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REVIEW ARTICLE

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Recent progress in materials development and biological properties of GTR membranes for periodontal regeneration

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Abstract

Chronic periodontal is a very common infection that instigates the destruction of oral tissue, and for its treatment, it is necessary to minimize the infection and the defects regeneration. Periodontium consists of four types of tissues: (a) cementum, (b) periodontal ligament, (c) gingiva, and 4) alveolar bone. In separated cavities, regenerative process also allows various cell proliferations. Guided tissue regeneration (GTR) is a potential procedure that favors periodontal regrowth; however, some limitations (such as ineffective hemostatic property, poor mechanical property, and improper biodegradation) are also associated with it. This review mainly emphasizes on the following areas: (a) a summarized overview of the periodontium and its immunological situations, (b) recently utilized treatments for regeneration of distinctive periodontal tissues; (c) an overview of GTR membranes available commercially, and the latest developments on the characterization and processing of GTR membrane material; and 4) the function of the different non-polymeric/polymeric materials, which are acting as drug carriers, antibacterial agents, nanoparticles, and periodontal barrier membranes to prevent periodontal inflammation and to improve the strength of the GTR membrane.

KEYWORDS

antimicrobial properties, bone tissue regeneration, GTR membrane, nanomaterials, periodontitis

1 | INTRODUCTION

Guided tissue regeneration (GTR) procedure has become an important process for regeneration of periodontal tissue treatment that utilizes the membranes as mechanical barriers to produce a distance across the flaws and subsequently allows bone regeneration (He et al., 2017). Membranes utilized in GTR must be biocompatible with suitable degradation summary, satisfactory physio-mechanical characteristics, and adequate sustained power (Porrelli et al., 2021; Swami et al., 2021). However, this technique collapse in clinical use due to contamination (Venkatesan et al., 2021) that is initiated by either microbial settlement at the injury area or external body reactions causing by the implanting substances (He et al., 2017; Shi et al., 2014). Periodontitis is an extremely widespread chronic provocative infection that can lead to infective damage of the periodontal hard and the soft tissues (Swami et al., 2021), maximum bone resorption, gradual attachment loss, and finally the tooth loss (Barbeck et al., 2020; Xu et al., 2017). Periodontium, once harmed, has a minimal capability for regeneration (Chen et al., 2016;

Lian et al., 2019; Pihlstrom et al., 2005). Guided bone regeneration and guided tissue regeneration membranes follow clinical protocols to regenerate harmed periodontics tissues that are lost because of periodontal disease (Toledano-Osorio et al., 2021), tooth extraction, and periodontal wounds (Porrelli et al., 2021). GBR/GTR membranes should be porous for adequate nutrient approval and cellular variation (Venkatesan et al., 2021). Usually, the membranes are distributed into two classes: *i*) non-resorbable membrane and *ii*) bio-resorbable membrane (Ahmadi et al., 2020; Barbeck et al., 2020; Mei et al., 2007; Villar & Cochran, 2010). Non-resorbable membranes (like extended polytetrafluoroethylene (e-PTFE)) are mostly eliminated after implant through a second surgery; on the contrary, bio-resorbable membranes (like collagen-based membranes) do not require to remove as well as these membranes can have ability to maintain their structural identity during repairing process. This desirable quality has currently build bio-resorbable membranes capable for GTR/GBR treatments (Ahmadi et al., 2020; Chakraborti et al., 2011; Mei et al., 2007; Russo et al., 2019). But, the rapid deterioration of the present resorbable membranes is the key task leading to deterioration before perfect tissue regeneration (Pihlstrom et al., 2005). Therefore, different studies focused on this targeted flaw and reported new kinds of membranes with greater mechanical strength and controlled degradation rate (Ahmadi et al., 2020; Bottino et al., 2011; Veronese et al., 1999; Yang et al., 2009). An ideal GTR membrane should possess the following promising features: appropriate mechanical strength, biocompatibility, active osteogenic property, and antibacterial strength (Pilipchuk et al., 2015; Zahid et al., 2019).

Currently, some new protocols, *for example*, incorporation of growth factors (GFs) are adopted and modified to remove the barriers that hinder the membrane properties. GFs can enhance the regenerative procedure and hence accelerate the tissue's regeneration mechanism. In the periodontal process, growth factors involving bone morphogenetic protein (BMP-2) and platelet-derived growth factor (PDGF) are mostly utilized to enhance the healing process (Ahmadi et al., 2020; Caballé-Serrano et al., 2019). Periodontics regeneration is described morphologically as the regeneration process of teeth-supporting tissues, involving the cementum, periodontal ligament, cementum, and the alveolar bone, over a formerly contaminated root cover (American Academy of Periodontology, 2001). Platelet-rich plasma (PRP) performs through alpha granules degradation in platelets cells, which hold the manufactured and enveloped (GFs) (Marx et al., 1998; Petrungaro, 2001). The alpha granules combine with the platelet cell membrane, where the GFs accomplished to a biologically active state by the accumulation of the carbohydrates cross chains and the histones proteins.

In the present study, we first overview periodontal tissue regeneration approaches involving tissue engineering and guided tissue regeneration. Next, we review the drug delivery systems, nanoparticles (NPs), and biomaterials that have been formed to enhance the biological and mechanical properties of guided tissue regeneration membrane for periodontal regeneration. We emphasize the improvement of the progressive bio-inspired scaffolding biomaterials and the temporospatial handling of the multi-drug delivery system. Moreover, we review the functions of the biomaterials and drug delivery systems periodontal tissues regeneration that involve the alveolar bone, PDL, and the cementum. After all, our views on the use of biomaterials and drug delivery system to renovate the categorized and efficient periodontium are delivered as signs for the future improvement of this field. The present study would offer useful evidence for the strength of the GTR/GBR membrane.

2 | MATERIALS ADVANCEMENTS IN THE FABRICATION OF GTR MEMBRANE

Periodontal regeneration in coordination with the tissue-engineering approach, it is important to study two necessary substances: controlled drugs delivery systems and the scaffold **(**Figure 1). Two approaches are followed for periodontal regeneration process, that is, tissue-engineering strategy and the GTR. GTR has been extensively utilized for periodontal treatment in clinical systems. It follows a regenerative surgical procedure which includes the process of raising, planning root surfaces, scaling, putting barrier membrane for some time underneath gingiva, and mucous-gingival flap around affected teeth (Gottlow et al., 1984).

The tissue-engineering strategy uses bioactive molecules to construct a biomimetic system, scaffolds progenitor/stem cells to induce new tissue formation.

This approach for periodontal regeneration depends upon the type of biomaterials, thus classified into scaffold-free and scaffold-based strategies. In scaffold-free strategy, either cell aggregates or cells are transferred to a wound area deprived of a cell-carrier. Many kinds of cells, involving adipose-derivative stem cells (ADSCs) (Yamano et al., 2014), bone marrow-derivative dental pulp stem cells (DPSCs) and bone marrow mesenchymal stem cells (BMSCs) (Requicha et al., 2014), and the dental pulp stem cells (DPSCs) were been verified for dental regeneration (Liang et al., 2020; Yamano et al., 2014). It was described that sheet therapy tempted new bone development phenomenon in contrast to the cell suspension in swine periodontal defect cell (Hu et al., 2016).

