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Prospective and challenges of locally applied repurposed pharmaceuticals for periodontal tissue regeneration

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Periodontitis is a persistent inflammatory condition that causes periodontal ligament degradation, periodontal pocket development, and alveolar bone destruction, all of which lead to the breakdown of the teeth's supporting system. Periodontitis is triggered by the accumulation of various microflora (especially anaerobes) in the pockets, which release toxic substances and digestive enzymes and stimulate the immune system. Periodontitis can be efficiently treated using a variety of techniques, both regional and systemic. Effective therapy is dependent on lowering microbial biofilm, minimizing or eradicating pockets. Nowadays, using local drug delivery systems (LDDSs) as an adjuvant therapy to phase I periodontal therapy is an attractive option since it controls drug release, resulting in improved efficacy and lesser adverse reactions. Choosing the right bioactive agent and mode of delivery is the foundation of an efficient periodontal disease management approach. The objective of this paper is to shed light on the issue of successful periodontal regeneration, the drawbacks of currently implemented interventions, and describe the potential of locally delivered repurposed drugs in periodontal tissue regeneration. Because of the multiple etiology of periodontitis, patients must get customized treatment with the primary goal of infection control. Yet, it is not always successful to replace the lost tissues, and it becomes more challenging as the defect gets worse. Pharmaceutical repurposing offers a viable, economical, and safe alternative

for non-invasive, and predictable periodontal regeneration. This article clears the way in front of researchers, decision-makers, and pharmaceutical companies to explore the potential, effectiveness, and efficiency of the repurposed pharmaceuticals to generate more economical, effective, and safe topical pharmaceutical preparations for periodontal tissue regeneration.

KEYWORDS

periodontitis, biological regulation, biomaterials, bioengineering, tissue remodeling

1 Introduction

Periodontitis, a prevalent inflammatory illness, has been designated by healthcare professionals as the third-greatest contributor to mortality in humans, behind only cancer, heart disease, and brain disorders. Its prevalence is between 5% and 25% of the worldwide population, whereas mild periodontitis affects almost 60% (Papapanou and Susin, 2017). Furthermore, the prevalence and frequency of periodontitis are greater among those with limited resources and elderly people. Persistent periodontitis hurts the standard of living and is associated with worry, inadequacy, lack of tolerance, bad odor, and other symptoms. These implications may result in social hurdles and some difficulties with function, including chewing problems.

Mechanical debridement is the primary therapy for periodontitis now. Scaling, and root planning (SRP) physically eliminate harmful microbiota and slow the regrowth of periodontitis-causing bacteria. Nevertheless, due to inadequate visibility into the micro-organisms that reside deeply in the periodontal defect, and the dental intricate structure, SRP cannot entirely eradicate infections (Jhinger et al., 2015).

Furthermore, periodontitis, as an irritation linked with bacteria, can result in alveolar bone loss and destruction of tissues. As a result, SRP can enhance the effectiveness of other medications by combining them with antimicrobial treatments, anti-inflammatory medications, and therapies that stimulate bone and tissue regeneration. The total course of treatment is dependent not only on the medication characteristics but also on the delivery device and routes of delivery (Rams and Slots, 2023). In this setting, the article focuses on the utilization of locally applied repurposed drugs in the management of periodontal illnesses, highlighting current problems and prospective study prospects.

2 Pathogenesis of periodontitis

Periodontitis is an inflammation illness with complex causes. In 1997, Page and Kornman devised a traditional framework to explain the complicated etiology (Baru et al., 2024). The traditional theory was constantly changed over the next 20 years to develop the current theory according to novel insights. It is now acknowledged that pathologic dysbiosis is crucial, but not the only reason for the emergence of periodontal diseases. The illness is produced by complicated interactions between dysbiosis and the immunological reaction of the host. There are several fresh perspectives concerning the progression of periodontitis according to modern theory. Obtaining and sustaining therapeutic wellness necessitates an optimal microbiome in which intricate interrelated interplay between the biofilm and the immunological response emerge (Nasiri et al., 2023). If the fragile equilibrium between the dysbiosis and the host reaction is disrupted, a greater host reaction will be generated. Excessive inflammatory cascades are frequently produced, overpowering their opposing competitors and causing periodontal destruction (Trindade et al., 2023). This condition is known as gingivitis because it has not progressed to the periodontitis phase (Meyle and Chapple, 2015). Once bacteria have accumulated to produce dysbiosis, inflammatory cascades take over at the current lesions (Herrmann and Meyle, 2015; Jain et al., 2008). When the chemotactic and bactericidal activities are disrupted, and neutrophils are unable to generate pro-resolving lipid cytokines, the excessive immune reaction causes tissue destruction and adhesion loss, resulting in periodontitis (Sonnenschein and Meyle, 2015). Patient behaviors, drugs, and environmental impacts including lifestyle are examples of changeable variables. All of these variables may give rise to the formation of periodontitis (Petersen and Ogawa, 2005). Periodontitis is a complicated oral disease with various pathogenic variables, including heredity, gender, certain systemic disorders, and epigenetic impacts. Patient behaviors, drugs, and environmental effects like lifestyle are examples of changeable parameters (Yousefi et al., 2020; Liang et al., 2020).

While dental implants possess successful outcomes over time, problems related to poor treatment preparation and implementation, material failure, and infection have been described (Rokaya et al., 2020). The primary biological problem is peri-implantitis, which is defined as an infectious disease triggered by microbiological colonies affecting the tissues enclosing implants, marked by clinical indicators of inflammatory and radiological loss of bones (Belibasakis and Manoil, 2021). A significant proportion rate has been found, and the number of patients impacted could be approximately twenty percent (Diaz et al., 2022). Several therapy approaches have been proposed to treat peri-implantitis. Nevertheless, no advantage of a specific therapy over another has been established, and advanced techniques were unable to show extra advantages over simple therapies (Ramanauskaite et al., 2022).

3 Topical drug carriers for management of periodontitis and peri-implantitis

Both systemic and topical delivery are essential ways of medication administration. The implementation of a systemic approach in the management of oral dysbiosis has demonstrated some benefits during the last half-century (Rokaya et al., 2020). Nevertheless, systemic medication administration can cause issues that include dysbacteriosis, and poor biodistribution. Furthermore,

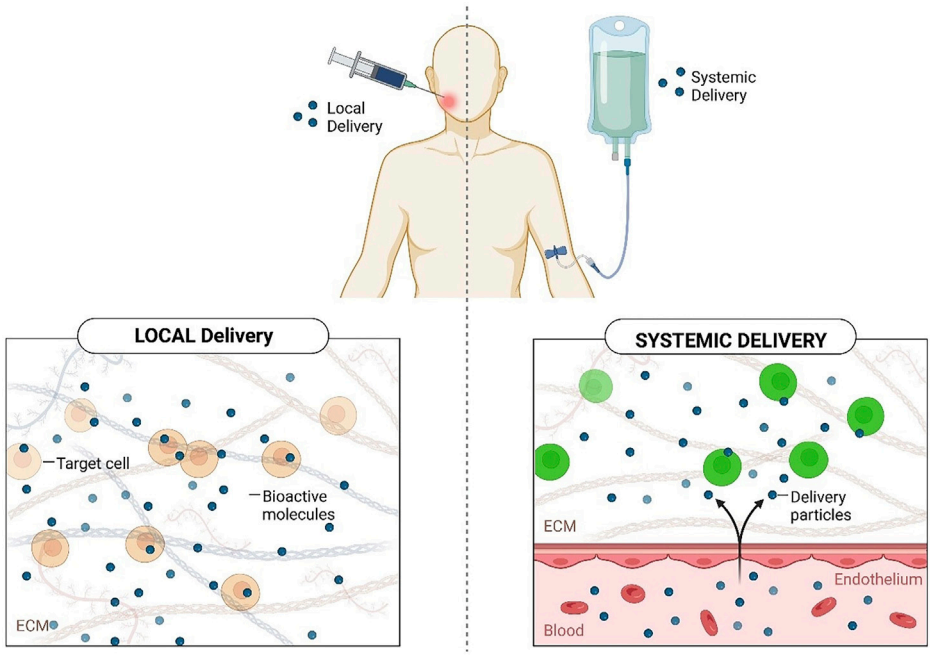

FIGURE 1
Comparison between local and systemic drug delivery.

to acquire and sustain an efficient level, a large dosage is frequently delivered, which could cause toxic effects, digestive discomfort, and resistance to them (Figure 1) (Atia et al., 2024b; Atia et al., 2024a; El-Nablaway et al., 2024a; El-Nablaway et al., 2024b).

Because of the evident difficulties of systemic administration, it is critical to adopt LDDS for improved periodontitis management and avoidance.

Peri-implant disorders, like periodontal illnesses, are mostly caused by tooth plaque. Periodontal health is controlled by a variety of variables, including oral hygiene, genetics and epigenetics, overall health, and diet (Monje et al., 2022). Peri-implantitis and periodontitis lesions contain Gram-negative anaerobic bacteria. Nevertheless, peri-implantitis has a greater greater variety of bacteria than periodontitis (Taymour et al., 2024). Furthermore, peri-implantitis is primarily infiltrated by inflammatory cells, and it commonly doesn't have a protective tissue layer around the bone, which is typical of periodontitis (Sadek et al., 2024). Peri-implantitis lesions were twice as big, exhibited greater blood vessels, and had an infiltration in the connective tissue than periodontitis (Carcuac and Berglundh, 2014). Peri-implantitis had a 97% higher concentration of matrix metalloproteinases (MMP), such as MMP-8, but chronic periodontitis had just a 78% increase compared to healthy gingiva (Zhang et al., 2018). Additionally, peri-implantitis tissue includes extracellular matrix antibodies (Papi et al., 2017). Peri-implantitis progresses more quickly than periodontal disease, resulting in quicker and more extensive bone loss. Peri-implantitis causes a nonlinear kind of continuous bone degradation over time, possibly due to changes in bacteria at the implant locations, the host's defensive mechanism, and the absence of a periodontal ligament (Hasturk and Kantarci, 2015).

Topical placement of LDDS in the periodontal pocket can produce an adequate quantity of pharmaceutical medicines for a longer duration of time. When juxtaposed with systemic administration, LDDS has additional benefits including avoiding problems within the digestive system and bioavailability by administration at a particular location, greater effectiveness, and fewer adverse reactions by managing the release of medication, and enhanced compliance among patients through decreased periodic dosing. Given these benefits, LDDS has been studied as a method for periodontitis therapy in the past few decades (Viglianisi et al., 2023).

4 Drugs integration strategies in drug delivery systems

Several approaches, including direct loading, combining, and surface/chemical interaction, have been developed to introduce various medicines into scaffolds for therapeutic purposes (Figure 2) (Tallawi et al., 2015). These strategies have significant benefits and downsides in terms of production procedures, scaffold design and required scaffolding dimensions, customized treatments, controlled drug release, and specific medical applications.

