Advances in Periodontal Drug Delivery Systems and the Role of Probiotics in Periodontitis Treatment

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Abstract

Periodontitis is a group of inflammatory diseases which results the destruction of tooth-supporting tissues and affects 20-50% of the global population. Different bacterial enzymes are released into the periodontal pockets as a result of the proliferation of varied microflora, particularly anaerobes, which affect the body's immune response. A key component of treating periodontitis is mounting along with routing. Soluble at the site of infection, nonoperative controlled-release formulations reduce the requirement for systemic dosage by providing an affordable, non-toxic, biocompatible, and long-term therapeutic alternative. To successfully deliver a drug variety, several polymer-based systems can be used, i.e., strips, microparticles, fibers, nanoparticles, films, and nanofibers. This paper reviews the potential benefits and limits of using periodontal pockets as a medication delivery platform to create an appropriate dental localized dose form. The microorganisms called probiotics are present in the human body's alimentary canal and saliva. Recent studies on the usage of these organisms in treating periodontitis have substantially sparked the interest of researchers due to the positive metabolic effects of these organisms. Therefore, more study is needed to understand better how probiotics function physiologically and to manage periodontal disease over the long term.

Keywords: Periodontitis, controlled drug delivery, Microflora, Nanocarriers, Mucoadhesion, Probiotics.

Significance | This review discussed the periodontitis and its prevalence in gum inflammation and bone loss. Local drug delivery systems offer effective treatment, enhancing patient care.

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Introduction

Ensuring healthy lives and promoting well-being for all people of all ages is the goal of SDG 3. There are several studies demonstrated a connection between oral health and general health. Oral disease and the common non-communicable diseases have co-existing modifying risk factors. Additionally, Oral health is connected with economic, environmental, cultural, and social problems. Implementing oral health care, universal health coverage, and oral health problems could be good for oral health and general health and well-being. Taken together, oral health is the initial step to SDG3 (Huang, et al. 2022). A class of more common oral disorders known as periodontitis affects people of all ages, races, nationalities, and socioeconomic backgrounds. It is estimated to affect 20-50% of the global population and is a serious public health concern (Nazir et al. 2020). It is among the most common chronic diseases in the world (Kotb et al. 2023). The degenerative and inflammatory conditions affecting gums, periodontal ligaments, alveolar bone, and dental cementum are together referred to as “periodontitis” (Nguyen et al. 2023). Bacterial proliferation, resulting from subgingival plaque buildup, is the primary reason. The migration of gingival epithelium along the tooth surface creates a gap between

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the gingiva and the tooth. This area is referred to as the "periodontal pocket". Bacteroides inhabit this pocket and as the severity of the disease goes on increasing the microflora changes from gram-positive to negative anaerobic bacteria. Periodontal structures are damaged by harmful by-products and enzymes produced by periodontal bacteria, such as collagenases, fibrinolysins, leucotoxins, and other proteases, as well as by the host immunological response that is elicited. When we talk about periodontitis, we usually mean inflammation-causing plaque-related conditions like gingivitis and periodontitis. The mild stage of the condition known as gingivitis is brought on by a buildup of supragingival plaque and is characterized by redness, swelling, and minor bleeding in the marginal gingiva. If the condition is not addressed Gingivitis develops into periodontitis, a persistent inflammation that creates a periodontal pocket and modifies normal osseous architecture (Samal et al. 2021). If left untreated, periodontitis will proceed into an inflammatory reaction which leads to anaerobic bacteria proliferation in the subgingival, destroying the soft tissues and bone that support teeth, ultimately leading to tooth loss (Hajishengallis et al. 2020).

Periodontal damage is caused by a broad variety of periodontal infections, under the influence of *Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis Actinobacillus actinomycetemcomitans* along with *Camphylobacter rectus, Tannerella forsythia, Treponema denticola, Aggregatibacter actinomycetemcomitans* (Visentin et al. 2023).In a disease state, the body produces inflammatory mediators such as chemokines, C-reactive protein, and lipopolysaccharides, which are found in the cell walls of gram-negative bacteria, as well as antibodies and activates T-lymphocytes, neutrophils, and plasma cells (Riaz et al. 2023)Neutrophil granulocytes secrete matrix metalloproteinase, whereas IL-1 stimulates fibroblasts. This leads to increased collagen deterioration and cytokine and chemokine activation. TNF-α increases osteoclast activity by inhibiting collagen synthesis. Release of Antibody and Production of Receptor Activator of Nuclear Factor Kappa-B Lymphocytes Activate Osteoclasts (Aoki et al. 2023).

In contrast to aggressive periodontitis, which develops throughout adolescence and accelerates bone resorption three to four times quicker than chronic periodontitis, chronic periodontitis is the most frequent kind of the disease and is linked to plaque and calculus. There are several known risk factors that can lead to periodontitis, including smouldering, anxiety, diabetes, willingness, host immunity, endometriosis, along with deteriorating. Increased risk factors associated with Periodontitis can be related to infective myocarditis, coronary infarction, swipe, diabetes, acute disease of the lungs, and spontaneous abortion (Liccardo et al. 2019).