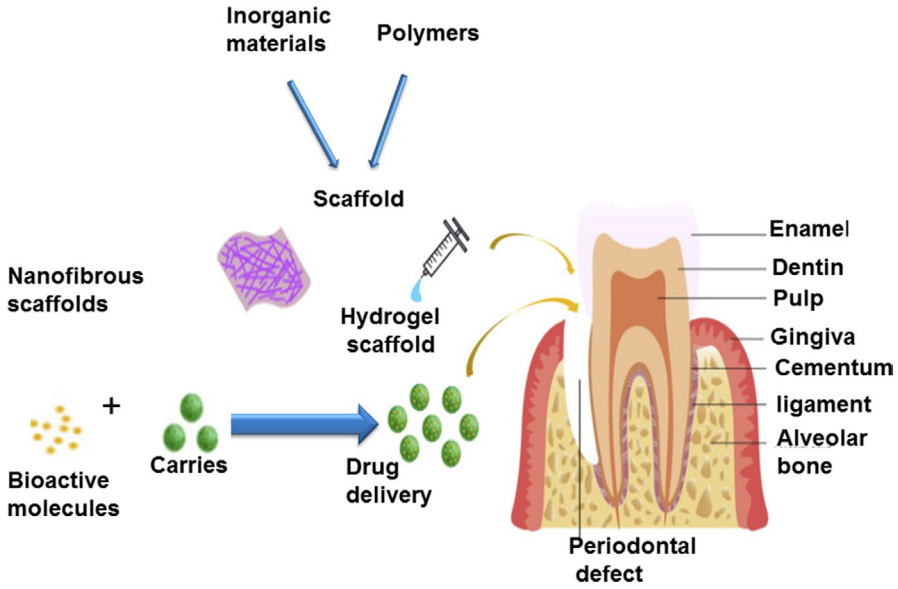

FIGURE 1 Representation diagram of the scaffolds of a tissue-engineering approach, anatomy of periodontal tissues, drug delivery system, and periodontal defect (Liang et al., 2020)

Cell sheet protocol is only capable of regenerating a tissue layer with a simplest arrangement. If the complex structural design of periodontium using soft tissue PDL and two hard tissues (alveolar bone & cementum) are involved for the regeneration of alveolar bone complex and PDL cementum, then the only feasible approach is the use of a scaffold-based. To imitate the periodontal structures, multiphase scaffolds with distinct characteristics in every part are requisite. Especially, chemical composition, the architecture, cellular or the biochemical arrangement in every portion required to be tailored to attain periodontal complicated healing (Jiang et al., 2015; Park et al., 2017). Explanations of scaffolding design and the biomaterials are described based on the quantity of growth factors and drugs. In a mono-drug delivery procedure, a growth factor or a drug is used to accomplish a specific target (Cai et al., 2018; Liu et al., 2015). BMP-2 was utilized to accelerate mandibular bone defect repair and enhance bone regeneration (Song et al., 2016). The bioactive agents can be mixed-up with biomaterials through non-covalent approaches, like ionic complexation and physical entrapment. However, the burst release cannot handle by these approaches, which is not favorable for the drug delivery procedures. After the fabrication process, the activity of the bioactive agents frequently decreases (Liang et al., 2020) (Table 1).

Different natural biomaterials, for example, heparin sulfate and heparin glycosaminoglycan are in the extracellular matrix (ECM) possess binding areas that induce powerful contact with bioactive molecules. In this way, these glycosaminoglycan defends the bioactive molecules (like growth factors). Hence, protect from proteolytic degradation, resulting extended and sustainable release and denaturation. Based upon this function for bone-tissue regeneration, recently another approach is developed, that is, hierarchical nano-spheres encapsulated microspheres (Liang et al., 2020; Ma et al., 2015). By this approach, BMP-2 and heparin bounding was encapsulated in a gelatin nano-spheres heparin-conjugated system, which was more immobilized within microsphere nanofibers (Figure 2). This method permits the control growth factor delivery system into only one injectable microsphere (Liang et al., 2020). BMP-2 contains binding sites with heparin, and this binding controls its sustained release of heparin and stabilizes the BMP-2. In addition, the encapsulation in gelatin nano-spheres and immobilization on nanofibrous microspheres aped the design of collagen fibers and provided various universal properties, that is, controllable degradation rate, better surface area, and less value of density with high porosity. The ECM-aped nano-fibrous design increased new tissue formation, proliferation, bone marrow-derivative mesenchymal stem cell adhesion, and differentiation (Chang et al., 2018; Wang et al., 2017). BMP-2-loaded hierarchical microsphere nanofibers provided exceptional carrier properties and remarkably increased bone regeneration, as confirmed via in vitro study. With an injectable biomimetic scaffold, the combination of controlled growth factor carriage offers new visions into the scheme of cell-instructive scaffolds (Liang et al., 2020).

Distribution of an osteogenic agent with the removal of the contaminations is the best process for periodontal treatment. Additional demands of the GTR technology are effectively satisfied by the dual-drug delivery system (DDDS). It is a feasible approach for periodontal treatment as the dual-drug delivery procedure can consecutively discharge osteogenic and antimicrobial drugs. In previously reported work, through phase separation and thermal-induced process, they effectively introduced a 3-D dual-drug delivery system scaffold loaded with naringin (NAR)

TABLE 1 Various drugs and the GFs utilized for the periodontal regeneration process (Liang et al., 2020)

Bioactive molecule	Properties	Characteristics	Application in Periodontal regeneration	[Ref]
Drugs				
Statins Sim-vastatin (SMV) Atorvastatin (ATV)	It reduces the action of the coenzymes Reductase, usually utilized for the cholesterol enhancement and lipid increasing process	Preventing the action of the osteoblasts cells Enhance the level of the bone morphogenic factor−2 Prevent the β-Hydroxy β-methylglutaryl-CoA	Gels charged along Statins Sim-vastatin decrease the dental diseases	Liang et al., 2020; Martande et al., 2017; Bertl et al., 2018)
Metformin	Used for the treatment of the diabetes	Increase the bone regeneration and the osteogenic activity	Inhibit the periodontal diseases	Wang et al., 2018; Pradeep et al., 2017)
(GFs)				
Platelet-derived growth factor	Four isomeric consists of dimer of A, B, and C chain: Platelet-derived GF-AA, platelet-derived GF-AB, platelet-derived GF-BB, platelet-derived GF-CC Two receptors: α and the β	Increase the cells movement according to the chemical response and increase the osteogenic activity	Increase the bone and the periodontal regeneration	Liang et al., 2020; Yamano et al., 2014)
Fibroblasts (GFs)	Promote the cellular activity of the cells	Enhance the cell division activity during mitosis, promote osteogenesis action	In the periodontal patients, it increases the bone regeneration process	Liang et al., 2020; Khoshkam et al., 2015)
Stromal-cell-derived factor−1	Also known as the C-X-C chemokine ligand 12 (CXCL12) and its receptors(CXCR4)	Promote the bone regeneration	Increase the process of the bone regeneration	Cai et al., 2018; Liu et al., 2015; Ji et al., 2013)
BMP protein class	Resemble to the transforming GFs-β class and have more than twenty types of the proteins. These proteins can be different or same proteins with each others	Promote the osteogenesis, bone regeneration, and the wound healing activity	Indicate regeneration in bone formation	Liang et al., 2020; Yin et al., 2017; Ern et al., 2017)