4.1 Direct loading

The direct loading method requires submerging the scaffolding in a medicinal solution, which allows chemicals to attach to the framework through physical adsorption and/or absorption. Biomaterials containing bone morphogenic protein-2 (BMP-2), for instance, are a viable method of inducing bone development. DeConde et al. demonstrated the effectiveness of bio active scaffolds

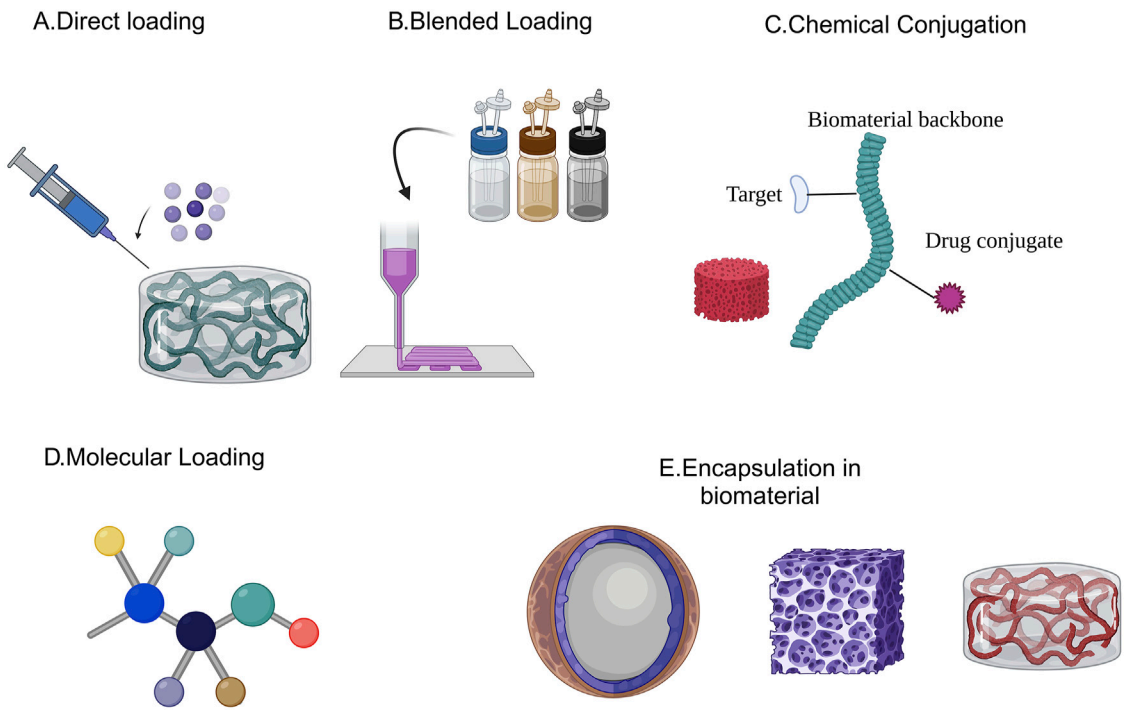

FIGURE 2
Different techniques for incorporation of pharmaceuticals within drug carriers.

treated with BMP-2 in osseous healing in mandibular lesions in rats (Reis, 2019). The downside of this method is that the capacity for carrying is strongly dependent on the scaffolding design, involving the dimensions of the particles, scaffolding unbound volume, moisture absorption, and medicinal physical qualities (e.g., molecular capacity) (Wang et al., 2019).

4.2 Blended loading

Unlike direct loading, blending involves integrating medications into the scaffolding framework before constructing the 3D design. This is often performed through the combination of pharmaceuticals and a polymer in a common media that will be used to construct the scaffolding. This method has the advantage of being adaptable to different scaffold biomaterials, pharmaceuticals, and production techniques (Calori et al., 2020). In this regard, electro-spinning has been employed to build nanofiber scaffoldings for nerve regeneration utilizing a combination of vitamin B5 and PLCL/silk composites (Ye et al., 2019). Blending techniques can also be utilized to develop scaffolds with additive manufacturing technologies for purposes that require complex architectures. Additionally, this carrying method has negligible effect on the pharmacokinetic pattern.

4.3 Chemical and surface conjugation

Chemical conjugation of biologically active substances to scaffolding elements or surfaces enables the removal of variations between biologically active substances, scaffolding, pharmaceutical loading, and, most importantly, the controlling of breakdown rate for ongoing, induced, or upon request medication discharge (Jiang et al., 2019). Scaffolding surfaces, for example, can be changed to induce purposeful biological reactions that aid in drug binding. In contrast to traditional scaffolding, the development of these bioactive components has been reported to increase the integration of bioactive cues, while also lowering the immediate impact and expanding the discharge length (Freeman et al., 2021).

Chemical conjugation and surface enhancement can help in establishing covalent bonds to scaffolds, allowing medicines to remain on the scaffold constituents or surface. Due to the particles' remarkable adhesion, the biochemical immobility method is appropriate for postponed and prolonged delivery of medical drugs. It additionally restricts the chemical composition of the pharmaceuticals that can be loaded. Furthermore, unless significant scaffold breakdown allows for effective release characteristics, the immobilizing approach may not be appropriate for drugs that need to be ingested or interact with cell nuclei (Fu and Yang, 2023).

4.4 Loading bare biomolecules versus encapsulation/loading

Medicinal compounds can be integrated into scaffoldings in their basic state or entrapped in (or conjugated with) an array of nanocarriers. The latter technique has been utilized to circumvent compatibility concerns between scaffolding and therapies by adding biological components into nanoparticles (NPs) prior to their

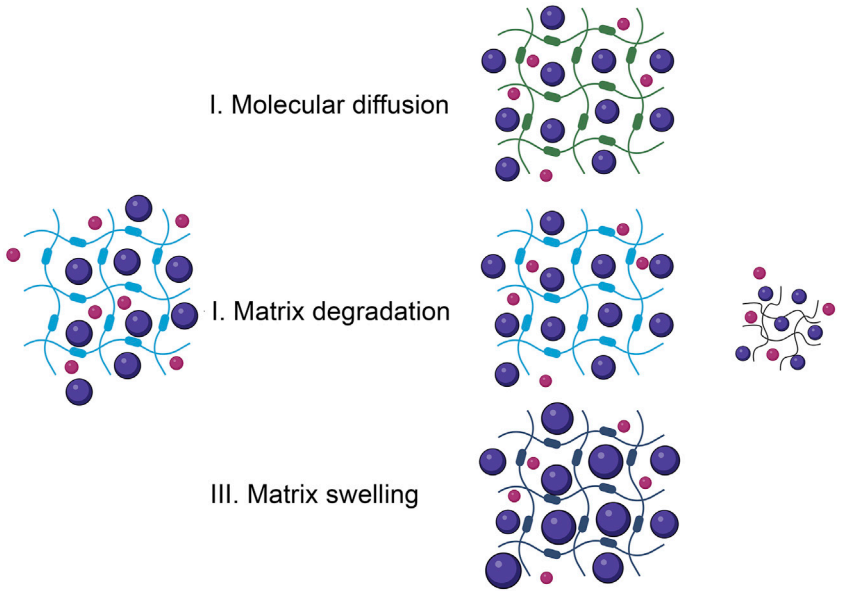

FIGURE 3
Different mechanisms of drug release.

insertion into frameworks (Xu and Burgess, 2012). Loaded particles can then be introduced into a polymeric matrix before or after scaffolding formation, utilizing the methods outlined above for direct loading, blended loading, and chemical attachment. Multifunctional nanoparticles are another way to put a wide range of medications into frameworks. Yang et al. demonstrated the utilization of painted scaffolds as a carrier for biological molecules, influencing biological activity (Yang et al., 2010).

5 Strategies for drug release

It is critical to create 3D scaffolds that match the physiological, mechanical, and metabolic functions of ECM. Scaffolds are supposed to execute a number of functions, such as signaling cellular development and activity and transporting biological and medicinal chemicals. The medication delivery approach in porous scaffolding devices can be controlled by either passive or active transportation of bioactive substances in the bioconstructs (Figure 3) (Rocha-García et al., 2016).

5.1 Diffusion

The concept of molecular diffusion can be applied to improve medication pharmacokinetics in porous carriers. This phenomenon involves the movement of particles from a large quantities region to a low-volume area. To study the release mechanism in the framework, it is assumed that the pharmaceutical molecules are surrounded by inactive membranes and that the velocity of diffusion is constant (Ridolfo et al., 2020). The volume of the matrix in numerous scaffoldings may affect diffusion speed because a larger free volume allows more water to penetrate the scaffolding, allowing for more drug diffusion and desorption. Mesh dimensions, in addition to open space, are an important factor that might limit the specific dimensions of targeted therapeutic substances (Wanat, 2020). To overcome this drawback, mesh size can be modified by varying the amounts of polymers and cross-linking agents employed in scaffolding assembly.

5.2 Burst effect

Another common method of administering drugs is burst release. This signifies the unregulated initial distribution of a large amount of medication. For some therapies, including wound healing, such an impact has been used as an optimal medicine administration technique, where an initial quick release may speed up healing processes and minimize discomfort in patients (Isik et al., 2020). Yet for certain medicinal uses, fast release might be harmful to patients. The quick release has been connected to multiple variables, such as drug-loading situations and the properties of hydrogels and bioactive substances (Mirzaeei et al., 2022).

To mitigate the detrimental consequences of burst release, several strategies have been devised, such as employing cross-linked coatings, increasing the crosslinking proportion in the hydrogel, and developing polymeric blends (Zupancic et al., 2016), Heterogeneous packaging of medicinal components with increased levels in the scaffolding, In molecular submerging, increasing the density of the overlaying layer, as well as constructing a layer-by-layer structure with various medicine and polymer ingredients (Ren et al., 2023).

5.3 Affinity-based releasing strategy

The interaction between medications and frameworks can be controlled to alter pharmaceutical pharmacokinetics in scaffolding. The structure, permeability, and structure of the scaffolding have

TABLE 1 The advantages and the limitations of drug repurposing.

