Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(4), 1789-1816 | ISSN:2251-6727

Recent Advances in Local Drug Delivery

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(Received: 16 June 2025 Revised: 20 July 2025 Accepted: 04 August 2025)

KEYWORDS

Periodontiis, Local drug delivery, Fibers, Strip and film, gels, Nano particles.

ABSTRACT:

Periodontitis is characterized by destruction of periodontal ligaments by inflammatory process leading to development of periodontal pockets, loss of attachment and the resorption of the alveolar bone that results in breakdown of the teeth's supporting structures. The development of various microorganisms, especially anaerobes, in the pockets leads to periodontitis by triggering the immune system and producing toxins and enzymes. To effectively treat periodontitis, a variety of local and systemic strategies have been employed. Reducing or removing pockets, bleeding on probing (BOP), and bacterial biofilm are all necessary for a successful course of treatment. Nowadays, a promising approach to treating periodontitis is the use of local drug delivery systems (LDDSs) as an adjuvant therapy to scaling and root planing (SRP). By regulating medication release, LDDSs increase efficacy and reduce side effects. The key to a successful periodontitis treatment strategy is choosing the right bioactive agent and administration method. In order to identify present issues and potential avenues for future study, this review concentrates on the use of various LDDSs and its recent advances with different properties in the treatment of periodontitis, whether or not systemic diseases are present.

1. Introduction

Periodontitis is a chronic inflammatory condition that affects tooth-supporting structures which is characterized by probing depths (PD), clinical attachment level (CAL) loss and bone resorption. The condition is caused by a combination of changes in the microbiota of the gingival pockets and an inappropriate immunological response from the host.[1] Bacterial infection and microbial plaque cause the inflammation to start. In the periodontal pocket, the bacteria create a highly structured and complicated biofilm. Later, the biofilm extends below the gingiva, making it challenging to remove during routine oral hygiene procedures. Gram negative anaerobic bacteria make up the majority of the periodontitis-related microflora.[2]

However, in some cases due to the complex anatomy of the root and the site of the lesion, traditional therapies such as mechanical debridement to remove the subgingival flora and provide clean, smooth, and biocompatible root surface may hinder the treatment and prevent the sufficient removal of the bacterial load. To avoid recolonization, supragingival plaque management is crucial.According to multiple clinical studies, scaling and root planing combined with good dental hygiene can, in most cases, stop periodontal disease in its tracks by altering the subgingival plaque. Oral hygiene is crucial for a positive outcome after therapy because patients with unsatisfactory plaque management during or after treatment typically have reccurring periodontitis.[2]

Sanz et al.'s recommendations state that the following measures should be followed for stage I, stage II, and stage III periodontitis treatment[3]. According to Herrera et al· management of various conditions that exacerbate periodontal disease, such as diabetes, cardiovascular disease, and/or quitting smoking, as well as sub gingival instrumentation conducted by the clinician , stage IV of periodontitis requires surgical correction of the bone defects and multidisciplinary intervention, including temporary control of secondary occlusal trauma, orthodontic therapy, rehabilitation of the edentulous spaces, and tooth-supported or implant-supported dental prostheses. To manage the infection, scaling and root planing (SRP), also called as supragingival and subgingival instrumentation, and strict at-home dental hygiene are needed. In reality, the aforementioned techniques eliminate the etiological microbiological component of periodontitis since the pathogenic bacteria are arranged in biofilm.[4]

Periodontal disease can be treated with supplementary systemic or local host-modulating medications in addition to the mechanical removal of the biofilm. Modulating the molecule release is crucial for achieving the greatest outcomes with the lowest risk for the chosen pharmaceutical therapy.Due to this, it has been suggested that a local drug delivery system (LDDS) be implemented in conjunction with

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JCHR (2025) 15(4), 1789-1816 | ISSN:2251-6727

SRP.A number of medical specialties, including the treatment of local infections of the vagina, nose, eye, and skin, utilise LDDSs as a promising therapeutic approach. It has been shown that maintaining an effective drug concentration in the periodontal pockets for a long enough period of time is crucial for the treatment of periodontitis. Due to this LDDS is a valuable tool for local adjunctive pharmacological periodontal therapy.[5]

Local drug delivery systems attempt to reduce dose frequency in order to improve patient compliance and quality of life, in addition to offering a mechanism for sustained and targeted distribution of drug molecules or bioactive therapeutic compounds (Toker et al., 2019). The benefit of autonomous regulation of drug release from the site of placement is provided by the sophisticated nanotechnology based drug carrier systems, which are particularly effective.[5] (Rathor et al., 2017).

2. STRATEGIES FOR MAINTENANCE OF GOOD ORAL HYGIENE

By practicing oral hygiene, it is generally possible to prevent the disease's earliest symptoms.

- **Brushing and flossing**

  Brushing and flossing are the first line of defence against microorganisms in the mouth cavity. The American Dental Association (ADA) advises twice-day brushing for two minutes and daily flossing. Effectively combats gingivitis and treats periodontitis [6]

- **Supragingival irrigation**

  Supragingival irrigation improves the efficiency of tooth brushing and helps to reduce gingival inflammation in people who do not practise proper dental hygiene. A positive link was discovered between supragingival irrigation, which could be accomplished with either acetyl salicylic acid (ASA) or water, and illness severity reduction.[7]

- **Subgingival irrigation**

  By reducing plaque toxicity, impeding subgingival plaque maturation, or even by washing away loose plaque, subgingival irrigation reduces gingival inflammation even when plaque levels remain unchanged.Pocket irrigation improves various clinical measures, such as pocket depth and gum bleeding, and can lower the bacteria burden in the pocket.[8]

- **Mechanical therapies for the treatment of periodontal diseases**

  Scaling the teeth is a successful strategy for treating and preventing gingivitis. Cleaning out plaque, calculus, and stains from the crown and root surfaces of teeth is a part of periodontal scaling operations.[9]

3. CHEMOTHERAPEUTIC AGENTS USED FOR THE TREATMENT OF PERIODONTAL DISEASES

Various chemotherapeutic agents used for treating periodontal disease are following:

- **Host modulation therapy (HMT)**

  Host modulatory therapy (HMT) aims to change the host response to reduce the levels of damage.[10]A number of host modulatory medicines are available, including growth factors, bisphosphonates, anti-inflammatory medications, enamel matrix derivatives, and doxycycline at sub-antimicrobial doses. Each of these substances has the ability to alter the host reaction and obstruct the immune system's damaging components. Tetracyclines arecollagenase inhibitors, biphosphonates lower osteoclast cell activity, and anti-inflammatory medications can block prostaglandins and cytokinins.[11]

- **Antimicrobial therapy**

  Since bacteria are the primary etiological component for periodontal disease, using antimicrobial therapy in conjunction with mechanical therapy is a solid biological strategy for treating the condition. The systemic antibacterial treatment can undoubtedly produce many beneficial results.[12]

- **Localized intra-pocket drug delivery systems**

  Less undesirable side effects, higher value, and improved patient compliance make intra-pocket drug delivery systems very alluring.The appeal of using localised drug delivery systems to treat periodontal diseases stems from the fact that they allow for greater accessibility to the periodontal cavity and deliver medications at concentrations that are bacteriostatic or bactericidal for prolonged periods of time to produce the desired clinical effects.[13]

  The fundamental prerequisite for local drug delivery to be effective is that the agent must reach the base of the periodontal pocket and that the concentration must be maintained there by measures like a reservoir for long enough for the antibacterial action to take place. **Dr. Max Goodson** and colleagues initially presented the idea of controlled release medication administration for the treatment of periodontitis in the year 1979.

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JCHR (2025) 15(4), 1789-1816 | ISSN:2251-6727

4. CLASSIFICATION OF LOCAL DRUG DELIVERY SYSTEM

Various classification systems of local drug delivery systems were evolved:

A. Based on the Application Rams and Slots1996:[14]

Personally applied (Patient self-care application)

i. Nonsustained subgingival drug delivery: Drug system that dosen'nt prolong for extended period of time.

- Home oral irrigation
- Home oral irrigation jet tips
- Traditional jet tips
- Oral irrigation (water pick)
- Soft cone rubber tips (Pickpocket)

ii. Sustained subgingival drug delivery: Drug system that is designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose.

Professionally Applied in Dental Office:

Nonsustained subgingival drug delivery

- Professional pocket irrigation

Sustained subgingival drug delivery

- Controlled release devices
- Hollow fibers
- Dialysis tubing
- Strips
- Films

B. Based on the Duration of Medicament Release Greenstein and Tonetti 2000[15]:

- **Sustained release devices**
  - These devices provide drug delivery for less than 24 h
  - Require multiple applications
  - Follow first-order drug kinetics
- **Controlled release devices**
  - Drug release is for more than 24 h
  - administered only once
  - Follow zero-order drug kinetics
  -

C. Depending on degradability [16]:

- Non-degradable devices (First generation)
- Degradable devices (Second generation)

D. Langer and Peppas 1989[17]:

Classified controlled drug release polymeric systems based on their mechanism of action.

1. Diffusion Controlled Systems
   a. ➢ Matrices
   b. ➢ Reservoirs
2. Chemically Controlled Systems
   a. ➢ Erodible systems
   b. ➢ Pendant chain systems
3. Solvent Activated Systems
   a. ➢ Osmotic systems
   b. ➢ Swelling controlled systems
4. Release Induced by External Forces

E. Kornman(1993) has classified the Controlled Release Local Drug Delivery System as[18]:

- ➢ Reservoirs without a rate controlling system like hollow fibers, gels and dialysis tubing.
- ➢ Reservoirs with a rate controlling system like erodible polymeric matrices, micro-porous polymer membrane, monolithic matrices and coated drug particles.

F. Depending on the Origin:

- ➢ Allopathic or chemical local drug delivery
- ➢ Herbal or ayurvedic local drug delivery

.G. According to WHO Guidelines, Herbal Medicines Can Be Categorized Into Four Categories [19]:

- ➢ Based on their evolution, origin, and forms of current usage as under:-
- ➢ **Category 1:** These indigenous herbal medicines are used by local communities or region and are very well-known by the local population through ages in context to composition, treatment, and dosage.
- ➢ **Category 2:** This group consists of herbal medicines in systems and is well-documented and based on long-time usage on theories and concepts that are duly accepted by the respective countries. Example – Ayurveda Siddha and Unani.
- ➢ **Category 3:** This consists of Modified herbal medicines which have been modified in relation to their shape, dose, administration mode and composition. These medicines have to meet the national regulatory requirements in terms of their safety and efficacy.

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JCHR (2025) 15(4), 1789-1816 | ISSN:2251-6727

- **Category 4:** Imported products with a herbal medicine base include all the imported herbal medicines (raw materials and products). The national authority of the importing country should have safety and efficacy data.