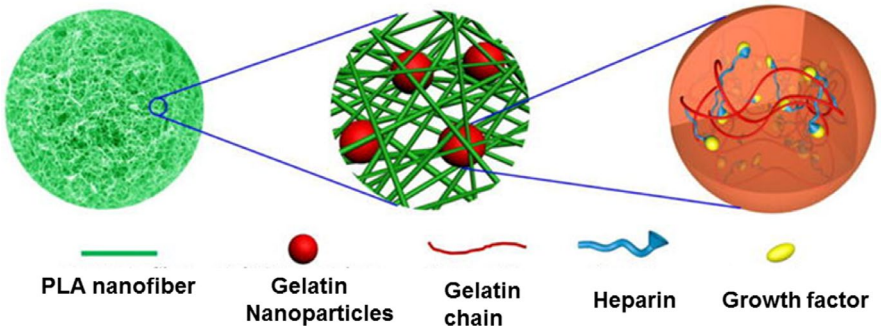

FIGURE 2 Scheme Representation of the microsphere nanofibers for regeneration of bone, showing BMP-2 encapsulation into heparin-conjugated gelatin nano-spheres that are more adjusted/settled in nano-fibrous PLLA microspheres (Ma et al., 2015)

and metronidazole (MNA). NAR and the MNA were discharged in a successive organized design with MNA discharged quickly, and NAR was discharged in a more regular pattern (Guo et al., 2017). In the fabrication of GTR electrospinning membrane, numerous features are developed: (a) wide adaptability and common techniques; (b) with a different structure it can modulate fiber mats that enhance the attachment of the cell, achieves continuous and precise delivery of local drug and increases the loading of drug (Kojić et al., 2017; Park et al., 2015; Sedghi et al., 2018). A novel kind of spinning known as the coaxial electrospinning technique has generated an exclusive core/shell arrangement (He et al., 2020; Nie et al., 2017). By coaxial electrospinning, loaded drugs in the shell portion and core portion correspondingly can realize at the same period. So, coaxial electrospinning is appropriate in spinning the multifunctional dual-drug delivery system as GTR membranes (He et al., 2018, 2020).

Dental membranes bioceramics have gained massive interest as they improved bioactivity, biological and physio-chemical characteristics of the membrane. Numerous researches have combined bioceramics like bioactive glasses (BG), hydroxyapatite (HA), and calcium phosphate (CP) in dental field because of its important biological characteristics like osteoinductivity and osteoconductivity and capability to minimize the natural inorganic bone constituent (Heinemann et al., 2010; Hu et al., 2016; Li et al., 2008). For bone healing/reparation uses and dental membranes, beta tri-calcium phosphate (β-TCP) has been used as an outstanding bioceramic in several medical places because of its excellent osteo-conductivity, bioactivity, and extreme in vivo resorb ability that are beneficial for effective regeneration process (Rad et al., 2017; Soheilifar et al., 2014; Yang et al., 2015). Numerous forms of the membranes including fibers, gels, foams, and mats, synthesized by a range of procedures involving electrospinning, particulate leaching, freeze-drying, self-assembly, solvent casting, and molding have been utilized (Hurt et al., 2014; Rad et al., 2017; Saleem et al., 2011). The capability of the fibrous structure to mimic ECM with a huge porous structure possessing interconnected pores and a huge surface-to-volume ratio make nanofibers attractive for dental applications (Matsumoto et al., 2001; Rad et al., 2017; Saleem et al., 2011).

Bioactive glass is comprised of mostly SO_2 as an amorphous biomaterial that displays biodegradation. Bioactive glass can discharge Ca and Si ions, improving the action of osteoblast and produce an association with bones. It has been revealed that bioactive glasses enclosed in biodegradation membranes stimulate the deposition of minerals on the surface of osteoblast cells. But, increased pressure and temperature-based manufactured procedures exhibit high brittleness, poor elasticity due to these reasons maximum bioceramic stay as limitations to be utilized in dental regeneration (Sasaki et al., 2021).

In gene therapy, two major approaches are involved in the periodontium regeneration ex vivo and the in vivo distribution. Though in vivo distribution is a single step, its treatment power is less and shows a high host immune response. Ex-vivo, on the other side, is a double step mechanism where tissues and cells of interest can be removed, and improved in vitro location, strength, and effectiveness of the transduced cells can be large but expensive and hardworking.

Though gene therapy in dental regeneration is at the birth phase and needs a further suggestion for medical trials, the treatment efficiency of gene therapy in the dental regeneration process can develop promising therapeutic opportunities and increase probabilities of integrated well-designed periodontium regeneration (Woo et al., 2021).

Carbon nano-tubes (CNTs) not only promote the regeneration process but also perform as a stable mechanical part (Mei et al., 2007). Currently, CNTs showed great capacity in the biomedical field because of their contribution to their distinctive chemical, physical, and mechanical characteristics. In vivo reports showed definite bioactivity of multi-walled carbon nanotubes (MWNTs)

with numerous cells, particularly for the osteoblast cells. Many researchers have uncovered that hydroxyapatite enhanced the biological characteristics of PLLA, and the nano-sized hydroxyapatite crystallites were well adjusted on the multi-walled carbon nanotubes surface.

Hydrogel is a crosslinked macromolecule polymer with hydrophilic strength and reasonable absorption properties. Different kinds of biomolecules can be designed as hydrogel. The benefits of a hydrogel structure involve bioactivity, higher amount of water, and flexibility in construction mechanism. Numerous kinds of hydrogel have been utilized for the periodontium regeneration. When biphasic calcium phosphate (BCP) with collagen membrane was associated using Hydroxypropylmethyl cellulose (HPMC), resulted membrane exhibit the outstanding results including prevention of soft tissue attack into periodontium flaws and significant regeneration of bones.

A major restriction of hydrogel in the tissue-engineering technology is the poor mechanical strength. To avoid the hurdle to some degree, numerous surveys utilized chemical modification (Woo et al., 2021).