Significance	Obstacles	Reference
Guarantees security	Insufficient knowledge of legal requirements	Jourdan et al. (2020)
It reduces both time and expenses	Inadequate economic motivations	Jourdan et al. (2020)
Marketing potential: rising global revenue spurs growth in markets	The likelihood of failing evidence of concept trials for new purposes is one of the clinical trial concerns	Padhy and Gupta (2011)
Out licensing possibility: novel applications while retaining ownership of the old purpose	Patent restrictions prevent the selling of repurposed molecules	Padhy and Gupta (2011)
Unmet therapeutic requirements can be met by developing novel uses for current pharmaceuticals to treat unusual conditions and attacking tumors with non-cancer therapy	Evaluation of financial requirements	Padhy and Gupta (2011)

significant effects on the discharge kinetics in passive drug delivery, with little interaction between the drug and the scaffolding. Further biochemical communications can be developed between the scaffolding and the drug to increase control over the release process and kinetics. Chemically, this includes the hydrolysis-mediated degradation of polymeric components, as well as enzyme activity (Abedi et al., 2022). However, particular blends with significant promise for the therapeutic molecule(s) can be incorporated into the polymer results in an extended-release pattern. Cyclodextrins are a well-known macromolecule family that has a strong affinity for numerous therapeutic chemicals (CDs) (Mealy et al., 2015). It exhibited the sustained administration of a drug (L-tryptophan) in a CD-adjusted hyaluronic acid (HA) hydrogel for 21 days. The releasing kinetics showed a prolonged progressive pattern, with only 20% of the medicine delivered following 24 h, compared to 90% in standard HA hydrogel. As an alternative technique, NPs have been integrated as a pharmaceutical transporters, allowing for greater flexibility in tailoring the pharmacokinetic pattern by modifying the NP-polymer interconnections. For instance, after strengthening with silicate NPs, the medication delivery rate of hydrogels was lowered, indicating that NPs limit drug diffusion, decrease swelling, and/or inadequately adhere to the drug. The linkages between the active ingredient and the NP, or the NP and the framework, as a drug transporter, can be changed to control release (Zhang et al., 2022a).

5.4 Stimulus-based discharge

5.4.1 Releasing mechanism relying on the scaffolding

In conjunction with passive monitoring, modulation of scaffolding has been developed for different medical purposes by exploiting their sensitivity to external components like acidity and natural stimuli such as glucose (James et al., 2014). For example, a temperature-sensitive polymer scaffolding was used to distribute drugs like aspirin (Du et al., 2018b), erythropoietin (Xu et al., 2019a), and ornidazole (Ravishankar et al., 2017) to treat periodontal disease.

5.4.2 Discharge method dependent on the loaded components

NPs can be used as a signaling molecule to initiate drug release when subjected to initiating conditions such as light. The photothermal heating of AuNPs in a thermally sensitive hydrogel permitted light-controlled drug release. When subjected to near-infrared (NIR) light, carbon nanostructures, and graphenematerials exhibit a photo thermal effect, which has been utilized for light-triggered pharmaceutical dissolution (Trucillo, 2022).

6 Drug repurposing

Repurposing a drug entails employing medicines that have been approved by regulatory bodies for a new application. To be licensed for sale, a novel drug must meet stringent standards. Due to the many physicochemical properties of chemical entities, as well as the difficulty of expanding production, finding a drug along with improving it needs substantial investment (Vaidya et al., 2019). This limitation also permits pharmaceutical businesses or educational organizations to utilize already-approved medications quickly and successfully for an unfamiliar purpose to which those suffering from that disease have yet to access (Table 1).

All toxicity, experimental, and clinical trial efficacy data for a repositioned medicine are readily available, allowing the researcher to reach an objective decision at every step of pharmaceutical research, and developmental approaches (Pan et al., 2022; Alghonemy et al., 2024; Mohamed, 2024). The accessibility of current knowledge on safety, efficacy, and the right distribution approach significantly reduces investigation expenses and a period leading to less effort required to successfully bring a recycled drug to the marketplace (Abdel Nasser Atia et al., 2022).

Because of the tremendous potential of a shorter development process, several drug companies are currently utilizing medication repurposing to reassemble authorized, as well as previously unsuccessful substances, into fresh medications for a range of medical conditions (Badria, 2020).

7 Repurposed drugs for local periodontal regeneration

There is a plethora of pharmaceuticals that could be repurposed for implementation in periodontal regeneration (Figure 4).

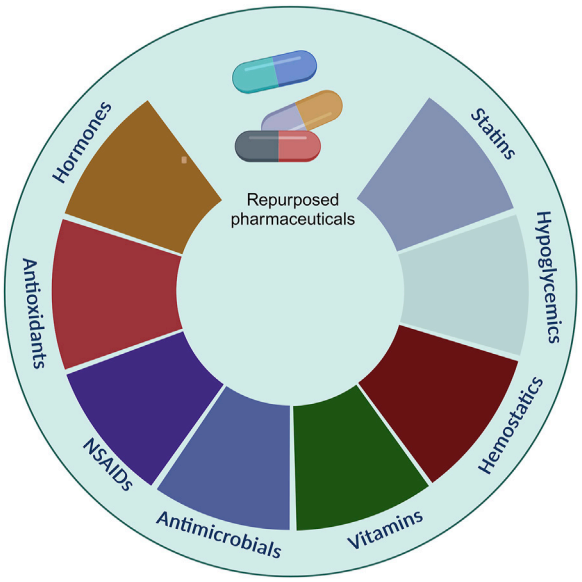

FIGURE 4
Examples of repurposed pharmaceuticals for periodontal regeneration.

7.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

They are medications that are widely employed to manage pain, decrease inflammatory conditions, and lower fever (Díaz-González and Sánchez-Madrid, 2015). NSAIDs showed promise in periodontal regeneration (Table 2) (Preshaw, 2018).

7.1.1 Acetylsalicylic acid (ASA)

It is additionally referred to as aspirin and can accelerate bone healing. Numerous publications have been written about its physiological functions, the vast majority of which are linked to other immune system regulation, including T-cell inhibition, MSC longevity prolongation, and immune regulation ability enhancement (Liu et al., 2011). ASA-based chitosan hydrogels showed long-term dispersal for more than 14 days, enhancing PDLSC replication and bone formation (Zhang et al., 2022b). CS/b-GP/G/EPO/RLX hydrogels are effective for treating periodontal disease (Xu et al., 2019b).

7.1.2 Ibuprofen (IBU)

Ibuprofen has anti-inflammation characteristics similar to aspirin but causes considerably less digestive pain. Thermo-

TABLE 2 Application of locally delivered repurposed NSAIDs for periodontal regeneration.

NSAIDs	Carrier	Model	Outcome	Reference
Aspirin	CS/ β -GP/G hydrogel	Rats	Excellent cytocompatibility. Anti-inflammation and periodontal regeneration effects	Xu et al. (2019b)
	hydroxyapatite/tricalcium phosphate (HA/TCP)	Mice	Enhanced osteogenesis	Wu et al. (2019)
	Platelet-rich fibrin	Rats	Prolonged discharge of aspirin/salicylic acid. Encouraged periodontal ligament mesenchymal cell growth and movement	Du et al. (2018a)
		Human PDLSCs	ASA increased the activity of markers linked to cellular growth, and osseous regeneration	Abd Rahman et al. (2016)
	Tetra-PEG hydrogel	PDLSCs Mice calvaria bone defects	Increased PDLSCS multiplication, and osteogenic differentiation	Zhang et al. (2019)
Meloxicam	CS/PVA/HA electro-spun fibers and films	Epithelial cells of African green monkey (VERO)	Sustained release of meloxicam	Yar et al. (2016a)
	3D chitosan Scaffold	L929 mouse fibroblasts	The scaffold had a porous structure Cytocompatibility *in vitro* Meloxicam is released continuously	Nowak et al. (2019)
Ibuprofen	PCL/PVA/COL Nanofiber	*In vitro*	Outstanding cytocompatibility Sustained drug release	Limoee et al. (2019)
	PLGA/CHX chlorohexidine	Human oral epithelial cells P. gingivalis strain. male C57BL/6J mice	TNF-release suppression Bactericidal activity	Batool et al. (2019)
	Calcium-deficient hydroxyapatite/ tricalcium phosphate (β-TCP)	*Escherichia coli* Albumin denaturation method Swiss 3T3 fibroblast cells Rat cranial defects	Outstanding biocompatibility Anti-inflammation, and antimicrobial activity	Madhumathi et al. (2018)
Piroxicam	CS/PVA/HA nanofibers	*In vitro*	Prolonged release of piroxicam, and optimal biomechanical properties	Farooq et al. (2015)

CS, chitosan; β-GP; Beta-glycerophosphate, G, gelatin; EPO; erythropoietin; RLX, raloxifene; TCP, tricalcium phosphate; PCL; polycaprolactone, PVA; polyvinyl alcohol, TNF; tumor necrosis factor alpha, CHX; chlorohexidine, PEG; polyethylene glycol, PDLSCs, Periodontal ligament stem cells; Col, Collagen; Cs; Chitosan; HA, hydroxy apatite.

TABLE 3 Local applications of statins in periodontal regeneration.

Statin	Scaffold	Model	Outcome	Reference
Atorvastatin	thermosensitive chitosan hydrogel	*In vitro* and *In vivo*	BSP2 upregulation in osteoblasts highlights atorvastatin's healing properties	Pradeep et al. (2016a)
	Methylcellulose gel	Diabetic humans	Enhanced periodontal regeneration, and bone fill	Kumari et al. (2016)
Lovastatin	1 Cs/epigallocatechin-3-gallate membrane	Dogs	Lovastatin long-term distribution aided osteogenesis. EGCG14-CS had promise antibacterial action; and promoted periodontal repair	Lee et al. (2016a)
	2 Polyurethane (PUR)	Rats	The quantity of NFB was much higher in lovastatin-PUR specimens	Yoshii et al. (2010)
Fluvastatin	PGA	Rabbits	Enhanced osteogenesis, and osseointegration	Moriyama et al. (2008)
	Gelatin hydrogel	Rats	Significant osteoinduction	Tanabe et al. (2012)
	Collagen graft	Rabbits	Simvastatin-collagen scaffolds induced osteogenesis	Wong and Rabie (2003)
	Gelatin hydrogel	Rats	Enhanced angiogenesis, and osteogenesis	Fukui et al. (2012)

CS, chitosan; PUR, polyurethane; PGA, poly glycolic acid.

sensitive microgels carrying metronidazole (MET) and ibuprofen (IBU) displayed excellent MET discharge for 8 h and sustained IBU release for up to 48 h, demonstrating that they could be used in periodontal regeneration (Pham et al., 2021).

7.1.3 Meloxicam

Meloxicam helps to keep cartilage and bone in place. Noncytotoxic electro-spun (e-spun) chitosan (CS)/poly vinyl alcohol (PVA)/hydroxyapatite (HA) fibers and films filled with meloxicam were discovered, encouraging cellular division. These features, together with these compounds' immune system regulation capacity, hint at possible utility in periodontal therapy (Yar et al., 2016b).

7.1.4 Piroxicam

CS/PVA/HA nanofibers loaded with PX resulted in prolonged release of PX, and optimal biomechanical properties (Farooq et al., 2015).

7.2 Statins

Statins are potent drugs for cholesterol reduction that work by inhibiting a critical component of the cholesterol manufacturing process. They have made significant advances in the avoidance of cardiac events. Statins have anti-inflammatory and immune-modulating capabilities since they suppress the generation of inflammatory cytokines like interleukin 1 (IL-1) and interleukin 6 (IL-6), as well as tumor necrosis factor (TNF) (Koushki et al., 2021). Since Mundy et al. initially explored statins' bone anabolic effects nearly 15 years ago, there has been a vigorous hunt for potential applications to bone catabolic illnesses like osteoporosis (Mundy et al., 1999).