H. Based on the Types of Local Drug Delivery System [20]:

- Fibers
- Films
- Strips
- Gels
- Vesicular liposomal systems
- Microparticle systems
- Nanoparticle systems

5. TERMINOLOGIES USED FOR LOCAL DRUG DELIVERY

Terms used to describe medications administered directly to the subgingival area. Others actually have very different meanings and therapeutic implications, while some of the terms are synonyms.The terms used most frequently are as follows: [18]

- **Targeted Delivery**: When delivery of agents is referred to specific cells.
- **Local Delivery**: When drug delivery is more specific or targeted delivery but not at cellular level.
- **Site specific Delivery**: The terms local and site specific delivery are interchangeable with targeted delivery but do not convey the same level of cellular precision. However, in periodontics, local delivery or site-specific delivery are valid terms to represent the administration of currently accessible medications to the subgingival region.[21]
- **Controlled Delivery / Controlled Release:** These are designed to release a drug slowly for more prolonged drug availability and sustained drug action.
- **Sustained-release**, prolonged-release, timed-release, slow release, sustained-action, prolonged-action, or extended-action
- **Topical drug delivery:** Topical" application of a drug is a form of local delivery. Topical application generally refers to delivery of an agent to an exposed surface [21]
- **Local delivery devices**: The systems designed to deliver agents locally into the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time.
- **Controlled-release local delivery devices:** Utilising the controlled-release technologies mentioned above or other comparable technologies, "controlled-release local delivery devices" ensure therapeutic concentrations of the antibiotic in the subgingival area for at least 3 days after a single application.
- **MIC (Minimum Inhibitory Concentration):** It is the lowest concentration of a drug that will inhibit the visible growth of a microorganism after overnight incubation. [21]

Type of Administration [22]

- **Systemic**

  Advantages: Some patients may prefer conventional drug- administration; well-known associated risk; no need of second intervention and cheap.

  Disadvantages: Low bioavailability of the drug; need for frequent doses; gastrointestinal issues; dysbacteriosis; drug resistance; interaction with other systemic administrated drugs.

- **Local Drug Delivery System**

  Advantages: High bioavailability of the drug; controlled drug release; bypass of the hepatic metabolism; no gastrointestinal issues; reduction in frequent doses; mini-invasiveness of some LDDSs; high compliance of the patient; use of drugs that are not compatible with systemic administration (ex. Chlorhexidine); no interaction with other drugs.

  Disadvantages: Difficulty of management of some types of LDDS, some of them have difficulty to provide

6. DESCRIPTION OF VARIOUS TYPES OF LDDSS IN PERIODONTITIS TREATMENT

6.1 FIBERS AS A LOCAL DRUG DELIVERY

Fibres are a reservoir-type delivery system that is loaded with the therapeutic drug of choice, put circumferentially into the periodontal pocket by an applicator, and kept in position by cyanoacrylate glue or a periodontal dressing. As fibres for local drug delivery systems, a range of polymers have been proposed and researched, including natural polymers such as chitosan, zein, and gelatin, as well as synthetic polymers such as poly(e-caprolactone), polyurethane, polypropylene, cellulose acetate propionate, and ethyl vinyl acetate.[23,24] Goodson et al. proposed hollow fibres impregnated with tetracyclines in 1979. The local administration of tetracyclines

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JCHR (2025) 15(4), 1789-1816 | ISSN:2251-6727

loaded in hollow fibres allowed the systemic administration of less than 1/1000 of the normal quantity of tetracyclines. Nonetheless, the long-term concentration duration was a constraint of this formula.[25] Tonetti et al. proposed different types of fibres that would have circumvented the a forementioned limit, such as an ethyl vinyl acetate fibre loaded with 25% tetracycline that maintained steady levels of medication for 10 days.[26]

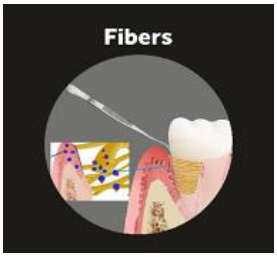

Fig: 1 Fibers as local drug delivery credits to Rajeswari et al [24]

To avoid this, the market has seen the introduction of biodegradable fibres such as collagen fibres [27] .It is vital to highlight the recent advent of an intriguing process for producing polymeric nanofibers with discomfort because it required another procedure to remove them, and wound healing excellent biological characteristics, known as electrospinning.[28](Fig:2)

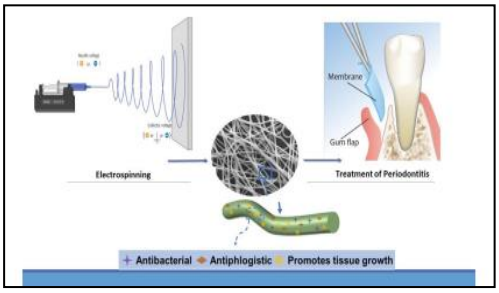

Fig: 2 The procedure of electrospinning to make nanofibers Amato M et al [22]

Ze He et al.[29] tested PLGA nanofibers loaded with tea polyphenols (TP), which are active compounds present in tea and are mainly composed of catechins and their derivatives, which have shown good influences on periodontitis treatment.Finally, fibres are one of the oldest types of LDDSs. They are appropriate for difficult-to-reach locations, however if non-biodegradable fibres are used, they must be removed following treatment, resulting in gingival redness. Furthermore, new directions are being directed to progressively smaller forms, such as nanofibers, and other medications employed in addition to antibiotics, such as TP.[30,31]

6.2 STRIPS AND FILMS AS A LOCAL DRUG DELIVERY

Strips and films (SFs) are thin matrix bands that contain medicines dispersed throughout the polymer. SFs are excellent at matching the form and size of the periodontal pocket and, as a result, are simple to insert with minimal discomfort for patients; they are put in the interproximal periodontal pocket area.In order to solve this issue, novel bioabsorbable materials such as poly-hydroxybutyric acid and poly lactic-co-glycolic acid (PLGA), atelo collagen, gelatin, chitosan/PLGA, and others were introduced. They were tested and yielded positive results. Non-biodegradable SFs diffused the medicinal agent. Meanwhile, biodegradable SF released from diffusion and erosion.Antibiotic and antiseptic drug-loaded SFs have been examined, with satisfactory long-term concentration maintenance and clinical improvements in gingival health.[32] Friesen et al. evaluated the effectiveness of SRP paired with tetracycline-loaded strips over SRP alone in 2002 and proved the significant of SRP paired with tetracycline-loaded strips over SRP alone in 2002 and proved the significant efficacy of numerous strips over a single strip in reducing probing depths. Despite the fact that chlorhexidine-loaded strips have previously been associated with the least efficacy in periodontal treatment when compared to other molecules [33.] Paolantonio et al.found that sites treated with chlorhexidine chips had a significantly higher reduction in probing depths ($p< 0.01$) than sites treated with SRP alone.[34]

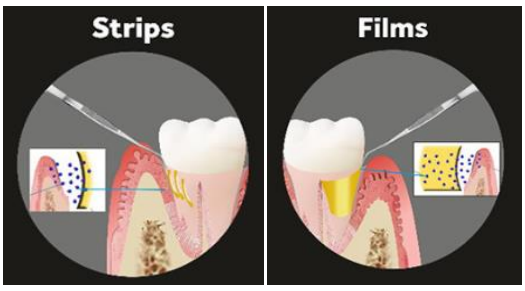

Fig: 3 Strips and Films as Local drug delivery credits to Raieswari et al [24]

SFs are finally manufactured using the same materials as fibres. Their release rate varies depending on their dimensions as well as their application. Fibres, in fact, are appropriate for inaccessible and most remote places. Meanwhile, SFs are wider and hence better suited to bigger pocket regions.[35]

6.3 MICROPARTICLES AND NANOPARTICLES AS A LOCAL DRUG DELIVERY

6.3.1 MICROPARTICLES

Microparticles are spherical polymer structures with diameters ranging from 1 to 1000 µm that are loaded with a medication that spreads equally throughout the

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polymer matrix. They are simple to give and provide a sustained release of the medicine, but they are not easily absorbed in the targeted region. They are administered via different carrier systems such as chip, dental pastes, gel system, and direct injection into the pocket.[24]Materials of natural origin, modified natural compounds, and synthetic polymers, classified as biodegradable and non-biodegradable, have been proposed as microparticle materials.[23]

Tetracycline-loaded (lactic-co-glycolic acid) (PLGA) microparticles are commonly employed, although they have the following drawbacks: Loading efficiency is low for encapsulating highly water-soluble drugs into PLGA microspheres/nanospheres as well as PLGA's slow degradation rate, result in the presence of empty microspheres/depots at the site of periodontal pockets for a long time after the loaded minocycline is completely released.[36,37]

Pichayakorn et al. evaluated cross-linked chitosan microparticles containing metronidazole (MTZ) in their search for the optimal microparticle formulation. The MTZ-MPs demonstrated an entrapment efficiency of 59.40% and a protracted release profile[38]. Another study looked at the drug release of MTZ-MPs in hydrogels and films versus drug powders. This analysis was based on a prior work, which found that chitosan-based hydrogels and films have outstanding properties for local drug delivery in the oral cavity, such as mucoadhesiveness, biocompatibility, and biodegradability.[39] In the study of Gad et al. [76], the use of solid lipid microparticles (SLMs) seems intriguing. Due to its physiologically well-tolerated nature, high compatibility, avoidance of organic solvents, ability to modify target drug release, increased drug stability, high drug load, and capacity for large-scale production using a high-pressure homogenization technique, SLMs have gained particular attention in the medical field [40].ARESTIN, a novel sustained-release version of minocycline microspheres for subgingival implantation, was recently approved by the FDA for local delivery.[41]

Fig:4 Microparticles and Nanoparticles as local drug delivery credits to Rajeswari et al [24]

6.3.2 NANOSYSTEMS

Nanosystems are distinguished by their extremely small sizes, which make them suitable for locations where other types of LDDSs do not reach, such as the pocket area below the gingiva. They are either directly injected into the pocket or delivered through different carrier systems (such as gels).[41]Micellas, metallic and polymeric nanoparticles, liposomes, and nanofibers are among them. They are ideal due to their large loading capacity and favourable surface-volume rate. Some of them contain antibacterial capabilities, which could be useful in treating periodontitis because it is caused by bacterial aetiology. Metallic nanoparticles, in particular, are used in dentistry due to their antibacterial activity and bone regeneration capabilities.[23,24,42,43]Polymeric nanoparticles loaded with minocycline via emulsification-diffusion demonstrated good results, with 96% of the minocycline released after 12 days and excellent clinical outcomes in terms of periodontal repair.[44]Chitosan, a natural substance with nontoxic, highly biodegradability and antibacterial characteristics has been widely employed in the production of nanoparticles.[45] Xu et al. for example, created doxycycline-loaded chitosan nanoparticles with a mean particle size of 50 nm, which demonstrated 75% entrapment efficiency and a 28% loading power. The results showed that the preparation had good cell compatibility, superior antibacterial activity against P. gingivalis, and effective downregulation of inflammatory factors.[46] De Freitas et al.[47]investigated the synergistic effect of aPDT along with Methylene blue (MB) loaded with PLGA nanoparticles on human dental plaque bacteria in vitro (planktonic and biofilm phases) and in vivo (patients with chronic periodontitis).The decision to test the above-mentioned combination takes use of nanoparticles' excellent penetration and sustained drug release capabilities which could have improved aPDT's antibacterial efficacy.[48,49] **Hayakumo et al**. found that ozone nanobubbles produced by nanobubble technology can be used as subgingival irrigation due to their antibacterial qualities. **Cafferata et al.** found that using nanocarriers for periodontal disease treatment, such as PLGA, chitosan, and silica-derived nanoparticles, was effective. This study discovered that host modifying substances given by nanodrug delivery devices had immunomodulatory effects.[50]Leung et al. reported on the effects of nano-chlorhexidine on oral bacterial biofilms and found that the formulation was effective against the biofilm of periopathogenic bacteria. **Sánchez and colleagues** investigated five distinct pharmacological methods using nanoparticles doped with doxycycline, zinc, calcium, and silver on hydroxyapatite biofilm. When tested in vitro on a subgingival biofilm model, polymeric PolymP-n Active nanoparticles in combination with silver and doxycycline had the strongest antibacterial/antibiofilm impact.[51]The production of silver nanoparticles using the leaf extract of Justicia glauca,

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which is primarily responsible for the reduction of silver nitrate, exemplifies the diversity of nanoparticle composition. On periodontal and caries associated microorganisms, silver nanoparticles had a substantial antibacterial effect.[51]The application of nanotechnology in a gel delivery system represents a novel pharmacological combination. **Aithal et al** developed and tested a bioabsorbable, controlledrelease nanoemul gel of quercetin as an antibacterial agent. **Madi et al** used nano doxycycline gel as an adjuvant to scale and root planing and discovered that the nanogel had an antiinflammatory effect by improving both clinical metrics and inflammatory markers over a three month period.

