applied sciences

MDPI

Review

Guided Tissue Regeneration Membranes: Review of Innovations and Applications in Immunocompromised Patients

Man Hung [1,2,3,*], Katherine Sanders [1], Aditya Deshpande [1], Roshni Trivedi [1], Connor Schwartz [4] and Amir Mohajeri [1]

[1] College of Dental Medicine, Roseman University of Health Sciences, South Jordan, UT 84095, USA
[2] Department of Orthopaedic Surgery Operations, University of Utah, Salt Lake City, UT 84108, USA
[3] Division of Public Health, University of Utah, Salt Lake City, UT 84108, USA
[4] Library, Roseman University of Health Sciences, South Jordan, UT 84095, USA
* Correspondence: mhung@roseman.edu; Tel.: +1-801-878-1270

Abstract: Guided tissue regeneration (GTR) membranes are pivotal in regenerative medicine. While their effectiveness is established in general populations, their application in immunocompromised patients, such as those with diabetes or cancer, remains underexplored. This review evaluated evidence on GTR membranes in immunocompromised settings, focusing on their mechanisms, outcomes, and challenges posed by systemic conditions. A systematic search identified studies on GTR use in these populations. Inclusion criteria were peer-reviewed articles in English on human samples or relevant preclinical models. Of 218 articles, 5 met the criteria. These highlighted advancements in GTR technologies, such as stem cell integration, growth factor-enriched scaffolds, and scaffold-free tissue engineering. Stem cell-based approaches improved regeneration, especially with biomimetic designs incorporating bone morphogenetic protein-2. Innovations like microcavity-rich scaffolds enhanced angiogenesis and osteogenesis, while scaffold-free constructs minimized immunogenicity and supported functional tissue regeneration. Preclinical models demonstrated GTR membranes' potential for addressing large-scale tissue deficits in compromised environments. GTR membranes show promise for immunocompromised patients, but further research is needed to validate their clinical efficacy, address patient-specific challenges, and evaluate long-term outcomes. These technologies could transform regenerative medicine, providing sustainable solutions for high-risk populations.

Keywords: guided tissue regeneration; immunocompromised patients; diabetes; cancer; regenerative medicine

check for updates

Academic Editor: Rossella Bedini

Received: 27 December 2024
Revised: 15 January 2025
Accepted: 22 January 2025
Published: 23 January 2025

Citation: Hung, M.; Sanders, K.; Deshpande, A.; Trivedi, R.; Schwartz, C.; Mohajeri, A. Guided Tissue Regeneration Membranes: Review of Innovations and Applications in Immunocompromised Patients. *Appl. Sci.* **2025**, *15*, 1145. https://doi.org/10.3390/app15031145

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Guided tissue regeneration (GTR) is a cornerstone in the field of regenerative medicine, serving a critical role in restoring lost or damaged tissues [1]. Central to this approach is the use of barrier membranes that direct the growth of specific tissues while simultaneously preventing the infiltration of unwanted cells into the defect site [2]. These membranes create a microenvironment conducive to tissue regeneration by isolating the injured area and promoting the proliferation, differentiation, and migration of cells essential for repair [3]. Over the past few decades, GTR has evolved significantly with the development of advanced materials, including resorbable and non-resorbable membranes, each offering distinct advantages. Resorbable membranes, often composed of polymers such as polylactic acid or collagen, are designed to degrade naturally over time, eliminating the need for

surgical removal [4]. Non-resorbable membranes, such as those made of expanded polytetrafluoroethylene, provide robust mechanical support and durability but require additional surgical procedures for removal [5]. These technologies have demonstrated considerable efficacy in enhancing wound healing and tissue repair, particularly in periodontal and bone regeneration [6]. However, despite these advancements, their application in high-risk populations, including immunocompromised individuals, remains insufficiently studied and represents a critical gap in the current literature.

