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Review Article

Materials advances in GTR membrane: A comprehensive review



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الملخص

يُعدّ تجديد الأنسجة الموجّه جزءا هاما من علاج أمراض اللثة. ويستخدم أغشية حاجزية لتوجيه تجديد بنى اللثة المفقودة بشكل انتقائي. وتعتمد فعالية تجديد الأنسجة الموجّه بشكل أساسي على الخصائص الطبيعية للمواد المكونة لهذه الأغشية. تستعرض هذه المراجعة تطور مواد الأغشية، بدءًا من الأنواع التقليدية غير القابلة للامتصاص وصولاً إلى البوليمرات والمركبات الحديثة القابلة للامتصاص الحيوي. وينصبّ التركيز بشكل كبير على التقنيات الجديدة التي تهدف إلى تحسين النتائج السريرية. وتشمل هذه التقنيات تطوير سقالات نانوية ليفية مغزولة كهربائيا، وإضافة عوامل حيوية فعّالة مثل مضادات الميكروبات (مثل الجسيمات النانوية المعدنية) وعوامل النمو لتسهيل الشفاء ومنع العدوى. في الختام، على الرغم من أن المواد الحالية قد حسّنت من إمكانية التنبؤ بالتجدد، إلا أن مستقبل تجديد الأنسجة الموجّه يعتمد على تطوير أغشية ذكية متعددة الوظائف توفر حاجزا فيزيائيا وبيئة حيوية فعّالة مُتحكّم بها لتنظيم عملية الشفاء بدقة.

الكلمات المفتاحية: تجديد الأنسجة الموجّه؛ مواد نانوية؛ النشاط الحيوي؛ الامتصاص

Abstract

Guided Tissue Regeneration (GTR) is an important part of periodontal therapy. It uses barrier membranes to selectively direct the regeneration of lost periodontal structures. The effectiveness of GTR is mainly based on the natural properties of the materials that make up these membranes. This review examines the evolution of membrane materials, transitioning from traditional non-resorbable types to contemporary bioresorbable polymers and composites. A big focus is on new technologies that are meant to improve clinical outcomes. These involve the development of electrospun nanofibrous scaffolds and the incorporation of bioactive agents such as antimicrobials (e.g., metallic nanoparticles) and growth factors to facilitate healing and prevent infection. In conclusion, while current materials have improved the predictability of regeneration, the future of GTR relies on the development of intelligent, multifunctional membranes that provide both a physical barrier and a controlled bioactive environment to precisely orchestrate the healing process.

Keywords: Bioactivity; GTR membrane; Nanomaterials; Resorption

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Impact Statement

The research on guided tissue regeneration (GTR) membranes holds significant importance in the field of regenerative medicine and dentistry. This review advances existing knowledge by emphasizing the natural properties of membrane materials and their influence on tissue regeneration effectiveness. By analyzing recent innovations in bioresorbable polymers, composites, and the integration of bioactive agents such as antimicrobials and growth factors, this study provides a comprehensive understanding of how these materials enhance clinical outcomes. The insights gained contribute to the development of more biocompatible and multifunctional GTR membranes that optimize the healing process, reduce complications, and improve predictability in periodontal and bone regeneration procedures. Ultimately, this research supports the evolution of advanced biomaterial designs that can lead to better patient outcomes and more reliable regenerative treatments.

Introduction

The restoration of maxillofacial and alveolar tissues after traumatic injury, tumor resection, or periodontal disease represents a significant challenge in clinical dentistry. These defects often result in both functional and aesthetic compromises, affecting the overall quality of life of patients. The most recent estimate from the Centres for Disease Control and Prevention (CDC) says that 47.2% of persons 30 years and older in the U.S. have some type of periodontal disease. Periodontal disease becomes more prevalent with advancing age, affecting 70.1% of persons aged 65 and older.[1] Periodontitis an inflammation of periodontium is characterised by the degradation of alveolar bone, periodontal ligament, cementum and gingiva as a reaction of bacterial buildup. It cause inflammation of soft tissues along with progressive, irreversible bone loss potentially leading to tooth loss and implant failure in the presence of bone abnormalities.[2] Periodontium, in optimal conditions tend to restore a functioning and harmonious periodontium, ensuring the restoration of alveolar bone, reconstruction of cementum, and reattachment of the periodontal ligament. However, attaining this intricate rebuilding needs a carefully coordinated process that encourages the regeneration of certain tissues while limiting the invasion of undesirable cells, notably epithelial cells, which can inhibit bone and ligament repair.[3]

Periodontium is a specialized tissue complex which plays critical role in oral health maintenance. it is composed of alveolar bone, periodontal ligament, cementum, and gingival epithelium, which interact dynamically to support tooth stability and function.[4] This intricate structure may be undermined by specific pathological conditions, including periodontitis, trauma, or tumor-associated resections, resulting in tooth loss and requiring advanced regenerative therapies.[5] Melcher was the first to propose guided tissue regeneration for the treatment of periodontal defects.[6] The idea of guided tissue regeneration membrane is based on the use of such a partially permeable membrane that restricts the movement of unwanted epithelial and gingival connective tissue into the healing site and allows the entry of periodontal and osteogenic cells to repopulate and regenerate alveolar bone and cementum.[7]

To achieve clinical acceptable regenerative outcome an ideal GTR membrane should possess properties such as biocompatibility, non-cytotoxicity and high tissue tolerance. Recent progress in GTR membrane technology has focused on combining the biological and mechanical characteristics of these membranes to enhance clinical results. Innovations have led to the formation of such composite membranes that use both natural and synthetic materials, as well as antimicrobial agents and growth factors. Such composite membranes facilitate tissue healing and prevent infection of healing sites.[8] Farman et al. (2023) fabricated a composite GTR membrane utilizing eggshell powder, polylactic acid, and polyethylene glycol, exhibiting favorable mechanical properties and biocompatibility for periodontal applications.[9]

The incorporation of antimicrobial agents into GTR membranes also play a crucial role in effective postoperative healing and infection prevention.[10] It has been confirmed from different studies that the integration of substances such as zinc oxide nanoparticles and lignin into membrane materials can confer antimicrobial characteristics. Bilal et al. discovered that lignin-based membranes effectively impede bacterial proliferation, thereby reducing the risk of infection in periodontal anomalies.[11]

Furthermore, researchers have also studied the incorporation of growth factor into the GTR membrane and found that it has the ability to enhance tissue healing. Different growth factors including morphogenic proteins stimulate the proliferation and differentiation of cells involved in tissue repair. Consequently, the incorporation of these growth factors in GTR membranes facilitate the continuous release at the defect site, thereby enhancing tissue regeneration. Mirzaeei et al. in his research assessed the impact of growth factor-loaded membranes in guided tissue regeneration (GTR), highlighting the capacity of growth factors to accelerate periodontal tissue regeneration.[12]

In recent years, increasing emphasis has been placed on sustainability-driven biomaterial development in periodontal regeneration, particularly through the utilization of bio-derived and waste-origin materials. Emerging evidence demonstrates that naturally sourced hydroxyapatite derived from fish bone, camel bone waste, eggshells and other biogenic residues may provide a sustainable alternative to synthetic ceramics while retaining favorable osteoconductivity and bioactive characteristics.[13–15] These materials not only support circular bio economy principles but also exhibit nanoscale architecture and ionic compositions resembling native bone mineral, enhancing their regenerative potential. Recent investigations have additionally explored graphene-based reinforcement and bioactive peptide functionalization of such materials to further improve osteogenesis, antimicrobial function and cell signaling, expanding the concept of GTR membranes from passive barriers to instructive regenerative platforms.[8,16]

Despite extensive literature on guided tissue regeneration membranes, most existing reviews focus either on conventional material classifications or isolated modification strategies, with limited integration of multifunctional bioactive systems, sustainability-driven biomaterials and translational challenges. The novelty of the present review lies in critically synthesizing conventional, advanced and emerging GTR membrane materials within a unified framework encompassing composition, functionalization strategies, regenerative performance and translational potential. In addition, this review identifies persisting knowledge gaps and future research priorities for development of next-generation clinically translatable membranes.

Materials and methods

This narrative review was conducted to explore the recent progress done in guided tissue regeneration (GTR) therapy for periodontal issues. A comprehensive literature search was done using different search engines such as PubMed, Scopus, Google Scholar, and Web of Science. Recent publications done from 2020 to 2025 were mainly focused. The keywords used were new GTR membranes made from materials like PLA, PCL, collagen, and bioactive substances, as well as ways to make them, such as electrospinning and 3D printing. The review encompassed in vitro, in vivo, and clinical studies evaluating mechanical properties, biocompatibility, and regenerative outcomes. The main findings obtained from the selected studies were combined to underscore emerging trends in membrane design, including antimicrobial properties, hydrogel-based membranes, and nanofiber technologies. Methodology of the relevant studies was evaluated for reproducibility. The review gives a full look at the latest developments in GTR membranes and points out areas for future research to make periodontal regeneration better.

A historical perspective on periodontal regeneration techniques

In 1970's for the first time after periodontal surgery a physical barrier was placed along the root surface in order to restrict epithelial down growth.[17] Before this innovation, clinicians employed two primary treatment modalities: free palatal grafts harvested from the patient and bone grafts as tabulated in Table 1 (autologous, allogenic, or synthetic) placed into the periodontal defect.[17,18] However, both of these treatment modalities demonstrated limited success in achieving true periodontal regeneration, with clinical outcomes typically restricted to periodontal healing characterized by long junctional epithelium formation rather than actual regeneration of lost periodontal tissues.

Subsequent analysis of clinical and preclinical evidence led to the hypothesis that the primary limitation of these early techniques was the absence of compartmentalization between the periodontal defect and the surrounding soft tissues. This deficiency permitted non-osteogenic and rapidly proliferating epithelial and connective tissue cells to repopulate the defect site preferentially, thereby impeding the regenerative process. Addressing this biological challenge, a series of seminal studies by Nyman et al. introduced the concept of guided tissue regeneration (GTR), a technique founded on the principle of selective cell repopulation. This innovation aimed to exclude undesired cell types while allowing cells with regenerative potential—principally from the periodontal ligament, alveolar bone, and cementum—to repopulate the defect, thus promoting true periodontal regeneration.[19]

Recent advances include hydrogels and electro spun nano fibrous membranes as promising GTR scaffolds that replicate the extracellular matrix and support bioactive compound delivery[10,20](Figure 1). Electrospun nanofibrous

Table 1: Grafts and their uses.