The depth of the periodontal pocket determines the disease's severity, which can be moderate (3-4 mm), mild (<3 mm) or severe (≥5 mm). The bacterial etiology harboring this pocket plays a major role in treating the disease. As the problem is very much dependent on the bacterial flora and is restricted to the pocket, the therapeutic success of a drug depends upon the pocket control and local approach rather than the conventional mechanical method. The efficacy of local drug delivery can be emphasized under the following points.

- Site-specific drug delivery
- Avoidance of GI tract-related problems
- Safer drug delivery route
- The efficacy of the drug is increased.
- Increase of retention period
- It offers a greater bioavailability.
- Non-invasive and painless drug delivery

However, this approach is limited by

- Local irritants cannot be used.
- Limited dose due to small area.
- Administration of peptide is limited.
- High manufacturing cost of patches.

An extensive study for drug delivery has been carried out for ameliorating periodontal disease which provides local delivery of drugs and long-term maintenance therapy. Novel controlled drug delivery devices can precisely control the rate of drug release. The ideal local drug delivery system should be easy to use, release the medication in a controlled manner, maintain the drug concentration for a prolonged period, be biodegradable and biocompatible, and not irritate the tissues. By using a variety of polymers, these formulations have proved to be superior due to nontoxicity, biocompatibility, nonimmunogenicity, biodegradability, stability, and low price.

2. Pathophysiology of Periodontitis

Periodontitis is a complex clinical condition that results from the interaction between the subgingival biofilm and the host's immune system response to the bacteria challenge. The disease progresses through various stages, starting with the absorption of salivary polypeptide, followed by bacterial invasion, plaque calcification, gingivitis, pyorrhea, periodontal pocket formation and, ultimately, periodontitis, which can lead to tooth loss.Fig.1 and Fig.2 (Samal et al.2021).

3.Current treatment Modalities

There are various ways to treat diseases such as surgical procedures, mechanical therapy, and the use of pharmacological agents(Jain et al.2023; Deporte et al. 1988; Freeman et al.1988). Medications are used to manage periodontitis, which includes antimicrobials that alter the microbial flora in the periodontal environment and host response modulating agents that modify the host's response, such as reducing enzymes, cytokines, prostaglandins, and osteoclast activity (Krayer et al. 2010). The different modalities for treatment is illustrated in Fig 3.

3.1. Strategies for Maintenance of Good oral hygiene

Regular brushing and flossing are the primary ways to reduce microbes in the oral cavity. The American Dental Association (ADA) recommends brushing twice a day for at least 2 minutes and flossing once a day(Ryan et al.2005). This route can effectively reduce gingivitis and treat periodontitis. However, many people do not follow this protocol, and a result, more than 50% of adults suffer from gingivitis(Bader et al. 1998; Oliver et al. 1998).

3.1. 1. Supragingival irrigation

Supragingival irrigation can increase the effectiveness of tooth brushing and help reduce gingival inflammation in patients who do not follow good oral hygiene practices. Studies have shown that there is a positive correlation between supragingival irrigation (using either acetyl salicylic acid or water) and a reduction in disease severity. Therefore, regular supragingival irrigation with either 0.3% ASA or water in addition to usual oral hygiene routine can be a valuable supportive remedy for patients with moderates to severe periodontitis(Fleming et al.1995)

3.1.2. Subgingival irrigation

The role of subgingival irrigation in the treatment of periodontitis is still up for debate. Various studies have shown that subgingival irrigation, either alone or combined with root planning, can reduce the number of harmful bacteria in the gums. Despite not affecting plaque levels, subgingival irrigation can help reduce gum inflammation by diluting plaque toxicity, intervening with subgingival plaque maturation, or possibly washing away unattached plaque(Lang et al. 1981; Lang et al. 1981)

3.2. Mechanical therapies for the treatment of periodontal diseases

Plaque is a combination of bacteria, minerals and food residue that accumulates on teeth. Some plaque hardens into calculus, which can cause inflammation and an ongoing state of gingivitis. To treat periodontitis, a nonsurgical procedure called scaling and root planning is used. This procedure involves removing plaque, calculus, and stains from the crown and root surface of teeth(Giusto et al.1997). Manual scaling and root planning can be challenging and time-consuming, especially in deep pocket sites with complex and unfavourable root morphology. To overcome these difficulties, power-driven ultrasonic mechanical instruments have been developed. These instruments enable the operator to reach into furcation more efficiently and to go through the depth of the pocket more conveniently, making scaling and root planning more effective(Clifford et al.1999).

3.3. Chemotherapeutic agents used for the treatment of periodontal diseases

3.3. 1. Host modulation therapy (HMT)

Clinical data from recent research has revealed that bacterial plaque, toxins produced by them, and the host's inflammation-immunity response are responsible for the degeneration of periodontal tissue. To prevent the destruction caused by these factors, Host Modulation Therapy (HMT) is used to modify the host response [8]. Several host modulatory drugs, enamel matrix derivatives, and growth factors. All these agents can modify host-response and block the destructive aspects of the immune response. Anti-inflammatory drugs can inhibit prostaglandins and cytokinins, while tetracyclines act as collagenase inhibitors and bisphosphonates reduce osteoclast cell activity (Rajababu et al. 2009). Recently, the FDA has approved a new therapy that involves systemic administration of drugs to be used in conjunction with scaling and root planning (Oringer et al. 2002).