The importance of GTR extends beyond conventional applications, as it offers a targeted and potentially transformative approach to addressing complex tissue defects in patients with compromised health. Among high-risk populations, individuals with diabetes mellitus and cancer present unique challenges that complicate tissue healing and regenerative outcomes [7]. Diabetes mellitus, characterized by chronic hyperglycemia, is a metabolic disorder associated with a cascade of physiological impairments that hinder wound healing [8]. Elevated blood glucose levels disrupt critical processes such as collagen synthesis, angiogenesis, and re-epithelialization [9]. These disruptions are compounded by persistent low-grade inflammation, which further impairs the body's natural repair mechanisms [10]. Additionally, hyperglycemia has been shown to alter macrophage function, resulting in delayed resolution of inflammation and an increased risk of chronic wound development [11]. Similarly, cancer patients, particularly those undergoing chemotherapy or radiotherapy, face significant barriers to healing due to their immunosuppressed state [12]. Chemotherapy reduces cellular proliferation, a key requirement for tissue repair, while radiotherapy damages surrounding healthy tissues and impairs angiogenesis, leading to delayed wound healing [13]. Both treatments also increase the susceptibility to infections, which can further compromise the regenerative process [14]. The combined impact of these factors underscores the need for specialized strategies to enhance tissue repair and regeneration in these vulnerable populations.

Recent innovations in GTR membrane technologies offer promising solutions to the challenges faced by immunocompromised patients. Bioactive membranes, which are engineered to release therapeutic agents such as growth factors, have shown the ability to enhance cellular proliferation, differentiation, and angiogenesis—key processes essential for effective tissue repair [15]. For example, membranes incorporating bone morphogenetic protein-2 (BMP-2) or vascular endothelial growth factor (VEGF) have demonstrated enhanced osteogenesis and vascularization in various preclinical studies [16]. Additionally, antibacterial membranes represent a critical advancement, addressing one of the most significant concerns in immunocompromised patients: the heightened risk of infection [17]. By incorporating antimicrobial agents such as silver nanoparticles or antibiotics, these membranes not only promote tissue regeneration but also provide a protective barrier against microbial colonization and biofilm formation [18].

Despite these advancements, there remains a significant gap in the literature regarding the use of GTR membranes in immunocompromised populations. Most studies to date have focused on healthy individuals or general populations, with limited investigation of how these technologies perform under the altered physiological conditions associated with immunocompromised patients. The few existing studies that address these populations often do so indirectly, using preclinical models or focusing on specific aspects of the regenerative process [19,20]. As a result, there is a lack of comprehensive understanding regarding the efficacy, safety, and long-term outcomes of GTR membranes in these high-risk groups. Furthermore, the heterogeneity within immunocompromised populations, such as variations in glycemic control among diabetic patients or differences in cancer treatment regimens, adds another layer of complexity that is rarely addressed in current research.

The need for a systematic evaluation of GTR membranes in immunocompromised patients is further emphasized by the growing prevalence of these patients worldwide [21]. According to the International Diabetes Federation, approximately 537 million adults were living with diabetes in 2021, a number expected to rise to 643 million by 2030 [22]. Similarly, global cancer incidence continues to increase, with an estimated 19.3 million new cases and nearly 10 million deaths reported in 2020 [23,24]. These trends highlight the urgency of developing effective therapeutic strategies to manage the complications associated with these conditions, including impaired tissue regeneration. The integration of advanced GTR membranes into clinical practice for these populations holds the potential to significantly improve patient outcomes, reduce healthcare costs associated with chronic wounds, and enhance the quality of life for millions of patients [25].

This scoping review aims to address the critical gap in knowledge by providing a comprehensive review of the current evidence on the use of GTR membranes in immunocompromised patients. Furthermore, it seeks to identify key research gaps and proposes future directions to optimize GTR membrane strategies for these high-risk populations. The findings of this review can inform both clinical practice and future research, ultimately contributing to the development of targeted and effective regenerative therapies for immunocompromised individuals.