Type	Source	Advantages	Limitations
Autograft	Patient's own tissue	Possesses osteogenic, osteoinductive, and osteoconductive properties; no risk of immunological rejection as it contains viable cells and biological matrices.	Associated with donor site morbidity, limited quantity of available bone, and relatively fast resorption.
Allograft	**From another human donor**		
Demineralised freeze-dried bone allograft (DFDBA)	Processed human bone	Exhibits osteoinductive and osteoconductive capabilities.	Risk of infection transmission and immune reaction.
Freeze-dried bone allograft (FDBA)	Processed human bone	Provides osteoinductive and osteoconductive benefits.	Potential for immunological rejection and infection.
Xenograft	Bone derived from other species (commonly bovine)	Primarily osteoconductive, providing a scaffold for new bone growth.	Risk of immunogenic response and possible infection; may be slowly resorbing or non-resorbable.
Alloplast	**Synthetic materials**		
Sintered hydroxyapatite (HA)	Laboratory-synthesised calcium phosphate	Osteoconductive scaffold supporting bone regeneration.	Tends to resorb slowly or may remain indefinitely.
β-Tricalcium phosphate (β-TCP)	Synthetic ceramic	Offers osteoconductive properties.	Undergoes rapid resorption, which may outpace new bone formation.
Natural-based products (e.g., coral, chitosan)	Naturally derived biomaterials	Provide osteoconductivity with minimal immunogenicity.	Often exhibit slow resorption or may not resorb completely.

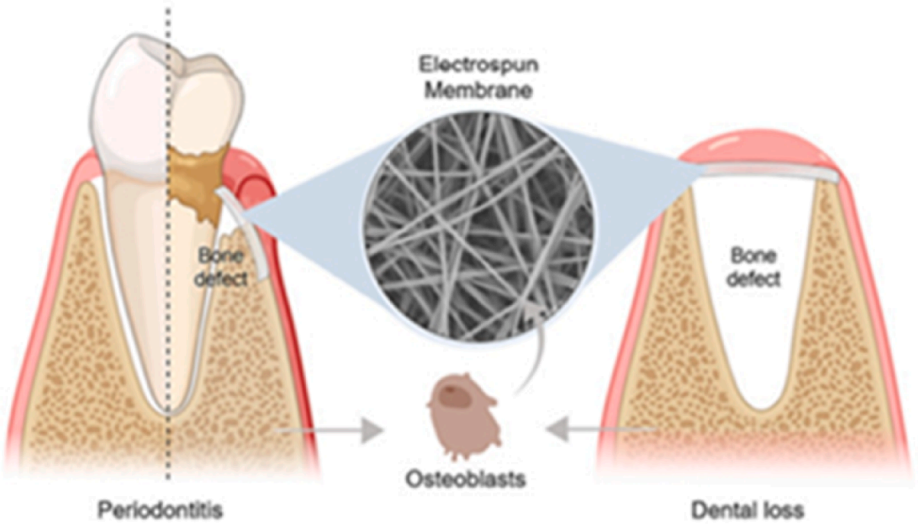


Figure 1: Electrospun membrane[36].

membranes show resemblance to the extracellular matrix with enhanced biocompatibility and controlled porosity, thereby promoting cell adhesion and proliferation. In addition to their barrier function, these membranes perform multifunctional drug delivery when combined with antimicrobial, anti-inflammatory, and osteoinductive agents, significantly promoting regeneration along with controlled drug-delivery.[20,21]

Guided regeneration therapy

The prime objective of periodontal regeneration is to re-establish a functional periodontal attachment apparatus, including newly formed cementum with inserting periodontal ligament (PDL) fibres, alongside alveolar bone regeneration. To achieve this, two primary surgical techniques have been employed: Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR).[22] The theoretical foundation for periodontal regenerative procedures was introduced in the late 1980s by Nyman et al. (1990), building upon Melcher's hypothesis, which proposed that the outcome of periodontal wound healing depends on the type of cells that first repopulate the root surface. True periodontal regeneration can be achieved if regenerative cells from the alveolar bone or the periodontal ligament (PDL), are directed specifically to the site of defect.[6,19]

Numerous studies involving humans and animals have validated this theory, affirming the core principles of the directed regeneration technique. GTR therapy involves the application of a biocompatible membrane over the periodontal defect. This membrane helps in permeation of precursor cells from residual PDL, alveolar bone or vascular supply restoring the periodontal structure and restricting the quick growth of gingival epithelium and connective tissue into the defect area.[5,17]

Guided Bone Regeneration (GBR) involves similar method as GTR but differ in way that they are used for repairing the alveolar bone defects, especially before or during the placement of dental implants.[5,17] Like GTR, GBR helps new bone grow by using a membrane to keep soft tissue from invading the bone defect. This method is also used to repair furcation defects, intrabony lesions, and to maintain alveolar ridges after tooth extractions. Depending on the particular therapeutic scenario, either resorbable or non-resorbable membranes may be utilized in GBR. The goal of both GTR and GBR is to encourage the creation of new bone while re-establishing a new cementum with functionally orientated PDL fibers connected to the alveolar bone [5]These processes collectively demonstrate Melcher's theory that regenerative cells can actively aid in the regeneration of alveolar and periodontal tissues when they are directed to a problem site.[6]

Later, Gottlow et al. successfully used the technique on a broader group of patients, confirming the efficacy of these regenerative treatments.[23,24] Over the last three decades, several researches have rigorously verified the biological and theoretical foundations of GBR,with a plethora of clinical trials and detailed systematic reviews proving its clinical effectiveness.[25–27]

In contrast to traditional surgical techniques like open-flap debridement, which is usually employed to treat intrabony defects and mild to moderate furcation involvements, guided regeneration procedures provide significant advantages in terms of maintaining alveolar bone and fostering periodontal regeneration.[17,28,29] Bone augmentation procedures also make dental prostheses, like implants and permanent dentures, work better and look better. They also fix contour problems that happen when teeth are lost and phonetic issues caused by gaps formed between prosthesis and gingival tissue.[17,30]

Biologic principles of guided tissue regeneration therapy

The success of tissue engineering depends upon certain essential biological components, including a supportive biomaterial scaffold, adequate vascularization, a sufficient supply of progenitor cells, and the presence of regulatory signals in appropriate quantities and patterns.[31,32] Cells having external stimulus like growth factors and morphogens contribute primarily in the development and differentiation

of new tissues through proliferation and production of matrix.[33] Angiogenic signals facilitate new vascular networks that are necessary for supplying nutrients and maintaining the regenerated tissue.[34] Furthermore, three-dimensional structure of biomaterial scaffolds is essential for guiding tissue organization and cell migration.[17,35] In this context, the microstructural characteristics of scaffolds—including porosity, pore size, and mechanical properties—are equally important, as they directly influence cellular adhesion, proliferation, migration, and differentiation, thereby enhancing regenerative outcomes.[36]

The wound healing process after periodontal surgery completes in thress stages typically similar to other incisional wounds. Firstly, a fibrin clot develops around the flap's edge and the root surface which is later on replaced by a connective tissue matrix attaching itself to the root surface. Instead of a desired connective tissue attachment, a lengthy junctional epithelial attachment may form if the fibrin clot's tensile strength is prematurely exceeded.[17,37–39] Because of the involvement of several specialized cell types, avascular root surfaces, a variety of microbial flora, and intricate stromal–cellular interactions, periodontal wound healing is intrinsically more difficult than soft tissue healing elsewhere.[40] The application of guided tissue regeneration membranes addresses this complexity by acting as a selective barrier, preventing rapid epithelial downgrowth and favouring repopulation of the defect by slower-growing periodontal ligament and bone cells, thereby promoting true regeneration rather than repair.[17,38]

Once a barrier membrane is placed plasma proteins quickly adsorb onto the tissue membrane interface, facilitating the accumulation of precurssor cells and growth factors that are necessary for tissue healing.[5] This protein-rich environment supports selective cell recruitment, particularly of periodontal ligament-derived progenitor cells and osteogenic cells, thereby initiating organised tissue regeneration. Additionally, membrane bioactivity can be enhanced through the incorporation of functional components such as nanofillers and composite materials, which improve cellular responses and promote osteogenic differentiation.[36] For instance, multifunctional membranes incorporating antibacterial and osteogenic agents have demonstrated the ability to simultaneously inhibit microbial colonisation and enhance both soft and hard tissue regeneration.[41]

The clinical rationale for executing cortical perforations is supported by the fact that the majority of the vascularization within the protected location comes from arteries coming from bone marrow. These intramarrow penetrations increase the likelihood of effective bone regeneration by promoting bleeding, offering a framework for cellular migration, and facilitating the entry of osteogenic and angiogenic cells.[5,17,38] Adequate vascularisation is critical for sustaining regenerative processes, as it ensures nutrient delivery, waste removal, and overall tissue viability. Furthermore, recent advances such as asymmetric or Janus membranes provide differential surface functionalities, enabling selective promotion of desirable cell types while simultaneously inhibiting unwanted cell infiltration and bacterial contamination, thereby optimising the regenerative microenvironment.[42,43]

The mechanical properties and biodegradability of membranes are also carefully tailored to align with the kinetics of tissue healing. Strategies such as polymer blending and collagen cross-linking have been employed to prolong barrier function while maintaining biocompatibility and preventing adverse host responses.[44] Additionally, advanced fabrication techniques, including electrospinning of bioactive composite materials, have been utilised to enhance both mechanical strength and osteoinductive potential, further supporting periodontal regeneration.[45]