3.3.2. Antimicrobial therapy

Controlling disease progression through mechanical methods and surgical debridement is not always effective in removing all microbes present in the periodontal pocket and tissues. This can result in residual microbes in the periodontal environment re-colonizing after 8 weeks of treatment (Ryan et al. 2005). Therefore, using chemotherapeutic agents in addition to mechanical and surgical debridement can be more effective. Bacteria are the main cause of periodontal disease, and using antimicrobial therapy alongside mechanical therapy is a good biological rationale for treating it. Systemic antimicrobial treatment can be effective, but it is currently only prescribed for rapidly progressing or refractory periodontitis (Slots et al. 1990). Multiple doses of systemic can have drawbacks, such as erratic antibiotic concentration at the targeted site, a quick drop in the plasma drug concentration below the therapeutic index, and the development of antibiotic resistance. In addition, high antibiotic doses can cause several side effects in patients. Due to these drawbacks, localized intra-pocket drug delivery systems have been developed for the treatment of periodontal diseases.

4. Local Drug Delivery Systems

The release of topically administered drugs, which are recommended as adjuncts to periodontal therapy, is controlled using a topical drug delivery system. To manage scaling and root planning—adjuvant medication use—they are administered directly into the periodontal pocket. The optimal characteristics of a local drug delivery system should include biodegradability, biocompatibility, simplicity of administration, regulated drug release to sustain stable concentration over an extended period of time, and non-irritativeness (Rajeshwari et al. 2019). There are several intrapocket medication delivery systems on the market, i.e., Fibers, strips and films, microparticles, Nanosystems, gel, membranes, and scaffolds for the treatment of periodontitis (Amato et al. 2023), as shown in Figure 4.

4.1. Strip and Films

The thin matrix bands known as strips and films are where the medications are dissolved into the polymer. Strip and Films are inserted in the periodontal pocket (Fig 4) and are an excellent combination along with size with respect to the periodontal pocket. As a result, they are simple to insert and cause little discomfort for Patients (Rajeshwari et al. 2019). Acrylics loaded with various antibiotics were the first materials suggested for use in the creation of strips and films. These materials demonstrated a notable drug release on the first day following insertion, followed by a prolonged release over the course of 4-5 days. Due to their non-biodegradability, they came with the drawback of requiring a second operation for removal- a challenging process by crevicular fluid softening, which irritates the gums. New bio-absorbable materials, such as polylactic-co-glycolic acid (PLGA), poly-hydroxybutyric acid, atelocollagen, chitosan/PLGA, and gelatin, along with others, were developed to get around this drawback. They underwent testing with positive findings (Wei et al. 2021). Diffusion was used to liberate the medicinal chemical from non-biodegradable Strips and Films.

Researcher has shown that Strip and Films containing antibiotics and antiseptics can effectively maintain concentration over the long run and enhance gingival health clinically. Advanced tetracycline-loaded Scaling and root planning-associated strips over Scaling and root planning alone showed that numerous strips are much more effective in reducing probing depths than a single strip. Despite the fact that other molecules have been linked to a lower efficacy in treating periodontal disease than chlorhexidine-loaded strips there is a notably greater reduction by using the chlorhexidine chips with the probing depths ($p < 0.01$) as opposed to site specific with Scaling and root planning alone.

Lastly, the ingredients used to create strips and films are the same as those used to create fibers. Their release rates vary, as do their diameters and applications; some are more suited for bigger pocket areas than others (Joshi et al. 2016).

4.2. Fibre

Fibre remains the inventory consignment device that is filled with the desired medicinal substance, applied inside the tooth pocket affected by periodontitis using an associable, which kept in place with a periodontal dressing (Rajeshwari et al. 2019).

Many polymers, including synthetic ones such as poly(ε-caprolactone), polyurethane, polypropylene, cellulose acetate propionate, and ethyl vinyl acetate, as well as natural polymers such as chitosan, zein, and gelatin, have been proposed along with research as fibers for local drug delivery (Wei et al. 2021; Rajeshwari et al. 2019). Upon use and testing, every one of them had antibacterial medications.

Since the earliest type of fibres were not recyclable, they were linked to discomfort as a lower grade interruption was required to withdraw it, and gum redness was linked to wound healing (Wei et al. 2021). Collagen fibers, for example, and other biodegradable fibers were brought to market to prevent this. Highlighting the recent development of an intriguing process termed electrospinning- which produces polymeric nanofibers with enhanced biological properties is crucial (Khorshidi et al. 2016).

A fibrous structure like a native extracellular matrix is created with this process, and they can be functionalized to transport chemical medicines, bioactive agents, or inorganic substances (Liu et al. 2018). Poly (L-Lactic acid) and collagen are materials with properties that make them appropriate for electrospinning processing. Indeed, they are incredibly biodegradable and biocompatible (Zhang et al. 2022).