2. Methods

This scoping review was carried out following the framework provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [26] to ensure a methodical, clear, and reproducible process. The primary aim of the review was to investigate and synthesize the existing evidence regarding the use of GTR membranes in patients with compromised immune systems. This review emphasized assessing healing outcomes, membrane efficacy, and potential limitations while identifying unexplored areas in the current body of knowledge. To accomplish these objectives, the methodology included several key steps: defining the research question, creating a thorough search strategy, selecting and evaluating studies based on predefined inclusion and exclusion criteria (Table 1), extracting pertinent data, and synthesizing findings.

Table 1. Inclusion and exclusion criteria for article selection.

Inclusion Criteria	Exclusion Criteria
• Published peer-reviewed articles in English • Human sample-based studies • Focused on the use of membranes for tissue regeneration	• Abstracts without a full text • Review articles (literature review, narrative review, scoping review, systematic review, meta-analysis) • Opinion articles (letter to editor, editorial comments, opinion) • Articles not written in English • Conference proceedings

The research question guiding this review was as follows: what is the current evidence on the healing effects of membranes used for guided tissue regeneration in immunocompromised patients? This question was designed to provide a broad understanding of the literature while addressing the specific objective. A comprehensive search strategy was employed to identify relevant studies across multiple electronic databases, selected for their broad coverage of the biomedical literature (Table 2). These databases included PubMed, Web of Science, Cochrane Library, Ovid, and Scopus. The search strategy combined controlled vocabulary, such as Medical Subject Headings terms, with free-text keywords to

ensure a wide capture of studies. Key terms included "guided tissue regeneration", "barrier membranes", "immunocompromised", "tissue healing", and "wound regeneration", along with related synonyms. Boolean operators such as AND, OR, and NOT were used to refine the search, and database-specific terms were applied to restrict results to peer-reviewed articles published in English. The search period extended from the inception of each database to the date of search to ensure comprehensive coverage.

Table 2. Database search strategy.

Database (Date of Search)	Search Strategies	Number of Articles Found
PubMed (7 November 2023)	((“Membranes, Artificial”[Mesh]) OR (“Tissue Scaffolds”[Mesh]) OR (“absorbable membrane”[tiab]) OR (“absorbable membranes”[tiab]) OR (“Semi-absorbable membrane”[tiab]) OR (“Semi-absorbable membranes”[tiab]) OR (“non-absorbable membranes”[tiab]) OR (“non-absorbable membrane”[tiab]) OR (“Barrier Membrane”[tiab]) OR (“Barrier Membranes”[tiab]) OR (“synthetic membrane”[tiab]) OR (“synthetic membranes”[tiab])) AND ((“Guided Tissue Regeneration”[Mesh]) OR (“Bone Growth”[tiab]) OR (“Tissue Engineering”[Mesh]) OR (“Guided Tissue Regeneration, Periodontal”[Mesh]) OR (“Bone Regeneration”[Mesh]) OR (“Nerve Regeneration”[Mesh])) AND ((“Immunocompromised Host”[Mesh]) OR (“immunodeficiency”[tiab]) OR (“immunocompromised”[tiab]) OR (“immunosuppressed”[tiab])) NOT ((“Review”[Publication Type]) OR (“Meta-analysis”[Publication Type]) OR (“Systematic review”[Publication Type]) OR (“Case reports”[Publication Type]) OR (“Editorial”[Publication Type]) OR (“News”[Publication Type]) OR (“Newspaper Article”[Publication Type]))	66
Cochrane Library—Clinical Trials (7 November 2023)	(((Artificial Membranes) OR (Artificial Membrane) OR (Tissue Scaffolds) OR (Tissue Scaffold) OR (absorbable membrane) OR (absorbable membranes) OR (Semi-absorbable membrane) OR (Semi-absorbable membranes) OR (non-absorbable membranes) OR (non-absorbable membrane) OR (Barrier Membrane) OR (Barrier Membranes) OR (synthetic membrane) OR (synthetic membranes)) AND ((Guided Tissue Regeneration) OR (Bone Regeneration) OR (Bone Regenerations) OR (Periodontal Guided Tissue Regeneration) OR (Guided Periodontal Tissue Regeneration) OR (Tissue Engineering) OR (Nerve Regeneration) OR (Nerve Tissue Regeneration) OR (Nervous Tissue Regeneration) OR (Neural Tissue Regeneration)) AND ((Immunocompromised Host) OR (Immunosuppressed Host) OR (Immunocompromised Patient) OR (Immunocompromised Hosts) OR (Immunosuppressed Hosts) OR (immunodeficiency) OR (immunocompromised) OR (immunosuppressed))):ti,ab,kw	2
Ovid (7 November 2023)	((Artificial Membranes) OR (Artificial Membrane) OR (Tissue Scaffolds) OR (Tissue Scaffold) OR (absorbable membrane) OR (absorbable membranes) OR (Semi-absorbable membrane) OR (Semi-absorbable membranes) OR (non-absorbable membranes) OR (non-absorbable membrane) OR (Barrier Membrane) OR (Barrier Membranes) OR (synthetic membrane) OR (synthetic membranes)).ti,ab. AND ((Guided Tissue Regeneration) OR (Bone Regeneration) OR (Bone Regenerations) OR (Periodontal Guided Tissue Regeneration) OR (Guided Periodontal Tissue Regeneration) OR (Tissue Engineering) OR (Nerve Regeneration) OR (Nerve Tissue Regeneration) OR (Nervous Tissue Regeneration) OR (Neural Tissue Regeneration)).ti,ab. AND ((Immunocompromised Host) OR (Immunosuppressed Host) OR (Immunocompromised Patient) OR (Immunocompromised Hosts) OR (Immunosuppressed Hosts) OR (immunodeficiency) OR (immunocompromised) OR (immunosuppressed)).ti,ab.	1