Wool keratin and PLGA are two brilliant biomedical materials. In the area of GTR technology, these two biomaterials have promise uses (Caffesse et al., 1994; Katoh, Shibayama, et al., 2004; Kurtiş et al., 2002; Nakata et al., 2014; Zhang et al., 2016). But, due to the deficiency of the natural strength of molecular recognition sites on the PLGA side, they can bound the PLGA application in the medical area to a specific point and inhibit the specific cell adhesion (Chen et al., 2006; Hsu et al., 2006; Zhang et al., 2016). Therefore, materials with higher cell affinity, for example, hydroxyapatite and collagen, are mostly reformed with PLGA for the enhancement of biocompatibility (Kawazoe et al., 2009; Li, Zheng, et al., 2009). Wool keratin is a natural biomaterial (Tachibana et al., 2002, 2005; Yamauchi et al., 1996; Zhang et al., 2016). It can cause biodegradation of the nontoxic products in vivo and in vitro without producing immune and inflammatory reaction (Yamauchi et al., 1996; Zhang et al., 2016). Further, it has better treating performing and can be managed into different shapes (Katoh, Tanabe, et al., 2004; Li, Li, et al., 2009; Yang et al., 2009). But, keratin biomaterials have usually low mechanical strength, that is, the pure wool keratin membranes show brittleness (Gou & Yang, 2011; Zhang et al., 2016). Therefore, to fabricate composite GTR membranes wool keratin is combined with PLGA. However, wool keratin can decrease the rate of PLGA-induced sterile infection and can increase the bioactivity and cell affinity of PLGA. The mechanical features of wool keratin can be improved by PLGA, thus fabricating an Ideal GTR membrane according to requirements (Zhang et al., 2016). A bilayer-graded membrane, having bottom layer of PLGA and wool keratin non-porous membrane and the upper layer of PLGA/wool keratin porous membrane, was manufactured by the procedures of the solvent casting and electrospinning. The porous layer promotes the regeneration process, and the dense layer can prevent the gingival epithelium and connective tissue from communicating root surface: reform periodontal ligament, cementum, and the alveolar bone; form new connection; and finally attain the regeneration of periodontal tissue. Then, the resultant membranes were utilized in guided tissue regeneration surgery on the beagle dogs. The research will function as a basis for more knowledge of bilayer wool keratin/PLGA membrane for treatment of dental diseases and GTR application (Zhang et al., 2016).

Biodegradable polymer (BP) has also been used in the dental regenerative methodology as biomaterials in the form of powders or a scaffold for tissue engineering, micro-particles to stimulate local tissue repair or solutions. The previous data presented that inorganic coating was capable to increase differentiation and mineralization on the implant surface, cell proliferation, and initial cell adhesion (Chi et al., 2019). Further, to preserve post-extraction alveolar ridge volume, electro-spun polylactic acid (PLA) and polycaprolactone (PCL) membranes are loaded with resveratrol as promising nanomaterials. The two membranes were capable to discharge resveratrol in a sustained and tunable manner and with various kinetic functioning instantaneously on two fronts: 1) allows new bone formation and 2) counteract bone resorption (Chi et al., 2019).

3 | INCORPORATION OF ANTIMICROBIAL AGENTS IN GTR TO IMPROVE THE BIOLOGICAL PROPERTIES

Various antimicrobial agents and nanoparticles were used which have been discussed in detail below.

3.1 | Addition of antimicrobial drugs

In the periodontal protocol, a biodegradable drug loading GBR/GTR membranes can lead to more promising damaged tissue regeneration providing a relatively benign environment. (Chen et al., 2013; Gottlow et al., 1984; Jia et al., 2016; Nyman et al., 1982; Naqvi & Drlica, 2017). Drug-loaded GBR/GTR can inhibit bacterial colonization and eliminate microorganism's infection on the root surface (Gilchrist et al., 2013; Jia et al., 2016, Naqvi et. al., 2018). Electrospinning is a prevalent method for the fabrication of drug-loaded biodegradable membranes (Bhardwaj & Kundu, 2010; Jia et al., 2016). The resultant fibers possess a huge surface area and volume ratio and a 3D network

structure that can increase the adhesion, porosity, growth of the cells, and proliferation (Jia et al., 2016; Sill & Von Recum, 2008). Further, the drug can be covered directly by the electrospinning procedure and mixed a polymer and drug solution; thus, fibers can be utilized as transporters in measured drug delivery system (Jia et al., 2016; Kumbar et al., 2006; Son et al., 2014). Electro-spun membranes can be divided into different shapes and sizes that make them appropriate for the different kinds of clinical treatments (Luong-Van et al., 2006; Zamani et al., 2013). To control the cell differentiation and adhesion, electro-spun nanofibrous membranes can offer chemical and physical indications and stimulate regeneration (Chen et al., 2011; Jia et al., 2016). All these structures make electro-spun nanofibrous membranes extensively utilized in the biomedical area (Jia et al., 2016).

One of the common antibiotics is doxycycline hydrochloride (DOX). Because of the minor amount, it is vigorous against mostly periodontal pathogens (Garrett et al., 2000). It has the ability to inhibition of bone absorption collagenase, anti-inflammatory action.(Chaturvedi et al., 2013). Reported literature research had displayed that DOX with root planning had a beneficial result on periodontal treatment (Garrett et al., 2000). The outcomes exhibited that the class used with the doxycycline hydrochloride and SRP-loaded nanofibers were profoundly improved than the group used with the only SRP (Chaturvedi et al., 2013). Current research is meant to yield the nanofibrous membranes having the antimicrobial DOX by the electrospinning procedure, which can treat periodontal infection (Jia et al., 2016).

An antimicrobial drug, *that is*, methamphetamine (MET) normally applied in the medication of periodontal treatment (Bottino et al., 2012; Freeman et al., 1997). Metronidazole benzoate performs upon anaerobic Gram-positive and anaerobic Gram-negative bacteria (*P. gingivalis*) (Bottino et al., 2012; El-Kamel et al., 2007; Naqvi, 2021). Certainly, the incidence of periodontal pathogens, *for example*, *P. intermedia* and *P. gingivalis* may adversely affect the accomplishment of tissue regeneration (Bottino et al., 2012; Haffajee & Socransky, 1994; Pihlstrom et al., 2005; Slots et al., 1999). Thus, to improve periodontal tissue regeneration, it is imperative to handle the control bacterial infection of the periodontitis flaw (Bottino et al., 2012). The most common antibiotic agent tetracycline has been confirmed to increase membrane characteristics due to its safety profile and efficiency in periodontal treatment (Zahid et al., 2019). Tetracycline is utilized as an anti-collagenase, wound healing, and anti-inflammatory properties (Petrungaro, 2001). They prevent metal catalyzing protease enzyme, involving breakdown of the peptide bond, which performs a part in harming bioabsorbable collagen membranes and connective tissue (Petrungaro, 2001).

To inhibit the anaerobic bacteria, Metronidazole (MNA) is commonly used that can settle during contamination in the GTR membrane (Xue et al., 2014b; Xue et al., 2014a). So, to reduce the early burst discharge, electrospinning protocol can be applied to manufacture Metronidazole-loaded gelatin/PCL nanofibers (He et al., 2015). In recent research, the main purpose was to manufacture a GTR membrane with an antibacterial property by electrospinning technique. The resultant GTR membrane would be predictable to inhibit the inflammatory response and to achieve sustainable drug delivery during the regeneration process. Gelatin and PCL were chosen as the coating reagent and scaffold substance. Genipin was used as a cross-linking agent to stop the liquefying of gelatin core. Metronidazole was selected as an antimicrobial means since it is mostly utilized for the cure of periodontal infections. At this time, we especially concentrated on two features of the GTR membrane: (a) drug loading amount on drug delivery behavior and the effect of the core/sheath structure and (b) advancement of tissue affinity yielded by gelatin coating. The membrane's surface biocompatibility, hydrophilicity, antibacterial activity, surface, morphology, and drug delivery behavior were entirely studied. The current study is accepted to offer beneficial new awareness into the improvement of drug-loaded GTR membranes (He et al., 2015).