Statins can also promote osteoblast formation by increasing bone morphogenetic protein-2 (BMP-2) levels, which are thought to be an inducer for osteoblast transformation and bone creation (Dalcico et al., 2013). They may additionally boost bone tissue formation by activating the vascular endothelial growth factor (VEGF) (Balli et al., 2014). Statins, because of their anti-inflammatory and osteo-inductive capacities, have been proven to be helpful in the enhancement of osteogenesis in human periodontal ligament cells (Table 3) (Mundy et al., 1999). Statins enhance osteogenesis by promoting the division and transformation of osteoblasts, while also protecting these cells from apoptosis. Additionally, statins reduce osteoclastogenesis by inhibiting the differentiation of osteoclasts (Pacheco-Pantoja and Alvarez-Nemegyei, 2014; Moshiri et al., 2015).

7.2.1 Mechanism of actions of statins

Statins have periodontal regeneration-promoting characteristics, such as being anti-inflammatory (Satny et al., 2021), promoting the growth of bones (Figure 5), inhibiting tissue metabolizing enzymatic processes, and possessing antimicrobial capabilities (Hennessy et al., 2016; De Giorgi et al., 2023).

7.2.1.1 Statins promote osteoblast development by increasing BMP-2

Statins stimulate new bone formation (NBF) by increasing BMP-2 transcription. Lipophilic statins, such as simvastatin can stimulate the BMP-2 gene regulator; whereas more hydrophilic statins, including pravastatin, do not (Wan Hasan et al., 2020; Li et al., 2023). At the cell membrane, BMP-2 interacts with a particular type II receptor, forming a complex by engaging a type I receptor. The compound of BMP-receptor II and BMP-receptor I (activated serine/threonine kinase receptors) Smad proteins are phosphorylated (Wu et al., 2021). Statins may boost Runx2 gene activity via increasing Runx2 expression, which leads to the differentiation of MSCs into osteoblastic cells (Hong et al., 2020).

7.2.1.2 Statins promote osteoblast development and bone matrix mineralization by decreasing the synthesis of FPP and GGPP

Statins modulate downstream byproducts of mevalonate (for example, FPP and GGPP). FFP diminishes during statin-stimulated osteoblast development. Exogenous FPP expression prevents osteoblastic cell differentiation. Lovastatin, for example, lowered the amounts of both FPP and GGPP in cultured cells in a dose-related way (Nes, 2011). GGPP has also been linked to statin-initiated bone formation. GGPP mRNA and protein levels have

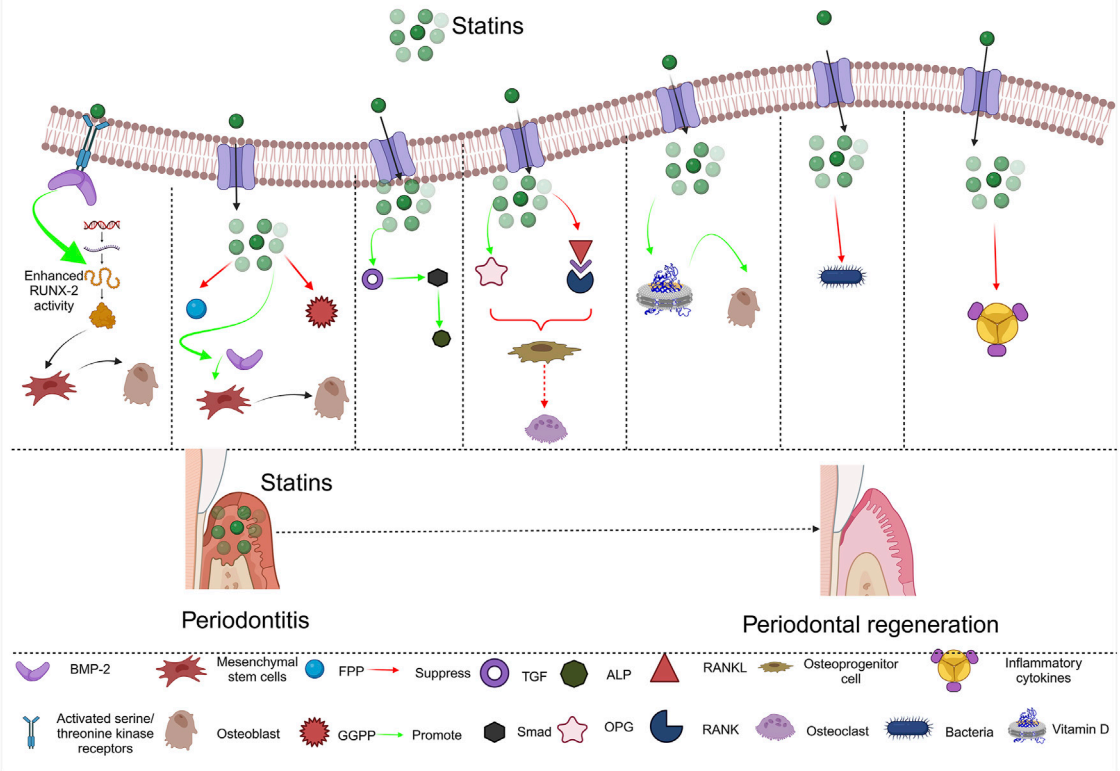

FIGURE 5
Mechanism of action of statins in periodontal regeneration.

been demonstrated to decrease during mineralization in MC3T3-E1 cells. Geranyl-geraniol (GGOH), which is transformed to GGPP in the cells, suppresses the differentiation of MC3T3-E1 cells, indicating that GGPP may have an adverse effect on osteogenesis (Weivoda and Hohl, 2011). Pitavastatin-treated osteoblasts expressed more BMP-2 mRNA *in vitro*, but this impact was reversed when subjected to mevalonate or GGPP (Tai et al., 2013). Simvastatin also raised BMP-2 mRNA expression and accelerated MC3T3-E1 cell transformation into osteoblastic cells; nevertheless, cells primed with GGPP inhibited simvastatin-triggered differentiation (Zhong et al., 2011).

7.2.1.3 Statins suppress osteoblastic apoptosis via the TGF/Smad3 signaling system

Statins protect osteoblasts from apoptotic processes through the TGF/Smad3 signaling pathway. TGF stimulates Smad3 by launching several actions that result in the stimulation of a specific enzyme (Neve et al., 2011). By producing matrix proteins and enhancing ALP functionalization and mineralization, Smad3 promotes osteogenesis. Statins increase Smad3 expression in osteoblasts, which may help to prevent dexamethasone-induced apoptosis.

7.2.1.4 Statins suppress osteoclastogenesis by increasing er transcription via the OPG/RANKL/RANK signaling cascade

Statins influence osteoclast regeneration by modulating the OPG/RANKL/RANK signaling pathway. There is a link between statins and estrogen (ER) (Song et al., 2008). It has been demonstrated that countering the BMP-2 monoclonal antibody did not completely inhibit ALP activity, whereas estrogen receptor-alpha (ER-α) protein concentrations boosted following dose-dependent simvastatin treatment of mouse BMSCs, implying that simvastatin preserves BMD by inducing either ER or BMP-2. Simvastatin enhanced Er expression in the bone in a synergistic way with estrogen in ovariectomized rats (Song et al., 2008; Nyan et al., 2007; Chen et al., 2010; Albu et al., 2013). They could boost OPG mRNA concentrations while decreasing RANKL gene expression in mouse bone cells (Chamani et al., 2021).

7.2.1.5 Statin-vitamin D interactions

Two clinical investigations found that rosuvastatin medication boosted 25-hydroxyvitamin D levels considerably (Yavuz et al., 2009; Ertugrul et al., 2011). This might explain why, in some clinical investigations, the boost in bone mineral density with statin therapy was mediated by an elevation in vitamin D concentrations. Nevertheless, fluvastatin (Ertugrul et al., 2011), and simvastatin (Rejnmark et al., 2010) administration has no effect on the concentrations of 25-hydroxyvitamin D. The process underpinning statins' impact on vitamin D has not been determined, however, the shared catabolic route for statins and vitamin D may be to blame (Ertugrul et al., 2011). CYP enzymes may potentially affect the influence of vitamin D on statin actions. As a CYP enzyme inducer, vitamin D may boost the metabolism of statins (Bhattacharyya et al., 2012). Active CYP metabolites, such as those seen in atorvastatin, may potentially aid in therapeutic success.

7.2.1.6 Antimicrobial activity of statins

About 700 species colonize the mouth cavity. Although some are regarded as commensals, persistent biofilm formation is the cause of caries, gingivitis, and other dental problems. Statins have antibacterial action, and some studies have found statins to be effective against oral microbes, especially those found in the subgingival colonies, even at reduced levels (Kamińska et al., 2019).

Kaminska et al. revealed in 2019 that statins had antibacterial activities, mostly lowering their production, which may imply a modification in microbial activities. The existing biofilm, on the other hand, was less impacted, with enhanced bacterial viability, despite a drop in *P. gingivalis* and *T. forshythia*. As pathogens declined, the abundance of *S. gordonii* increased, resulting in a shift in populations between harmful and nonpathogenic bacteria. As a result, these results suggest that statins have a significant role in managing the oral biofilm, lowering bacterial load in favor of a greater physiologic microbiome (Kamińska et al., 2019).

7.2.1.7 Impact of statins on immunological attributed inflammation

The formation of dysbiosis biofilm can trigger an increased host response, resulting in the loss of periodontal tissues. If no treatment intervention is implemented, pathogenic bacteria and the imbalanced immune-inflammation-mediated reactions feed each other, resulting in a self-perpetuating loop. When the inflammatory process advances to the alveolar bone in response to a pathogenic stimulation, it stimulates the initiation of bone resorption. The adaptive immune system additionally serves a crucial function in host tissue defense, but, when left unchecked, it may lead to periodontal deterioration.

Statins influence T cell development and antigen presentation in the adaptive immune system. *In vitro*, atorvastatin and simvastatin increased the number of human regulatory T cells (Tregs) and induced CD4 differentiation into Tregs (Petit et al., 2019; Mausner-Fainberg et al., 2008; Kagami et al., 2009). Statins have varying impacts on the release of inflammation-associated mediators. Simvastatin and rosuvastatin reduce IL-6 and IL-8 levels. Simvastatin, on the other hand, enhanced the expression of IL-4, IL-5, and IL-13 in T cells.

They have been proven in animal experiments to be able to suppress the generation of inflammatory mediators in the periodontal pocket of rats, correlating with specific findings observed in *in vitro* research (de Araújo Júnior et al., 2013; Jin et al., 2014b; Jin et al., 2014a; Messora et al., 2017). That's why they are widely implemented in periodontal therapy approaches for their pleiotropic beneficial effects, on both of prevention of inflammation, and the promotion of regeneration.