Table 2. *Cont.*

Database (Date of Search)	Search Strategies	Number of Articles Found
Scopus (7 November 2023)	TITLE-ABS (((artificial AND membranes) OR (artificial AND membrane) OR (tissue AND scaffolds) OR (tissue AND scaffold) OR (absorbable AND membrane) OR (absorbable AND membranes) OR (semi-absorbable AND membrane) OR (semi-absorbable AND membranes) OR (non-absorbable AND membranes) OR (non-absorbable AND membrane) OR (barrier AND membrane) OR (barrier AND membranes) OR (synthetic AND membrane) OR (synthetic AND membranes)) AND ((guided AND tissue AND regeneration) OR (bone AND regeneration) OR (bone AND regenerations) OR (periodontal AND guided AND tissue AND regeneration) OR (guided AND periodontal AND tissue AND regeneration) OR (tissue AND engineering) OR (nerve AND regeneration) OR (nerve AND tissue AND regeneration) OR (nervous AND tissue AND regeneration) OR (neural AND tissue AND regeneration)) AND ((immunocompromised AND host) OR (immunosuppressed AND host) OR (immunocompromised AND patient) OR (immunocompromised AND hosts) OR (immunosuppressed AND hosts) OR (immunodeficiency) OR (immunocompromised) OR (immunosuppressed))) AND (EXCLUDE (DOCTYPE , “re”) OR EXCLUDE (DOCTYPE , “ch”) OR EXCLUDE (DOCTYPE , “cp”)) AND (LIMIT-TO (LANGUAGE , “English”))	79
Web of Science (7 November 2023)	(TI = (((Artificial Membranes) OR (Artificial Membrane) OR (Tissue Scaffolds) OR (Tissue Scaffold) OR (absorbable membrane) OR (absorbable membranes) OR (Semi-absorbable membrane) OR (Semi-absorbable membranes) OR (non-absorbable membranes) OR (non-absorbable membrane) OR (Barrier Membrane) OR (Barrier Membranes) OR (synthetic membrane) OR (synthetic membranes)) AND ((Guided Tissue Regeneration) OR (Bone Regeneration) OR (Bone Regenerations) OR (Periodontal Guided Tissue Regeneration) OR (Guided Periodontal Tissue Regeneration) OR (Tissue Engineering) OR (Nerve Regeneration) OR (Nerve Tissue Regeneration) OR (Nervous Tissue Regeneration) OR (Neural Tissue Regeneration)) AND ((Immunocompromised Host) OR (Immunosuppressed Host) OR (Immunocompromised Patient) OR (Immunocompromised Hosts) OR (Immunosuppressed Hosts) OR (immunodeficiency) OR (immunocompromised) OR (immunosuppressed)))) OR AB = (((Artificial Membranes) OR (Artificial Membrane) OR (Tissue Scaffolds) OR (Tissue Scaffold) OR (absorbable membrane) OR (absorbable membranes) OR (Semi-absorbable membrane) OR (Semi-absorbable membranes) OR (non-absorbable membranes) OR (non-absorbable membrane) OR (Barrier Membrane) OR (Barrier Membranes) OR (synthetic membrane) OR (synthetic membranes)) AND ((Guided Tissue Regeneration) OR (Bone Regeneration) OR (Bone Regenerations) OR (Periodontal Guided Tissue Regeneration) OR (Guided Periodontal Tissue Regeneration) OR (Tissue Engineering) OR (Nerve Regeneration) OR (Nerve Tissue Regeneration) OR (Nervous Tissue Regeneration) OR (Neural Tissue Regeneration)) AND ((Immunocompromised Host) OR (Immunosuppressed Host) OR (Immunocompromised Patient) OR (Immunocompromised Hosts) OR (Immunosuppressed Hosts) OR (immunodeficiency) OR (immunocompromised) OR (immunosuppressed)))	70