3.2 | Addition of polymeric antimicrobial agents

Structurally nano-engineered antimicrobial peptide polymers (SNAPPs), a recent group of antibacterial agent has recently developed, as revealed in Figure 3. They showed action against *Acinetobacter baumannii* (Gram-negative) bacteria (Chi et al., 2019).

It is feasible that in accumulation to recognized periodontal microbes in the etiopathogenesis of periodontal diseases, a non-oral bacterial class like *Acinetobacter baumannii* may also show a function (Dasilva-boghossian et al., 2011). The antibacterial activity of SNAPPs proceeds through unregulated ion interchange through the cytoplasmic membrane (Chi et al., 2019; Abbas et. al., 2021). Accordingly, in reducing the growing danger of Gram-negative bacteria, SNAPPs exhibited huge capability as inexpensive and successful antimicrobial mediators (Chi et al., 2019). Previous research analyzed single-class biofilms (Kolenbrander et al., 2010). But, single-class biofilm is not illustrative of the natural biofilms (Hall-Stoodley et al., 2004). As compared to the single species, multiclass biofilms are more difficult to attain, because against pathogens multispecies biofilms are extremely unaffected than the single species (Zollinger et al., 2015). Further,

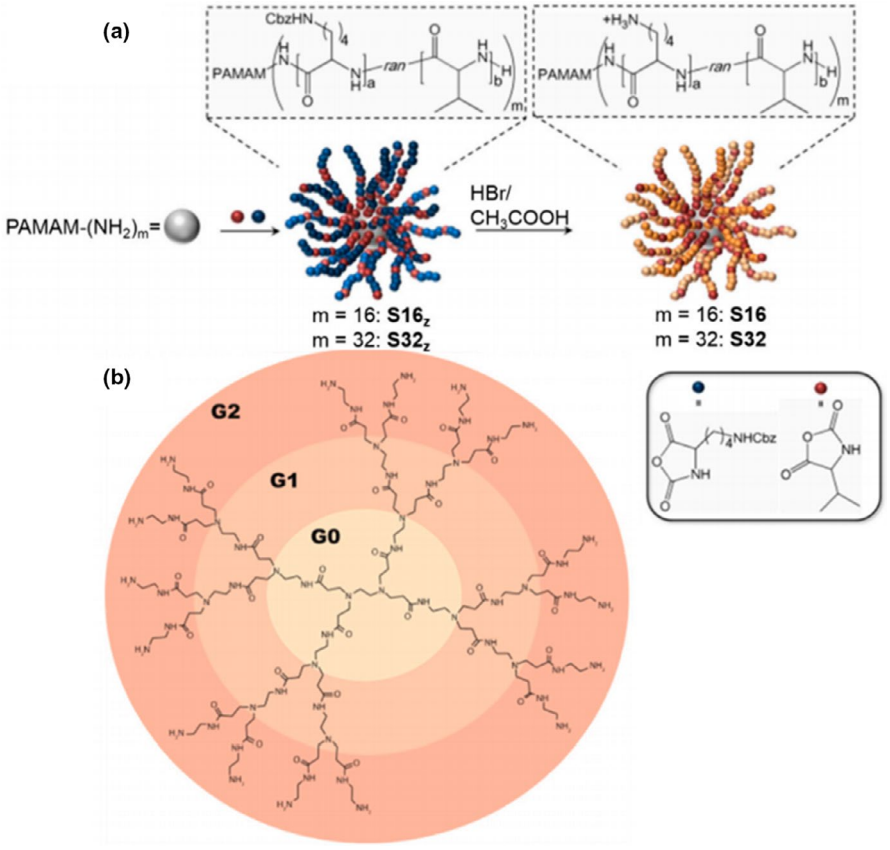

FIGURE 3 SNAPPs synthesis protocol. (A) By ring-opening polymerization of lysine and valine N-carboxyanhydrides (NCAs). Process was instigated from the terminal amines of poly (amido amine) (PAMAM) dendrimers. (B) 2nd and 3rd generation PAMAM dendrimers with 16 and 32 peripheral primary amines were used to synthesize 16- and 32-arm SNAPPs, respectively (Chi et al., 2019)

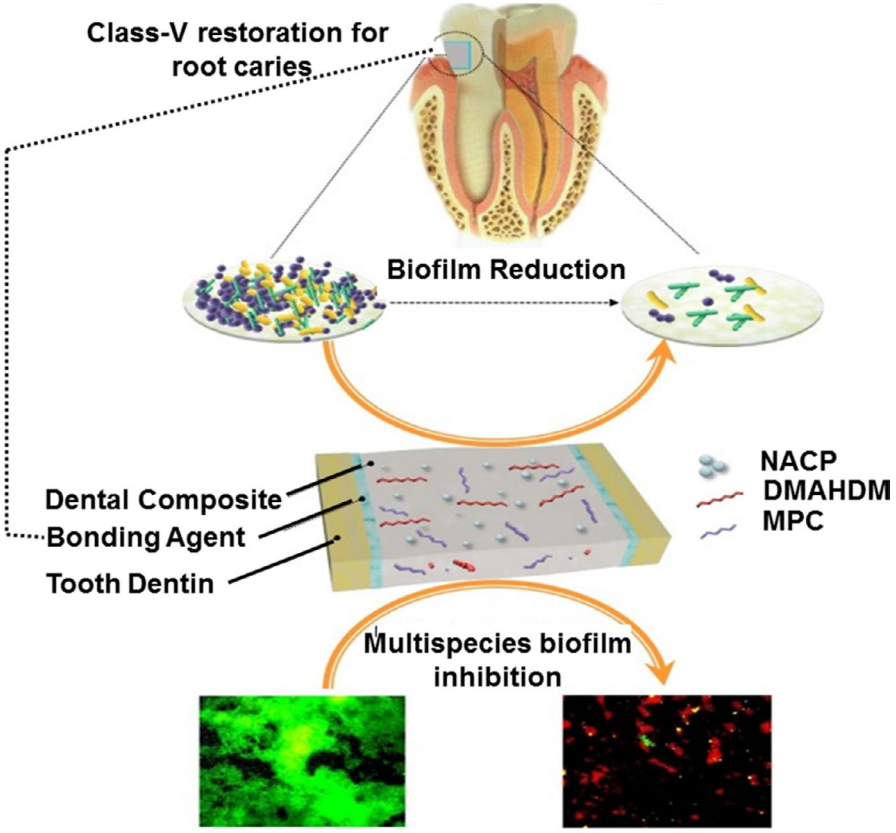

FIGURE 4 An antibacterial approach utilizing dual agents in dental composite (Wang et al., 2019)

the biofilm make-up affects the result of periodontal therapies (Fujise et al., 2002) and destroys the efficiency of antimicrobial mediators (Zollinger et al., 2015). Hence, current research studied the results of the amount of class of species in the dental biofilm on the reduced efficiency of the film (Wang et al., 2019). Further, the outcome of dual agents dimethylaminohexadecyl methacrylate and methacryloyloxyethyl phosphoryl choline (DMAHDM +MPC) as compared to the single species on the prevention productivity was studied as a purpose of the number of classes in periodontitis film for the first time (Chi et al., 2019, Zhang et. al., 2020). Figure 4 explains the anti-biofilm scheme. The bioactive combination decreased the adsorption of the protein in magnitude and remarkably decreased the biofilm feasibility (Chi et al., 2019).