As time went on, more research, such as the randomized clinical study by Chhina et al.,2015, evaluated using biochemical and clinical measures that patients with chronic periodontitis receiving treatment with Scaling and root planning in addition to the effects of tetracycline fibers were superior to those SRP alone. It does not follow that Scaling and root planning is a poor treatment choice exclusively. For early to moderate periodontitis, it really is effective. Regarding the severe type of the disease, tetracycline Local drug delivery system fibers, in conjunction with Scaling and root planning, represent a viable treatment option. In conclusion, one of the earliest types of Local drug delivery systems is fibre. Although non-biodegradable fibres must be removed after treatment, they are appropriate for inaccessible locations and can cause gingival redness.

4.3. Nanosystems

Due to their extremely small sizes, Nano systems is suited for locations like the pocket area beneath the gum lines where conventional Local drug delivery forms are not effective. They are applied directly to the pocket region or by various delivery methods, such as gel, as described in reference (Rajeshwari et al. 2019) (Fig.4). Micellar particles, liposomes, nanofibers, metallic and polymeric nanoparticles are among them. They feature an advantageous surface-volume rate and a large loading capacity, making them ideal. As periodontitis has bacterial etiological aspects, several of them have also demonstrated antibacterial qualities, which may be helpful in treating the condition.

Metallic nanoparticles are used in dentistry due to their antimicrobial activity and bone regeneration properties. (Wei et al. 2021; Rajeshwari et al. 2019,). Nevertheless, because of their cytotoxicity and non-degradability, they cannot be used for periodontal therapy (Park et al.,2010; Inkielewicz-stepniak et al. 2014); instead, other materials are preferable.

We should draw attention to the growing significance of liposomes as a vehicle for managing patients' periodontal inflammation. Moreover, liposomes can modify drug pharmacokinetics and bio distribution, enhance drug absorption into cells, and release encapsulated medication in a regulated fashion (Allen et al. 2013). But statins are an example of a different class of medication that has demonstrated efficacy when administered locally to treat periodontitis (Isilay Ozdogan et al. 2018). To conclude, there are numerous medication types that can be put onto nanocarriers that show promise for usage in this type of technology. Although nanoparticles offer a plethora of benefits, they are not without drawbacks. Actually, their formulas lack stability, their production method is highly complex, and they are expensive (Wei et al., 2021).

4.4. Scaffolds

Scaffolds have been introduced to treat bone deficiencies with the same goal as membranes. They are better because they do not have the primary drawback of absorbable membranes, which is a weakness that prevents enough spontaneous endurance to outside intensity. Those involved position towards the damaged region to preserve room for the regeneration of periodontal tissue later on (Carlson- Mann et al. 1996).

Stem cells can be included in the scaffold to facilitate their distribution, as they are becoming more and more important in periodontal regeneration (Amato et al. 2022). In order to promote periodontal regeneration, Baba et al. 2016 documented the benefits of implanting autologous mesenchyme stem cells(MSCs) with a biodegradable three-dimensional(3D) woven fibrous composite scaffold and platelet-rich plasma(PRP) in periodontal regeneration. It evaluates the safety of formulations and three measures of clinical attachment level, pocket depth, and linear bone growth. All improved, indicating good clinical outcomes. It is important to note that even while scaffolds are a useful therapeutic alternative, future trends may favour a scaffold-free strategy that uses stem cells either alone or in conjugation with growth factors (Ouchi et al. 2020).

4.5. 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 gingival fiber wounds (Sheikh et al. 2017). They can be coupled with certain therapeutic drugs to strengthen these functions, hence gaining the designation of Local drug delivery system (Liang et al. 2020). First, membranes that weren't biodegradable were used. Then, as a second surgical procedure was required to remove them, they were gradually abandoned.

These days, ingestible membranes have replaced older, non-resorbable membranes. They have a proliferation influence, which was held by an operational film and medications that promote osteogenesis. In periodontal polyglycolide, regeneration, and GTR, collagen, polylactide, or their copolymers are now utilized as membranes. Because of its benefits, such as its ability to engage and activate gastrointestinal fibroblast cells, prevent immunological reactions, and have hemostatic power, collagen is the most often employed substance. Collagen membranes have been shown to stimulate fibroblast DNA formation, and compared to other membrane surfaces, osteoblasts show greater adhesion to the collagen membrane surface. A core nanofiber membrane has recently been developed as a periodontitis treatment.

4.6. Gels

Gels are widely used in dentistry because of their many benefits, which include high biocompatibility and bioadhesivity, ease of administration, and ease of production. They are inserted into the periodontal site using wide port needle syringes. These days, in situ-produced gels that undergo liquids to semisolid state transition in response to stimuli like temperature changes or solvent effects, constitute the most current innovation in gel formulations (Dong et al. 2016). Gels are effective drug delivery devices, but one major drawback has been reported: the medication is released rather quickly after being collected. Because of this, Scientists have created formulations for a blend of gels and alternative medication administration methods. The development of a tunable and injectable local delivery system was undertaken, with subsequent in vitro and in vivo testing conducted on rats. The system was successfully designed, constructed, and evaluated for its efficacy (Wang et al. 2020).