The process of selecting studies was conducted in two separate stages. In the first stage, the titles and abstracts of retrieved articles were screened for relevance. Two independent reviewers evaluated each study based on the preset inclusion and exclusion criteria. Articles that satisfied the initial criteria were then subjected to a thorough full-text review in the second stage. During this phase, the same two reviewers assessed the studies for final inclusion, resolving any differences through discussion or by consulting a third reviewer when needed.

Clear inclusion and exclusion criteria were established to ensure the quality and relevance of the selected studies. Inclusion criteria included studies examining the use of GTR membranes in patients with weakened immune systems, reporting healing outcomes such as tissue regeneration or infection prevention, involving human samples or relevant preclinical models, and published as original research in peer-reviewed journals in English. On the other hand, exclusion criteria consisted of review articles, meta-analyses, and

opinion pieces; studies not published in English; research that did not focus on GTR membranes or was unrelated to immunocompromised populations; and studies lacking insufficient methodological detail or with incomplete outcome data.

Data extraction was performed using a standardized form specifically created for this review. The extracted information included details such as study characteristics (author(s), publication year, study location, research design, and sample size), population characteristics (patient conditions like diabetes or cancer and their immunocompromised status), intervention details (types of GTR membranes, materials used, and additional therapeutic components such as growth factors or antimicrobials), key findings, and any limitations or recommendations noted by the authors. To ensure accuracy and consistency, one reviewer conducted the data extraction, which was then independently validated by a second reviewer. Any disagreements were resolved through mutual discussion and agreement.

The extracted data were synthesized and presented narratively to offer a thorough summary of the findings. This synthesis included grouping studies by characteristics such as patient population, GTR membrane type, and research design. A thematic analysis was carried out to identify shared trends and recurring patterns in the results. Reported healing outcomes were compared across studies to highlight trends, strengths, and limitations in the evidence. Research gaps were also identified, particularly in areas where evidence was inconsistent, lacking, or inconclusive.

By using this structured and transparent approach, this review aimed to deliver a comprehensive and reliable synthesis of the evidence regarding GTR membranes in immunocompromised patients, contributing to the advancement of knowledge and informing clinical practice in this essential field.

3. Results

The systematic search identified a total of 218 articles, from which 64 duplicates were removed. After screening the title and abstract of the remaining 154 articles, 144 studies were excluded due to their focus on non-human models, irrelevance to GTR membranes, or lack of applicability to immunocompromised populations (Figure 1). A full-text review of the remaining 10 articles identified 5 studies that met the defined inclusion criteria. These studies focused on experimental applications of GTR membrane technologies in preclinical models and human sample-based research relevant to immunocompromised individuals.

