the use of antibiotics lies in the fact that specific micro-organisms cause periodontal diseases and that the concentration of antibiotic in vivo can exceed the concentration required either to kill or inhibit the pathogens. Antibiotics may be prescribed for periodontal patients who do not respond to conventional mechanical therapy, for patients with acute periodontal infections associated with systemic manifestations, for prophylaxis in medically compromised patients, and as an adjunct to surgical and non-surgical periodontal therapy<sup>[45,46]</sup>.

**Table 1:** It shows various antimicrobial agents and their activity.

Antibiotic	Moderate Activity	High Activity
Penicillin	Streptococcus sp.	Bacteroides Porphyromonas
Oxacillin	Actinomyces	Porphyromonas
Amoxicillin	Capnocytophoga	-
1 <sup>st</sup> generation cephalosporin	Streptococcus sp.	Capnocytophoga
Macrolide	Staphylococcus	Eikenella
Clindamycin	Staphylococcus	-
Tetracyclin	Eikenella	Streptococcus gp A Prevotella
Gatifloxacin	Streptococcus	Prevotella Porphyromonas sp.

Systemic antibiotics reaches the deep periodontal pockets and furcations and destroy the micro-organism residing in the gingival area<sup>[51]</sup>. However the side effects caused due to the high doses required for systemic action makes its use unfavourable<sup>[52]</sup>.

### 3. Local Drug Delivery:

It is of mainly two types. It either delivers drug locally in the periodontal pocket or act as a controlled release system which has the drug action for a prolonged period of time at desired site of action <sup>[53]</sup>.E.Ramadan et al. developed metronidazole bioadhesive matrices for localized delivery of the drug in periodontitis in order to prevent systemic side effects <sup>[54]</sup>.

The main advantage of local drug delivery is the ease of application, selective targeting, enhanced treatment results <sup>[44]</sup>. However certain disadvantages are also associated to it. Local drug delivery doesnot often cause complete elimination of the pathogens which can later lead to the recolonization of the micro-organisms at the targeted sites<sup>[55]</sup>.

Mouth wash require an initial high concentration & multiple application to prove its effectiveness <sup>[1]</sup> Local delivery can alter the pathological condition thus improving the clinical symptoms <sup>[44,56]</sup>.Peridex and Listerine antiseptic mouthwashes are clinically proven and ADA accepted <sup>[42]</sup>. Chlorhexidine gluconate is available at 0.12% in US but can stain teeth and tongue and can as well promotesubgingival calculus formation <sup>[57,58]</sup>. Listerine is a fixed combination of thymol (0.064%) ,eucalyptol (0.092% ), methyl salicylate (0.060%), and menthol (0.042%)<sup>[59]</sup>.

### 4. Laser therapy:

Lasers have become a very important mechanism in general dentistry, especially for soft tissue procedures in chronic periodontitis. Lasers, such as Nd:YAG and Er:YAG, achieve a reduction in the number of periodontal pathogens and pocket depth<sup>[60,61]</sup>.

Two types of diode lasers have been studied for their effects Periodontal Therapy, the diode laser and the low level diode laser.Low Level Laser Therapy elicits beneficial cellular and biological responses. On a cellular level, metabolism is increased, stimulating the production of ATP. This in turn normalize cell function and promote tissue healing<sup>[62]</sup>.

#### **Surgical Approach:**

This approach is undertaken to remove the etiological factors and regenerate the lost periodontal tissue <sup>[44]</sup>.

Flap surgery: it is done when even after the antibiotic therapy periodontal pockets still persists which includes tissue grafting <sup>[63]</sup>.

### **Host modulation approach:**

It is a new approach which is introduced in dentistry. With respect to periodontitis which is caused by bacteria, the individual who harbors the bacteria is the host. Now it is possible to modulate the response of the host towards these bacteria by using chemotherapeutic agents. They are used as an adjunct to non-surgical therapy. The only systemic host modulating agent approved by FDA is Periostat. Platelet -derived growth factor combined with a resorbable synthetic bone matrix (GEM 21S) is approved recently by the FDA<sup>[42]</sup>.