The exact identity of the effector cells in charge of periodontal regeneration is still up for discussion. Evidence reveals that in the presence of growth stimulus PDL-derived cells may undergo differentiation into cells that resemble cementoblasts or osteoblasts. Some other researches revealed that PDL cells have the ability to control mineral deposition and avoid unwanted ankylosis during regeneration.[46–48] On the other hand, numerous in vitro and in vivo investigations have found that PDL cells exhibit very little osteoblastic activity, primarily attributing cementum-like tissue development to osteoblasts.[49,50] These differenced might be caused by the intrinsic variability of PDL cell populations, differences in experimental setup, and the inability of in vitro models to accurately replicate in vivo settings. Despite these differences, there is a general agreement upon a fact that PDL cells are the primary regeneration cell source, with modest input from nearby bone cells.[17,38,47]

Requirements of GTR/GBR membrane

For a successful GTR/GBR treatment the barrier membrane used should meet a set of clinical and biological parameters that promote predictable tissue regeneration. These requirements obtained from considerable experimental and clinical research, can be summarized (Table 2) as follows:

Cell Exclusion: The fundamental role of membrane is to act as a barrier against unwanted epithelial and connective tissue cells by restricting their migration onto the defect site and allowing precursor cells with regenerative potential to colonise the area. This selective exclusion provides an optimal environment for bone and periodontal tissue repair[3]

Space Maintenance (Framework): Space preservation in critical in larger flaws. Rigid or semi-rigid frameworks are used in such clinical conditions to avoid the collapse of membrane into the defect. Bone graft materials can be used in conjunction with the membrane to offer extra structural support while preserving the necessary regeneration space.

Porosity: For proper cell migration, proliferation, and vascular infiltration ideal pore structure is required as the membrane's porosity has a direct effect on tissue integration and regeneration. A high-pore, linked architecture encourages cellular ingrowth while also controlling the exclusion of undesired cell types[51,52]

Degradation profile: The membrane should have degradation rate similar to the body's natural healing process, usually four to six weeks for soft tissue regeneration and longer for bone abnormalities. The membrane should ideally resorb completely after the healing is completed, leaving no byproducts behind which can impede tissue remodeling or trigger inflammatory reactions[53,54]

Stabilization: The membrane should stay firm in its place during healing. It should resist displacement caused through mechanical forces such as mastication, soft tissue movement

Table 2: Requirements of GTR/GBR membrane.

Membrane Property Requirement	Clinical Importance
Cell exclusion	Acts as physical barrier against epithelial and connective tissue cells while allowing precursor cells with regenerative potential to colonize the defect site. Provides optimal environment for bone and periodontal tissue repair.
Space maintenance (framework)	Rigid or semi-rigid structure prevents membrane collapse into larger defects. Maintains critical regeneration space for bone graft materials to provide structural support.
Biocompatibility	Non-cytotoxic material ensures integration with host tissues without inflammatory response or allergic reactions. Essential for predictable clinical outcomes.
Non-immunogenicity	Minimizes foreign body response and allows natural healing without immune compromise.
Appropriate resorption rate	Bioresorbable membranes must resorb synchronously with new tissue formation—premature resorption compromises barrier function; delayed resorption prolongs inflammation.
Permeability	Permits passage of nutrients and growth factors to regenerating tissue while maintaining barrier function against soft tissue ingrowth.
Mechanical strength	Sufficient rigidity to maintain space during healing; flexibility to adapt to defect contours without causing tissue damage.
Integration with grafts	Synergistic effect with bone graft materials enhances regenerative space maintenance and cellular repopulation.

or tension created by flap. To achieve stabilization certain fixation tools should be used that reduces the micro movements as well as maintain the membrane placement.

Clinical Manageability: The membrane must have sufficient physical properties to allow ease of handling, trimming, adaptation, and secure implantation within the surgical site. Clinical manageability is a critical factor influencing intraoperative efficiency and regeneration success, particularly in complex or constrained anatomical locations.

Biocompatibility: To reduce postoperative difficulties, the membrane must be biocompatible, with little to no inflammatory reaction. Any material that causes adverse reactions can risk the regenerative outcome, extend healing time, increase patient morbidity, and raise overall therapy costs.

Classification

Contemporary GTR membrane classification has now expanded beyond the traditional resorbable/non-resorbable dichotomy as it no longer captures the complexity of contemporary membrane system. Barrier membranes can be classified on the basis of.

1. Biodegradability
2. Sustainability and bio-derivation
3. Functional modifications

Classification based on biodegradability

Non-resorbable membranes

Non-resorbable membranes have been instrumental in the progression of guided tissue regeneration (GTR) and guided bone regeneration (GBR) methodologies, primarily serving as physical barriers that inhibit the swift migration of epithelial and connective tissue cells into periodontal and osseous defects, thus promoting the repopulation of the wound area by slower-growing regenerative cells, such as periodontal ligament and bone-forming cells.[55] Non-resorbable membranes, initially launched in the 1960s and 1970s, were engineered to mimic the physical properties of the substituted tissue while reducing host toxicity. In the 1982 experiments by Nyman et al., cellulose acetate was one of the first materials used in the form of Millipore bacterial-filter membranes; however, despite showing proof of concept, its toxicity made it unsuitable for clinical use.[5,56] Expanded polytetrafluoroethylene (e-PTFE) membranes were first used in the 1990s. Despite showing consistent regeneration results, e-PTFE had significant exposure rates and necessitated a second surgical excision. Dense PTFE (d-PTFE) membranes were created to solve these problems. Even when exposed, these provided acceptable bone repair, streamlined explantation, and enhanced microbiological resistance. Titanium mesh and titanium-reinforced e-PTFE and d-PTFE membranes were then added to improve the stiffness required for defect space maintenance. These, however, also presented difficulties in aesthetic zones and required further surgical retrieval. In GTR and GBR techniques, non-resorbable membranes, such as CA, e-PTFE, d-PTFE, and titanium-reinforced versions, have been frequently used. They enable slower-migrating regeneration cell types and act as effective barriers to soft tissue growth.[5,54]

i. Cellulose acetate

Cellulose acetate (Millipore®, Burlington, MA, USA), the pioneer synthetic membrane for guided tissue regeneration (GTR), derives from the acetylation of cellulose hydroxyl groups, yielding mono-, di-, or triacetate forms with acetyl ratios of approximately 29%−48%.[7] Built upon the promising traits of chemical inertness, thermal stability, high tensile strength, pliability, modest hydrophilicity, favorable tissue compatibility, economic viability, and biomass source, the polymer appeared ideal for periodontal use.[7,54] Following these characteristics, Nyman and coworkers (1982) tested cellulose acetate membranes to mechanically exclude epithelial and gingival fibroblast layers, thereby directing periodontal regeneration. Despite the rational foundation, clinical handling difficulties, casuistic cytotoxicity, and membrane breakage limited outcome reproducibility, ultimately excluding cellulose acetate from normal practice.[5] Attractive alternatives then

monopolized the field, including machined expanded and high-density polytetrafluoroethylene (e-PTFE and d-PTFE), which accommodate granular and titanium-backed configurations while possessing prolonged biostability and physical ductility, and are now uniformly regarded as the gold standard for guided regeneration protocols applied to periodontal and mandibular bone defects.[5,57]

ii. Expanded Polytetrafluoroethylene (ePTFE)

Expanded polytetrafluoroethylene (e-PTFE) is synthetic, bioinert polymer made composed of fluorine atoms joined to a lengthy carbon backbone, renowned for its exceptional biocompatibility and chemical stability in medical applications.[3] The distinctive structural design facilitates integration with bone and connective tissues at the peripheries of periodontal lesions, while effectively inhibiting the migration of gingival and epithelial connective tissue cells, rendering it a significant material in guided tissue regeneration (GTR) treatments.[58] The structure of e-PTFE membrane is dual-layered having open microstructure of thickness 1 mm with 90 % porosity and occlusal layer of thickness 0.15 mm with about 30% porosity. This dual layered structure provides balance between prevention of epithelial invasion and osteogenesis promotion.[7] Although e-PTFE got beneficial effects, but beside these effects these membranes have a dense barrier function which compromises the blood perfusion, leading towards periodontal complications such as early spontaneous gingivitis and gingival dehiscence.[59]

Different researchers have evaluated the clinical efficacy of e-PTFE membranes in regenerative therapies, particularly upon achieving primary closure. The 100−300 mm wide opening of microstructure membrane promotes the growth of collagen fibers and facilitate the easy transportation of essential nutrients, thus improving the mechanical stability and stimulation of new bone formation during early healing phase.[60] On the other hand, the occlusive component, which is distinguished by pore diameters smaller than 8 μm, serves as a strong barrier to prevent unwanted soft tissue cells from entering the bone regeneration site. A major disadvantage of e-PTFE membranes, however, is their comparatively high exposure rate, which has been estimated to be between 30 and 40 percent. This can lead to infection and fibrous tissue infiltration, ultimately jeopardising the results of bone regeneration.[54] Additionally, because they are not resorbable, they require a second surgical procedure to remove, which presents hazards such bacterial contamination and exposure of the newly produced bone, especially if the membrane is removed too soon or left in place for a long time.[61]

iii. Dense polytetrafluoroethylene (d-PTFE)

In order to overcome the drawbacks of expanded PTFE (e-PTFE) membranes, dense polytetrafluoroethylene (d-PTFE) membranes were created and first used in 1993. Even when exposed to the oral cavity, d-PTFE's 0.3 micron pore size inhibits microbial penetration while permitting the flow of oxygen and other tiny molecules that are necessary for healing. In spite of membrane exposure, this characteristic permits efficient bone repair. Furthermore, because of their low tissue adhesion, d-PTFE membranes are readily retrievable, simplifying post-operative care.[62] Clinically, they are useful for rapid implant placements, extensive bone defects, and alveolar ridge preservation, especially when tension-free primary closure cannot be achieved, protecting the mucogingival junction and soft tissue contouring. Nevertheless, drawbacks include a propensity to deform, decreased collagen synthesis, and elevated glycosaminoglycan buildup, all of which might postpone healing.[7]

Research has demonstrated that d-PTFE and e-PTFE membranes perform similarly in vertical bone augmentation and ridge preservation; however, d-PTFE has the advantage of being simpler to remove because of its non-adherent surface.[63] With pores smaller than 0.3 microns, its high-density structure allows it to be used in cases with severe ridge atrophy while lowering the possibility of graft contamination during membrane exposure.[3,62] Despite of these advantages, the stiffness of d-PTFE's might limit its flexibility under functional strain, while fixing it is a time consuming process. As a solution titanium foil membranes have been suggested, which provide better stiffness and surgical manageability.

iv. Titanium mesh and titanium foil

Titanium in a form of titanium foil or titanium mesh have been commonly used in non-resorbable GBR membranes. Titanium mesh is valued for its mechanical qualities, such as strength, stiffness, and flexibility. Primarily developed and used in 1960s for trauma patients titanium mesh was later modified for bone augmentation in dental implantology.[64] It is because of these qualities that titanium mesh is capable of promoting bone regeneration by conserving the area for osteogenesis and inhibiting bone resorption during the healing process.[65] In a recent study conducted by mateo et al. it was discovered that titanium mesh can promote considerable amount of bone gain, with an average horizontal bone increase of 4.95 ± 0.96 mm and a mean buccal plate thickness of 3.25 ± 0.46 mm after 12 months of follow-up. However, one major problem associated with titanium mesh is that the risk of infection and graft contamination increases when it's exposed.