Inhibiting single species biofilm, DMAHDM composite was more effective in the biofilms improving the amount of the species, the inhibition efficacy decreased. MPC addition into the DMAHDM mixture enhanced the efficiency as opposed to the multiclass species biofilms. (MPC +DMAHDM) the dual agent nanocomposite, with the protein-repellent anti-biofilm functions, is capable to stop the periodontitis microbes, defend the periodontal cells, and the treat root caries (Chi et al., 2019). Besides, three bioactive agents (DMAHDM for anti-biofilm activity, MPC for the protein-repellent, and the amorphous calcium phosphate NPs for the process of remineralization) were merged to inhibit the periodontal diseases (Wang et al., 2017). So, in the dental polymer, dual use of MPC and DMAHDM could operate together to increase the prevention ability of the periodontal microbes (Chi et al., 2019).

3.3 | Silver nanoparticles

Research on AgNPs has developed an arising area recently. A major reason for this outgrowth is that AgNPs can be synthesized by mediating their growth process and nucleation by utilizing various synthetic reagents. Second, with molecular capping agents, silver NPs can be functionalized explicitly, such as chemical and proteins groups. Third, AgNPs have a powerful antimicrobial influence that increases clinical therapy results (Schmalz et al., 2017). The purpose of this review is to introduce a new sequence of the electro-spun nano-fibrous scaffolds for the application of the GTR membrane. These nanofibers are constructed on either a mixture of the poly(caprolactone) (PCL), polylactic acid (PLA), and cellulose acetate (CA) polymers. Moreover, various concentrations of hydroxyapatite nanoparticles and the green-synthesized (AgNPs) were fused into the scaffolds to increase their bone regeneration and antibacterial action (Figure 5). The resultant NPs in nanofibrous scaffolds were projected for their antibacterial mechanism, cell feasibility, regenerative capability for the tissue, and physicochemical properties. The purpose of this methodology is to fabricate efficient and simple GTR/GBR scaffolds having biodegradable, antibacterial, and osteo-conductive properties (Abdelaziz et al., 2020).

Therefore, homogenous AgNPs with morphology, well-ordered size, and function can be considered as multifunctional particles in various periodontal regenerations. AgNPs can be mixed with acrylic for irrigating solution, titanium coating in dental graft treatment, preparation of detachable dentures in prosthetic action, and composite resin for direct renovation (Yin et al., 2020). Moreover, due to the capability to deliver the silver ions, AgNPs can kill germs (Schmalz et al., 2017; Yin et al., 2020). The features of the GTR/GBR scaffolds can vary considerably depending upon their morphology and fabrication. Moreover, the porosity of scaffolds is a significant factor influencing the regeneration process. Periodontitis is a widespread acute infectious disease produced by different categories of microbes. Through the biofilm and suppression of inflammation, a sufficient contamination mechanism is necessary for periodontal therapy (Halkai et al., 2017; Yin et al., 2020). Silver nanoparticles in comparison with

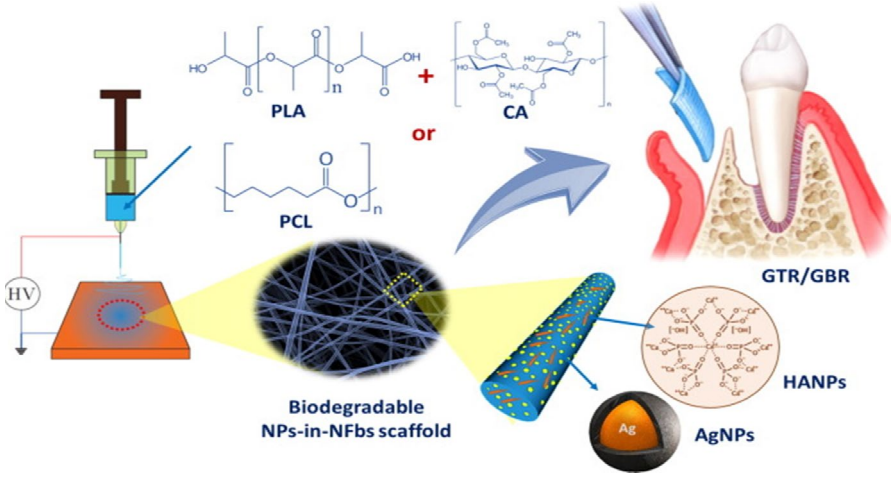

FIGURE 5 Schematic representation of the development of a novel sequence of electro-spun nanoparticles in nanofibrous GBR/GTR scaffolds for improved bone regeneration and antibacterial activity (Abdelaziz et al., 2020)

traditional antibiotics contain antibacterial applications without the development of bacterial resistance (Alam & Al Riyami, 2018; Yin et al., 2020). When combined with antibiotics, Ag NPs considerably increase antibacterial mechanisms. Significantly, inactive antibiotics store a high antimicrobial action toward the bacterial strength when they combine with AgNPs (Alam & Al Riyami, 2018; Yin et al., 2020).