### **Various Drug Delivery Systems:**

#### 1. Fibers

Hollow fibers, monolithic fibers & resorbable base material are used which changes the microflora in periodontal pockets & proves instrumental in decreasing the inflammation. It requires the removal of carrier after the drug is released<sup>[64]</sup>. They have good drug holding capacity as well as easy evacuation of the drug<sup>[44,65]</sup>. To retard drug release, drug impregnated monolithic fibres were developed by adding drug to molten polymers, spinning at high temperature and subsequent cooling<sup>[65]</sup>. Tonetti et al. reported that EVA fibres containing 25% tetracycline hydrochloride maintained a constant drug level. Goodson first developed a hollow fiber of cellulose acetate filled with tetracycline which reduced the spirochete number and improved the clinical signs when placed into periodontal pocket. However the hollow fiber system released the drug very rapidly and was not very successful at sustaining the drug release<sup>[44]</sup>. Carbon nanofibres are usually preferred owing to their characteristic features which good mechanical properties, chemical stability, high aspect ratio and surface properties that allow easy functionalization with more biocompatible hydrophilic groups. Carbon fibres conjugated with tricalcium phosphate nanoparticles using polyacrylonitrile fibres was prepared by (Liu et al., 2010)<sup>[66]</sup>.

#### 2. Chip

It consists of active ingredient in combination with homogeneous polymer base which is effective in treating plaque & inflammation beneath the gingival margin<sup>[6]</sup>. Fouad et al. developed a biodegradable periodontal chip containing thymoquinone in a chitosan base for targeted delivery in chronic periodontitis. Results were more promising when it was given as an adjunct to scaling and root planning<sup>[67]</sup>. FDA has approved the use of a gelatin chip containing

chlorhexidine and a minocycline polymer formulation along with ethylene vinyl acetate fiber containing tetracycline to be used for scaling & root planning <sup>[44,48]</sup>.

### 3. Films, strips & compacts

Films are the matrix type delivery system in which the drug is distributed throughout the polymeric membrane and the drug release occurs diffusion or by dissolution method<sup>[68]</sup>.

They are prepared by either solvent casting or direct milling and are applied onto the cavity within the cheek mucosa where they exert their action. They have ease of application & minimum pain along with dimensions that fits well in the periodontal pocket <sup>[44,69]</sup>.Olgun and coworkers prepared antimicrobialpolycaprolactone composite films containing 12.5% silica and 0.15% silver nanorods which showed destruction of E. coliand S. aureus. The results were comparable with the composite films containingtriclosan with respect to antimicrobial activity <sup>[70]</sup>.Shin and associatesdeveloped chitosan–hydroxyapatite film for periodontal therapy where hydroxyapatite was incorporated as nanoparticles into chitosan film.The rapid healing property ofchitosan and bone remodelling tendency of hydroxyapatite showed synergistic effect.Hydroxyapatite offers advantage in the later phases of periodontal diseases where bone

degeneration takes place<sup>[47]</sup>.Films based on synthetic biodegradable polymers such as poly (lactide-co-glycolide) (PLGA) containing tetracycline have been developed for modulated-release of drug inthe periodontal pocket.The dimensions and shape of the films can be easily controlled according to the dimensions of the pocket to be treated.Non-biodegradable ethyl cellulose based films for the delivery of chlorhexidine diacetate, metronidazole, tetracycline and minocycline have been developed. Tissue adhesive implants were made using nbutyl-2-cyanoacrylate.Ornidazole dental implants containing ethyl cellulose, hydroxy propyl cellulose, hydroxy propyl methyl cellulose, eudragit-RL-100are also developed <sup>[44]</sup>.KatiyarAviral et al. developed a sustained release lomefloxacin hydrochloride film by solvent casting method for the local delivery of antibiotic<sup>[72]</sup>.Umadevi et al. fabricated biodegradable film of ciprofloxacin for sustained release<sup>[73]</sup>.

### 4. Injectable system

They fill the entire pocket upon delivery so have a wide range of action. They are easily applied and are cost saving .An injectable delivery system should be able to fill the pocket, thus reaching a large proportion of pathogens <sup>[44]</sup>.