7.2.2 Atorvastatin

Atorvastatin is a statin medication intended to decrease the amount of cholesterol in the blood (McIver and Siddique, 2023). In the past few years, the different features of atorvastatin have been investigated for their possible use in the treatment of a variety of inflammatory and immune-related diseases, including periodontitis.

There have been several investigations on the topical delivery of atorvastatin for periodontal treatment, notably with gel devices (Pradeep et al., 2016b; Elavarasu et al., 2012). Nonetheless, atorvastatin has a limited bioavailability due to its weak water solubility. Atorvastatin chitosan gel could counteract inflammatory cytokines and promote bone regeneration (Işılay Özdoğan et al., 2018).

7.2.3 Lovastatin

Lovastatin is employed for the treatment of coronary heart disease, high cholesterol levels, and congenital excessive cholesterol levels in adolescents. Chitosan membranes containing epigallocatechin-3-gallate and lovastatin demonstrated high alkaline phosphatase functionality as well as antibacterial action against prevalent infectious microbes, leading to improved bone repair (Lee et al., 2016b).

7.3 Hemostatic agents

ε-aminocaproic acid (εACA) is a plasmin-plasminogen antagonist that is synthesized. Fibrin- εACA–Cs could increase cementogenesis and osteogenesis by modifying fibrin biodegradability, hinting that they could be used therapeutically to promote periodontal regeneration (Park et al., 2017).

7.4 Hypoglycemic drugs

7.4.1 Metformin

Metformin is the first-line therapy choice for hyperglycemia in type 2 diabetes. It stimulates the AMPK process, which is a critical energy sensor that induces autophagy and controls metabolic processes in cells to preserve energy balance. To improve the survival of cells, autophagy efficiently inhibits the apoptosis-activated protein caspase-8 (Jiang et al., 2021). The autophagic pathway has been shown to moderate excessive cellular ROS-induced impairment to sustain cellular homeostasis and safeguard the survival of cells during stress. Metformin has been shown to improve osteogenic differentiation and mineralization *in vitro* and increase bone density *in vivo*, in addition to its protective impact (Zhang et al., 2021; Zhang et al., 2024; Ha et al., 2024). Furthermore, it is utilized in conjunction with phase I therapy to address periodontal abnormalities, with considerable repair results (Pradeep et al., 2013; Akram et al., 2018).

7.4.1.1 Mechanism of action of metformin

Following metformin application, the primary known antidiabetic mode of activity is mitochondrial respiratory chain (complex I) inhibition, resulting in oxidative phosphorylation separation and enhanced AMP/ATP ratio. Therefore, a boost in the AMP/ATP ratio activates 5′ adenosine monophosphate-activated protein kinase (AMPK), and AMPK is capable of controlling many additional enzymes (Shafiei-Irannejad et al., 2017). Insulin activates insulin receptor substrate 1 (IRS1) via activation of the insulin receptor (IR), resulting in amplification of the glucose transporter (GLUT) in the cell membrane and enhanced glucose absorption (Chopra et al., 2012). AMPK enhances insulin sensitivity by allosterically activating IR and IRS1 (O'Neill, 2013). Though AMPK improves nutrition intake by increasing responsiveness to insulin, it does not operate as completely as insulin and suppresses anabolic reactions

(Friedrichsen et al., 2013). Surprisingly AMPK shifts the body's metabolism into a catabolic state, creating energy and ATP to maintain normal cell function while increasing insulin sensitivity, glucose, and lipid metabolism, and decreasing gluconeogenesis, particularly in the liver.

Recent research has demonstrated that metformin is potentially bone-promoting *in vitro* after activating AMPK, leading to osteoblastic transformation, bone matrix production, and osteoblast proliferation. According to one investigation, AMPK may induce osteogenesis in MC3T3-E1 cells and decrease adipogenesis in 3T3-L1 cells via the AMPKGfi1-OPN axis (Wang et al., 2016). Another research found that AMPK can inhibit RANKL-induced osteoclast development (Lee et al., 2010). In the setting of two mediators, M-CSF and RANKL, osteoclasts are formed by multinucleated big cells (monocyte-macrophage lineages) (Sun et al., 2021).

Metformin also lowers hepatic lipids by inhibiting lipogenesis and improving lipid metabolism. Metformin, in general, can regulate cell development, division, and death via a variety of signaling mechanisms (Shafiei-Irannejad et al., 2017).

7.5 Relocated hormones for periodontal tissue engineering and bone regeneration

Growth factors' oriented treatments are expensive and can induce adverse events and immunologic responses in some people. To compensate for these drawbacks, different hormones have been developed and evaluated as effective substitutes for growth factors. They are cheap to generate, easy to engineer and create, and have little immune response because of their adaptability (Table 4) (Visser et al., 2016).

Numerous hormones contribute to the growth, development, and preservation of both periodontium and bone. In general, hormonal influences on periodontal health, bone growth, and maximum bone mass are significant (Stutz et al., 2020; Ortiz-Sánchez et al., 2021). Hormones are molecules produced by the body's hormone-producing glands and discharged into the circulatory system, where they are delivered to certain target cells to exert the effects they have. Hormones can function as transmitters or as complicated organizers of several vital activities that involve blood volume and pressure controlling, advancement, and reproduction (Fraser et al., 2022; Swanson et al., 2022). The subsequent hormones were discovered to be associated with periodontal regeneration.

7.5.1 Thyroxin

Thyroxin is a crucial molecule that serves several biological tasks in our bodies (Hulbert, 2000). One of these is its ability to promote vascular growth through a multitude of techniques (Aleem et al., 2017). It triggers the synthesis of angiogenesis facilitators by activating integrin v3 (Murk et al., 2013). Thyroid hormones have an impact on cell metabolism in addition to cellular multiplication (Sirakov et al., 2013). Chitosan composites encased in different amounts of thyroxin were shown to be cytocompatible, and these pro-angiogenic hydrogels offer a wide range of potential uses in periodontal regeneration (Malik et al., 2020).

7.5.2 Adiponectin (AN)

It is a hormone generated by fat cells and is commonly associated with blood glucose management and lipid oxidation. Nevertheless, it serves a variety of other physiological needs (Nguyen, 2020). AN is now believed to have the ability to act as a beneficial bone density regulator, angiogenic booster, and osteoclast inhibitor (China et al., 2018; Huang et al., 2021). AN reacts with cementoblasts (OCCM-30), influencing cell movement, division, and cementogenesis partially via the Mitogen-activated protein kinase (MAPK) signaling system (Yong et al., 2020). P38, ERK1/2, and JNK suppression resulted in the stimulation of AN-mediated movement and development to variable degrees, whereas MAPK suppression resulted in enhanced mineralization to different extents (Rodríguez-Carballo et al., 2016; Yong et al., 2021). All of this promotes cell growth and cementogenesis. AN delivery in rabbits led to higher mineral levels, durability, and harder bone structure regionally, implying fresh and quicker bone production (Jiang et al., 2011). The rabbits in the research experienced distraction osteogenesis, a surgical approach of expanding bone by slicing it and progressively tugging the fragments separated over time with a mechanical device. The fundamental processes of AN-stimulated bone repair in surgically created gaps were determined to be the attraction and clonal proliferation of cells responsible for creating bones under mechanical stimuli (Yang et al., 2019).

Furthermore, two AN-receptors were recently discovered as being activated by osteoblasts, suggesting that AN has primary roles in bone metabolic processes, such as encouraging division and increasing osteogenesis (China et al., 2018). Because bone formation depends on proper blood flow, vasculature is an essential part of bone development and functionality. The AN has been shown to impact physiological reactions in endothelial cells in an ischemia environment to enhance angiogenesis (Adya et al., 2015). Ouchi and colleagues found that treatment of AN promoted angiogenesis in mouse and rabbit studies (Ouchi et al., 2004). AN has been shown to treat periodontitis because of its anti-inflammatory and bone-healing properties (Wang et al., 2021). APN has the ability to promote bone formation by upregulating the enamel matrix derivative-induced production of development and osteoinduction-related proteins (Nokhbehsaim et al., 2014).

7.5.3 Oxytocin (OT)

OT is a key anabolic hormone present in mammals during nursing that has both regional and systemic effects on bone remodeling (Colaianni et al., 2012). Bone cells contain OT receptors, and OT is implicated in the mechanism of bone remodeling, as it has been shown to inhibit bone loss while increasing bone creation (Breuil et al., 2021). Furthermore, OT increases osteoblastic development and function, resulting in greater bone production and improved bone structure (Feixiang et al., 2023). Decreased oxytocin levels in the blood have been linked to osteoporosis after menopause.110,111 and have been discovered to be involved in bone equilibrium (Breuil et al., 2011). Therapy with OT has been demonstrated to raise calcium levels within cells and to control the activation of osteoblast production and consequently the generation of bones in rats. Furthermore, in mice, ablation of the OT receptor led to the formation of OP. According to an investigation conducted by Jee et al., OT increases bone loss and results in a favorable bone metabolism throughout alveolar bone repair in

TABLE 4 Hormones utilized locally for bone and periodontal tissue engineering.

Hormone	Original application	Repositioned implementation	Reference
Thyroxin	Thyroid carcinoma and dysfunction	Revascularization and new blood vessel formation	Malik et al. (2020)
Oxytocin	Bleeding after childbirth, labor stimulation, and imperfect, or unavoidable abortion	Increased bone formation	Park et al. (2014)
Dexamethasone	Rheumatism, hematologic/hormonal problems, allergies, and skin diseases, Visual issues, breathing issues, digestive problems, tumors, and allergic responses	Enhanced bone marrow activity and bone formation enhancement	Zhou et al. (2020)
Androgens	Estrogen generation, sexual desire, and bodybuilding	Improved implant Osseo-integration and bony deformity correction	van de Ven et al., 2021b
Parathyroid Hormone	Calcium/Phosphorus homeostasis	Enhances ALP activity and mineralization	Ning et al. (2019)
Insulin	Management of type I diabetes	Accelerated bone healing, and regeneration	Wang et al. (2018b)
Selective Estrogen Receptor Modulators	Postmenopausal osteoporosis the management and avoidance	Cellular growth, calcification capabilities, and function of ALP have all improved	Mu et al. (2018)
Erythropoietin	Management of severe anemia	Anti-inflammation and periodontal therapeutic characteristics	Xu et al. (2019b)
Estrogen	Ovaries dysfunction Hypogonadism in women	Markers of cellular proliferation and the development of osteoblast were improved	Wang et al. (2018a)
Melatonin	Management of sleep deprivation	Bone formation, and development in preosteoblast cellular lineages	Huang et al. (2020c)
Calcitonin	Management of increased calcium levels, and Paget`s disease	Lowers osseous destruction via regulating osteoclastic activity	Wada-Mihara et al. (2018)
Adiponectin	Regulation of blood glucose management and lipid oxidation	-Reduces inflammation - Possesses anti-apoptotic properties -Promotes the division of osteoprogenitor cells and osteoblasts. Promotes the osteoblastic transformation of HPDL cells.	Fang and Judd (2018), Iwayama et al. (2012)
Angiotensin	Management of volume and blood pressure	-Decreases inflammation -Promotes proliferation of periodontal cells -Enhanced bone regeneration	Singh and Karnik (2016)
Cortisol	Natural hormone released in response to stress, and fear	-Decreases inflammation - Promotes bone regeneration	Botelho et al. (2018), Warren et al. (2014)

Human periodontal ligament; HPDL.

female rats (Jee and Ma, 1997). It promotes bone formation by increasing osteoblast growth, osteoclast activity, and BMP2 expression.