Currently, there are only a few dental applications for nanoparticle drug delivery systems. More research is needed to expand these applications, including the diagnosis and treatment of oral cancer, the use of nanoparticles in toothpastes and mouthwashes as an adjuvant to non-surgical periodontal treatments, the administration of local anaesthesia, and the management of dental hypersensitivity.[50]

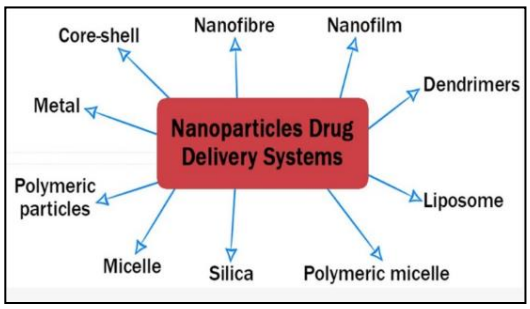

Fig: 5 Nanoparticles as local drug delivery credits to Lal A et al

6.4 GELS AS A LOCAL DRUG DELIVERY

Gel refers to a broad range of medicinal dosage forms. A gel is often characterised as a solid, jelly-like material that, in a steady state, exhibits (nearly) no self-flow but that, in response to an applied force, may flow. Its matrix's fluid qualities might be either soft or rigid. Certain gels might experience swelling and distortion due to their hydrogel nature. A thermogel, also known as a thermoreversible gel, is one whose fluidity is susceptible to variations in ambient temperature. When it comes to the flexibility of administering the medication into the periodontal pocket, this kind of administration clearly provides a therapeutic benefit.[51]With numerous advantages, including excellent biocompatibility and bioadhesivity, ease of administration, and ease of manufacture, gels are widely used in dentistry. They are inserted into the periodontal site using wide-port needle syringes.[24]They may be made from a variety of polymers, including chitosan, carbopol, and carboxy methyl cellulose. Particularly for the treatment of periodontal disease, chitosan is a substance that is frequently utilised in dentistry.It has been used as a gel, producing positive clinical results and being efficient against periodontal infections such as Porphyromonas gingivalis. Its biological features, including as antibacterial, anti-inflammatory, and wound healing qualities, make it useful.[52]A different kind of injectable degradable gel was clinically evaluated. It was made of a polylactic-glycolic acid copolymer matrix added with 35% tetracycline.After one week, there was a noticeable decrease in periodontal microbial infections; however, this reduction was no longer significant. The treated pockets showed a considerable reduction in probing depth.[32] When used as intrapocket drug delivery systems, thermosensitive gels have strong flow qualities at ambient temperature, but they harden at pocket temperature. These drug-delivery gels provide improved penetration into pockets that may not all have the same architecture, as well as improved pocket attachment. An ornidazole and doxycycline-containing thermosensitive gel of crosslinked chitosan-vanillin microspheres was developed.[53]

Fig: 6 Gel as a local drug delivery credits to Rajeswari et al [24]

An injectable, thermosensitive gel containing erythropoietin and aspirin was developed and evaluated by **Xu et al**. The gel was simple to make, had good biocompatibility, and could release the active ingredient continuously for at least 21 days. Additionally, there exist intriguing research on gels that include encapsulated osteogenesis medicines[54] **Phaechamud and Setthajindalert** produced cholesterol gels to include doxycycline as the active agent and N-methyl pyrrolidone as the solvent. The gels were simple to inject into the intended spot, according to the authors. These mechanisms suppressed oral microorganisms, including P. gingivalis.[51] Green tea catechins were the active ingredient in the thermo reversible gels developed by **Chava and Vedula,** and subsequently by **Yuvaraja et al,.** Green tea extract is rich in polyphenols, which may be useful in treating periodontal disorders due to its antibacterial and anti-inflammatory actions. The extract has demonstrated antibacterial activity in vitro and has improved clinical parameters when compared to controls in patients receiving green tea gel treatment.[55] **Yang et al.** recently

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discovered a novel kind of injectable gel. They employed liquid crystals, which behave like liquids yet have molecules arranged in a way resembling crystals. The authors created fluid precursor formulations that absorb gingival crevicular fluid and change into a viscous gel upon injection. **Wang et al**. developed a tunable and injectable local delivery system in rats by loading poly (lactic-co-glycolic acid) (PLGA)-drug microspheres into a thermo-reversible polyisocyanopeptide (PIC) hydrogel. New thermo-reversible PIC hydrogels have been shown to be easier to penetrate deep and irregular pockets.[22] **Lu et al.** developed I2@COF-HEC hydrogel, which they then suspended in hydroxyethyl cellulose gel. The study conducted by **Qi et al**. is among the most current. It used the concept of oxidative self-polymerization to load Turkish Galls effective ingredient (TGEC, T) into nanoparticles (T-NPs). T-NPs were crushed into a thermosensitive in situ hydrogel; under periodontitis circumstances. Concluding that gels are widely used in periodontal therapy, and several formulations either by themselves or in conjunction with other LDDS—are being developed and evaluated.[22]

6.5 MEMBRANES AND SCAFFOLDS AS A LOCAL DRUG DELIVERY SYSTEM

6.5.1 MEMBRANES

Bone resorption is the result of apical biofilm advancement in periodontitis. To remedy these kinds of bone abnormalities, it is crucial to promote bone regeneration. Membranes have been created and used to make it feasible. They function as barriers that aid in the healing of periodontal tissues' wounds. They can also be coupled with certain therapeutic substances to strengthen these functions, so gaining the designation of Local drug delivery system.[56]The first membranes introduced were non-biodegradable ones. Then, as a second surgical procedure was required to remove them, they were gradually abandoned.

Fig: 7 Membrane and its placement in order to act as a barrier credits to Amato M et al [22]

A core-shell nanofiber membrane has recently been developed as a periodontitis treatment. In order to create this membrane, **Liu et al.** loaded recombinant human bone morphogenetic protein-2 (BMP-2) into the core and an inhibitor (SP600125) into the polymeric micelles of the shell. The outcomes were really encouraging Due to these excellent results, this formulation represents a potential therapeutic option for the treatment of periodontitis in the future.[57] Despite the fact that membranes such as LDDS filled with growth factors or other antibiotic membranes have also been investigated as therapeutical agents that cause bone regeneration. **Ho et al.** investigated an amoxicillin (AMX)-loaded PDLLA electrospun nanofiber antimicrobial membrane. They put it to the test.in rats, both in vitro and in vivo.[58]

6.5.2 SCAFFOLDS

Scaffolds, similar to membranes, have been created to treat bone deformities. They are preferred because they eliminate the major limitation of absorbable membranes: the lack of mechanical resistance to external pressures. They are implanted in the afflicted region to keep the space open for future periodontal tissue regeneration.

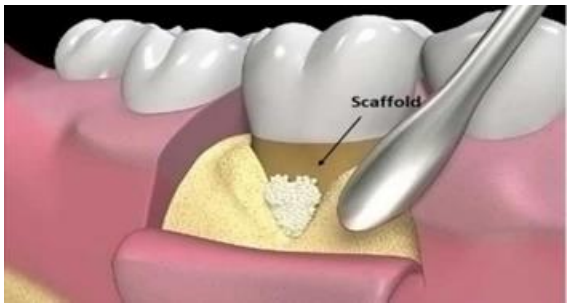

Fig: 8 Scaffold and its placement credits to Amato M et al [22]

A tetracyclines-loaded chitosan scaffold has been tested, detecting a higher loading capacity when the percentage of chitosan and glutaraldehyde was higher. **Liao et al.** investigated the antibacterial and controlled-release capabilities, osteogenic and cementogenic effects in vitro, and a mesoporous hydroxyapatites/chitosan (mHA/CS) composite scaffold loaded with recombinant human 20 g/mL amelogenin (rhAm) in vivo. The findings showed an inhibitory impact on Fusobacterium nucleatum and Porphyromonas gingivalis, boosting bone repair in vitro and cementum regeneration in vivo, suggesting a future therapeutic use. **Ma et al.** evaluated GAL-coated scaffolds for periodontal regeneration in vitro and in vivo in rats. The findings were encouraging, having excellent periodontal regeneration characteristics.Stem cells are gaining importance in periodontal regeneration and can be incorporated into the scaffold to promote their delivery. **Baba et al**. demonstrated the benefits of the implantation of autologous mesenchymal stem cells (MSCs) with a biodegradable three-dimensional According to **Golub et al.** Tetracycline decreased collagenase activity, collagen

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degradation, and bone resorption. According to **Maiden et al.,** in vitro testing has demonstrated that a number of likely periodontal pathogens, such as Fusobacterium nucleatum, P. gingivalis, Eikenella corrodens, Wolinella recta, and A. actinomycetemcomitans, are susceptible to localised Tetracycline concentrations that are completed in periodontal pockets using a controlled launch device**.** According to **Betty N.A. Vandekerckhove**, Tetracycline-impregnated fibre treatment transformed refractory spots into stable areas. Tetracycline administered locally may be effective in preventing recurrent illness due to both its antibacterial activity and its secondary effects on collagen degradation. **Terranova et al.** reported that tetracycline treatment of root surfaces markedly enhanced binding of fibronectin and fibroblasts**.**[62]Tetracycline as LDD compared to placebo demonstrated statistically significant improvements in clinical periodontal markers, such as CAL and PD, for patients of moderate to severe chronic periodontitis, according to a meta-analysis. The use of tetracycline as LDD in nonsurgical periodontal treatment can expand due to its efficacy, affordability, and ease of usage.[63](3D) woven-fabric composite scaffold and platelet-rich plasma (PRP) in periodontal regeneration.They evaluated the formulation's safety, and favourable clinical outcomes were indicated by improvements in three parameters: clinical attachment level, pocket depth, and linear bone growth(LBG).