Drug-loaded poly (lactic-co-glycolic acid) microspheres were embedded in a thermo-reversible polyisocyanopeptide (PIC) hydrogel. There are natural agents among the recently examined compounds. The current study conducted by (QI et al. 2022) successively loads Turkish gall ingredients into Nanoparticles by the technique of oxidative self-polymerization. Turkish-Nanoparticles were crushed into a thermosensitive in situ hydrogel; under periodontitis circumstances, 42.29± 1.12% of Turkish galls effective constituent, was continuously freed from it in 96 hours. Turkish-Nanoparticles have the effect of causing bacteria to lyse. In actuality, they were in favor of massive ROS production without endangering periodontal tissue. Although research into finding an appropriate antibiotic alternative medicine is still in its early stages, these promising results bode well for future investigations.

4.7. Microparticles

Microparticles have been proposed using natural materials, natural compounds that have been changed, and synthetic polymers that fall into two categories: biodegradable and non-biodegradable (Wei et al. 2021). An intrapocket delivery system for minocycline was developed by Wu et al. 2018 as an adjuvant to scale and root planning. The ca^{2+}, along with sulphate-bearing biopolymer and utilization of ion pairing by complexation of minocycline study, looked at the possibilities of future periodontal research by using Microparticles. In addition to in vitro studies, clinical research has also been conducted on the use of microparticles as a method of local drug delivery in the treatment of periodontitis. In the study by (Gada et al. 2017), the use of solid lipid microparticles is interesting. Due to their physiologically well-tolerated nature, high biocompatibility, avoidance of organic solvents, ability to modify and target drug release, increased drug stability, high drug content,

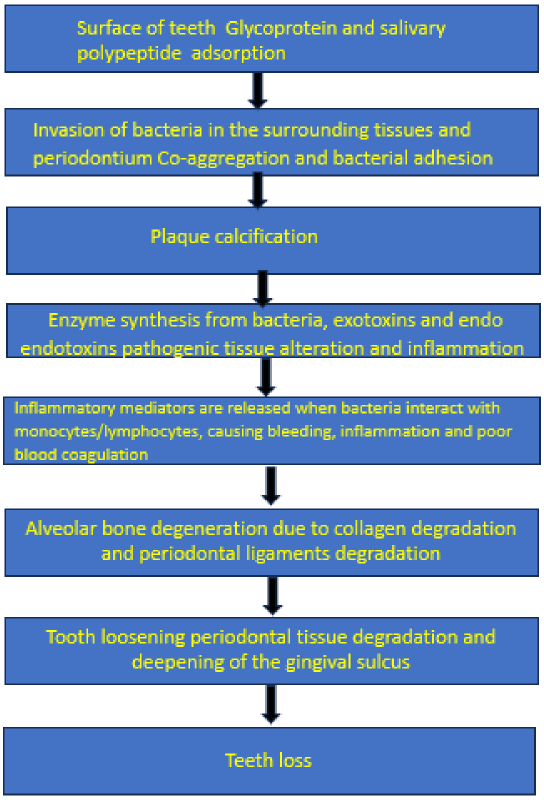

Figure 1. Schematic representation of Stages of Periodontal disease.