The findings from these studies highlighted advancements in the design and use of GTR membranes for tissue regeneration in environments affected by systemic conditions (Table 3). Several key themes emerged, showcasing innovations in membrane engineering, incorporation of biological agents, and applications in complex regenerative scenarios.

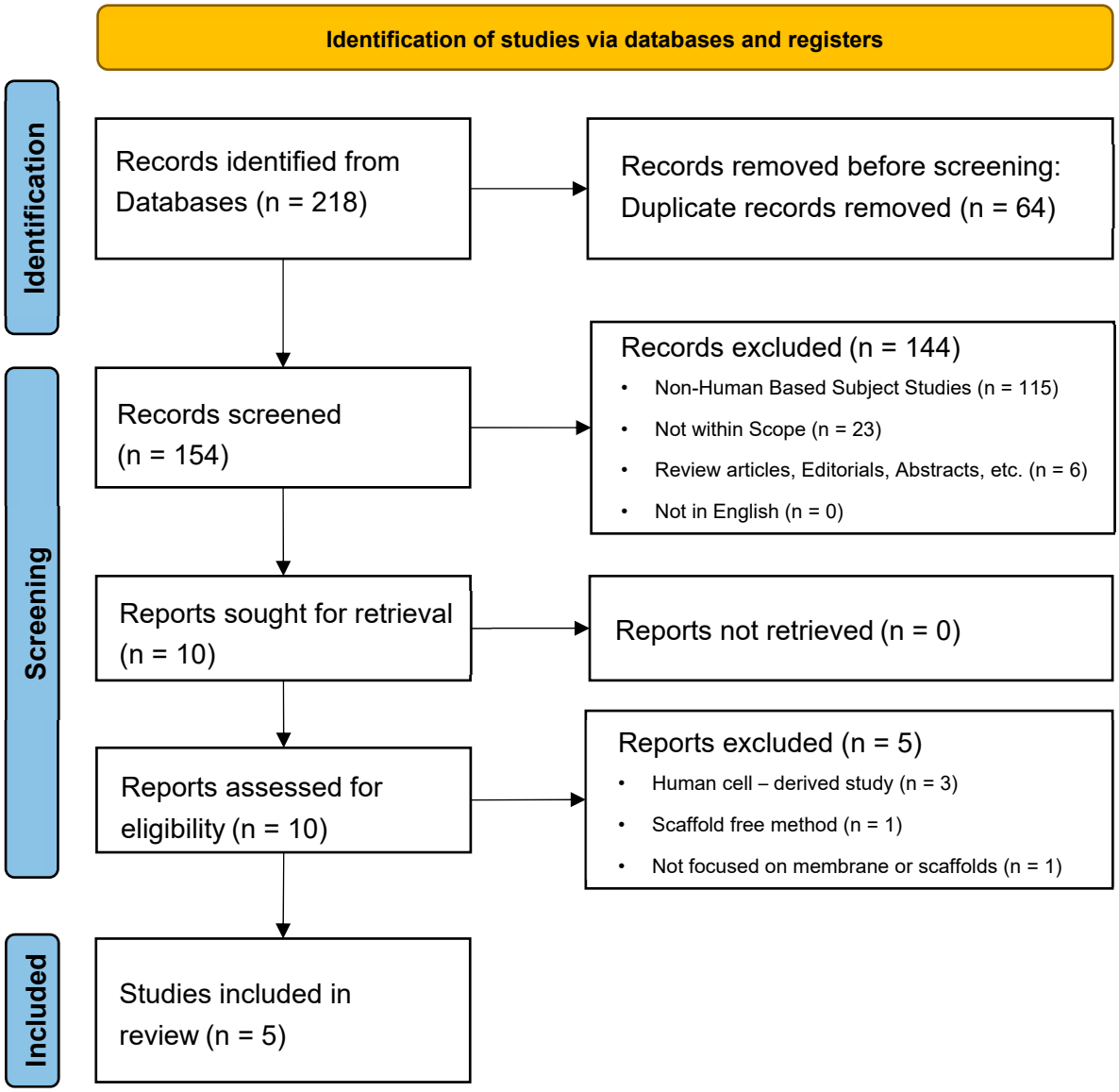


Figure 1. PRISMA flow diagram of article selection.