#### 5. Injectable gels(in-situ gel)

They have high bioavailability & can effectively adhere to the mucosa in the oral cavity and eliminated through normal catabolic pathway<sup>[44]</sup>.In situgelling drug delivery systems are greatly in use.Poloxamer, carboxymethyl cellulose,Carbopol, alginate, hydroxypropylmethyl cellulose(HPMC), chitosan etc are some of the most commonly employed polymersfor in situgelling systems.The major advantage ofthis system is the low consistency of the formulation at its sol state andthus enabling easy delivery at the site of application along with prolonged residence time<sup>[74]</sup>.When the sol system reaches the periodontal pocket,it gets transformed to a gel by a stimulus thus releasing the drug at the desired site<sup>[71]</sup>.Garala et al. developed a chlorhexidine hydrochloride temperature sensitive in-situ gel containing poloxamer 407 and carbopol 934P. It showed a sustained release pattern and exerted its effect for upto 6 hours<sup>[75]</sup>. Prakash et al. developed levofloxacin in-situ gel by different concentration of gellan gum and poloxamer 407 using ion and temperature sensitive methods which greatly reduced the dose size and frequency along with systemic side effects and improved patient compliance<sup>[76]</sup>.A biocompatible and biodegradable syringeable in-situ gel formulation of Ornidazole having controlled release characteristics for direct placement into the periodontal pocket was developed using Poloxamer 407(Pluronic F-127) to inject without incision by Swati et al.<sup>[77]</sup>.

#### 6. Microemulsion gel

Swaroop.et.al developed sartranidazolemicroemulsion gel. This increased the penetration ability of the drug along with duration of action.Microemulsion alone or in conjunction with in situ gelling system is instrumental for drug delivery in periodontitis.They offer advantage of long contact time with the periodontal pocket owing to the mucoadhesive polymer used in the formulation<sup>[78,79]</sup>.

#### 7. Vesicular systems

They are studied to target periodontal biofilms<sup>[44]</sup>. This system offers advantages such as reduced side effects, minimum drug degradation on administration and improved bioavailability<sup>[71,80]</sup>.SuccinylatedConcanavalinA (lectin)-bearing liposomes (proteoliposomes) have been found to be effective for the delivery of triclosan to periodontal biofilms<sup>[44]</sup>.Lectin-bearing liposome systems were studied for their activity against gingivitis and dental

plaque by Vyas.et.al <sup>[69]</sup>.Robinson and coworkers reported on the affinity and specificity of immunoliposomes to reduce dental plaque <sup>[44]</sup>.

## 8. Nanoparticulate systems

They have high dispersibility in an aqueous medium, controlled release rate along with small size which owes its use in periodontitis <sup>[44,65]</sup>. They also have a reduced dosing frequency which increases patient compliance and have uniform drug distribution over extended period of timeincreasing retention of the formulation through bioadhesion. <sup>[81]</sup>.Thesenanoparicles prepared can also be incorporated in hydrogel matrix to develop a new delivery system <sup>[82]</sup>. An example of recent application can be cited as formulation of metronidazole benzoate using thiolated chitosan (TCS)-poly(methacrylic acid) where the retention time could be increased at the absorption site <sup>[83]</sup>.Nanoparticulate system provides a natural microenvironment to the regenerating cells and help them proliferate.They also help in the delivery of bone density regulator eg alendronate sodium <sup>[84]</sup>Composite nanoparticles based onglycidyl methacrylate (GMA) and natural polymers like gelatin/dextran was developed.Bone morphogenetic protein (BMP) was immobilized on to nanoparticle composites containing dextran-GMA/gelatin <sup>[85]</sup>. Endodontic treatment can also be done using nanoparticles such as PLGA nanoparticles loaded with methylene blue as photosensitizer <sup>[86]</sup>.Nanoparticulate delivery systems provide protection for agentssusceptible to degradation or denaturation in regions of variable pH <sup>[87]</sup>.