6.6 ANTIMICROBIAL AGENTS USED IN LOCAL DRUG DELIVERY

6.6.1 TETRACYCLINE

Tetracycline-containing fibre is the first local medicine delivery technology. Administered as a supplement to periodontal disease therapy, tetracycline is a broad-spectrum bacteriostatic medication that treats chronic bacterial infections such as acne vulgaris. Tetracycline fibre local medication consists of 0.5 mm diameter monofilament ethylene/vinyl acetate copolymer fibres that contain 12.7 mg of tetracycline per 9 inches and hydrochloride that disappears uniformly, allowing for continuous tetracycline release after 10 days.[60]Resorbable tetracycline fibres were made using a collagen film that is commercially available, called Periodontal Plus AB. With a two-year shelf life, this product contains 25 mg of pure fibrillar collagen and roughly 2 mg of gamma-sterilized evenly impregnated tetracycline HCL. It releases tetracycline, which takes eight to twelve days to breakdown. It also has the advantage of biodegradability.[61]

Fig: 9 Periodontal AB plus (Tetracycline fibers) credits to Dang AB et al [61]

6.6.2CHLORHEXIDINE

Chlorhexidine (CHX) is a bisbiguanide antiseptic with four chlorophenyl rings and two biguanide groups joined by a central hexamethylene bridge. At pH levels over 3.5, it is di-cationic, having two positive charges on either side of the hexamethylene bridge.It is effective in vitro as an antimicrobrial agent against both Gram-positive and Gram-negative bacteria, including aerobes and anaerobes, as well as yeasts and fungi.[64]It works by affecting the integrity of bacteria's cell membrane, and its method of action includes plaque inhibition, bacteriostatic and bactericidal effects, substantivity, and pincushion effect. When a low dosage is employed, the bacterial cell's cellular transport is harmed due to the formation of holes in the cellular membrane (Bacteriostatic). At greater concentrations, the fluid enters the bacterial cell and kills the bacterium (Bactericidal).Substantivity is the capacity of medications to adsorb onto and bind to soft and hard tissues, and it was originally described in the 1970s.[64] **Ma, et al.** discovered that in patients with periodontitis, scaling and root planing plus chlorhexidine chips produced superior clinical results than scaling and root planing alone. 1.5% chlorhexidine in a xanthan gum matrix makes up the chlorhexidine gel. When used in conjunction with scaling and root planing, chlorhexidine gel is a more effective therapy for periodontitis than these methods alone. The growth of supragingival calculus and dark discoloration of the teeth, restoration materials, and dorsum of the tongue are the most significant adverse consequences.One theory for tooth discolorations is the production of coloured metal sulphides and non-enzymatic browning (Maillard reactions).[65] The gold standard for anti-plaque and anti-gingivitis agents is chlorhexidine. Chlorhexidine is available in two forms as a local antibacterial for periodontitis treatment: gel and chip.

6.6.2.1CHLORHEXIDINE GEL

The 1.5% CHX gel contanining 0.5% fast releasing chlorhexidine gluconate and 1% slow-releasing chlorhexidine dihydrochloride comprising Chlosite TM gel is based on xanthan. When administered into the periodontal pocket by a

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0.5 ml syringe needle, xanthan is the ideal substrate for the creation of a stable gel. It is well tolerated and breaks down naturally after 15 to 30 days at the application site.[66]

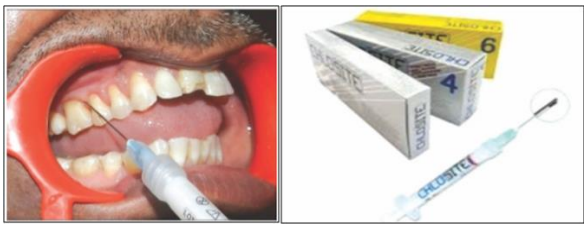

Fig: 10 Chlorhexidine gel as a local drug delivery credits to Grover HS et al [66]

6.6.2.2CHLORHEXIDINE CHIP

Chlorhexidine is administered in the periodontal pockets using the PerioChip® controlled-release medication delivery technology. It is the only locally applied antiseptic that the FDA has approved for use as a supplement to SRP treatments to lessen the depth of the probing pocket or as a part of a regular maintenance regimen for periodontal disease (Ryan, 2005) [65]Periochip is a tiny chip made of water, glycerine, and a biodegradable hydrolyzed gelatin matrix that has been crosslinked with glutaraldehyde. Each chip also contains 2.5 mg of chlorhexidine gluconate. Measuring 4.0 x 0.5 x 0.35 mm and contained in a biodegradable matrix of hydrolyzed gelatin, it is a tiny, orange, brown chip that has received FDA approval.[67]**Machtei et al. 2011** conducted a research to evaluate the safety and effectiveness of often applying the PerioChip® and Flubiprofen Chip® (FBP) in individuals with chronic periodontitis. When compared to the FBP chip, the PerioChip® responded more quickly.[68]

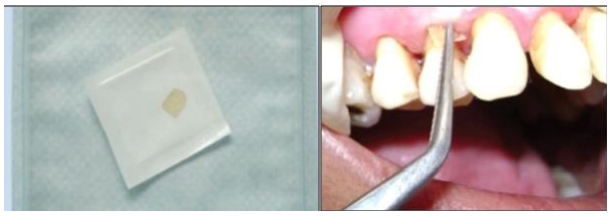

Fig: 11 Chlorhexidine chip as a local drug delivery credits to Bogdanovska L et al [68]

6.6.2.3 CHLORHEXIDINE VARNISH

Varnishes have evolved during the last decade. They are one of the most successful forms for professional chlorhexidine administration since they are simple to use, do not require patient cooperation, and, while having a disagreeable odour, do not cause discolouration. They are a new type of vehicle for antibiotic administration in the treatment of oral infections. A sufficient amount is delivered and kept at the site of action, reducing the related side effects.[69] As a result, they appear to be highly promising as vehicles for local drug delivery in the periodontal environment.Chlorhexidine varnishes are available in quantities of 1% (Cervitec), 10% (chlorzoin), 40% (EC 40), and 20% (Bio C).

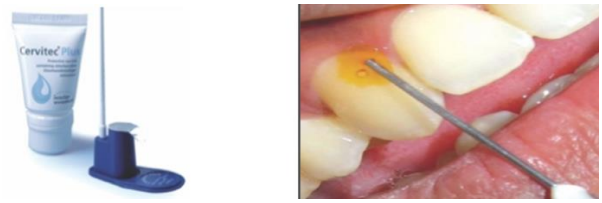

Fig: 12 Chlorhexidine Varnishes as a local drug delivery credits to Puig Silla M et al [69]

6.6.3 METRONIDAZOLE

Metronidazole is a widely used broad-spectrum antibiotic that is effective against the majority of periodontal infections. Because anaerobic bacteria are thought to be the primary cause of periodontitis, metronidazole particularly targets anaerobic microorganisms used in the treatment of chronic periodontitis. First became available for the treatment of trichomoniasis in the late 1950s. Its therapeutic usage has been expanded to include anaerobic bacterial infections.[70] Metronidazole is now one of the most extensively utilised antibacterial compounds in the treatment of periodontal disorders such as aggressive periodontitis and chronic progressive periodontitis that do not respond satisfactorily to conventional therapy. The presence of antimicrobials in periodontal tissues is more important in the treatment of periodontitis. It reaches gingival crevice fluid at amounts equivalent to plasma.[71] Metronidazole has been used to treat gingivitis, acute necrotizing ulcerative gingivitis (NUG), chronic periodontics, and aggressive periodontitis in clinical trials.It is utilised as a stand-alone treatment as well as in conjunction with root planing, surgery, or antibiotics.It has effectively treated NUG. When combined with thorough mechanical debridement, metronidazole has been used as an adjunct in the treatment of aggressive periodontitis, particularly localized juvenile periodontitis. This approach reduces the number of gram-negative anaerobic rods and spirochetes, such as P. intermedia, P. gingivalis, and T. forsythia.[70]

Delivery systems of Metronidazole

a. **Irrigation devices/system**

Prior research has employed many MET formulations for local administration, including 0.5% MET in dialysis tubing and supragingival and subgingival jet irrigation with 0.05% MET.(Macaulay WJ, Newman HN 1986) But the little gains shown with dialysis tube and jet irrigation

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could be the result of low MET concentrations that don't provide the best bactericidal action, or the medication might not have been in the sulcus long enough to be useful. [72]

b. **Non-biodegradable delivery systems**

Previous research (Yeung FI, Newman HN 1983), have assessed the effectiveness of MET using acrylic resins saturated with 40% MET concentration. MET-saturated acrylic strips have the potential to enhance clinical parameters; nevertheless, there are various drawbacks that hinder their clinical application. These include the possibility of the strips breaking loose from the sulci, tissue irritation, and the requirement for a clinician to insert and remove the device (Greenstein G 1993) [72]

c. **Biodegradable delivery systems**

The inadequacies of irrigation and non-biodegradable methods led to the development of MET in the form of collagen and polymer-impregnated MET (Metrogène) and sustained release gels (Elyzol).Since Elyzol, a 25% MET, is accessible as a biodegradable gel that solidifies into a semi-solid state upon contact with gingival crevicular fluid, it circumvents many of the aforementioned problems associated with slow release devices. There have also been reports of using other gels, such chitosan.[72] (Akncbay H, Senel S, Ay ZY 2007)

6.6.3.1 METRONIDAZOLE GEL (ELYZOL)

This topical medicine uses an oil-based metronidazole 25% dental gel (glycerol mono-oleate and sesame oil). Metronidazole gel, a resorbable and biodegradable antibiotic, contains 25% metronidazolebenzoate. A syringe and blunt cannula are required to provide this fluid. The gel is applied to the pocket in a thick consistency, liquidized by body heat, and hardened again to produce crystals when in contact with water.The preparation contains metronidazole-benzoate, which is easily converted into active substances by esterases in GCF. Microbiological investigations show that this local delivery system has minimal benefits on reducing total anaerobic bacteria colony forming units in subgingival plaque.[72]

Fig: 13 Metrogyl DG Gel credits to Himaja G et al.

Yellanki SK et al. (2010) studied six batches of metronidazole gels made using natural, biodegradable polymers chitosan, guar gum, and locust bean gum at varying concentrations.Researchers found that using natural polymers to prepare metronidazole gels can effectively treat periodontal disease, reduce dosing frequency, increase bioavailability, and improve patient compliance while minimizing side effects.

Pandit N et al. (2013) examined the effectiveness of subgingivally administered minocycline microspheres and 25% metronidazole gel as an adjuvant to scale and root planing (SRP) in treating chronic periodontitis. The study found that using minocycline microspheres with metronidazole gel improves probing pocket depth (PPD) and clinical attachment level (CAL) in periodontitis patients compared to SRP alone.

Bergamaschi et al. (2016) studied the effectiveness of Metronidazole, either locally as a gel or systemically as a pill, as a supplement to full-mouth periodontal debridement (1 hour of ultrasonic calculus/plaque removal) in smokers with chronic periodontitis. The study found that using metronidazole (gel or pill) in addition to periodontal debridement resulted in comparable clinical and microbiological improvements in smokers with chronic periodontitis up to 6 months after therapy.