Despite being researched for a variety of uses in medicine, the influence of oxytocin on local bone formation has not been addressed, most likely due to its brief duration of action and vulnerability to dissolution (Wang et al., 2024). A polymer hydrogel scaffolding containing spherical oxytocin hormone and biphasic calcium phosphates enhances calvarial bone healing in rats (Akay et al., 2020). Additionally, OT-encapsulated β-TCP promotes osteogenesis in rats with calvaria bone abnormalities through an osteoinduction mode of action (Park et al., 2014). It promoted osteogenic growth, division, and aggregation of PDLSC *in vitro*. In addition, the effect of OT on osteogenic progression was linked to the ERK and AKT processes. As a result, OT could be beneficial in restoring periodontal tissues (Ge et al., 2019).

7.5.4 Dexamethasone (DEX)

DEX has been shown to improve osteoblast growth and osseous formation by increasing genes linked to osteoblasts (Chen et al., 2018; Jørgensen et al., 2004). DEX has long been used as an osteoinductive agent because of its high consistency and osteogenesis (Martins et al., 2010; Li et al., 2015). Excessive DEX amounts, on the other hand, could impede osteoblastogenesis and have potentially adverse reactions (Arafa et al., 2023). Consequently, it has limited further functional utility in bone tissue engineering. Thus, sustained DEX discharge is necessitated to maximize efficiency, meanwhile minimizing detrimental impact on osseous healing. Injectable dexamethasone-loaded hydrogels show promise as an injectable drug repository for bone regeneration treatment in situations of persistent inflammatory reaction (Chauhan et al., 2021).

7.5.5 Angiotensin

Angiotensin is generated in the liver and discharged in an inert condition, where it is divided by the enzyme renin and transformed to angiotensin I, and then fragmented again by the angiotensin-converting enzyme (ACE) into angiotensin II (Guang et al., 2012). Angiotensin is essential for volume and blood pressure management (Almeida et al., 2020). Endothelial cells can produce angiotensin

away from regulation of vascular homeostasis (RAS). Angiotensin I promoted the breakdown of bones in the coexistence of osteoclasts and osteoblast cells, according to the researchers. This study suggests that RAS could possess a function in bone breakdown regulation (Hatton et al., 1997).

Saravi et al. (2020) reported that inhibiting RAS in a laboratory animal might reduce periodontal bone degeneration and inflammatory severity. It has been found that diverse tissues and organs of rats may manufacture angiotensin separately from circulatory RAS. Surprisingly RAS is expressed regionally in rat gingival tissue, allowing for the production of angiotensin II *in vitro* (Santos et al., 2009). It could impact bone deterioration in periodontitis, although greater renin synthesis could raise periodontal vulnerability. Moreover, (Santos et al., 2009), highlighted how bacteria stimulate the production of the gingival RAS, leading to a proinflammatory microenvironment with higher angiotensin II levels, that may lead to the decline in bone density seen in periodontitis. Addressing RAS's inflammatory function can give a new viewpoint for therapeutic studies and periodontitis therapy. RAS has been utilized in the treatment of inflammatory illnesses (Al-Azzawi et al., 2022).

7.5.6 Androgens

Males' main sexual hormone and anabolic element is testosterone. In human beings, testosterone is important in the male reproductive systems like the testes, in addition to in the stimulation of further sexual features including enhanced musculature and density of bones (Kuhn, 2002). PLGA-coated pericardial implants or membranes combined with topical progressive application of more testosterone and alendronate could be a feasible strategy for inducing local bone formation, resulting in improved implant osseous-integration and bone defect and fracture healing (van de Ven et al., 2021a). In mice, testosterone administered with a framework enhances bone formation in the same way that Bone Morphologic Protein-2 does (Cheng et al., 2013).

7.5.7 Parathyroid hormone (PTH)

PTH is a significant driver of osseous remodeling in addition to being a controller of calcium-phosphate balance (Arnold et al., 2021). It stimulates osteoblasts to produce a range of growth factors while reducing osteocytes' synthesis of sclerostin and DKK, two anti-osteoclastic and Wnt signaling antagonists. Moreover, it could have a secondary impact by encouraging osteoclasts to achieve degeneration of bones (Kikyo, 2024). PTH increases RANKL selectivity for osteoclast surface receptors while also increasing osteoblast RANKL synthesis, resulting in osteoclast activation (Sun et al., 2020).

PTH consumption has anabolic, and catabolic effects on bones. Massive quantities encourage the decomposition of bones, whereas low and irregular quantities encourage bone formation and mineral accumulation. PTH has been proven to significantly expedite fracture healing (Eastman et al., 2021). As a consequence, localized PTH supply to osseous defects could represent a viable alternative to auto transplantation (Wojda and Donahue, 2018). According to contemporary investigation, PTH improves the bony strength of the jaw and improves soft tissue repair and bone filling following exodontia (Kuroshima et al., 2013). PTH was found to possess a beneficial impact in periodontal disease animal models, by suppressing inflammation (Stutz et al., 2020). PTH dramatically decreases gingival inflammation while also suppressing bone loss. PTH administration increases bone formation via a boost in osteoblast amount, in addition to mineralized matrix accumulation via impacts on precursor division, cellular death, restriction, and lining cell stimulation, according to human and animal research (Jilka, 2007; Wein and Kronenberg, 2018).

Furthermore, investigations revealed that PTH directly promotes osteoblastic viability signaling and that the delayed death of osteoblasts is a substantial contribution to the enhanced osteoblast quantity, at least in mice (Wein and Kronenberg, 2018). Ji-Hye Kim observed that occasionally administering PTH to DM-rats with periodontitis decreased alveolar bone loss while increasing bone growth. This data implies that PTH treatment prevented bone loss caused by diabetes by stimulating bone growth. The use of the proteins SDF-1alpha and PTH increased bone growth. SDF-1alpha also promotes PDL regeneration. Multiple investigations have been conducted to investigate the effect of PTH on dental implant longevity and bone assimilation. Bellido et al.104 artificially caused osteoporosis in rabbits and assessed overall bone loss and decreased mineral levels in their jaws (Du et al., 2016). PTH injection, on the other hand, virtually totally corrected these unfavorable outcomes, restoring the jawbone to almost normal levels. Research on mongrels discovered greater amounts of bone remodeling surrounding dental implants put in the jaw in the PTH-treated group (Kim et al., 2020). A work exploring PTH-coated titanium dental implants in rats presents a possibility that may be close to usage in dentistry (Lai et al., 2017). The results showed enhanced bone growth surrounding the PTH-coated implants. As a result, our findings imply that PTH may be a potential treatment for enhancing the integration of dental implants in humans. Nevertheless, the rate of PTH delivery differs throughout research, thus determining the best interval and dose to enhance bone formation should be a top focus (Kuroshima et al., 2013). Huang et al. created an optimized delivery approach by combining a parathyroid hormone analog (PTHrP-2) with a mesoporous bioactive glass framework. In BMSCs, PTH-loaded scaffolding promoted bone formation and development. Moreover, the PTHrP-2/scaffold had decreased osteoclasts than the unaltered peptide-loaded matrix (Huang et al., 2020a). Ning et al. developed an injectable Gelatin hydrogel for sustained abaloparatide delivery. It boosted bone development and the content of minerals (Dang et al., 2017).

7.5.8 Cortisol

Cortisol, a steroid hormone generated by the adrenal glands, enters the circulation, crosses the cell membrane, and translocates to attach to cell nucleus receptor proteins, causing variations in gene transcription (Chaudhuri, 2019). Cortisol is released in response to stress. Insecurity, worry, hemorrhage, discomfort, reduced blood glucose, disease, and malnutrition are common stress triggers. Because of responding to cortisol, muscle, liver, and adipose tissue deplete their nutrition store. Cortisol levels that are chronically raised cause muscle and bone degeneration, as well as compromised endocrine and immune system functionality (Stefanaki et al., 2018). Stress is a component that contributes to the beginning of sickness.

Chronic and acute stress appear to hinder tissue healing in rats. Previous research has found that prolonged stress impedes recovery, in addition to the development of the bone matrix and collagen fibers, as well as a reduction in the number of osteoblasts. Rat periodontium experimental models have revealed that anxiety enhances vulnerability and exacerbates periodontitis, PD. Several studies have found a link between stress indicators, inflammation, and periodontal disease (Warren et al., 2014). Comparably, the advancement of periodontitis is linked to stress as a cause. It has been shown that stress seems to relate to microbial colonization.

Nevertheless, salivary cortisol levels are unrelated to stress. As a result, stress and the consequent rise in cortisol could lead to the advancement of periodontitis (Siqueira et al., 2015). Cortisol inhibits parathyroid hormone's resorptive activity, which promotes an increased number of progenitor cells and their transformation into osteoclasts. As a result, cortisol limits bone resorption *in vitro* by decreasing precursor cell capacity to produce osteoclasts.

7.5.9 Insulin

Insulin is a hormonal medication for Diabetes type I (Vanea et al., 2014; Maratova et al., 2018). Insulin/IGF-1 has been shown *in vivo* to stimulate vascularity and provide nutrition for osteogenesis (Hynes et al., 2013; Paglia et al., 2013; Rabinovsky and Draghia-Akli, 2004). Insulin, by boosting the amount of bone-formation cells, may successfully promote localized skull bone development in mice (Cornish et al., 1996), and is capable of regulating osteoclastic activities (Thomas et al., 1998). Innovative insulin-loaded interactive injectable materials have been found and might be used to treat osteoarthritis, notably as a low-cost stimulator/alternative to BMP-2 approaches (Krajcer et al., 2022).

Kido et al. (2017) conducted a study on diabetic rats and discovered a link between periodontitis and diabetes. They also discovered that diabetes may trigger aberrant gingival fibroblast growth. Insulin resistance contributes to the advancement of periodontitis in diabetics. They concluded that reduced fibroblast growing and moving induced impaired gingival wound healing in diabetic rats. Fibroblast malfunction can be produced by excessive glucose-induced insulin resistance via oxidative stress. A growth factor with an architecture so close to insulin that it has been termed insulin-like growth factor-1 (IGF-1) may be produced from the liver by human growth hormone stimulation, but also by bone cells (Klein, 2014).