**Table 2: Summary of various drug delivery systems<sup>[71]</sup>.**

Drug delivery system	Drugs used	Polymer used
Nanoparticulate system	Minocycline Triclosan	PLGA
Films	Ciprofloxacin	Chitosan
Chips	Tetracycline Chlorhexidine Doxycycline Metronidazole	PLGA HPC, Acrylic polymer HPC, Methacrylic acid Poly-(2-hydroxyethyl)- methacrylate
Gels	Metronidazole Doxycycline Tetracycline	Chitosan PLA & N-methyl 2-pyrrolidone HEC & PVP
Fibers	Amoxicillintrihydrate Tetracycline HCl Chlorhexidine	Polyvinyl acetate Cellulose acetate Cellulose acetate
Implants	Tinidazole Doxycycline	PLA PLA

**Plant Based Medicines**<sup>[88-92]</sup>**Table 3: It shows different type of plant based medicine and their activity against different microorganism.**

Plant	Activity Against
<i>Droserapeltata</i> (dorseraceae)	S.mutans
<i>Abiescanaden</i> (pinaceae)	Streptococci
<i>Pinusvirginiana</i> (pinaceae)	Streptococci
<i>Rosmarinusofficinalis</i> (laminaceae)	Streptococci
<i>Coptidis rhizome</i> (ranunculaceae)	P.actinomycetes
<i>Melaleucaalternifolia</i> (myrataceae)	S.mutans&P.gingivalis
<i>Psoreleacorylifolia</i> (fabaceae)	Gram –ve& +ve bacteria
<i>Propolis</i>	S.mutans

Botanicals e.g., Acacia catechu, Cinnamomumzeylanicum, Droserapeltata possess anti-microbial activity against S.mutans thus preventing periodontitis<sup>[93,94]</sup>. The botanicals which have a phenolic group constituent in it have anti-inflammatory and prostaglandin synthetaseinhibiting activity by functioning as a scavenger of free oxygen radicals<sup>[93-96]</sup>. These are some the important plant derived products that are used for the treatment of periodontitis since ages.

The in-vitrobactericidal activity of the Harunganamadagascariensisleaf extract (HLE) was studied on the oral bacterialstrains which is one of the major cause of dental caries and gingivitis infections. Here HLE-loaded PLGA nanoparticles were prepared usinginterfacial polymer deposition following the solvent diffusion method<sup>[97]</sup>.

**Certain Marketed Preparations**<sup>[98]</sup>

Product	Active Ingredient	Manufacturer
Elyzol	Metronidazole	Dumex ltd., Denmark
Actisite	Tetracycline HCl	Alza corp., USA
Periochip	Chlorhexidine	Dexcel Pharm Inc, Jerusalem
Periocline	Minocycline HCl	Sunstar Inc., Japan
Periostat	Doxycyclin hydrate	CollaGenexPharma, Penn

1. Atridox: It is a gel based system which forms a biodegradable implant.10% Doxycycline Hyclate was used and released the drug for 7 days.
2. Actisite: This system has tetracycline preloaded in hollow ethylene/vinyl acetate fibers.The tetracycline is released from the fiber over a period of 7 to 10 days.
3. Periochip: It is a biodegradable chip made of hydrolyzed gelatin impregnated with 2.5 mg of the antibiotic chlorhexidine gluconate.The chip itself will biodegrade and dissolve in about 8 to 10 days time.
4. Arestin:These are microspheres of Minocycline HCL (each micosphere containing 1 mg of the minocycline) which are to be injected into the pocketthereby releasing the Minocycline in a sustained manner.
5. Elyzol: This is a metronidazole based gel/strip which can be placed in the periodontal pocket<sup>[93]</sup>.
6. Periostat : It is doxycycline capsule,an inhibitor of matrix metalloproteinases, as an adjunct therapy to scaling and root planing in the treatment of periodontitis<sup>[99]</sup>.

### **Conclusion:**

Thus this review contains the number of ways in which periodontitis can be overcome including the antibiotics and recent advances such as nanoparticulate systems. Quite a few plant sources can also be employed in this respect. These methods are convenient and have higher degree of patient compliance as compared to surgical procedures.

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