Ag NPs prepared using appropriate topping molecules that can stimulate the prevention influence against bacterial species that mainly are a reason of periodontal inflammations. Against oral anaerobic pathogenic bacteria, micro-sized AgNPs showed greater antimicrobial application. GTR membrane with (AgNPs) decreased the dispersion of the bacteria and adherence, the action of intrabony flaws utilizing GTR membrane with silver NPs can progress the clinical treatment(Chi et al., 2019). AgNPs were described to contains an antimicrobial influence, by growth factors (Singh et al., 2018). To treat gingival wounds, periodontal treatment coated with AgNPs can be applied (Prasetyo et al., 2019; Yin et al., 2020). AgNPs can be mixed with acrylic resin to stop the development of pathogenic bacterial species like *Staphylococcus aureus*, *E*. coli, and *Streptococcus mutants* (de Castro et al., 2018; Yin et al., 2020). Some researchers are worried about the toxic behavior of AgNPs. The toxic behavior of AgNPs and antibacterial properties are not been fully understood up till now. Many researchers consider that AgNPs can frequently discharge Ag ions to kill microorganisms. With AgNPs, a growing amount of periodontal resources are being established for periodontal, prosthetic, endodontic, restorative, implant, and orthodontic therapy. Various laboratory analyses described that AgNPs have adverse effect on cells of human body. However, the clinical importance of the possible poisonousness of Ag NPs remains unidentified. Additional surveys are necessary because scientific suggestion is quiet inadequate (Yin et al., 2020). Novel multilayered membranes have gained wide consideration and perform huge impacts on tissue regeneration (Lu et al., 2016; Silva et al., 2014; Zhang et al., 2020). Multilayered functional materials loaded with nano-hydroxyapatite were formed to stimulate the bone and tissue regeneration process (Bottino et al., 2011; Zhang et al., 2020). Scaffolds loaded with drugs inhibited periodontal inflammation and eliminated pathogenic micro-biota (Farooq et al., 2015). So, the films with the new structures, which express hemostatic properties and effective biological functions, have expected inadequate attraction. Polycaprolactone (PCL) is a linear, resorbable aliphatic polyester and semicrystalline, extensively utilized in the tissue regeneration process because of its outstanding biocompatibility and mechanical strength (Farooq et al., 2015; Zhang et al., 2020). According to the literature, the minor leak on restoration margins offers cavities for the settlement by oral microbes, resultant in the secondary caries.

This causes the healing failure and requirement for the renovation replacement. Issues can be avoided by a combination of antibacterial sources like silver nanoparticles to the adhesive method and composite resign (Figure 6). Data show that the silver nanoparticles incorporated into the composite resins do not affect its biological and mechanical strength and give important antibacterial activity, at a small concentration. Therefore, the rate of development of recurrent caries under composite resins due to minor leaks can be decreased by the antimicrobial results of the silver nanoparticles holding healing substances. Therefore, the accumulation of the various biodegradable materials can benefit to progress these deficits. Gelatin is a natural ecofriendly polymer gained from the hydrolysis process of collagen (Ward & Courts, 1977). It is economical and highly biocompetible in biomedical fields and pharmaceuticals (Jiankang et al., 2009). Nevertheless, the fast degradation rate and the low mechanical properties prevent its long-lasting development. According to the previous knowledge, mixed GEL (PG) with composite materials of PCL can attain the balancing benefits. The composite scaffolds can recognize favorable mechanical strength hydrophilicity and appropriate degradation process. A natural polysaccharides chitosan is utilized in various clinical applications, involving wound healing, nerve regeneration, and bone repairing (Jiankang et al., 2009; Naqvi et. al., 2020). CS has good biocompatibility, minimal host immune rejection, an antibacterial effect on oral pathogens, and biodegradation,(Dimartino et al., 2005; Rabea et al., 2003). Besides, CS improved cell adhesion (Sogias et al., 2008), differentiation of fibroblast, keratinocytes, and endothelial cells (Tchemtchoua et al., 2011). Previous data revealed that chitosan made positive ions and networked with negative ions on RBCs; furthermore, it stimulates platelets and attains adequate hemostasis (Vickers, 2017). Electrospinning due to resourceful and effective protocol has been widely employed in dental regeneration (Cui et al., 2010). Electrospinning fibers can produce bioactive materials that can stimulate the extracellular matrix (ECM) to support the adhesion of cells and structural arrangement (Li, Sharama, et al., 2009). The electrospinning procedure has recently proved colossal potential in GTR/GBR applications (Qasim et al., 2017).

3.4 | Nanoparticles of amorphous calcium phosphate

Besides the antimicrobial agents, nanoparticles of amorphous calcium phosphate were also played an important

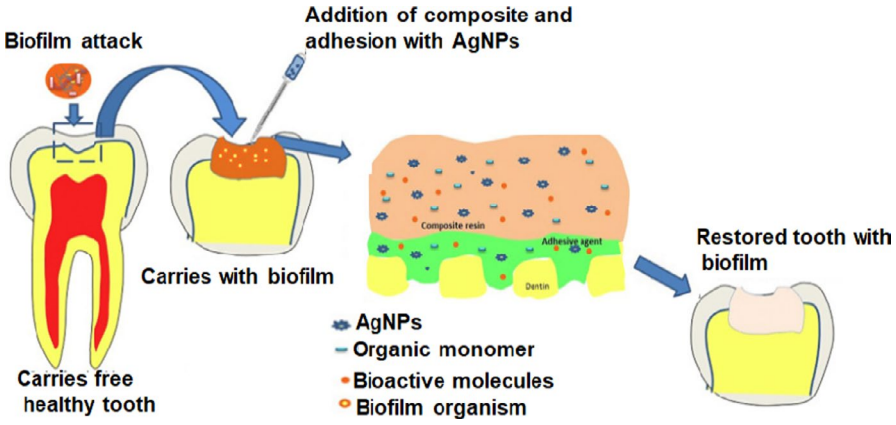

FIGURE 6 Addition of silver nanoparticles to the adhesive system eliminates the biofilm organisms and inhibits the decay of tooth structure. It avoids microleakage, enhancing the durability of the restoration (Bapat et al., 2018)

role (Al-Dulaijan et al., 2018; Melo et al., 2013), while the NACP composite having small antimicrobial action was "active" and at a cariogenic low pH could remarkably enhance the P and Ca ion release, when these ions were mostly required to stop caries (Xu et al., 2011). Previously reported that NACP nanocomposites were remarkably re-mineralized and attained enamel lesions efficiency that was fourfold larger than that of a commercial fluoride-releasing control (Weir et al., 2012). According to previous study nanoparticles of amorphous calcium, phosphate composite could be revived frequently with phosphorus and calcium ions, which confirmed that it could constantly discharge calcium and phosphorus ions to suggest a long-lasting process of remineralization (Zhang et al., 2016). These ions form the complex are estimated to protect the root structures, support re-mineralize tooth roots, neutralize biofilm acids, and reduce root sensitivity (Chi et al., 2019).

3.5 | Nanoparticles of magnesium oxide NPs (nMgO)

In biomedical applications, recently magnesium oxide NPs (nMgO) have attained growing attention because of their multifold advantages including osteoinductivity and superior antibacterial activity. Because in the body, nMgO nanoparticles can be feasibly metabolized, it might have a huge capacity for orthopedic procedures (He et al., 2020; Liang et al., 2020).

3.6 | Mesoporous silica nanoparticles

Among numerous nano-carriers, mesoporous silica nanoparticles (MSNs) possess larger pores thus confirmed to carry excellent biocompatibility, (Xu et al., 2014) good protein carrying capability, (Xu et al., 2015) and excellent bioactivity maintenance (Xu et al., 2020). MSNs with large pores can hold a large number of proteins (Kao et al., 2014). Still, very little literature is available upon electrospinning membranes using MSNs with polymers and larger pores with twofold function (Xu et al., 2020). In the current scenario, synthesis of a membrane having dual-delivery capabilities and a peapod-like structure based on larger-pore MSNs-embedded core-shell nanofibers to instantaneously distribute antibiotics (gentamicin) and for GTR is discussed.