6.6.4 MINOCYCLINE

A semisynthetic derivative of tetracycline is minocycline. There are two drug delivery methods available for local use: a gel form and a microencapsulated microsphere form. Dentomycin is a gel-like bioabsorbable formulation of 2% minocycline HCl in an aminoalkyl methacrylate, hydroxyl-ethyl cellulose, triacetine, and glycerine matrix. The addition of magnesium chloride alters the characteristics of medication release. It falls under the category of sustained release systems, with an exponential decline in drug concentration that follows first order kinetics.[73]A polypropylene applicator helps deliver the drug into the pocket, where it remains subgingivally for twenty-four hours at a high concentration. When paired with mechanical therapy, adjunctive minocycline usage improved clinical measures, such as attachment level, compared to mechanical therapy alone, according to a 2005 meta-analysis(Bonito A.J,Lux L,Lohr K.N. 2005).[74]Minocycline is more potent and has a broader range of action used systemically in addition to mechanical debridement has been observed to help control chronic periodontitis. It also offered through local medication delivery systems.[75]

Cortelli et al. (2006) investigated the clinical effects of administering minocycline locally and conducting scaling and root planing on individuals with advanced chronic periodontitis. They observed that SRP combined with

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subgingival minocycline use resulted in a greater decrease at 270 and 360 days.

Killeen et al. (2016) investigated the impact of scaling and root planing in addition to minocycline microspheres in residual pockets and discovered that there was no significant advantage in utilising minocycline microspheres over scaling and root planing alone.

Tabenski et al. (2017) examined the effects of local minocycline microspheres or an antimicrobial photodynamic therapy on the microbiological and clinical healing of deep periodontal pockets. Neither the antimicrobial photodynamic therapy nor the minocycline microspheres had a statistically significant additional effect on the clinical and microbiological healing results in the deep periodontal pocket when compared to scaling and root planing alone.

6.6.4.1 ARESTIN

It is a microencapsulated polymer containing 1 mg of minocycline. In 2001, the FDA authorised Arestin® (OraPharma, Inc., Warminster, PA, USA), a microsphere formulation of minocycline. Each syringe includes 4 mg of 20-60 µm diameter bioresorbable microspheres, which is comparable to 1 mg minocycline base in a poly (glycolide-lactide) carrier. Initially in powder form, the polymer hydrolyzes upon contact with GCF and adheres to the periodontal pocket. Administration results in sustained release of minocycline concentration of 340 µg per mL for 14 days, above the MICs for periodontal bacteria.Both Periocline® (Sunstar, Osaka, Japan) and Dentomycin® (Lederle Dental Division, Gosport, Hampshire, UK) are biodegradable 0.5 mg minocycline ointments. They contain 10 mg of minocycline hydrochloride at a concentration of 2% within a matrix of hydroxyethyl cellulose, triacetine, aminoalkyl methacrylate, and glycerine.[76]

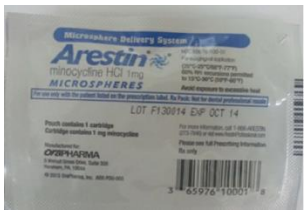

Fig: 14 Minocycline HCL (Arestin) for local drug delivery credits to Aboelsaad N, Ghandour R, Abiad

"Periofeel" is a commercially available bio-absorbable sustained local drug delivery system that contains 2% minocycline hydrochloride inside a matrix of aminoalkyl cellulose, a hydroxyethyl cellulose, methacrylate, triacetine and glycerine.Periofeel is a disposable polypropylene applicator that carries 10 mg of minocycline in 0.5 g of ointment (2% minocycline HCl). One benefit of local drug delivery systems is the ability to provide the medication sub-gingivally for 24 hours at a sustained release concentration. First-order kinetics dictates an exponential decline in the drug concentration.[77]

Kurimoto K and colleagues in 1990 clinical research in Japan resulted in the approval of minocycline hydrochloride as Periocline (Sunstar). **Maehara et a**l. reported that minocycline inhibits collagenase activity.**Williams RC et al., Van Steenberghe D et al., Jung DY et al., Atilla et al., and McColl E et al**. found a substantial reduction in gingival bleeding index.**Greenstein et al.** found that bleeding on probing is linked to histopathologic and bacterial changes associated with periodontal disease. Minocycline, an anti-inflammatory drug, enhances the benefits of the treatment. Research indicates that it binds to Ca++ and Zn++, inhibiting collagenolytic enzyme activity in inflammatory tissues. **Gabler and Creamer** found that minocycline suppresses neutrophil migration, O2-synthesis, and degranulation, all of which contribute to tissue damage during inflammation.[77]

Minocycline hydrochloride (MH) is regarded as an effective periodontal therapy due to its anti-collagenase capabilities and capacity to minimise soft tissue deterioration and bone resorption. (Heitz-Mayfield,2009; Pinon-Segundo et al., 2005). Polymeric nanoparticles have been introduced into periodontal treatment, with the potential to deliver active therapeutic medicines to periodontal pocket locations below the gum line that other delivery systems may be unable to reach due to their small size. (Kong et al, 2006)[78]

MINO-loaded electrospun PLGA membranes capable of a prolonged release of the antibiotic to ensure its sufficient concentration in periodontal pockets. MINO-PLGA membranes were predicted to encourage bone growth while maintaining their antibacterial properties. The current study shows that electrospun membranes can provide a therapeutic concentration of MINO over a 40-day period through an initial burst and persistent gradual release. This characteristic of MINO-PLGA accelerated bone regeneration, increasing the possibility of therapeutic applications.[79]

The 2% Minocycline (in MIN MC) is encased in a bioresorbable polymer called polyglycolide-co-dl lactide, which has a resorption period of around 21 days .Several studies concluded that using Minocycline microparticles (MIN MC) in addition to scaling and root debridement (SRD)led in a bigger reduction in bleeding on probing (BOP) and PPD, higher CAL gain, and a decrease in the quantities and proportions of red complex bacteria. In contrast, Tabenski L. et al.'s 12-month prospective RCT had radically different results. They evaluated whether antimicrobial photodynamic therapy (aPDT) or local application of MIN MC were more effective in treating periodontitis after SRD. Surprisingly,

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neither approach provided any meaningful extra benefit in the treatment of periodontal disease.[80]

6.6.5 DOXICYCLINE

Doxycycline is a well-known broad-spectrum antibiotic that has antibacterial properties against the subgingival microorganisms. Among its qualities, one notable trait is its capacity to bind to the dentin surface and remain substantial, hence maintaining bacteriostatic concentrations effective against the majority of periodontal infections. In vitro study indicates that Porphyromonas gingivalis, Prevotella intermedia, Campylobacter rectus, and Fusobacterium nucleatum are sensitive to doxycycline at 6.0 µg/ml. Doxycycline is effective against other periodontal bacteria at doses ranging from 0.1 to 2.0 µg/ml. However, biofilms require at least 50 times higher minimum inhibitory concentrations (MICs).In addition to its antibacterial action, doxycycline has been found to inhibit polymorphonuclear neutrophil-derived and bacterial-derived collagenases (matrix metalloproteinases, MMPs).[81]

Gad et al have developed a solid lipid microparticle encapsulating 5% w/w Doxycycline hydrochloride (DH) for treating periodontal problems. Pfizer developed doxycycline, a semi-synthetic derivative of oxytetracycline that exhibits broad-spectrum activity against common periodontal pathogens like spirochetes, Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans (Actinobacillus actinomycetemcomitans), and Prevotella intermedia.[82]

Subantimicrobial dosages of doxycycline prevent the periodontitis-causing matrix metalloproteases (MMPs) from acting on the gingiva and from degrading collagen.[138]Its local antibacterial activity against periodontal infections has been the subject of several investigations conducted throughout time. In order to give doxycycline hyclate locally by intrapocket infusion for the treatment of periodontal disease and regulated drug delivery, **Silvana Gjoseva et al.** developed chitosan microparticles (MPs) and ethyl cellulose (EC) coated Chitosan MPs.[82]

Marwa Madi et al developed subgingivally delivered nano-doxycycline periodontal gel, and its usage as an adjuvant to SRP was beneficial and improved both clinical measurements and inflammatory indicators for up to three months.Recently created chitosan/carboxymethyl chitosan nanoparticles with doxycycline exhibited excellent bacteriostasis against Porphyromonas gingivalis.

6.6.5.1 ATRIDOX®

It is a syringe-distributed, FDA-approved subgingival controlled-release 10% doxycycline gel device. Resorbable doxycycline gel system consists of two syringes of powder and liquid combined together 25 times. With its potential to down-regulate the matrix metalloproteinase.After receiving Atridox therapy, GCF levels peaked in two hours at 1,500–2,000. For eighteen hours, these levels stayed over 1000 µg/mL, after which they progressively decreased. [76]

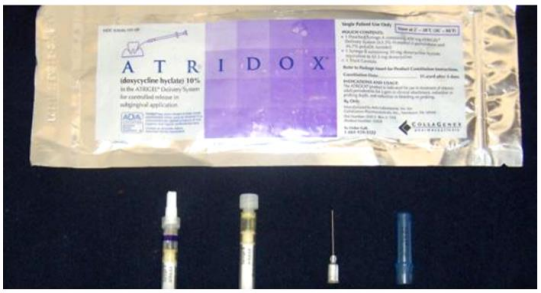

Fig: 15 ATRIDOX (Doxycycline Hyclate Gel 10%) Aggarwal S et al [82]

Walker et al. investigated the effects of a sustained-release, biodegradable gel containing 8.5% doxycycline on the patterns of antibiotic resistance and anaerobic flora in subgingival plaque and saliva. They found that the treatment decreased or eliminated the pathogenic species, which were primarily Gram-negtive bacilli.[83]

Numerous investigations on the topic of local DOX application have demonstrated the effectiveness of 10% DOX hyclate (Atridox®) as an antibacterial agent for reducing PPD and achieving the CAL. **(Sandhya, Y.P 2011, Jalaluddin; Ahamed, S et al 2013, Tonetti, M et al 2012)**

According to **Tomasi C and Jan LW** they found that controlled release doxycycline gel can partially counterbalance the deleterious impact of smoking on periodontal healing after non-surgical treatment. **Deo et al.** found that combining doxycycline hyclate 10% with SRP reduced PPD and increased CAL compared to SRP alone.

Ahamed et al. conducted a study in 2013 to assess how well-controlled local doxycycline administration performs as a complement to SRP in the treatment of chronic periodontitis. Combining SRP with 10% Atridox gel produced greater outcomes.[75]

Tonetti et al. (2012) examined the efficacy of slow-release doxycycline gel (SRD) and found that SRD may offer a temporary benefit in reducing inflammation and deep pockets in periodontal patients.