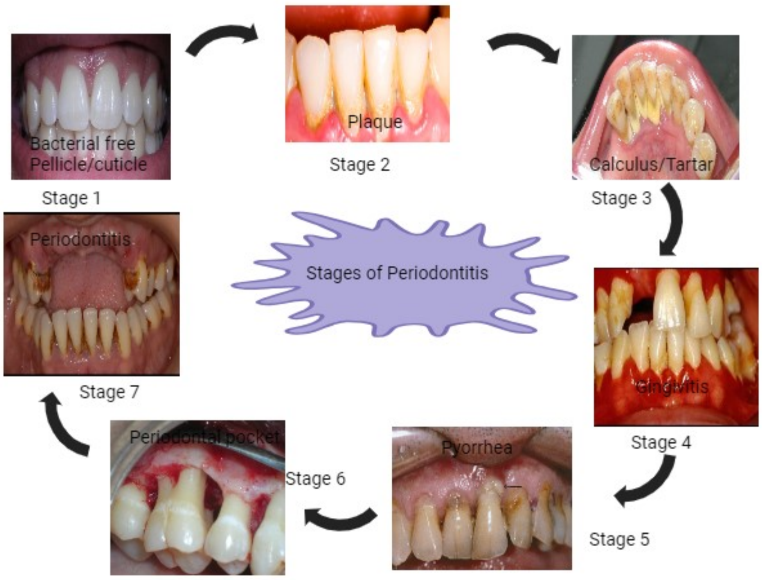

Figure 2. Figure shows stages of Periodontitis

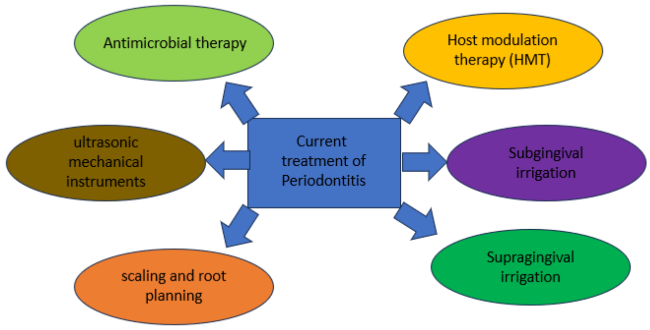

Figure 3. Schematic representation of Current treatments of Periodontitis

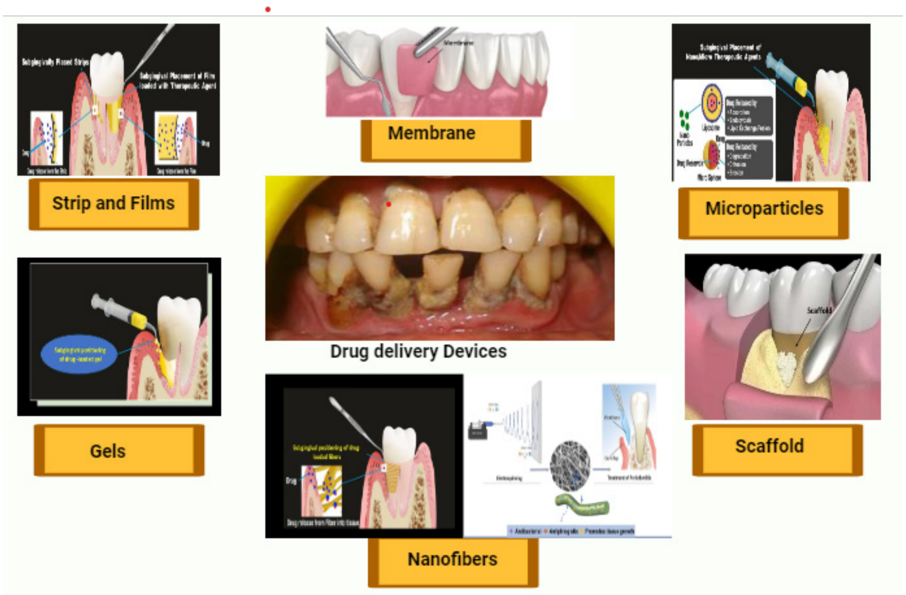

Figure 4. Diagrammatic representation of different types of Drug delivery devices

Table 1. Drug devices as Market product for periodontal treatment

Delivery Device types	Materials	Market Product as Drug	Reference
Strip and Films	Polyhydroxy butyric acid Hydroxypropyl cellulose	Hydrochloride or metronidazole Chlorhexidine diacetate	Deasy et al. 1989 Steinberg et al. 1990
Fibers	Ethyl vinyl acetate	Tetracyclines	Goodson et al. 1997
Microparticles	Sulfate/ Sulfonate bearing biopolymers	Minocycline	Wu et al. 2018
Nanoparticles	Chitosan	Doxycycline	Xu et al. 2020
Gels	Tetracycline loaded Chitosan	Tetracycline	Qasim et al. 2020
Membranes	Polyglycolide/polylactide	Collagen Membrane	Bunyaratavej et al. 2001
Scaffolds	Chitosan	Tetracycline	Qasim et al. 2020

Table 2. Each LDDS's indications and contraindications (Wei et al., 2021)

Types of Local Delivery Drug Systems	Indication	Contraindications
Strip and Films	Scaling and root planning adjacent, ideal for bigger pocket space	Surgical periodontal site repair and inaccessible posterior locations
Fibre	Scaling and root planning -adjacent and appropriate for inaccessible locations	Greater regions of pockets and surgical treatment of the periodontal site.
Nanosystems	Supplemental to scaling and root planning	The periodontal site was surgically corrected
Scaffolds	In addition to periodontal surgery repair	If surgical repair of the bone deficiency is not necessary
Gel	Supplemental to scaling and root planning	The periodontal site was surgically corrected
Membrane	In addition to periodontal surgery repair	If surgical repair of the bone deficiency is not necessary
Microparticles	Supplemental to scaling and root planning	The periodontal site was surgically corrected

Table 3. Probiotic species promoting periodontal health (Zhang et al., 2022).

Sl No	Genus/type	Species
1	*Lactobacillus*	*Lactobacillus acidophillus* *Lactobacillus brevis* *Lactobacillus casei* *Lactobacillus fermentum* *Lactobacillus gasseri* *Lactobacillus reuteri* *Lactobacillus rhamnosus* *Lactobacillus salivarius* *Lactobacillus johnsonii* *Lactobacillus fructosum* *Lactobacillus delbrueckii*
2	*Bifidobacterium*	*Bifidobacterium lactis*
3	*Streptococcus*	*Streptococcus salivarius* *Streptococcus dentisani* *Streptococcus cristatus* *Streptococcus gordonii* *Streptococcus sanguinis* *Streptococcus mitis*
4	*Weissella*	*Weissella cibaria*
5	*Recombinant probiotics*	*Recombinant Lactobacillus paracasei* *Recombinant L. acidophilus*

and capacity for mass production using high-pressure homogenization techniques, microsolid lipid particles have received special attention in medicine.