Additionally, the stiffness and sharp edges of the mesh's may cause irritation of mucosa and may impede the healing process.[25] Similar advantages are provided by titanium foil, a prefabricated titanium mesh substitute that is more flexible and customizable, making it appropriate for massive ridge faults. It has been beneficial in terms of non-permeability and biocompatibility, which helps keep the graft material from becoming contaminated.[54] However, titanium foil membranes can be difficult to adjust and secure in place, much like titanium mesh, which could make the surgical treatment take longer. However, titanium foil has demonstrated encouraging outcomes in terms of bone regeneration and stability, with studies reporting success rates as high as 88.2%.[64]

Absorbable membrane
Natural membrane

i. Collagen

Collagen, a principal constituent of the natural extracellular matrix (ECM), plays a fundamental role in maintaining

tissue architecture, promoting angiogenesis, facilitating cellular adhesion, and modulating wound healing processes.[66] Collagen is a specialized cell that is synthesized by osteoblasts in bone and fibroblasts in connective tissues. It is suitable for use in bioresorbable guided tissue regeneration (GTR) and guided bone regeneration (GBR) membranes because of its intrinsic biocompatibility, low immunogenicity, intrinsic bioactivity, and complete biodegradability.[67] Commercially available collagen membranes are predominantly derived from type I collagen, or a combination of types I and III, extracted from human, bovine, or porcine tissues such as tendon, dermis, pericardium, and skin.[62] However, the mechanical stability and dimensional integrity required for therapeutic applications are intrinsically absent from original collagen. Numerous physical and chemical cross-linking methods, such as UV irradiation, glutaraldehyde, genipin, carbodiimide, and diphenylphosphorylazide, have been used to improve collagen's biomechanical characteristics and resistance to enzymatic degradation in order to overcome these constraints.[62,68] Although cross-linking successfully prolongs membrane resorption periods, research has shown that remaining chemical agents may be cytotoxic, which could cause inflammation, hinder tissue integration, and change vascularization.[3]

Collagen membranes have several biological disadvantages despite their many benefits, including as hemostasis, chemotactic activity for periodontal ligament fibroblasts, and the capacity to prevent epithelial down growth. Notably, their risk of spreading zoonotic diseases, erratic degradation profiles, and low space-making capacity in comparison to non-resorbable membranes have all been well studied.[62] Recent studies have focused on producing functionally graded, multilayered membranes boosted with bioactive agents such as calcium phosphate nanoparticles, electro spun fibers, growth factors, and antimicrobials (16−19). This will help make things stronger, control how quickly they break down, and stop bacteria from growing. Moreover, the amalgamation of collagen membrane with osteoconductive bone grafts exhibits a synergistic effect by maintaining the regenerative space and promoting cellular repopulation within the defective region.[62]

ii. Gelatin

Gelatin is a polymer that comes from nature and is made by partially hydrolyzing collagen. It has gotten a lot of attention in biomedical applications because it is easy to get and work with, is biocompatible, and doesn't cost much to immunize.[69,70] Gelatin is considered a good choice for guided tissue regeneration as it exhibits better biological properties such as increased cell adhesion, proliferation, and tissue integration.[71,72] Despite of these advantages gelatin has restricted use in clinical settings because it is fragile and unstable in humid environment. In order to overcome these limitations, improve its mechanical properties, and regulate degradation rates, various cross-linking methods have been employed, including chemical modifications utilizing glutaraldehyde, N-hydroxyl succinimide, and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.[3,69] Gelatin membranes even after cross-linking usually possess low Young's modulus under moist conditions, making it unsuitable for load-bearing uses in regenerative dentistry.[3]

Although cross-linking of gelatin has significantly improved the mechanical stability and integrity of gelatin membranes, the cytotoxicity of chemical cross-linkers and the material's limited capacity to facilitate angiogenesis and bone regeneration remain uncertain. These membranes exhibit significant elasticity but inadequate rigidity in humid clinical environments, thereby restricting their autonomous application in guided bone regeneration (GBR) and guided tissue regeneration (GTR) procedures (Figure 2).[3] To address these inherent disadvantages, novel strategies have been developed to integrate gelatin with other biodegradable synthetic polymers or bioactive compounds.[73]

iii. Chitosan

To overcome the mechanical constraints of collagen based membranes researchers have explored alternative natural polymers for GTR/GBR membranes and found chitosan (CS) as a material of choice. Originating from the deacetylation of chitin present in crab exoskeletons, CS demonstrates positive biocompatibility, suitable rates of degradation, superior antibacterial qualities, the ability to heal wounds, adaptability in damp conditions, and economic viability.[74,75] Like collagen membranes, chemical cross-linking can enhance its mechanical characteristics and degradation profile. After 16 weeks in vitro, genipin-cross-linked CS electrospun membranes notably showed improved tensile strength (165% higher) and much less degradation (22% vs. 34%) in comparison to their non-cross-linked counterparts.[76,77] According to these characteristics and its innate antibacterial activity, CS membranes may be clinically useful for GTR/GBR applications.[78,79] The FDA has not yet approved CS for clinical dentistry uses, thus there are still restrictions because there are no human clinical trials or regulatory approval.[3]

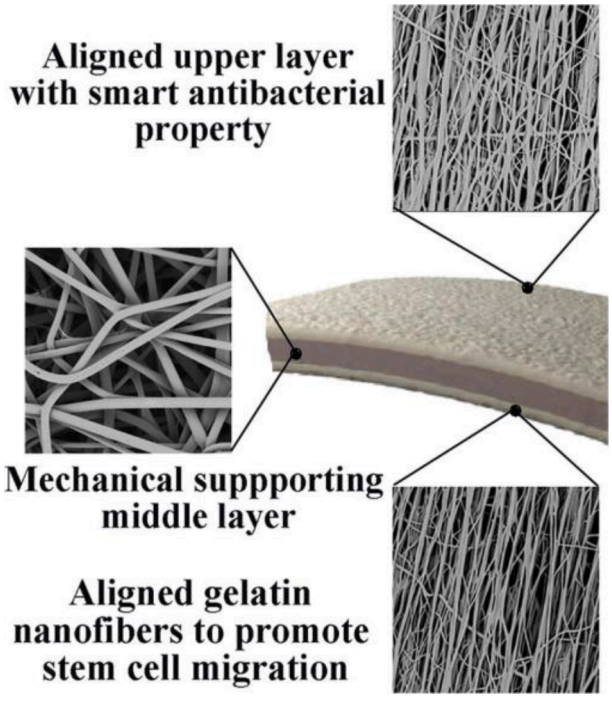


Figure 2: Modified gelatin based membrane[3].

Chitosan, a cationic, biodegradable, 1,4-linked 2-amino-2-deoxy-D-glucan polymer that is produced by deacetylating chitin, is valued for its antibacterial activity, osteoinductive potential, haemostatic properties, and biocompatibility.[80,81] Regardless of its inadequate mechanical strength and varying biodegradation rates, innovative production techniques such electrospinning and lyophilization have greatly enhanced its scaffold material performance.[82]

Synthetic. While synthetic polymers such as PCL, PLA, PGA, and PLGA exhibit promising physicochemical and biological properties in vitro and in preclinical models, their integration into clinical practice remains constrained. The majority of existing evidence is derived from laboratory-based or animal studies, with a relatively limited number of well-controlled human clinical trials assessing their long-term efficacy in GTR/GBR applications.

In clinical settings, synthetic polymer-based membranes have exhibited variable outcomes contingent upon their composition and structural design. Notably, PLA-based membranes have achieved moderate clinical success in periodontal regeneration, with results comparable to those of collagen membranes in specific indications. Conversely, polymers such as PCL, PGA, and PLGA are predominantly restricted to experimental or adjunctive applications due to limitations such as suboptimal degradation kinetics, inflammatory responses to acidic byproducts, and inadequate mechanical stability. Additionally, the absence of robust randomized controlled trials and long-term follow-up data constrains definitive conclusions regarding their clinical predictability.