IGF-1 has an important role in bone formation during adolescence and throughout life. IGF-1 has also been shown in rabbits to increase bone development around dental implants when combined with other growth factors (Zhou et al., 2017; Ortolani et al., 2014). Insulin may have bone-enhancing effects with osteoblasts having insulin-receptors, possibly boosting osteoblast development, because of their similarity in architecture (Klein, 2014).

In chondrocytes, GH regulates IGF-1 production, but in osteoblasts, parathyroid hormone (PTH) regulates it. Human osteoblasts synthesize IGFs. IGF-1 stimulates developed osteoblastic function without directly altering stromal cell development into mature osteoblasts. As a result, a minimal reduction in IGF-1 expression is thought to be required for apoptosis and the transformation of osteoblasts (Javed et al., 2020).

7.5.10 Estrogen

Estrogen is a naturally occurring steroid that affects the amount of bone and bone tissue homeostasis. The action of estrogen is intimately related to the control of osteoblastic multiplication and specialization. Furthermore, estrogen inhibits apoptosis in osteocytes and osteoblasts while promoting it in osteoclasts. Estrogen decreases osteoclastogenesis by lowering the generation of osteoclastic mediators. Furthermore, it stimulates the production of osteoprotegerin (OPG) by osteoblasts and osteocytes (Kearns et al., 2008).

17-estradiol (E2) attaches to estrogen receptors (ERs) in both bone cells and mesenchymal stem cells (MSCs). By increasing the activity of BMP-2, TGF-1, and IGF-1, estradiol may promote MSCs differentiation into osteoblasts and increase osteogenesis (Irmak et al., 2014). By encapsulation of E2 in an EDTA-adjusted nano composite, enhanced prolonged E2 discharge increased Alkaline phosphatase (ALP), osteopontin (OPN), osteocalcin (OCN), and calcium deposition in MC3T3-E1 preosteoblasts (Safari et al., 2021).

7.5.11 Selective estrogen receptor modulators (SERMs)

SERMs are non-steroidal chemicals that possess estrogen-like impacts on the skeleton, circulatory system, and lipid levels while additionally exhibiting anti-estrogenic actions on the breast and uterine system (Ott et al., 2002; Urano et al., 2017). They stimulate endochondral ossifying, osseous production, and bone remodeling, by acting estrogenically on the skeletal skeleton (Spiro et al., 2013).

7.5.11.1 Raloxifene

Raloxifene (RLX) is a selective estrogen receptor modulator (SERM), indicated to fight osteoporosis. Raloxifene has been demonstrated to have an estrogenic action on bones, in addition to increasing the preservation of bone integrity and improving bone mass density (BMD) (Ma et al., 2021). According to a lately published investigation (Zhang et al., 2017), RLX doses ranging from 0.1 to 10 g were tested *in vitro* utilizing a framework filled with PLGA microspheres carrying RLX. The findings showed that RAL discharge from microparticles was delayed and controlled, leading to improved cellular survival at all stages, significantly enhanced cellular proliferation, greater amounts of mineralized tissues, and boosted ALP functionality.

7.5.12 Melatonin

The function of melatonin (ML) in hard tissues has received plenty of interest (Leonida et al., 2022; Shino et al., 2016). ML might be related to the production of hard tissues like bone and teeth (Munmun and Witt-Enderby, 2021). ML promotes tissue calcification and alkaline phosphatase function (Liu et al., 2013). As was earlier stated, ML is used for its anti-aging, anti-inflammation, and anti-free-radical capacities (Köse et al., 2017; Fernández-Ortiz et al., 2020), and cytoprotection (Dos Santos et al., 2018; Fernández-Gil et al., 2017). When there is an increased level of ML, the production of inflammatory cytokines is reduced by modifying NF-κB functions, which adds to the signaling pathway. While the beneficial effects of ML on periodontal regeneration have been demonstrated in gingival fibroblasts in addition to lab animals, additional study is required (Dos Santos

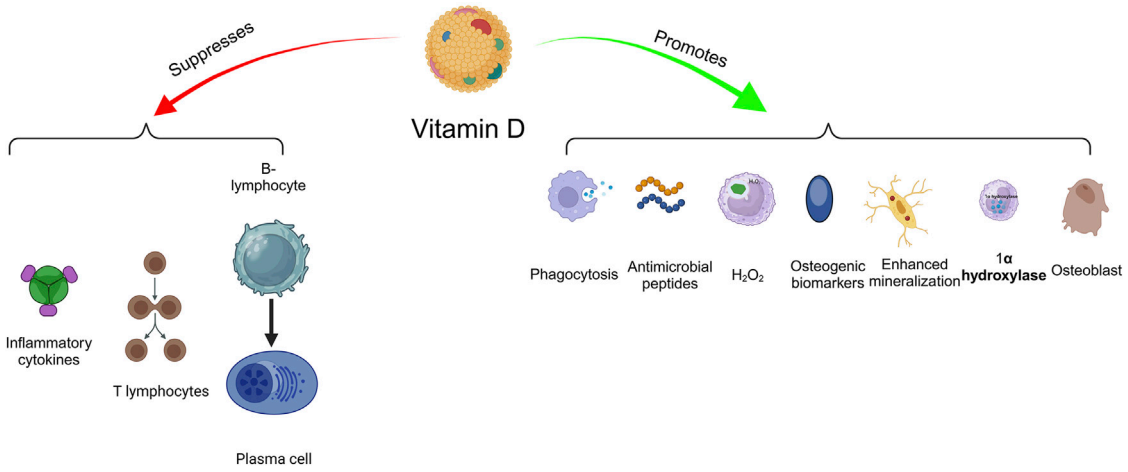

FIGURE 6
Beneficial effects of vitamin D on periodontal health.

et al., 2018). The circulatory half-life of ML is about 23 min (Givler et al., 2023).

ML-loaded chitosan particles can regulate Mel discharge throughout time, enhancing the osteogenic development of preosteoblast cells *in vitro* (Huang et al., 2020b). In diabetic rats, local injection of 2 mg ML gel is a promising therapy strategy for successful bone and PDL regeneration (Yousuf et al., 2013). ML appears to have the ability to be a good implant covering. When melatonin powder was administered for implantation regions in dogs, it significantly accelerated bone development and mineralization compared to control groups (Cutando et al., 2008).

7.6 Vitamins and antioxidants

7.6.1 Vitamins

7.6.1.1 Vitamin D

Vitamin D is a fat-soluble molecule that exerts a crucial function in regulating osteogenesis and strength, contributing to the maintenance of calcium-phosphorus ratios in the body (Figure 6). It attaches to cells through a vitamin D receptor (VDR), modulating the expression of several genes and cell responses. It enhances the mineralization of calcified tissues, and it aids in the retention of teeth in alveolar bone by strengthening periodontal tissue.

According to research, vitamin D has an anti-inflammatory impact on periodontal tissue via several methods. Furthermore, it promotes digestive and chemotactic activity of macrophages and regulates the 1-a-hydroxylase in monocytes, which is essential to vit D production as an autocrine agent, increasing the immune reaction and being a significant element of periodontal tissue reactions to dysbiotic infections (Lu, 2023).

In terms of inflammation, vitamin D enhances the suppression of proinflammatory cytokines. It has been demonstrated that vitamin D can reduce the synthesis of cytokines such as IL-17 by T-helper (Th) cells, which has been linked to an elevated risk of periodontitis. Taskan and Gevrek discovered that those with periodontitis had a reduced amount of VDR and fewer fibroblast cells than the normal group (Taskan and Gevrek, 2020). A new *in vitro* research study demonstrated vitamin D's anti-inflammatory and pro-mineralization benefits on periodontal tissue (Machado et al., 2020).

Periodontitis is also exacerbated by changes in the oral flora, which aggravate inflammation. It has been demonstrated to reduce the quantity of living *P. gingivalis* via activating autophagy (Hu et al., 2020). Other research indicates that elevated vitamin D concentrations reduce inflammatory amounts of cytokines such as RANKL, IL-1, and IL-6 (Han et al., 2019; Wang et al., 2020b; Li et al., 2019). Vit D has also been shown to be an important molecule in the maintenance of tooth mineralization and bone architecture.

Furthermore, vitamin D concentration was shown to be inversely associated with periodontitis severity. Numerous investigations have shown that vitamin D has a great capacity for both osteoinduction and odonto-induction. This compound has increased the levels of osteogenic biomarkers, and bone mineralization at low dosages (Mucuk et al., 2017). Bordini et al. developed a scaffold containing 1 nM 1, 25-dihydroxy vitamin D3. They observed that vitamin D3 may enhance the levels of odontoblastic markers (Bordini et al., 2020). Sattary et al. developed a polycaprolactone/gelatin framework containing HA nanoparticles recently. They observed that the incorporation of vitamin D into the scaffold blend boosts osteogenic growth and stiffening capability in hADSCs. On day 14, the combined effect of vitamin D and HA nanoparticles increased the osteogenic biomarkers in the PCL/Gel/nHA/Vit D3 scaffold group (Sattary et al., 2019).

7.6.1.2 Vitamin C

Because individuals cannot produce vitamin C, which is referred to as L-ascorbic acid, it must be obtained from a healthy diet (Padayatty and Levine, 2016). Plant-based foods, which are reliable providers of this nutrient, provide around 90% of the everyday need. It has to do with the production of collagen, which is essential for giving connective tissue firmness. As for the periodontal tissues, signs involve gum discomfort, tenderness,

and bleeding brought on by the vessels' brittleness, which might eventually result in tooth loss. Vit C promotes the development of collagen (Gref et al., 2020). Because vitamin C is required for the collagen stabilization approach, its shortage may result in structural disorientation, which relates to the deterioration of periodontal ligaments and, as a result, tooth loss. Furthermore, L-ascorbic acid is essential for endothelial cell activity and support. According to investigations, it promotes the division of endothelial cells, apparently because of its potential to boost type IV collagen production (Pizzicannella et al., 2021; Bai et al., 2021). The effect of vit C in collagen tertiary architecture stabilization is also critical. Moreover, it increases the movement of fibroblasts in the epidermis and the division of keratinocytes, which might boost wound healing caused by gingivitis by lowering inflammation within the gums (Rembe et al., 2018; Pullar et al., 2017).

Numerous functions of vitamin C also regulate immunity. This chemical can shield vital biomolecules from harm caused by contaminants, harmful substances, and free radicals by providing electrons since it is a powerful antioxidant (Marconi et al., 2021). The activity of neutrophils is also significantly impacted by vitamin C, which promotes their migration toward the infection and heightens internalization and bacterial death. Additionally, it encourages neutrophils to die and be absorbed by macrophages (Carr and Maggini, 2017).

Vit C is regarded as a crucial supplemental antioxidant for periodontal health because it eliminates excessive ROS. By causing the development of periodontal ligament progenitor cells, vitamin C is also essential for avoiding and minimizing the course of periodontitis. To lessen the detrimental impacts of diabetes on periodontium, vitamin C could be used topically to treat ligature wire-induced periodontitis in diabetic rats (Toraman et al., 2020). Locally administered vit C resulted in a significant decrease in inflammatory cells and epithelial thickness, as well as an increase in the quantity of freshly generated sub basal capillaries, and was an efficient supplementary approach in treating different forms of chronic gingival inflammation (Yussif et al., 2016).