5. Marketed drug delivery devices available for periodontal disease

We have outlined various delivery device of peridontal disease, their materials composed of, marketed drugs are desctibed in Table 1.

6.Advantages of a local delivery system for precise and effective periodontal treatment

It ensures minimum invasiveness and direct medication administration in the targeted location, acting immediately in the afflicted site and just that site, without harming other organs or waiting for the process of transporting such molecules. Since it avoids the hepatic metabolism, unlike drugs administered systemically, less medication is lost. It avoids the gastrointestinal problems that are common with oral medications, which can irritate the stomach mucosa or, in the case of antibiotics, induce dysbacteriosis of the intestinal system, which can result in diarrhoea. Since no portion of the molecule is metabolized by the liver, as was previously said, 100% of the molecule is effective, which is related to the decrease in dosage frequency. Because it is relatively simple to administer and allows the introduction of drugs that are not compatible with the systemic application, such as chlorhexidine, it improves patient compliance (Rajeshwari et al. 2019).

7. Challenges of Utilizing Local Delivery Methods for Periodontal Pocket Therapy

Some local drug delivery systems struggle to maintain control, and some struggle to supply drug concentrations that are high enough. The earliest examples need suffering during a second intervention to be removed since they are not biodegradable. High prices are sometimes linked to local delivery networks, which may limit their therapeutic use (Wei et al. 2021).

8.Indication and Contraindications

Table 2 lists the local delivery system's indications and contraindications.

9. Limitation of Local Drug delivery system

Bleeding can have a negative effect on the effectiveness of local drug delivery systems. If an LDD device is placed in a periodontal pocket immediately after root surface instrumentation, its efficacy is reduced. This is because the drug binds to the protein in the blood, which reduces its activity. A prime example of this is chlorhexidine, whose activity is reduced in the presence of organic matter such as blood. Additionally, the materials that the vehicle degrades into could interfere with the repair and regeneration of the periodontal tissues, which is an unwanted effect. The cost is also a possible barrier to the use of LDD in the management of periodontal disease (Eastham et al. 2014).

10. Role of Probiotics

Probiotics are eventually explored for intestinal disease. However, in recent decades probiotics have been used in oral health belonging to the genera *Lactobacillus, Bifidobacterium, Streptococcus, and Weissella.* Certain species like Bacillus *subtilis* and *Saccharomyces cerevisiae.* Several strains of *Lactobacillus reuteri*, *Lactobacillus brevis*, *Streptococcus salivarius*, have been made comericially viable for promoting oral health care (Allaker and Stephen, 2017). Probiotics can improve oral health such as dental caries, periodontal diseases, oral candida infection, and halitosis (Ince et al. 2015; Ohshima et al. 2016).

Probiotics are microorganisms that, when used in sufficient amounts, offer a number of benefits to the host, according to the World Health Organization (WHO). There are several kinds of probiotics used in dentistry, such as liquid, paste, and solid forms (Srinivasan et al. 2020, Nguyen et al. 2021). Probiotics can prevent periodontal disease in a few distinct ways. Inflammatory cytokines were found in higher concentrations in gingival regions containing a significant number of *P. gingivalis*. When gingival regions infected with *P. gingivalis* are treated with lactobacilli probiotics, the number of inflammatory cytokines is reduced (Nguyen et al. 2021). By colonizing epithelial cells and changing the pathogen bacteria, second probiotics can cling to the mouth mucosa. Finally, probiotics have the capacity to create chemicals such as reuttering, bacteriocin, and retrocyclin, which can inhibit the proliferation of peri pathogens (Srinivasan et al. 2020; Nguyen et al. 2021). In addition, probiotic strains secrete lactic acid, which stimulates the growth of probiotic bacteria and inhibits the development of harmful bacteria (Nguyen et al. 2021). Lactobacillus species, Bifidobacterium species, and Saccharomyces species are a few of the species that have been the subject of extensive research (Minic et al. 2021). Also, frequently present in the digestive system are these probiotics. The mouth cavity and intestinal lumen naturally contain Bifidobacteria, the first species. By monitoring the levels of BD-3, TLR4, and CD4 in gingival tissues, a study on *B. lactis* HN019 in rats with periodontitis claims that it can lower IL-1 BETA levels because of its immunological and antibacterial qualities (Invernici et al. 2020). There is an additional probiotic in addition to this. Beta glucans, which are produced by *Saccharomyces cerevisiae*, have been shown to promote phagocytic activity, inflammatory cytokinesis, and leucocyte activation, all of which improve periodontitis recovery (Garcia et al. 2016). Finally, Lactobacillus was found to produce metabolites such as 10-oxo-trans-11-octadecenoic acid and 1-hydroxy-cis-12-octadecenoic acid. As a gram-negative bacterium, 10-oxo-trans-11-octadecenoic acid has significant antibacterial activity (Furumoto et al. 2016; Sulijaya et al. 2019). Because of their capacity for colonization, biocompatibility, and gram-positive status, a number of novel species of Streptococcus have attracted the attention of researchers. An in vitro investigation using Streptococcus salivarius that was isolated from the saliva of healthy children revealed that K12 and M18 had the capacity to suppress periodontitis activities against *P. gingivalis, F. nucleatum*, and other bacteria (Zhang et al. 2022). Table 3 determines that different probiotic species promote periodontal health ((Zhang et al., 2022).