Future research is increasingly focused on overcoming these limitations through the development of composite and multifunctional membranes. Strategies such as incorporation of bioactive ceramics, surface modification to enhance cell adhesion, and fabrication of bilayered or gradient structures aim to improve both biological performance and mechanical stability. Additionally, advances in additive manufacturing and controlled drug delivery systems offer the potential for patient-specific, smart membranes capable of responding to the local microenvironment. However, the clinical translation of these innovations will require rigorous in vivo validation and well-designed clinical trials.

i. Polycaprolactone (PCL)

Polycaprolactone (PCL) is a semicrystalline, hydrophobic, biomedical synthetic polymer with favourable favorable mechanical characteristics, modifiable microstructure, and biodegradability (Wissing et al., 2017). The intrinsic hydrophobicity of PCL as compared to native extracellular matrix limits the ability of cell adhesion, proliferation, and bioactivity despite its many therapeutic uses (Croll et al., 2004). Polycaprolactone (PCL) membranes are increasingly employed in guided tissue regeneration (GTR) as barrier systems that inhibit epithelial downgrowth and promote selective periodontal regeneration. While the majority of evidence remains preclinical, emerging clinical observations suggest that PCL-based membranes, particularly when combined with bioactive components such as gelatin or zinc oxide nanoparticles, exhibit sufficient mechanical strength and antibacterial properties essential for regenerative success.[83,84] Furthermore, the incorporation of growth factors and antimicrobial agents has been investigated to further enhance regenerative outcomes; however, these approaches are predominantly confined to experimental and early translational stages. Despite these advantages, several limitations impede the widespread clinical adoption of PCL-based membranes. The slow degradation rate of PCL may not correspond with the dynamics of periodontal healing, potentially compromising timely tissue remodeling.[85] Additionally, the risks of bacterial colonization and structural instability in modified systems may negatively impact clinical outcomes.[83] More broadly, current PCL-based membranes do not fully satisfy all functional requirements, particularly in achieving an optimal balance between mechanical integrity, bioactivity, and tissue integration.[86] Numerous strategies have been adopted to overcome these limitations, such as surface modifications using plant extracts that significantly increase hydrophilicity and fibroblast adhesion, such as Pterodon pubescens and Arrabidaea chica. Additionally, sophisticated structural designs with antimicrobial and osteogenic qualities include core−shell nanofibres that contain gelatin, metronidazole, and nano-hydroxyapatite (NHA) (Wang et al., 2020), On the other hand, equine bone powders combined with nano-patterning enhance hydrophilicity and encourage the growth of dental pulp stem cells (DPSC) (Jang et al., 2019). Additionally, adding tricalcium phosphate (TCP) and bioactive glasses (BGs) to the PCL matrix enhances its mechanical integrity, wettability, and osteoconductivity. Although controlled drug release systems, like those that contain hydroxyapatite nanoparticles (HANPs) or metronidazole, have antibacterial properties, they must be carefully optimized to preserve structural features and biocompatibility (Shi et al., 2021; Münchow et al., 2019). The degradation rate of PCL is slow as compared to PLA and PGA. It may take up to three years for full resorption and it does not generate acidic degradation byproducts, which makes it suitable choice for long-term use (Wissing et al., 2017; Costa Salles et al., 2020; Munoz et al., 2021). Commercial copolymers, like Vivosorb®, combine lactic acid derivatives and PCL to improve degradation profiles, occlusivity, and biocompatibility (Munoz et al., 2021).

Future strategies aim to enhance both biological and mechanical performance through the development of multiphasic membrane designs capable of supporting simultaneous hard and soft tissue regeneration.[87] The incorporation of nanofillers and bioactive materials has demonstrated promise in enhancing osteogenic potential and cell adhesion,[86,88] while electrospinning techniques facilitate the fabrication of composite membranes with improved structural and functional properties.[89] Nonetheless, alternative materials such as collagen and polylactic acid-based membranes currently exhibit more consistent clinical performance in certain applications due to their favourable degradation profiles and handling characteristics.[36]

ii. Polyactic acid (PLA)

Polylactic acid (PLA) is a synthetic polymer that is biocompatible and biodegradable. It is widely used in biomedical and clinical applications due to its excellent degradation properties and versatility in scaffold construction.[90] It comes in three stereoisomeric forms: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), and poly(D,L-

lactic acid) (PDLLA), with PDLLA degrading more quickly within six months due to its amorphous structure.[91] Commercially available PLA-based GTR membranes, such as GUIDOR® Matrix Barrier, Atrisorb®, and Epi-Guide®, have distinct multilayered porous architectures, allowing selective tissue integration and nutrient permeation while maintaining barrier integrity for 5−12 months.[92] PLA membranes have demonstrated effective biocompatibility and mechanical stability in clinical GTR/GBR applications, with studies reporting reductions in probing pocket depth and gains in clinical attachment levels, although in some cases collagen membranes may yield superior bone fill outcomes.[36,93,94] The bioresorbable nature of PLA eliminates the need for a second surgical intervention, enhancing its clinical applicability.[36,93] Additionally, the incorporation of magnesium into PLA membranes has been shown to improve load-bearing capacity and corrosion resistance, further supporting their functional performance in regenerative procedures.[93]

Nonetheless, PLA's main drawbacks are its comparatively poor mechanical strength and acidic breakdown products, which can cause local inflammation over the course of protracted degradation phases that last up to a year.[95,96] Clinically, PLA membranes may also be associated with complications such as membrane exposure and soft tissue injury, which remain common concerns in GTR/GBR procedures and can compromise regenerative outcomes.[97] Furthermore, achieving an optimal degradation rate that aligns with new tissue formation remains a critical challenge influencing clinical success.[98] In order to get around these restrictions, scientists have altered PLA's physicochemical characteristics by adding bioactive substances like carbon nanotubes (CNTs), hydroxyapatite nanoparticles (HANPs), antibiotics, bioceramics, and bioactive glass (BG) to improve its mechanical performance, bioactivity, and antimicrobial activity.[96,99,100] Furthermore, improvements in osteoconductivity and cell proliferation have been made possible by the exact control of membrane porosity and mechanical properties made possible by fabrication innovations such as electrospinning, solvent casting, and 3D printing.[101] Magnesium-enhanced PLA membranes and composite constructions combining PLA with PCL or cellulose acetate have shown improved osteogenic potential, biocompatibility, and degradation control, hence bolstering its use in periodontal regenerative operations.[93]

The clinical success of PLA membranes is largely dependent on their ability to maintain space and support effective tissue integration, which are essential for predictable bone regeneration[98] 6. Future modifications are therefore focused on enhancing mechanical strength, optimising degradation kinetics, and improving antimicrobial performance through strategies such as incorporation of nanofillers and development of drug-loaded membranes.[36,98] While PLA-based systems show considerable promise, achieving an optimal balance between mechanical integrity, degradation rate, and biocompatibility remains a key challenge for improving long-term clinical outcomes.

iii. Polyglycolic acid (PGA)

Among biodegradable polymers, polyglycolic acid (PGA), an aliphatic polyester, has the quickest rate of decomposition and the fewest carbon units. Although it has good biocompatibility and breaks down in the body into carbon dioxide and water, elimination the need for second surgical procedure. But its expensive price and restricted market availability prevent it from being used independently as a barrier membrane (Shuai et al., 2020). Clinical studies have indicated that when combined with other materials, such as polyglactin 910, PGA membranes can contribute to improved outcomes, including reductions in probing depth and gains in clinical attachment levels in periodontal defects.[102] PGA is more frequently used in copolymerization with materials like PLA to modify degradation profiles and enhance mechanical stability because of its quick disintegration and acidic byproducts, which can cause inflammatory reactions.[103] However, its rapid degradation remains a significant limitation, as it may lead to insufficient structural support during the critical phases of tissue regeneration.[85] Although PGA exhibits adequate initial mechanical stability, this property diminishes quickly with degradation, potentially compromising its effectiveness as a long-term barrier membrane.[84] The breakdown of PGA promotes pore development in tissue engineering, increasing the exposure of bioactive ingredients and quickening scaffold resorption. For example, 3D laser printing will combine PGA with hydroxyapatite/poly-L-lactic acid (HA/PLLA) scaffolds, which will make them more porous and help apatite deposition (Shuai et al., 2020). It has also been noted that incorporating PGA fibers into collagen scaffolds enhances their physical properties and promotes cell adhesion in vitro (Toosi et al., 2019), confirming that it works as a functional supplement and not just a barrier membrane on its own.

Future modifications may involve combining PGA with other polymers or bioactive agents to enhance its mechanical properties and control its degradation rate.[85] Incorporating nanofillers into PGA membranes could improve mechanical strength and stability, enhancing cell adhesion and proliferation.[85] Despite these advancements, challenges related to rapid degradation and mechanical limitations persist, highlighting the need for continued research integrating nanotechnology and bioactive modifications to improve the clinical predictability of PGA-based membranes.

iv. Polyactic-co-glycolic acid (PLGA)

Polyactic-co-glycolic acid (PLGA) a non-toxic copolymer of hydroxyacetic acid and lactic acid possess biocompatibility and cytocompatibility similar to collagen membranes. These properties make PLGA favourable for use in biomedical engineering, tissue engineering, and drug delivery systems.[103,104] PLGA is widely utilised in guided tissue regeneration (GTR) membranes as a barrier material that prevents epithelial migration and facilitates periodontal ligament cell repopulation, thereby supporting periodontal and bone regeneration.[105] However, despite its favourable properties, its clinical performance remains influenced by intrinsic limitations such as hydrophobicity and limited bioactivity, which can hinder effective cell attachment and proliferation.[105,106] The physical and chemical properties of PLGA membrane can be altered either by altering the proportion of PLA and PGA or polymerization techniques.[103] In clinical settings, PLGA-based membranes