Xu et al in 2020 developed doxycycline-loaded chitosan nanoparticles. It was evaluated on cellular fibroblast cultures containing P. gingivalis. A fibroblast cell culture with untreated P. gingivalis served as the control group. After the

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study, the tested group had lower levels of cytokines than the control group. 84

Hu et al. conducted a trial research in 2019 and reported that employing doxycycline loaded on liposome as the delivery mechanism can minimise inflammation and induce bone regeneration.[85]

Wang et al. in 2020 studied the integration of bioactive compounds into polylactic-co-glycolic acid microspheres distributed in a thermo-reversible polyisocyanopeptide hydrogel. Doxycycline and lipoxin were charged independently in acid-terminated and ester-coated polylactic-co-glycolic acid.[86]

6.7 PHOTODYNAMIC ANTIBACTERIAL THERAPY (aPDT)

Photodynamic antibacterial therapy (aPDT) relies on the chemical effects of light. The light energy source, photosensitizer, and molecular oxygen are the three major components of photodynamic antibacterial treatment. Their interaction will cause a cascade of responses with therapeutic benefits**.**Nd:YAG lasers are useful in eliminating bacterial species like P. gingivalis because of their specific absorption of pigments. Additionally, endotoxins and other bacterial products might be less released when exposed to laser light. Therefore, photodynamic treatment aims to reduce inflammation and bacterial activity while also encouraging decontamination and periodontal site repair.[87]

By applying a photosensitizing substance to the periodontal pocket and irradiating it with a light source (laser or LED) at a wavelength appropriate for the used substance, the use of aPDT in adjunctive periodontal therapy can be increased after exposure to light, cytotoxic reactive oxygen species are generated, with effects involving protein, cell membrane, and bacterial organ damage.[88]

Periodontal treatment has explored a number of photosensitizing compounds, such as phenothiazine derivatives (methylene blue, toluidine blue), xanthens (erythrosine, eosin-Y, Bengal roses), riboflavin derivatives, indocyanine green, fullerene derivatives, and bordipiromethane.[89] Indocyanine green aPDT does not require oxygen to activate and release free radicals and singlet oxygen, and it is also known as photothermal treatment. Thus, indocyanine green may be more efficient than other photosensitizers in the periodontal pocket, which has low oxygen levels.[90]

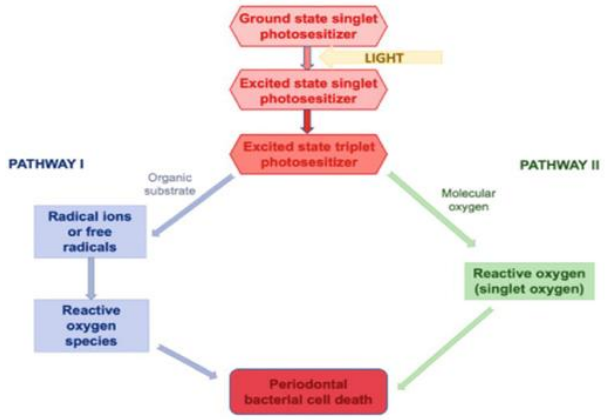

Fig: 16 Mechanism of action of Photodynamic antibacterial therapy credits to Jori G et al.[88]

Curcumin gel was found to have an antibacterial effect on P. gingivalis, P. intermedia, and A. actinomycetemcomitans in a clinical and microbiological study conducted on patients with periodontitis by **Sreedhar et al.** However, PDT enhanced the benefits of curcumin, which were further enhanced by repeated PDT sessions.[91]

Numerous periodontal disease-related bacteria' susceptibility to aPDT has been the subject of in-vitro investigations. Utilising aPDT has demonstrated the ability to decrease a number of bacteria linked to periodontal disease, including P. gingivalis, A. actinomycetemcomitans, and Fusobacterium nucleatum (F. nucleatum) in biofilms.[92]**(Prasanth et al., 2014; Kranz et al., 2015; Yoshida et al., 2017; Valle et al., 2019; Oruba et al., 2021)**

According to research, patients with HIV-associated periodontitis, diabetic patients with periodontitis, smokers, and those receiving orthodontic treatment with appliances that make plaque control difficult can all benefit from adjuvant treatment with aPDT. [92]**(Noro Filho et al., 2012; Theodoro et al., 2018; Alshahrani et al., 2020; Cláudio et al., 2021)**

Akram et al. in 2020 conducted a systematic analysis of the data pertaining to aPDT and laser irradiation as adjuvants to open flap debridement (OFD). The addition of aPDT to OFD resulted in improvements in periodontal parameters.

Moro et al in 2021 conducted systematic reviews of 22 RCTs comparing SRP alone to SRP combined with aPDT, with at least 3-month follow-ups. According to their findings, the relationship between SRP and aPDT was associated with a significant increase in clinical attachment level (CAL) and a decrease in probing pocket depth.Antimicrobial PDT (aPDT) contains photosensitizers that can target both Gram-positive and -negative bacteria by carrying a positive charge. These include porphyrins, phthalocyanines, and phenothiazines (e.g.,

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toluidine blue O and methylene blue). This suggests that aPDT may be useful in oral applications, particularly for periodontal treatment.[93]

6.8 RECENT ADVACES IN LOCAL DRUG DELIVERY

6.8.1CHITOSAN AS LOCAL DRUG DELIVERY

Chitosan effectively suppresses periodontal bacteria such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans **(Pichayakorn and Boonme, 2013)**[94] Research suggests that positively charged chitosan molecules may interact with bacteria' negatively charged cell membranes. Electrostatic forces alter the permeability of cell membranes, leading to an internal osmotic imbalance and restricting microorganism development. Hydrolysis of peptidoglycans in cell membranes can lead to leakage of intracellular electrolytes, including potassium ions, proteins, glucose, nucleic acids, and lactate dehydrogenase **(Goy et al., 2009; Koyano et al., 1998)**.[95]

Chitosan has been utilised as an antiseptic in dental applications, including gels (Bhattarai et al., 2010) and mouthwashes (Vilasan et al., 2013). Chitosan has been used for local drug delivery due to its absorbability, flexible properties, and cohesive threshold concentration, allowing for gradual release and optimal resorption (Bhattarai et al., 2010; Pichayakorn and Boonme, 2013; Benjamin et al., 2009). Chitosan's low cytotoxicity and anti-inflammatory and antibacterial qualities make it a promising alternative for non-surgical periodontal therapy.[95]

Chitosan, a deacetylated chitin derivative, is a popular semi-synthetic polymer for drug delivery systems. It has received a lot of interest in the pharmaceutical and biomedical industries due to its favourable biological qualities, which include non-toxicity, biocompatibility, biodegradability, and wound healing traits[96]

6.8.1.2 CHITOSAN BASED DRUG DELIVERY DEVICES

Chitosan microspheres have proven to be effective drug delivery carriers. They have the potential to be produced as a chip, part of a dental paste formulation, or directly injected into the periodontal pocket.[96]For periodontal therapy, **Sargon et al**. developed a microparticulate drug delivery method based on chitosan. There have also been reports of chitosan-based spray-dried microparticles loaded with clindamycin phosphate (CDP) for delivery in periodontal pockets.[97]

A novel chitosan/PLGA film delivery system for the periodontal distribution of ipriflavone was reported. For the treatment of periodontal diseases, **El-Kamel** developed mucoadhesive micromatricial chitosan/poly (ε-caprolactone) (CH/PCL) and chitosan films for a local, oral mucoadhesive metronidazole benzoate delivery system that the patient can apply and remove .

Chitosan gel and chlorhexidine gluconate film were reported at doses of 0.1 and 0.2%. The gels' flow properties made them suitable for local application on the oral mucosa and delivery into the periodontal pocket.[98]

Chitosan sponges have been explored for bone regeneration and for periodontal wound dressings that can administer antibiotics.99 **Lee et al**. demonstrated improved bone regeneration using a chitosan sponge containing platelet-derived growth factor-BB (PDGF-BB).[99]

Fibres, also known as thread-like devices, are reservoir-type systems put circumferentially into periodontal pockets with an applicator and attached with cyanoacrylate adhesive to allow for the prolonged release of the entrapped medicament into the pocket. **Yimin et al**. developed silver-containing chitosan fibres.The silver ions considerably improved the chitosan fibres antibacterial properties[100]

Chitosan-based nanoparticulates show great promise for enhancing periodontal drug delivery. Nanoparticles, due to their small size, have the ability to permeate places below the gumline that other medication carriers cannot reach.

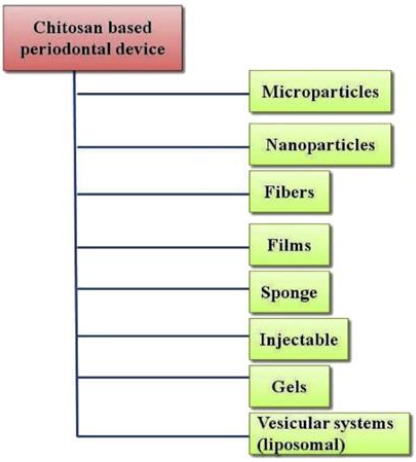

Fig: 17 Various chitosan-based periodontal drug delivery devices credits to Sah AK, Dewangan M,

6.8.2 LIPOSOMES AS A DRUG DELIVERY (VESICULAR SYSTEM)

Liposomes have been applied topically in dentistry to treat oral lesions, periodontitis, and to regulate the oral biofilm, hence reducing dental caries and gingivitis. Liposome compositions have been intensively studied for treating periodontitis. Local administration of liposome-encapsulated superoxide dismutase and catalase reduced periodontal inflammation in beagle dogs with experimentally induced

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periodontitis. To treat chronic periodontitis, a liposome formulation of minocycline was developed and tested on murine macrophages (ANA-1). [101]

Periodontal therapy was devised using pH-responsive quaternary ammonium chitosan (TMC)-loaded liposomes containing doxycycline. Rats were used to evaluate the effectiveness of the proposed formulations in treating periodontitis. The formulations demonstrated antibacterial efficacy against P. gingivalis and Prevotella intermedia, inhibited biofilm development, and hindered alveolar bone absorption in vivo.Local anaesthesia is generally used during periodontal treatment.[102]

Robinson and colleagues have also investigated the affinity and specificity of immunoliposomes for reducing dental plaque. Anti-oralis immunoliposomes had the highest affinity for S.oralis, and this affinity was unaffected by the net charge on the lipid bilayer or the amount of antibodies attached to the liposomal surface

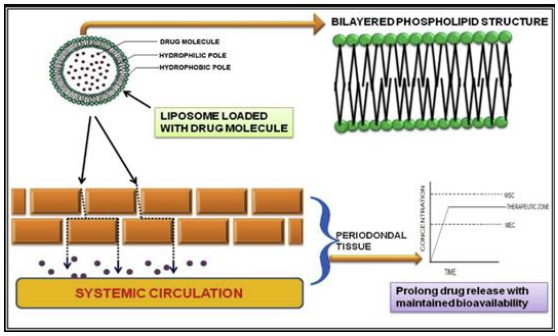

Fig: 29 Bilayered structure of liposome with penetration into the periodontal tissue credits to Sah AK, Dewangan M, Suresh PK[96]

Suganos et al.successfully developed "**Bubble liposomes**" as a carrier for gene or drug delivery. They next investigated the possibility of delivering genes into gingival tissues using ultrasound. Bubble liposomes and ultrasound can effectively transfer plasmid DNA into the gingiva, potentially improving periodontitis treatment[103]

6.8.3 GENE THERAPY AS LOCAL DRUG DELIVERY

Human gene therapy involves changing a gene's expression to change the biological features of cells. This technique can be utilised to regulate periodontal conditions and restore damaged periodontal apparatus through periodontal tissue engineering. Gene-based therapies involve introducing a gene into progenitor tissues to promote regeneration and repair, hence altering a deficiency.[104]

Gene therapy can help cure periodontal illnesses through immunisation, biofilm antibiotic resistance, alveolar remodelling, disease control, and treatment progression.Gene-based therapeutic approaches, along with tissue engineering, can help regenerate tooth-supporting components. Gene Activated Matrix (GAM) technique combines gene therapy with tissue engineering to administer cytokines and growth factors via plasmid genes. GAM systems function as a local gene depot, maintaining gene expression and enhancing growth factors in the microenvironment, resulting in tissue regeneration.