7.6.2 Antioxidants

7.6.2.1 Omega-3

Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are two examples of omega-3 PUFA that have been demonstrated to have a variety of benefits, involving anti-inflammatory, immunoregulatory, and antioxidant-enhancing qualities. Omega-3 PUFA has been found to be curative and preventive in the management of a variety of inflammation-related disorders (Stańdo et al., 2020).

7.6.3 Carnitine

L-Carnitine (L-C), a cofactor in β-oxidation of fatty acids, has been shown to promote the actions of human osteoblasts. It greatly raises osteoblast levels of collagen type I, bone sialoproteins, and osteopontin in addition to their function and multiplication (Marcovina et al., 2013; Terruzzi et al., 2019). L-C may assist in preserving the integrity of bones by preventing the effects of oxidative stress (Terruzzi et al., 2019).

7.6.4 Herbal products

Natural chemicals are currently generating increased attention. The general public's curiosity about herbal products has grown, particularly among people with chronic conditions (Alkhursani et al., 2023a; Alkhursani et al., 2023b). Products containing natural components offer extra anti-inflammatory and antioxidant characteristics that may enhance gingival health (Xue et al., 2018). Nevertheless, the variability of preparations may reduce the effectiveness of active and herbal medicines. Individual plants have mild antiseptic properties, thus mixing several herbs and chemicals may enhance their antibacterial actions. As a result, they could be utilized for the avoidance and management of early-stage periodontitis (Sadek et al., 2024).

7.6.4.1 Allium sativum (garlic)

Garlic is a natural plant that may be utilized as a cost-effective and safe alternative therapy. Garlic includes allicin, which could possess antimicrobial and anti-inflammatory effects. Furthermore, garlic extract has high biocompatibility and can promote cell development. It may enhance the vitality and replication of human gingival fibroblasts (Bramanti et al., 2018). Garlic has been shown to exhibit anti-proteolytic effects against *P. gingivalis* protease, as indicated by aged garlic extract (AGE), which shows high bacteriostatic properties against *P. gingivalis* and gelatin liquefaction following 250 μL/mL dosage delivery (Shetty et al., 2013).

7.6.4.2 *Aloe barbadensis* miller (aloe vera)

Aloe vera's therapeutic benefits extend over thousands of years (Darzi et al., 2021). Aloe vera has 75 elements, including minerals, enzymes, sugars, anthraquinone, and salicylic acid (Saleem, 2021). Aloe vera possesses antibacterial properties against *Streptococcus pyogenes* and *Enterococcus faecalis* (Ghasemi et al., 2020).

It is ideal for treating gingivitis and periodontitis because it contains an anti-inflammatory ingredient (C-glucosyl chromone), inhibits the COX pathway, lowers PGE2, and degrades the bradykinin inflammatory substance involved for pain creation (Taalab et al., 2023). It helps to minimize edema, bleeding, and gingival tissue irritation. It is useful in deep pockets where normal cleaning is difficult, and its antifungal characteristics can help cure denture stomatitis, aphthous ulcerations, and angular cheilitis. Administering it following extractions is a potent healer (Bai et al., 2023).

7.6.4.3 Amphipterygium adstringens

Amphipterygium adstringens is a Mexican indigenous plant from the Julianaceae family known as "Cuachalalate" (Beltrán-Rodríguez et al., 2021). According to recent research, the key chemical accountable for the plant's powers is (Sotelo-Barrera et al., 2022), that possesses antioxidant, anti-inflammatory, cancer-fighting, antiulcer, and antibacterial properties (Torres-Ortiz et al., 2023).

7.6.4.4 *Camellia sinensis* (green tea)

Camellia sinensis is a member of the Theaceae family, and its tiny perennial plants are frequently used to create green and black tea (Hazra et al., 2021). Green tea's benefits are linked to its polyphenol constituents (catechins). Epicatechin-3-gallate and epigallocatechin-3 gallate are the two most important catechins. Green tea has more polyphenols (30%–40% vs. 3%–10%) than black tea, which increases antioxidant capacity and has powerful anti-

inflammatory, antibacterial, antiviral, antimutagenic, and anti-aging properties (Tang et al., 2019). Green tea has a favorable effect on inflammation and periodontal disease. Thus, evidence suggests that green tea is capable of treating and avoiding periodontal disease (Liao et al., 2020).

7.6.4.5 *Cinnamomum zeylanicum* (ceylon cinnamon)

Cinnamon has been utilized as an herb for cooking and in traditional medicine. Cinnamon has been examined during pregnancy, diabetic control, and gynecological diseases (Heshmati et al., 2021). It possesses anti-inflammatory, antioxidative, antimicrobial, and properties (Almatroodi et al., 2020). Cinnamon is associated with a group of over 250 evergreen trees from the Lauraceae family (Suriyagoda et al., 2021). Numerous kinds have been investigated, particularly those related to oral medicine. Cinnamomum verum and Cinnamomum zeylanicum are two of the most widely researched cinnamon varieties. Cassia cinnamon, frequently identified as Chinese cinnamon or *Cinnamomum aromaticum*, is a well-researched spice. *C. burmannii* and *C. loureiroi* are two other important cinnamon species (Bandaranayake et al., 2023; Wang et al., 2020c).

Cinnamomum bark essential oil (CBEO) is rich in aromatic chemicals, including cinnamaldehyde and eugenol. CBEO and cinnamaldehyde have antimicrobial, anti-inflammatory, and anticancer activities (Wang et al., 2020a). According to Wang et al., the cinnamaldehyde in *C. zeylanicum* bark essential oil is effective against *P. gingivalis* (Wang et al., 2018c). Based on research, cinnamaldehyde is accountable for CBEO's antimicrobial activity (Wang et al., 2018c). The relative function of cinnamaldehyde was discovered by studying the cell microstructure, membrane integrity, and membrane characteristics (Chen et al., 2024). CBEO and cinnamaldehyde can permanently damage bacterial membranes, jeopardizing membrane functionality. When the cell membrane depolarizes, metabolism fails and bacteria die (Ivanišová, 2023). Propidium iodide uptake experiments revealed that the CBEO and cinnamaldehyde treatments damaged the bacterial membranes. The confocal microscopy investigation of *P. gingivalis* revealed PI incorporation, indicating a cell membrane rupture (Wang et al., 2018c). Microbes can be destroyed via this main method, which is called membrane damage (Meng et al., 2016). *P. gingivalis* may be vulnerable to membrane permeability produced by CBEO and cinnamaldehyde.

8 Future perspectives on periodontal regeneration

Periodontitis is the sixth most common chronic disease worldwide, imposing enormous costs on society and economies. Cognitive adaptation, risk factor control, and cause-related therapy have been considered the "gold standard" approach for managing periodontitis (Ren et al., 2023). Considering that host proinflammatory and immune reactions play important roles in the etiology of periodontitis and influence treatment responses, numerous adjuvant techniques have been developed to modulate host reactions and improve periodontal therapy and maintenance outcomes. We've already highlighted LDDS's benefits over systemic delivery (Sholapurkar et al., 2020). Additionally, they are appropriate for diabetic patients, who frequently have other linked systemic illnesses and necessitate several medications, increasing the risk of adverse responses if systemic administration is the sole choice.

As our understanding of periodontal disease and medicine administration has advanced, tailored delivery systems have been created to assist minimize the unfavorable systemic adverse reactions of drugs. Nanomedicines are on the rise, and their incorporation into effective periodontal therapies is possible, thanks to customized local drug delivery methods (Caporossi et al., 2020). Antibiotics and anti-inflammatory drugs administered to a specific location via nanoparticle-based local drug delivery systems are more likely to be successful since they come into direct contact with biofilms or host cells. Nanotechnology has produced outstanding outcomes in this field, and its increasing use as an adjuvant has fundamentally transformed the prognoses and outcomes of standard periodontal therapy procedures (Balta et al., 2021).

As a consequence, nanocarrier technology may soon dominate the pharmaceutical business as a whole. The present situation of this expanding field indicates that its potential is essentially limitless (Chen et al., 2022). As a result of a growing comprehension of the principles of microbial activity and development of periodontitis, there has been a noteworthy shift in periodontal pocket topical delivery strategies in periodontitis treatment.

As a result, both academics and clinicians are increasingly passionate about exploring novel therapeutic techniques that may promote periodontal regeneration (Makvandi et al., 2021). To get better treatment effects, drug delivery systems must be employed correctly to release beneficial pharmaceutical agents Prospective studies should concentrate on how to tailor local medication delivery systems in order to maximize prospective clinical procedures in periodontal care.

9 Conclusions and prospective outlook

The topical application of repurposed medicines offers a lot of promise for modifying oral bone and periodontal healing processes. Because of their beneficial consequences, these relocated drug delivery scaffoldings are predicted to have excellent therapeutic benefits in bone and periodontal problems. Nonetheless, clinical studies for this distribution technique are now being conducted. Nevertheless, given the capacity to enhance oral bone and periodontal tissue regeneration, these delivery strategies may soon be enhanced for professional use. As it was earlier noted, there have been significant advancements in enhancing the therapeutic outcome of oral bone and periodontal treatment. Scientific advances in tissue engineering technologies, particularly in periodontium and oral bone, have provided researchers with various viable options. These advancements hold the potential for developing clinically beneficial methods that not only regenerate oral bone but also restore the periodontium, preserving its architecture and functionality.

Author contributions

ME-N: Conceptualization, Data curation, Formal Analysis, Software, Validation, Visualization, Writing–original draft,

Writing–review and editing, Supervision. FR: Conceptualization, Data curation, Formal Analysis, Software, Validation, Writing–original draft, Writing–review and editing. ET: Conceptualization, Data curation, Formal Analysis, Software, Validation, Writing–original draft, Writing–review and editing, Visualization. AhA: Conceptualization, Data curation, Formal Analysis, Software, Validation, Visualization, Writing–original draft, Writing–review and editing. NT: Conceptualization, Validation, Writing–original draft, Writing–review and editing. MS: Conceptualization, Data curation, Software, Validation, Writing–original draft, Writing–review and editing. HS: Conceptualization, Data curation, Software, Validation, Writing–original draft, Writing–review and editing. LF: Conceptualization, Resources, Software, Visualization, Writing–original draft, Writing–review and editing. B-DI: Conceptualization, Data curation, Formal Analysis, Project administration, Software, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. ME-S: Writing–original draft, Writing–review and editing. EE: Software, Writing–original draft, Writing–review and editing. AfA: Writing–original draft, Writing–review and editing. MA: Writing–original draft, Writing–review and editing. C-CA: Writing–original draft, Writing–review and editing. GA: Conceptualization, Data curation, Formal Analysis, Software, Validation, Visualization, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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