are among the commonly employed synthetic barriers in GTR/GBR procedures, contributing to regenerative outcomes in a substantial proportion of patients undergoing these therapies.[36] Nevertheless, similar to other synthetic membranes, they are susceptible to bacterial colonisation, which may lead to premature degradation and compromise clinical success.[107] Notwithstanding these benefits, native PLGA by itself has drawbacks for guided tissue and bone regeneration (GTR/GBR) applications, chiefly because of its poor mechanical strength and rate of degradation. In order to address these issues, a number of studies have added bioactive substances and particles to PLGA matrices using methods including electrospinning to improve osteoconductivity, inhibit bacterial growth, and regulate cell infiltration rates.[108,109] Various modification strategies have been explored to overcome these biological limitations. For instance, incorporation of soluble eggshell membrane protein (SEP) into PLGA matrices has demonstrated enhanced cell attachment, spreading, and proliferation, indicating improved regenerative potential. Additionally, micro- and nano-patterned PLGA membranes have shown improved hydrophilicity and cell adhesion, which are critical for effective tissue integration.[106] For example, Higuchi et al. showed that PLGA membranes covered with hydroxyapatite (HA) can improve wettability, slow down degradation, and prevent local acidification by releasing calcium ions.[110] Similarly, Santos et al. found that a 60:40 ratio produced the best results, and that optimising the HA:TCP ratio inside PLGA membranes had a substantial impact on fibre morphology and bone regeneration performance.[111,112] Additionally, functional alterations that incorporate antimicrobial drugs have been investigated; however, these treatments frequently reduce tensile strength by altering the dynamics of drug release.[113] Furthermore, the incorporation of antibacterial agents such as lauric acid has been shown to enhance antimicrobial properties and biocompatibility, thereby reducing the risk of infection-related complications in clinical applications 4. According to Jin et al., depending on the LA:GA ratio, combining fish collagen and HA in PLGA matrices enhances mechanical integrity and degrading behaviour.[114] Furthermore, cutting-edge designs that combine structural and functional layers, like bi-layer scaffolds, have demonstrated promise and offer osteoconductive, antibacterial, and barrier qualities appropriate for clinical GBR applications.[115] While combining PLGA with polymers like polycaprolactone (PCL) provides additional opportunities for creating synthetic, multifunctional membranes, composite membranes of PDLLA/PLGA have also demonstrated efficient cell-occlusive and degradation properties, confirming their potential as barrier membranes in GTR.[109] Future modifications are increasingly focused on enhancing mechanical strength, optimising degradation kinetics, and improving osteogenic potential through the incorporation of nanofillers and other bioactive components.[116] In addition, advances in controlled drug delivery systems using PLGA are being explored to enable sustained and targeted release of therapeutic agents, thereby improving regenerative outcomes.[83] Despite these advancements, achieving an optimal balance between mechanical integrity, bioactivity, and degradation behaviour remains a critical challenge for maximising the clinical efficacy of PLGA-based membranes.

Semi absorbable membrane

i. Silk fibroin

Silk fibroin (SF) is a natural protein derived from silkworm cocoons or spider silk. It has certain advantages such as low inflammatory response, biodegradability, biocompatibility, and exceptional permeability to oxygen and water vapor which makes it a promising material for periodontal and regeneration purpose.[3,117] The bio−safety profile of silk fibroin is further corroborated by its non-toxic degradation byproducts, predominantly amino acids. It is evident from the histological experience and micro-computed tomography that silk fibroin membrane induces more bone growth as compared to PTFE and cross-linked collagen membranes. It also provides stability, space for bone growth and protection against membrane failure in moist conditions.[3,7]

Despite having certain advantages, silk fibroin is hard to handle and stretch due to brittleness in dry conditions (K. C. Chang et al., 2019). To resolve this issue plasticizers like glycerin and polyvinyl alcohol have been added followed by thermal annealing which makes the membrane more flexible, ductile and hydrophilic, with controllable degradation.[118]

These customized SF membrane with improved mechanical and physiochemical properties and considered to be more suitable for periodontal regenerative therapies. Animal studies have revealed that SF membranes have better tendency for bone healing than collagen based membranes. This supports their use as inexpensive and biocompatible barrier membranes for GTR/GBR operations.[117] Silk fibroin membranes can be tailored with particular mechanical and biological characteristics, making them a promising foundation for future regenerative therapies, particularly in addressing bone and periodontal disorders.[3]

Classification based on sustainability and bio-derivation

Recent advances in periodontal biomaterials have shifted attention toward sustainable and bio-derived systems as next-generation candidates for guided tissue regeneration (GTR), particularly where the aim is to combine regenerative performance with reduced dependence on petroleum-based polymers and improved environmental responsibility. In this context, biowaste-derived hydroxyapatite, marine-origin collagen, chitosan, silk fibroin, lignin, and polyphenol-containing biomaterials have attracted growing interest because they can be sourced from renewable or underutilized natural feedstocks and processed into membranes or scaffold components with intrinsic biological activity. This trend is especially relevant in periodontal regeneration, where membrane materials must not only function as a barrier but also support cell adhesion, vascular ingrowth, controlled biodegradation, and the creation of a biologically favorable wound microenvironment.

A major development in this area is the use of biowaste-derived hydroxyapatite, particularly from marine sources such as fish bone, fish scales, and other calcium-rich biological residues. These materials are attractive because they closely resemble the mineral phase of native bone and can provide osteoconductivity, ion-release potential, and a surface chemistry favorable to cell attachment and mineral deposition. Waste-derived hydroxyapatite has been reported

to support bone tissue engineering by providing a stable inorganic phase that can be incorporated into composite GTR membranes or particulate graft systems, thereby improving defect fill and supporting hard-tissue regeneration. The study on hydroxyapatite extracted from camel bone further reinforces the broader concept that naturally derived apatites can provide environmentally preferable alternatives to synthetic hydroxyapatite while retaining clinically relevant structural and compositional features, including carbonate substitution and trace ions that may contribute to osteointegration.[14,119] From a periodontal perspective, these features are desirable because they may promote early mineralization, improve scaffold bioactivity, and enhance the osteogenic potential of composite membrane constructs.[120,121]

Marine-derived collagen has also become increasingly important in this field. Collagen from fish skin, fish scales, and other marine tissues offers strong biocompatibility and low immunogenicity while avoiding some of the ethical, religious, and disease-transmission concerns associated with mammalian collagen sources. In periodontal regeneration, collagen remains one of the most biologically familiar membrane matrices because of its similarity to extracellular matrix architecture and its ability to support fibroblast attachment, cell migration, and hemostasis. Recent reviews have emphasized that collagen-based biomaterials can be tailored through molecular re-engineering to address their inherent weaknesses, particularly poor mechanical stability and rapid degradation, which are major concerns in barrier applications. Marine collagen is especially appealing because it adds the sustainability advantage of using underexploited marine byproducts while maintaining the biological features that make collagen useful for GTR.[122,123]

Chitosan and related marine polysaccharides are similarly promising because they combine biodegradability, mucoadhesion, antimicrobial potential, and ease of chemical modification. Chitosan can be blended with collagen or synthetic polymers to improve membrane handling and tensile performance while preserving a favorable cell-interactive surface. In composite periodontal scaffolds, chitosan is often valued not only as a structural component but also as a functional polymer capable of modulating wound healing and reducing bacterial colonization, both of which are highly relevant in the contaminated oral environment. When paired with calcium-phosphate particles or hydroxyapatite, chitosan-based systems can provide a hybrid membrane that better balances barrier function, bioactivity, and degradation kinetics.[13]

Silk fibroin represents another important sustainable biomaterial for GTR. Its rising popularity stems from the fact that it offers superior mechanical robustness relative to many natural polymers, while also exhibiting favorable processability and controllable degradation. Silk fibroin-based membranes are particularly attractive in periodontal applications because they can be engineered into dense, porous, or Janus-type architectures that separate soft-tissue exclusion from tissue-permissive surfaces. This structural flexibility helps address one of the core limitations of conventional natural membranes, namely inadequate stiffness or premature collapse in space-maintaining defects. Recent work on self-composite silk fibroin membranes for guided bone regeneration highlights how silk-based materials can be organized into multi-architecture constructs with intrinsic integrity, which is highly relevant to GTR where barrier performance and defect stability are both essential. More broadly, silk fibroin may be viewed as a bridge between sustainability and high-performance biomaterials because it offers a naturally derived protein platform that can be processed into clinically relevant forms without losing mechanical utility.[124]

Polyphenol- and lignin-containing biomaterials add yet another layer of functionality to the sustainability discussion. Lignin is abundant, renewable, and often obtained as an industrial byproduct, making it attractive from a circular-biomaterials standpoint. In periodontal biomaterial design, lignin and polyphenols may contribute antioxidant behavior, free-radical scavenging, and cross-linking reinforcement, which can improve scaffold stability and potentially support a more favorable healing response. Their phenolic chemistry also enables interactions with proteins and polysaccharides, which can strengthen composite matrices and reduce rapid dissolution. These advantages are especially relevant in GTR membranes because oxidative stress and inflammation are major features of periodontal wound healing, and materials that can moderate the local microenvironment may improve outcomes beyond simple barrier exclusion.[125]

A useful way to place these materials in context is to compare them with conventional collagen and PTFE membranes. Conventional collagen membranes remain widely used because they are biocompatible, easy to handle, and clinically familiar, but they may suffer from rapid enzymatic degradation, limited space maintenance, and variable mechanical integrity, especially in larger or non-contained defects. PTFE membranes, by contrast, provide excellent barrier function and dimensional stability, particularly in non-resorbable formats, but they are not bio-derived, do not contribute intrinsic bioactivity, and may require a second surgery for removal if non-resorbable designs are used. In this sense, sustainable natural membranes often offer a stronger biological rationale, whereas PTFE still remains superior when predictable structural maintenance is the overriding requirement. Thus, bio-derived membranes are not automatically better; their performance depends on whether they can simultaneously preserve space, resist collapse, and degrade in synchrony with tissue formation.

For this reason, many of the most promising sustainable GTR systems are not purely natural but hybridized. Bio-derived materials can be combined with electrospinning to produce nanofibrous membranes that mimic extracellular matrix architecture and improve cell attachment and nutrient exchange. Cross-linking, whether chemical, enzymatic, or physical, is frequently used to slow degradation, increase wet strength, and improve handling, especially for collagen- and gelatin-based systems. Three-dimensional fabrication approaches, including freeze-drying, additive manufacturing, and layered or Janus-type membrane design, can further improve porosity control, surface asymmetry, and space maintenance, thereby allowing one side to face the soft tissue and another to promote osteogenic regeneration. These technologies are particularly important because they allow sustainable biomaterials to overcome their traditional weaknesses without sacrificing bioactivity.[21,126]

The translational potential of sustainable GTR membranes is therefore substantial, but several challenges remain.