Three approaches to tissue engineering in periodontics are following:[105]

1.**Protein-based method.**: Periodontal tissue regeneration involves growth and differentiation factors such as TGF-β, BMP-2, 6,7,12, bFGF, VEGF, and PDGF. (Lee JY, Peng H 2002)

2. **Cell-based method.** : Studies have shown that mesenchymal stem cells can effectively repair massive bone defects that would not heal on their own. (Baum BJ, O'Connell BC 1995)

3. **Gene delivery method.**(CrombleholmeTM.2000): To address the short half-life of growth factor peptides in vivo, gene therapy employs a vector encoding the growth factor to promote tissue regeneration. Currently, two gene vector delivery techniques have been used for periodontal tissue engineering.

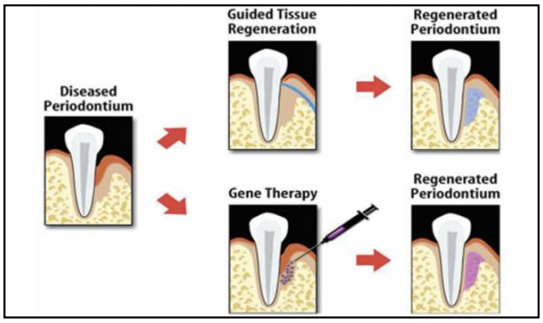

Fig: 30 Approaches for regenerating tooth supporting structure credits to Chatterjee A, Singh N, Saluja M.[105]

6.8.3.1 PLATELET-DERIVED GROWTH FACTOR GENE DELIVERY

PDGF is a chemotactic and mitogenic activator of osteoblasts, periodontal ligament cells, and gingival fibroblasts. PDGF can improve wound healing by promoting chemotaxis and mitogenesis. Transferring PDGF-BB into an adenovirus can provide prolonged availability of the factor at the healing site, promoting tissue regeneration in large periodontal defects.

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Animal studies indicate that recombinant human-derived PDGF can aid in vertical and horizontal bone regeneration. The FDA has approved its usage for periodontal regeneration.(Tian J, Li M, Lian F, Tong X 2017)[106]

- **Jin et al.** found that direct in vivo gene transfer of PDGF-B enhanced tissue regeneration in significant periodontal deficiencies.
- **Giannobile et al.** evaluated drug delivery techniques and innovative approaches for reconstructing oral and tooth-supporting components, specifically the periodontium and alveolar bone

6.8.3.2 BONE MORPHOGENETIC PROTEIN DELIVERY

Bone morphogenetic proteins microencapsulated in polyethylene glycol diacrylate (PEGDA) gels extend and distribute their expression at the problem location, according to animal investigations (Olabisi RM, Lazard ZW 2010). In order to treat periodontal disease and promote bone regeneration, researchers are examining the Cbfa gene, which produces the protein BSP (Bone Sialoprotein).[176]

a. **Franceschi et al**. studied BMP-7 Ad gene transfer for bone production both in vitro and in vivo.

b. According to **Dunn et al.,** Ad/BMP-7 gene delivery directly into vivo via a collagen gel carrier facilitated the effective healing of alveolar bone defects surrounding dental implants.

6.8.3.3 GENE THERAPY FOR PERIODONTAL TISSUE ENGINEERING

Tissue engineering strategies aim to regenerate functional tissue in the periodontal/implant region by delivering signalling molecules, cells, and scaffold/matrix to periodontal defects. TE/RM (Tissue engineering/regenerative medicine) has been employed in periodontal therapy to address limitations of traditional biomaterials and recombinant proteins.

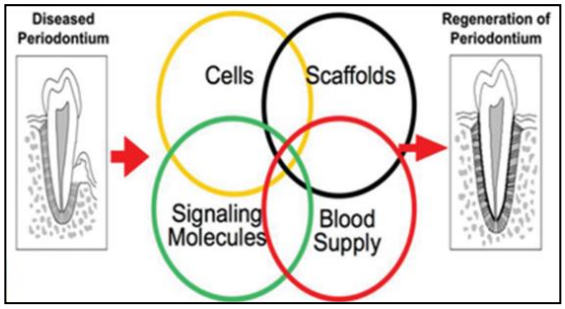

Fig: 31 Tissue engineering credits to Chatterjee A, Singh N, Saluja M [105]

FUTURE PERSPECTIVES

Designer drug therapy for treatment of periodontal disease **(CathyAJ)**

Genetic research can identify genes required for normal development, allowing for the development of "designer drug therapies" that target specific areas of the gene.

These designer drugs are safer than current medications as they only address the identified defect. Concluding that Gene therapy has promise in the field of periodontics. However, it does raise severe ethical concerns. Gene therapy is no longer a new concept. Comparing theoretical and hypothetical quotations to actual scientific study shows possible opportunities. More study is needed to fully understand the mechanisms and incorporate them into daily therapy options.

6.8.4 HYDROGELS AS LOCAL DRUG DELIVERY

Hydrogels made from natural and synthetic polymers are widely used in biomedical sciences to deliver powerful biological substances. These polymeric materials either have intrinsic antibacterial characteristics or are effective carriers for antibacterial drug delivery. Some hydrogels' biocompatibility, low toxicity, and biodegradability have made them a promising carrier for antibacterial medication delivery in periodontal disease.[107] The use of hydrogels as antibacterial agents or drug-delivery materials may be crucial in the worldwide fight against antimicrobial resistance. Hydrogel-based antibiotic drug delivery systems have demonstrated promise in the management of periodontal diseases in recent years.

The ability of hydrogels to respond to external stimuli, such as temperature, pH, light, ROS, or electric fields, and cause a reversible change in the hydrogel's structure and properties, is what makes them "smart." For the purpose of treating periodontitis, hydrogel drug delivery methods have evolved into **"Smart hydrogels"** in recent years. These hydrogels can react to physical, chemical, or biological cues. In the periodontal pocket, smart hydrogels with stimuli-response units enable reversible, in situ-triggered transitions between the fluid and solid states. The smart hydrogel backbone's triggerable drug-releasing components react to external or internal stimuli in the periodontal microenvironment. An instance of this is the creation of a glucose-responsive hydrogel for the treatment of diabetic periodontitis, using glucose oxidase (GOx) and CS as crossing agents.[108]

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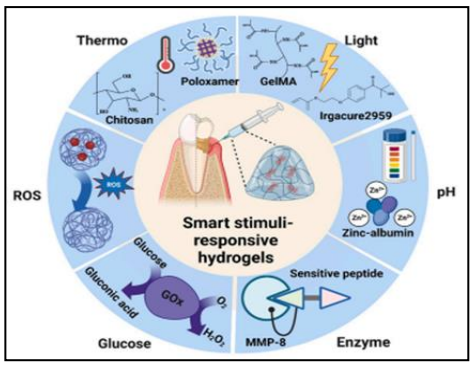

Fig: 32 Smart stimuli-responsive hydrogels for periodontitis credits to Wang Y, Li J et al[108]

Hydrogel-based antibiotic drug-delivery devices have demonstrated encouraging results in the treatment of periodontal diseases, providing targeted and prolonged release of antibiotics. Further study and development in this sector may result in more effective treatment choices for periodontal infections, ultimately improving patient outcomes and quality of life while addressing the rising issue of antibiotic resistance.[109]

6.8.5 METAL NANOPARTICLES

Metal nanoparticles (NPs) are a promising treatment option for periodontitis due to their capacity to improve photothermal and anti-inflammatory properties. Metal nanoparticles (NPs) with antibacterial and anti-inflammatory properties are being studied as potential therapies for periodontitis. Human periodontal fibroblasts treated to silver nanoparticles (AgNPs) smaller than 20 nm exhibited dose- and time-dependent cytotoxicity.[110]

6.8.5.1 GOLD NANOPARTICLES IN PERIODONTITIS

A study found that 45 nm AuNPs significantly reduced inflammation and improved the periodontal microenvironment by regulating cytokine production, macrophage polarisation, and differentiation of human PDL cells (hPDLCs). The interaction between AuNPs-conditioned macrophages and AuNPs-stimulated hPDLCs improved periodontal tissue differentiation in the LPS-activated macrophage-hPDLCs coculture system, in addition to the direct effects of AuNPs on hPDLCs. Using 45nm AuNPs can decrease the course of periodontitis and promote new periodontal attachment, bone, and cementum formation in periodontal defects.[110]

6.8.5.2 SILVER NANOPARTICLES IN PERIODONTITIS TREATMENT

Researchers used Oroxylum indicum (L) Kurz (OI) stem bark extracts as a reducing agent to synthesise AgNPs and examined their biological effects on hPDLSCs. The OI/AgNPs, ranging in size from 21.49 to 0.32 nm, were stable and spherical. Biosynthesis enhanced their biological and antioxidant properties. Research indicates that hPDLSCs with high cell viability collect OI/AgNPs. OI/AgNPs inhibited IL-1b secretion from LPS-hPDLSCs while increasing cell proliferation of H2O2-hPDLSCs. OI/AgNPs increased hPDLSCs' ALP activity and calcium concentration. Biosynthesized OI/AgNPs are non-cytotoxic, protect hPDLSCs from oxidative stress and inflammation, and promote osteoblastic growth, making them suitable for peri-implantitis regeneration therapy.[110]

6.8.5.3 ZINC NANOPARTICLES IN TREATMENT OF PERIODONTITIS TREATMENT

Zn nanoparticles' antibacterial properties help reduce biofilm growth .ZnONPs are effective against microorganisms. ZnONPs are more biocompatible than other nanoparticles, including Ag. However, due to the metal's inherent toxicity and the solubility of NPs based on its chemical properties, absorption, and ability to generate oxidative stress, high amounts of exposure may still be fatal. Using lower concentrations diminishes antibacterial effectiveness. ZnoNP-coated membranes eradicated pathogens that cause periodontitis. ZnoNPs shown antibacterial activity against S. aureus, S. mutans, P. gingivalis, and Fusobacterium nucleatum. The presence of F. nucleatum species led to enhanced and predictable periodontal regeneration outcomes.[110]

6.8.5.4TITANIUM DIOXIDE NANOPARTICLES IN TREATMENT OF PERIODONTITIS

Titanium dioxide (TiO2) nanoparticles are less than 100 nm. TiO2NPs, like other nanoparticles, have different surface chemistry and morphologies. TiO2NPs are known for their photocatalytic, antibacterial, and antiparasitic characteristics, distinguishing them from other metal oxide nanoparticles.Periodontitis is primarily caused by resistance to TiO2NPs' bactericidal and sterilizing properties. Due to TiO2NPs have excellent photocatalytic activity and chemical stability, making them ideal for enhancing the properties of polymer materials used to treat peri-odontitis.[110]