Functionalized MSNs with huge pores are used for encapsulation of large amounts of GFs and maintain their biocompatibility properties. With the coaxial electrospinning, an antibiotic-loaded polymer solution is utilized as a shell and an rhBMP-2-loaded MSNs solution is used as the core. Using the BMSCs regeneration ability biocompatibility is evaluated, and the antibacterial activity is analyzed against multi-resistant bacterial species. Core mesoporous silica nanoparticles provide a smart approach to reserve the biocompatibility of the drugs & GFs and the antibiotic with a rational arrangement (Xu et al., 2020).

3.7 | Zinc oxide (ZnO) nanoparticles

Zinc oxide nanoparticles (ZnO-NPs) are “usually known as save” by the food and drug administration (FDA) and have verified antimicrobial action toward a broad range of bacteria, involving antibiotic-resistant strains. Research accompanied by Münchow *et al*. described the antimicrobial efficiency of the PCL-Gel polymeric electro-spun membranes loaded with zinc oxide nanoparticles toward two bacterial species; their effects indicated strong prevention of the microbe's progression utilizing zinc oxide nanoparticles ratios of 5, 15, and 30 wt% (relative to the total polymer weight) and comparatively effective biocompatibility utilizing human dental pulp stem cells. But, although the antimicrobial strength of the NPs is favorable healing mediators, there are still problems concerning the probable long-lasting effect produced by an extreme delivery of the nanoparticles into human cells. To report this, a fabricated electrospun composite fiber of Gel loaded with zinc oxide nanoparticles (PCL-G-Zn membranes) and PCL at lower concentrations (1, 3, and 6 wt.%) using

TABLE 2 List of commercially available GTR/GBR membranes

Commercial membranes	Properties
Core- Tex	excellent space maintainer Comparatively rigid; controlling
High-density Gore-Tex	Permeability of smaller than 0.3 microns produces impermeable block to bacterial species
Cytoplast® TXT−200	High-density polytetrafluoroethylene (d-PTFE
Cytoplast® Ti−250	Titanium-reinforced high-density PTFE
Resolut LT®	Poly-dl-lactic/co-glycolic acid
Vicryl®	Polyglycolide/polylactide (9:1, w/w)
Atrisorb®	Poly-dl-lactide and solvent (N-methyl−2-pyrrolidone)
AlloDerm®	Collagen class-I resultant from human membrane
Bio-Gide®	Collagen derivative from swinish membrane
BioMend Extend®	Collagen Type-I derived from bovine tendon

the acetic acid as the sole solvent for making the electrospinning solution, trying to develop the biodegradable, biocompatible, and mechanically stable membranes with antibacterial strength and the lesser NPs concentrations. The thermal properties, water wettability, mechanical, and degradation properties of the PCLG- Zn membranes were analyzed in terms of their elemental chemical structure, morphology, and atomic structure. The capability of the PCL-G-Zn membranes to prevent bacterial biofilm creation and the planktonic bacterial growth against *S aureus* was examined. The capability of the membranes to withstand periodontal cell viability was assessed, showing human osteoblasts (hFOB) and gingival fibroblast (hGF-1) to the emitted products from membranes(Prado-Prone et al., 2020). Detail list of commercially available membranes with their properties is recorded in Table 2.

4 | CONCLUSION AND FUTURE PROSPECTS

Periodontitis is a chronic infectious syndrome that needs efficient therapies for biomedical applications. GTR is a favorable technique to stimulate the difficult regeneration of the tooth-supporting tissues. Present commercial GTR membranes are not able to provide appropriate beneficial effects and showed distinctive drawbacks, like low mechanical strength, less capability in stimulating the hierarchical periodontal regeneration process, and the inappropriate degradation rate, *etc*. Novel GTR membranes require three major desires to encounter clinical properties: (a) proper degradation, biocompatibility, and mechanical strength; (b) organized PDL regeneration activity and optimized alveolar bone; and (c) antibacterial activity. Appropriate additives and biopolymers should be designated to pledge their outstanding biocompatibility. Moreover, additives and biopolymers in appropriate ratios make it promising to control the degradation frequency of the membrane.

Synthetic polymers bearing good mechanical strength and natural polymers with good biomedical applications and electro-spun ability can be mixed to make good utilization of mutual benefits. The ability to stimulate periodontal regeneration is an important property necessary for guided tissue regeneration membranes. Electro-spun nanofibers, with the intrinsic capability to stimulate natural ECM, work outstandingly in persuading osteo differentiation. Carbon-based MWNTs and inorganic ceramics are supposed to provide tissue regeneration, which is feasible to improve the mechanical application at the same time. Moreover, efficient biomaterials, *that is*, GFs and proteins are also used to stimulate degenerative mechanisms. Inflammation is reflected as the main aspect involving GTR adversity in clinical employment. Adding multiple drugs develops the anti-inflammatory environment instantaneously and facilitates periodontal regeneration. Till now, different drugs and functional proteins like AMPs, NSAIDs, metal nanoparticles like the AgNPs, and the oxide components like ZnO, have been combined into electro-spun nanofibers to create an ideal anti-inflammatory environment and inhibit bacterial growth. To keep the control of the drugs release and the bioactivity, polymer-based factors involving, the weight of the component and polymer, and drugs-based factors involving drug loadings, the crystallinity of drugs and molecular weight should be considered in thought. With the progressively extensive use of antibiotics in the clinical stage, bacteria resisting property has come to be a prodigious challenge in microbial prevention; thus, it is necessary to search for further kinds of drugs to control periodontal inflammation efficiently and decrease bacterial resistance. Growth factors reduce rapidly in vivo which strictly reduces their clinical efficacy. Based on electro-spun nanofibers, the

release of the macromolecules is not required. To form efficient means for convenient liberation of GFs, and even apprehend the temporally distinctive discharge in the target period during the regeneration procedure, electrospinning techniques can be joined with other methodologies.

In periodontal tissue engineering, the stem cells like PDLCs play an essential part. The deficiency of sufficient thriving stem cells is the foremost reason involving the inability of spontaneous regeneration of dental cells. Stem cells can be cultured on a scaffold in vitro and then incorporated in damaged positions to impart adequate precursors for periodontal regeneration by employing tissue-engineering protocol. However, the basis of stem cells, the in vitro culture state, clinical effects, and the feasibility of stem cells are thought provoking for their clinical uses. The next stage is to choose appropriate stem cells and growth factors discover suitable amounts in scaffolds and enhance the feasibility of these stem cells for optimum periodontium regeneration.

5 | LITERATURE STATISTICS

The data sources are PubMed and google scholars. Whereever we used the graphics in the review article (if it is a complete figure or some part), prior permission was obtained through email from corresponding author or cited the reference.

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AUTHOR CONTRIBUTIONS

SUH, BB, and MSN collected and assimilated the literature from PubMed and Google search engines. SUH, SARN, ZA, SN, and NM drafted the manuscript for final submission. BA and AM help in revision.

COMPLIANCE WITH ETHICAL STANDARDS

Consent to participate and to publish.

DATA AVAILABILITY STATEMENT

All the cited literature will be made available upon request.

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