Source variability is a major issue, particularly for marine and biowaste-derived inputs, because differences in species, anatomical source, age, diet, and processing conditions can alter purity, crystallinity, and mechanical performance. Purification and sterilization must also be carefully controlled to avoid compromising structural integrity or introducing contaminants. Batch reproducibility, regulatory standardization, and scale-up for clinical-grade manufacturing are further obstacles that currently limit widespread translation. Moreover, sustainability should be interpreted as a complementary advantage rather than a surrogate for clinical efficacy. In periodontal regeneration, the decisive criteria remain space maintenance, predictable resorption, adequate barrier function, biocompatibility, and successful integration with host tissues and graft materials. Therefore, the most clinically relevant future direction is not the replacement of conventional membranes by natural ones alone, but the rational design of hybrid sustainable systems that integrate bio-derived components with engineered mechanical reinforcement and controlled degradation.

Classification based on functional modificatiosn

Antimicrobial drugs incorporation

Since microbial colonisation is still the main cause of GTR membrane failure, controlling bacterial infection is essential for successful periodontal regeneration.[23,127,128] By inhibiting bacterial adhesion and infection on root surfaces, drug-loaded GBR/GTR membranes provide a favourable environment for tissue regeneration.[129,130] To create biodegradable, drug-loaded membranes with a large surface area, three-dimensional porosity, and superior drug encapsulation effectiveness, electrospinning is a commonly used fabrication technique.[4,130] These nanofibrous membranes offer chemical and physical cues to regulate cell differentiation, adhesion, and proliferation, while also allowing for alterations in size and shape to satisfy diverse clinical needs.[130] Electrospun membranes have been treated with a variety of antimicrobial agents in order to enhance periodontal regeneration. Doxycycline hydrochloride (DOX), is a most commonly used antibiotic having anti-inflammatory and anti-collagenase properties. It is evident from literature that DOX has shown positive effect in periodontal therapy when used in combination with scaling and root planning.[4] Similarly results obtained from the studies conducted by Bottino et al. (2012), El-Kamel et al. (2007), and Naqvi (2021) showed mutual agreement upon loading of metronidazole benzoate into membranes adjacent to epithelial tissues can eradicate P. gingivalis like anaerobic pathogens. This greatly speeds up the healing of bones and gums. Metronidazole-loaded electrospun gelatin/PCL nanofibers have demonstrated long-lasting medication delivery throughout the healing process and strong antibacterial activity.[4] Furthermore, in the presence of A. actinomycetemcomitans and S. mutans, the incorporation of tetracycline hydrochloride and amoxicillin into PLA and polyethylene-co-vinyl acetate membranes enhanced periodontal ligament cell attachment; tetracycline enhances osteoblast chemotaxis and exhibits anti-collagenolytic activity for prolonged applications. Another novel and a broad spectrum antibiotic Nitazoxanide has been incorporated into PCL membrane to enable targeted localized therapy. These membranes were intended for use in GTR/GBR procedures, where maintaining a bacteria-free environment is critical for successful periodontal regeneration. The system is designed to provide sustained local release of the drug, thereby reducing infection risk and enhancing tissue healing and regeneration.[131] In addition to antibiotics, non-antibiotic antimicrobials such as chitosan nanoparticles and chlorhexidine have also shown synergistic antibacterial benefits in GTR, especially in periapical procedures, and when coupled within collagen membranes, they enhance tissue regeneration.[7]

Antimicrobial Peptides (AMPs) represent a sophisticated alternative to traditional antibiotics in GTR membrane technology, primarily due to their broad-spectrum efficacy and low risk of bacterial resistance. Research indicates that peptides such as "magainin 2" function through a rapid sterilization mechanism that physically ruptures bacterial membranes while maintaining high stability under physiological conditions[132] Figure 3. These "smart" therapeutic agents are uniquely effective against oropathogens and can eliminate established, drug-resistant biofilms where conventional treatments often fail.[133] To optimize their clinical application, AMPs are integrated into GTR scaffolds such as gelatin/chitosan nanofibrous membranes via electrospinning and microsphere encapsulation to ensure a controlled release that maintains a sterile environment without compromising the proliferation of bone marrow stem cells.[134] Furthermore, AMPs exhibit excellent biocompatibility and selective toxicity, destroying pathogens while remaining non-toxic to human keratinocytes and red blood cells, thereby ensuring safe and effective periodontal tissue regeneration.[135]

Growth factors

By attaching to particular transmembrane receptors on target cells, growth factors (GFs) direct cellular activity necessary for periodontal regeneration and play a crucial role in controlling tissue formation, repair, chemotaxis, cell proliferation, and angiogenesis.[136,137] By encouraging the development of cementum, periodontal ligament, and alveolar bone, bone morphogenetic protein-2 (BMP-2), platelet-derived growth factor (PDGF), transforming growth factor-β1 (TGF-β1), enamel matrix derivatives (EMD), autologous platelet concentrates (APC) and recombinant growth factors (rhPDGF-BB) have shown considerable regenerative potential in periodontal applications.[7,138] Concentrated GFs are delivered by platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) through platelet α-granules, promoting the repair of both soft and hard tissues.[4,7] Although cross-linking and heat treatments have been investigated to increase their stability and bioactivity for GTR usage, ordinary PRF membranes disintegrate quickly after two weeks.[54] Denser, more robust biomaterials with improved biomechanical and regenerative qualities have been produced by the creation of titanium PRF, concentrated growth factor (CGF), and advanced platelet-rich fibrin (A-PRF).[139] To improve the sustained release and stabilisation of GFs like BMP-2, controlled delivery systems have been introduced, such as hierarchical gelatin nanospheres encapsulated within microspheres conjugated

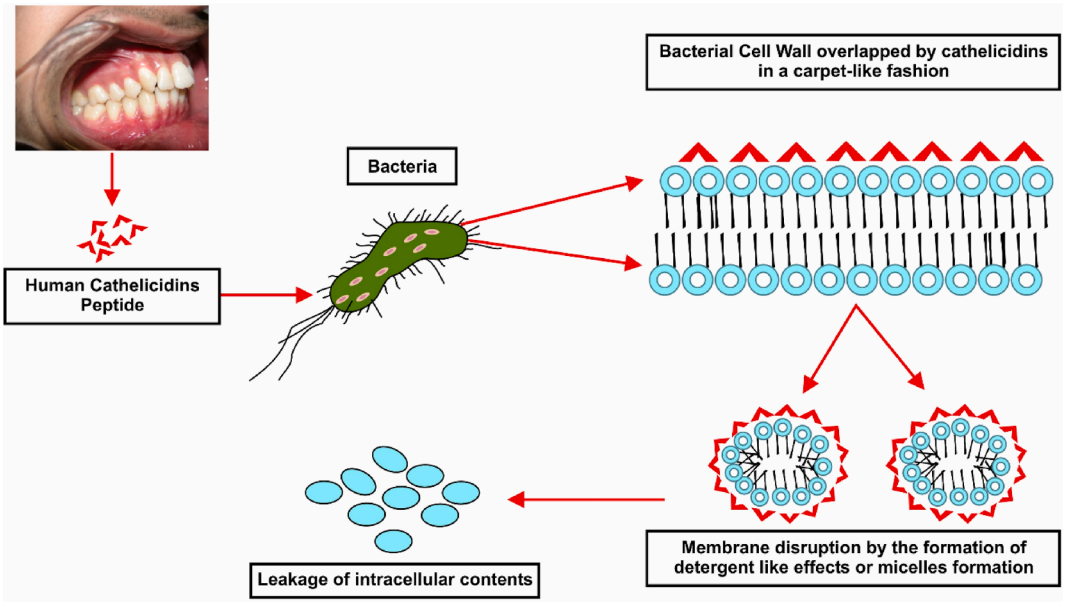


Figure 3: Mechanism of action of peptides (cathelicidins) against microbes[16].

with heparin. These systems improve the adhesion, differentiation, and formation of new tissue by bone marrow mesenchymal stem cells.[140,141] The available literature suggests that combinig the growth factors with graft materials provide limited but measurable improvements in selected clinical and radiographical parameters, particularly in probing pocket depth (PPD) reduction and radiographic bone level gain. The magnitude of benefit varies depending on the specific biologic agent, with PRF and growth factors showing a more pronounced response to grafts, while EMD yields comparable outcomes with or without grafts.[142] The long-term effectiveness of autologous plasma concentrates and their integration with bone-graft-implant complexes are still being studied, despite the fact that they exhibit encouraging results in soft and hard tissue regeneration.[54,143,144] Nevertheless, there are still useful ways to encourage local healing and accomplish real periodontal regeneration by including bioactive compounds into GTR membranes.

Metals

i. ZINC

Zinc (Zn) has emerged as a viable biomaterial in regenerative dentistry due to its superior mechanical, biodegradable, and biocompatible qualities.[145] Zn, an essential trace element, plays important roles in biological processes such as gene expression, signal transduction, and apoptosis regulation.[146] Zn ions (Zn^{2+}) stimulate osteogenic cell proliferation and differentiation by blocking bone-resorbing cells, leading to increased new bone production.[3,147] Furthermore, zinc promotes protein synthesis, activates aminoacyl-tRNA synthetase in osteoblasts, and maintains bone mass, all of which are essential for bone formation and mineralisation.[3] Pure Zn membranes have a favourable degradation profile with few by-products, and Zn-phosphate mineralised membranes have been shown to reduce inflammation associated with membrane exposure and provide antibacterial properties, promoting both soft and hard tissue regeneration.[145,148]

Zinc oxide nanoparticles (ZnO-NPs) have been approved safe by FDA. These nanoparticles have shown strong antibacterial activity including those bacterias which have shown resistance against antibiotics. Münchow et al. conducted a study demonstrating that PCL-Gel electrospun membranes coated with 5, 15, and 30 weight percent ZnO-NPs effectively inhibited microbial proliferation while maintaining biocompatibility with human dental pulp stem cells. Nevertheless, apprehensions persist regarding the possible cytotoxicity associated with excessive nanoparticle release. To address this issue, Prado-Prone et al. employed acetic acid as a solvent to fabricate electrospun PCL-Gel-Zn membranes with reduced ZnO-NP concentrations (1, 3, and 6 weight percent). The resulting membranes were strong, biodegradable, and had long-lasting antibacterial properties. These membranes significantly inhibited biofilm formation by Staphylococcus aureus and demonstrated favorable thermal stability, degradation resistance, and wettability characteristics. While keeping human osteoblasts and gingival fibroblasts alive.[87] Based on these results, it seems that membranes made of Zn and ZnO-NP could be good choices for GTR/GBR applications because they are antibacterial, promote bone growth, and reduce inflammation.