Nanoparticles have numerous potential applications for treating periodontal diseases Nanoparticles can effectively remove biofilm-encased periodontal bacteria. Clinical studies are needed to confirm whether nanoparticles can dissolve biofilms formed by periodontal bacteria **(Das V, et al.2023).**

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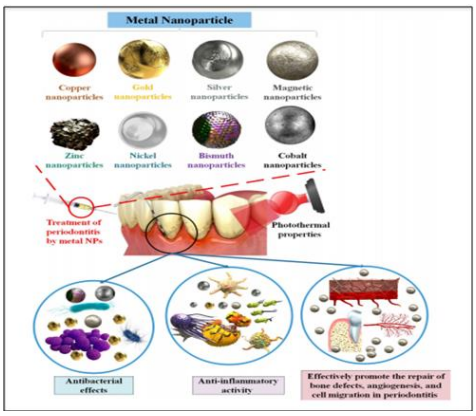

Fig: 33 Different types of Metal Nanoparticles credits to Nasiri K et al [110]

6.8.6 NATURAL AGENTS AS LOCAL DRUG DELIVERY

According to the Worth Health Organisation, 80% of the world's population relies on traditional medicine (herbal) for primary treatment. In developing nations, herbs and their derivatives account for 25% of all medical medications utilised. Herbal therapy has been used to treat oral problems such as periodontal disease for over 2000 years in China and India, two of the most populous countries.[111]

Herbal compounds with antibacterial characteristics are used in toothpaste to reduce bacterial adhesion and plaque formation. Plant parts with anti-inflammatory and antibacterial qualities can be utilised in dental treatments such as gels, mouth rinses, decoctions, and infusions.[112]

Various natural agents used as local drug delivery are as follows:

6.8.6.1 TURMERIC

Turmeric, also known as Curcuma longa, is a popular Indian spice. Lampe and Milobedzka identified curcumin, turmeric's principal bioactive component, in 1910. Curcumin has numerous biological properties, including antiinflammatory, antioxidant, anticarcinogenic, antiviral, and antibacterial effects. Curcumin's anti-inflammatory properties stem from its capacity to suppress the activities of cyclooxygenase 2 and lipoxygenase, as well as inflammatory cytokine production. Several studies have examined the effectiveness of curcumin as a treatment for periodontal disease.

In 2015 study was conducted in which curcumin gel (10mg/g) was utilised as a periodontal therapy, either with or without photoactivation and SRP. This study found that using curcumin gel in SRP treatment resulted in significant reductions in indices such as SBI, PPD, and CAL. **(Sreedhar A, Sarkar I et al 2015) [91]**

In a research of 30 patients with periodontitis, curcumin gel (2%) and chlorhexidine gel (0.2%) were found to be effective in improving SRP. This study found that curcumin gel was significantly more effective than chlorhexidine gel in reducing clinical markers of periodontitis. Curcumin gel was found to be more effective than chlorhexidine for treating mild to moderate periodontal pockets **(Hugar SS, Patil S 2016)[113]**

6.8.6.2 GREEN TEA

Green tea, derived from Camellina sinensis leaf, is widely taken as a beverage worldwide. Green tea contains polyphenols, primarily catechins. The chemicals have antibacterial, antioxidant, anti-inflammatory, and anticarcinogenic effects. Green tea catechins have antioxidant and antibacterial activities against periodontal pathogens, including P. gingivalis and Prevotella intermedia.

In 2009, an epidemiology investigation found a moderate negative connection between regular use of green tea and periodontal disease.**(Kushiyama M, Shimazaki Y 2009)[114]**

A clinical trial randomized 30 individuals into two groups. Both groups had the SRP technique, but one group was given the option of drinking commercial green tea twice a day for six weeks. After this period, subjects who ingested commercial green tea had considerably lower probing depth and Bleeding on probing compared to the control group**. (Taleghani F, Rezvani G 2018)[115]**

6.8.6.3 PROPOLIS

Honeybee propolis contains around 230 components, including flavonoids, cinnamic acids, and caffeic acid esters (phenethyl). Propolis has various natural qualities, including anti-inflammatory, antioxidant, antibacterial, antiviral, fungicidal, hepatoprotective, free radical scavenging, immunomodulatory, and antiglycemic actions. Propolis contains caffeic acid phenethyl ester, which contributes to its medicinal properties such as anti-inflammatory and antibacterial effects which makes it to be used in periodontal disease.

In a clinical study conducted by Sanghani et al. in 2014, 5 mg of propolis was added to SRP at 20 intervention sites The intervention group reported improved clinical periodontal parameters after a month. Improvement was also observed in microbiological measurements using F. nucleatum, P. gingivalis, and P. intermedia. The researchers came to the conclusion that improving clinical and microbiological parameters in patients with periodontitis with subgingival delivery of propolis to SRP was beneficial. (Sanghani NN, Bm S, S S 2014)

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6.8.6.4 ALOE VERA

Aloe vera (Aloe barbadensis) belongs to the Liliaceae family, contains minerals and vitamins with immunomodulatory, antiviral, anti-tumor, anti-inflammatory, anti-aging, and antioxidant activities. Aloe vera's characteristics have been used in dentistry to treat several oral disorders, including lichen planus, oral submucous fibrosis, stomatitis, alveolar osteitis, and periodontitis. Aloe vera's characteristics have led to studies evaluating its efficacy in treating periodontitis. Kurian et al. 2018 conducted a randomised clinical experiment with 90 participants divided into three groups: SRP and placebo gel, SRP + 1% metformin gel, and SRP + aloe vera gel.[117]

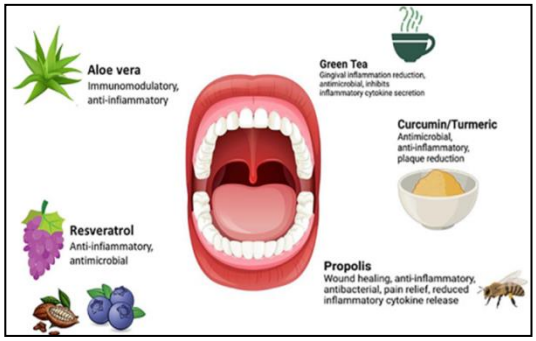

Fig: 33 Some of properties of herbal medicines for treating periodontitis credits to Viglianisi G et al

6.8.6.5 EUCALYPTUS EXTRACT

It enhances oral health. Euclyptus globulus leaf extracts (60% ethanol) have been shown to have antibacterial properties against numerous bacteria, including those found in the mouth. Ethanol extracts from E. globulus leaves inhibited the growth of periodontal bacteria such as Porphyromonas gingivalis and Prevotella intermedia. A study demonstrated that chewing eucalyptus gum improved signs of the condition, such as gingival bleeding, pocket depth, and plaque formation. Using toothpaste or tinctures with eucalyptus extract could improve periodontal health. (Nagata H, Inagaki Y 2008)[118]

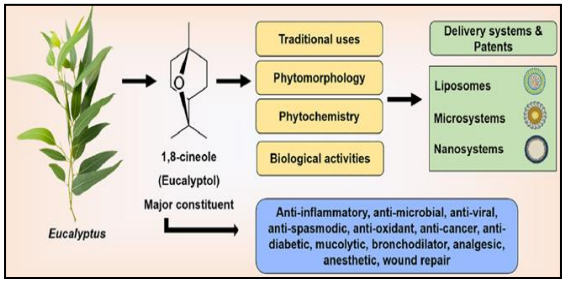

Fig: 34 Propertities of Eucalyptus credits to Chandorkar N et al.

6.8.6.6. NEEM LEAF

Neem leaf extract is beneficial in lowering bacteria and plaque levels, which contribute to the development of periodontitis It is proposed that bioactive materials found in neem cause the presence of gallotannins during the early stages of plaque formation, which may effectively reduce the number of bacteria available for binding to the tooth surface by increasing their physical removal from the oral cavity via aggregate formation.. The study showed that the gel containing neem extract significantly reduced plaque index and bacterial count compared to the control group.(Pai MR, Acharya LD, Udupa N. 2004) [119]

Fig: 35 Neem Leaf and twigs credits to Kala BS, Gunjan C

6.8.6.7. BLOODROOT

Bloodroot's natural alkaloids inhibit the growth of germs that cause periodontal disease. This herb, included in toothpaste and mouthwashes, helps reduce inflammation and prevent deep periodontal pockets, reducing bone and tooth loss.[120] Sanguinarine, an alkaloid found in bloodroot sap, has been shown to have antibacterial and anti-inflammatory actions, preventing plaque development and reducing gingival irritation and bleeding (Foster and Duke 2000, Miller 1988, Sanders 2002).

Fig: 36 Bloodroot (Botanical name: Sanguinaria Canadensis) credits to Taheri JB[121]

6.8.6.8. CHAMOMILE

Chamomile's therapeutic benefits have been used for centuries by cultures all over the world. Chamomile's anti-inflammatory and antibacterial characteristics aid to reduce inflammation in

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periodontal tissues as well as the bacterial load inside of the oral cavity. In dentistry chamomile is used as mouthwash to prevent periodontal disease.[120]

Fig: 36 Chamomile (Botanical name: Matricaria recutita). credits to Taheri JB[121]

6.9 DRUGS FOR OSSEOUS DEFECTS

6.9.1 ALENDRONATE

Alendronate, a new bisphosphonate, is a very strong inhibitor of bone resorption. The overall effect of alendronate on bone production could be described by its suppression of osteoclasts, which affects bone maturation and remodelling . Local drug delivery overcomes the majority of these issues by restricting the drug to the target site, resulting in little or no systemic uptake. Furthermore, the local drug delivery achieved can be substantially higher than feasible via the systemic route.[122]

6.9.2. SIMVASTATIN (STATIN)

Statins such as simvastatin (SMV), lovastatin, and pravastatin are selective competitive inhibitors of 3-hydroxy-2-methyl-glutarylcoenzyme A reductase Statins also appear to regulate bone formation by increasing bone morphogenetic protein-2 expression, inflammation, and angiogenesis, paving the way for new periodontal therapeutic approaches. Several animal studies indicated that SMV aids in regeneration of bone and has an anti-inflammatory impact when administered as local drug delivery.[123]

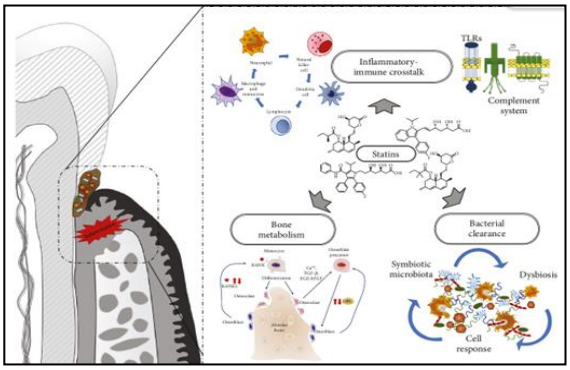

Fig: 37 Pleiotropic effects of statins in the context of periodontitis management credits to Petit C [124]

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