11.Probiotics & oral health

In 1965, Lilly and Stillwell introduced the term "probiotics," which they defined as "growth-promoting factors produced by microorganisms" (Lilly et al. 1965) Since then, the definition of probiotics has evolved. In 2002, the World Health Organization and the Food and Agricultural Organization of the United States came up with a new definition that is now widely accepted: probiotics are living microorganisms that can have a beneficial effect on the host when taken in sufficient doses (Hill et al. 2014). Originally used to treat intestinal diseases, probiotics have been shown to help control intestinal infections, relieve constipation and diarrhea, and improve lactose intolerance. However, their benefits extend beyond the intestines. They can contribute to maintaining a healthy urogenital system and fighting against diseases such as cancers, diabetes, obesity, and allergies.

In recent decades, extensive studies have explored the use of probiotics in oral disease treatment and oral healthcare. It has been found that the probiotics that contribute to oral health are mainly found in the genera Lactobacillus, Bifidobacterium, Streptococcus, and Weissella, as well as certain scattered species such as Bacillus subtilis and Saccharomyces cerevisiae. Several strains of *Lactobacillus reuteri*, *Lactobacillus brevis*, *Streptococcus salivarius*, and others have been commercially produced as oral health-promoting probiotics, all of which are microorganisms isolated from the oral cavity shown in Table 3 (Zhang et al. 2022). Studies have shown that probiotics can have a positive impact on common oral diseases such as dental caries, periodontal disease, oral candida infection, and halitosis.

12. The Role of Probiotics in Promoting Oral Health: Managing Periodontal Disease

The use of probiotics in periodontal therapy and care has become increasingly popular. Studies have shown that probiotics are effective in preventing periodontopathogens and improving a range of clinical indicators associated with periodontal health, including plaque index (PI), gingival index (GI), bleeding on probing (BOP), periodontal pocket depth (PPD), clinical attachment loss (CAL), and gingival crevicular fluid (GCF) volume. Moreover, probiotics can help reduce inflammation by regulating biochemical markers such as interleukin (IL)-1β, matrix metalloproteinase (MMP)-8, and tissue inhibitor of metalloproteinase (TIMP)-1. Various forms of probiotics are available for managing periodontal disease, including tablets, mouthwash, and toothpaste. However, probiotics used in periodontal therapy are usually in the form of tablets, while mouthwash and toothpaste are commonly used for periodontal health care (Zhang et al. 2022) (Table 3).

Future Direction in Probiotics

Probiotics have unique advantages and considerable potential in maintaining periodontal health. They offer more options for preventing and treating periodontal diseases. Probiotics have a role in periodontal therapy and healthcare by regulating host immune function and restoring the balance of periodontal microecology. Currently, the majority of periodontal health-promoting probiotics are derived from the classical probiotic genera Lactobacillus and Bifidobacterium. These probiotics are considered safe and effective for human health. However, there are concerns about their effectiveness and safety, so further research is needed to support the role of these probiotics, as well as probiotics derived from other genera or remodelled by genetic engineering techniques, in periodontal therapy and care.

13. Conclusion and outlook for the future

A variety of targeted drug delivery techniques have been developed to address periodontitis and improve the way medication is administered. These include strips, fibers, chips, films, microparticles, and nanoparticles, all of which are intended to minimize the negative effects that antibiotics can have on the body as a whole. Biocompatible, extended-delivery formulas that use biodegradable polymers have been created to lower the risk of antimicrobial resistance, decrease the necessary dosages, enhance therapeutic effectiveness, and minimize negative systemic effects in dental treatments. Thanks to their high surface-to-volume ratio, nanoparticles have proven to be one of the most effective antibacterial agents. They are useful in inhibiting the growth of certain microorganisms. In conjunction with scaling and root planning, these tools offer successful treatment of periodontitis. New techniques in periodontal pocket drug delivery systems hold promise as they offer a practical substitute for increasing patient compliance, although further research is still needed in this area. Probiotics are microorganisms found in the saliva of the mouth and digestive tract of the human body. Due to the beneficial metabolic effects of probiotics in the treatment of periodontitis, recent research on the use of these organisms in the treatment of the disease has attracted great interest from researchers. Thus, more research is needed to control periodontal disease in the long term and to better understand how probiotics work metabolically.

Author contribution

KB developed the hypothesis and wrote the initial draft, PM contributed to data curation and analysis, and HBS contributed to conceptualization and supervision. PM and IJD were credited for comprehensive edits, which all authors reviewed and approved.

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Competing financial interests

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