ii. Magnesium

The magnesium (Mg) membrane is another promising choice for guided tissue and bone regeneration (GTR/GBR) because it has better mechanical properties, can be completely broken down, and is safe for living things. When compared to silk fibroin and commercial biodegradable membranes, pure magnesium membranes have a higher tensile strength (183 ± 10.7 MPa). Higher tensile strength

values successfully prevents membrane collapse and promotes vertical defect repair.[3,149] Their breakdown results in the production of hydrogen gas and magnesium ions, which are both innocuous and naturally regulated by the body, guaranteeing non-toxicity and biosafety.[150] Additionally, because of their bone-like Young's modulus, magnesium membranes promote cell adhesion, proliferation, osteogenic marker expression, and bone regeneration without preventing stress shielding.[151] However, there are clinical limits due to their quick in vivo disintegration, evolution of hydrogen gas, and rise of pH.[152] To increase corrosion resistance, cytocompatibility, and mechanical stability, various techniques have been investigated, including alloying with Zn and Gd, surface modifications like Ca−P coatings, hydrofluoric acid treatment, plasma electrolytic oxidation, and integration with collagen.[153−155] Concerns about rapid degradation remain unresolved despite developments. In terms of strength and integrity, absorbable metal membranes such as magnesium perform better than polymers and ceramics. Pure magnesium is still a clinically desirable option because of its osteoconductivity, mechanical compatibility with bone, and wide range of biomedical applications, but it is still crucial to optimise its degradation kinetics[55] Figure 4.

iii. Silver

Silver nanoparticles (AgNPs) have recently gained a lot of interest recently because of its strong antibacterial abilities and probable use in membranes for GTR/GBR. The sustained release of silver ions, disruption of microbial membranes, induction of oxidative stress, and interference with intracellular biomolecules are the main ways that AgNPs, which are synthesized using chemical, physical, and environmentally friendly biological methods, demonstrate size- and morphology-dependent antimicrobial efficacy.[156,157] The nanofibers made up of polycaprolactone (PCL), polylactic acid (PLA), and cellulose acetate (CA) were reinforced with hydroxyapatite and silver nanoparticles to improve bone regeneration capability and antibacterial activity.[157] The AgNP's reinforced scaffolds promote tissue repair while reducing bacterial adhesion, biofilm formation and inflammation associated with periodontitis, making it an ideal option for periodontal tissue regeneration.[158,159] Release of Ag ions from AgNP's is responsible for its antibacterial activity. The use of these nanoparticles is leading towards a diverse range of applications. Besides periodontal therapy they are being used in implant coatings, prosthetics, restorative, endodontics and orthodontics and have shown effective results against endodontic infections, secondary caries, and peri-implantitis, while preserving mechanical integrity.[160,161] Along with the benefits there are some concerns about their cytotoxicity, potential for oxidative stress, and long-term environmental impact. Therefore precise control over nanoparticle concentration, size, and surface functionalization is necessary for maintaing optimal safety and therapeutic efficacy.[162] Consequently, GTR membranes based on AgNPs, having combined antibacterial, anti-inflammatory, and osteogenic qualities within biodegradable, mechanically robust scaffolds, establish a multipurpose tactic for periodontal regeneration.[4]

iv. Cerium

Cerium oxide nanoparticles (CeO_2 NPs) are another attractive option for guided tissue regeneration (GTR) membranes due to their multifunctional qualities, which include strong antioxidant, antibacterial, and osteogenic characteristics. Ren et al. revealed that through regulated Ce^{4+}/Ce^{3+} ion release and reactive oxygen species modulation, electrospun nanofibrous membranes loaded with CeO_2 NPs significantly improved osteogenic differentiation, angiogenesis, and bone regeneration.[163] In another study Aminmansour et al., added CeO_2 NPs to GelMA/PCL scaffolds and reported improved cellular proliferation, biocompatibility, and mechanical strength which is suitable for periodontal tissue engineering.[164] While in a study by Chatzimentor et al. the antibacterial effectiveness of CeO_2 NPs against important oral infections without causing

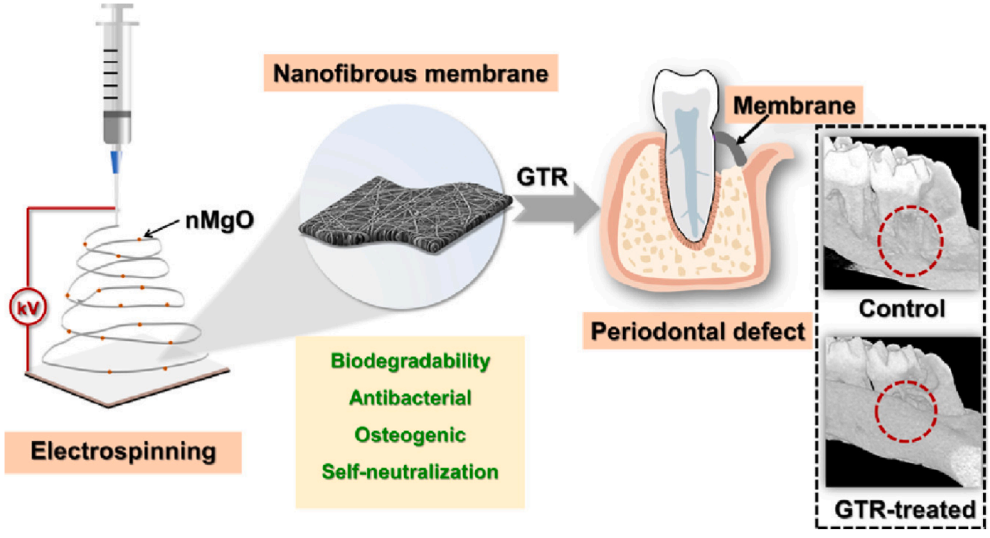


Figure 4: Magnesium oxide based membrane[167].

cytotoxic effects was further validated.[165] Although there is currently little direct use of cerium nanoparticles in GTR membranes, these results point to the possibility that they could improve membrane performance through increased mechanical stability, biocompatibility, and antibacterial activity. These findings are consistent with concepts shown in nanocomposite GTR membranes that use other nanoparticles, such as hydroxyapatite and carbon nanotubes.[166] Cerium nanoparticles are therefore considered as a feasible option for further improvement in periodontal regeneration techniques.

Current challenges, limitations and future directions

Despite major progress in GTR membrane development, several translational challenges remain unresolved. One major limitation involves balancing mechanical integrity with controlled degradation. Membranes that degrade too rapidly may lose barrier function before regeneration is complete, whereas slow-resorbing systems may impair tissue remodeling. Another persistent challenge concerns vascularization and integration within large or compromised defects. Although many bioactive modifications improve osteogenic behavior in vitro, consistent in vivo translation remains variable. Furthermore, antimicrobial additives and nanoparticle reinforcement may improve function but raise concerns regarding dose-dependent cytotoxicity, inflammatory responses and long-term biosafety. Manufacturing scalability and reproducibility also remain barriers to clinical translation, particularly for multilayer, electro spun and multifunctional smart membranes. Regulatory pathways for composite bioactive devices incorporating drugs, nanoparticles or biologics remain complex. Recent animal studies have begun addressing these challenges through biomimetic and multifunctional designs. Preclinical investigations demonstrate promising outcomes using graphene reinforced membranes, peptide functionalized scaffolds and ion-doped bio-derived composites showing enhanced bone fill, periodontal ligament organization and reduced inflammation. However, many of these studies remain limited by short follow-up periods, heterogeneous models and insufficient comparison with clinically established membranes.

Conclusion

GTR membrane technology has evolved from inert non-resorbable barriers to bioactive multifunctional structures. Contemporary resorbable polymers and bioactive composites with antimicrobial agents (metallic nanoparticles) and growth factors have significantly improved periodontal regeneration outcomes. Electrospun nanofibrous membranes have emerged as particularly promising due to their enhanced biocompatibility and controlled drug delivery capabilities. Advanced GTR membranes enable more predictable outcomes in periodontal and bone regeneration procedures. The integration of antimicrobial and anti-inflammatory agents reduces post-operative complications while promoting tissue regeneration, leading to improved functional and aesthetic restoration for patients with periodontal disease and bone defects. Future GTR development should focus on engineering intelligent, multifunctional membranes that combine optimal physical properties with biofunctional characteristics. Research priorities include exploring novel nanomaterials (cerium nanoparticles, hydroxyapatite, carbon nanotubes), hydrogel-based systems, and smart delivery mechanisms to achieve superior clinical outcomes and fully predictable periodontal regeneration.

The quest for an optimal Guided Tissue Regeneration (GTR) membrane has deriven a substantial transformation from passive, inert barriers to dynamic, bioactive structures. Current materials, including resorbable polymers and advanced composites, have significantly enhanced clinical outcomes; however, they serve merely as a transitional phase. The membrane's structure alone will not make periodontal regeneration truly predictable; it will also need to be biofunctional. The definitive trajectory for forthcoming advancements resides in the engineering of intelligent, multifunctional membranes that seamlessly amalgamate optimal physical characteristics with the regulated administration of therapeutic agents (antimicrobials, growth factors). This change from a passive barrier to an active participant in healing is the key to unlocking full and predictable periodontal regeneration.

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Conflict of interest

There is no conflict of interest for this study.

Ethical approval

There is no ethical issue as no animal and human involved in this study.

Authors contributions

RZ: original article writing, NHI and RAA: Supervision, TAK: Data Collection, MS: Write up, RZ: Data collection. NM: Conceptualization. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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