One notable finding was the incorporation of stem cells with GTR membranes to improve regenerative outcomes. Stem cells such as oral mucosa stem/progenitor cells (OMSFCs) and dental pulp stem cells (DPSCs) showed remarkable potential when combined with engineered membranes or scaffolds. These cells demonstrated self-renewal capabilities and differentiation potential, contributing to the development of complex tissues such as bone and periodontal structures [32]. The addition of bone morphogenetic protein-2 (BMP-2) pre-treatment in combination with biomimetic scaffolds significantly enhanced osteogenesis and mineralized matrix deposition [28]. Similarly, OMSFCs cultured using the neurosphere technique regenerated cementum-like structures and ectopic bone in non-hard tissue regions [27]. These studies emphasize the synergistic effects of combining stem cell-based therapies with bioengineered membranes, particularly in overcoming limited regenerative capacities in immunocompromised patients.

Table 3. Characteristics and findings from the reviewed articles.

Author (Year)	Country	Study Aims	Findings
Abe et al. (2015) [27]	Japan	To isolate NCSCs from oral mucosa using the neurosphere technique and to establish effective in vivo bone tissue regeneration methods.	OMSFCs have similar properties to NCSCs (self-renewing capabilities and multipotency); OMSFCs were able to generate ectopic bone tissues even in a region not naturally containing hard tissue; regenerated acellular-type hard tissues from the OMSFCs form cementum-like structures, and the use of the neurosphere culture technique allows for a more simplified method for isolating and culturing OMSFCs.
Bakopoulou et al. (2019) [28]	Greece	To investigate the potential of combining biomimetic chitosan/gelatin (CS/Gel) scaffolds with dental pulp stem cells (DPSCs) for orofacial bone reconstruction.	This study demonstrated the successful production of a nanocrystalline, mineralized matrix over time in both in vitro and in vivo settings, with CS/Gel-0.1 scaffolds showing more effective upregulation of osteo/odontogenic genes and enhanced bone formation when pre-treated with recombinant human BMP-2.
Barthel et al. (2012) [29]	United States	To develop tissue-engineered colons (TECs) from postnatal human organoid units and evaluate their potential for colon tissue regeneration by implanting them into immunocompromised mice.	A TEC was successfully generated from postnatal human organoid units implanted onto biodegradable scaffolds in immunocompromised mice, demonstrating differentiation into mature colon epithelium with supporting mesenchymal components, indicating a potential transition towards human therapy.
Basu et al. (2019) [30]	United States	To develop scaffold-free tissue constructs using periodontal ligament cells (PDLCs) that self-assemble into an organized multi-tissue structure mimicking the complex composition of periodontal tissues, specifically comprising a mineralized cementum-like core surrounded by a periodontal ligament (PDL)-like tissue.	Scaffold-free tissue constructs engineered from PDLCs demonstrated an organized multi-tissue structure comprising a mineralized cementum-like core and a PDL-like tissue, which maintained its structural and biochemical characteristics both in vitro and in vivo.
Graziano et al. (2007) [31]	Italy	To understand whether a microcavity-rich scaffold had distinct bone-forming capabilities compared to a smooth one.	Cells on the microcavity-rich scaffold released larger amounts of BMP-2 and VEGF into the culture medium and expressed higher alkaline phosphatase activity. The microcavity-rich scaffold enhanced cell adhesion: the cells created initimate contact with secondary microcavities and were polarized.

Scaffold architecture and material properties were identified as critical factors in successful tissue regeneration. Biomimetic scaffolds, such as chitosan/gelatin (CS/Gel) composites [28] and microcavity-rich designs [31], demonstrated superior performance in promoting cell adhesion, polarization, and growth factor release. These architectural features facilitated key cellular interactions and supported the deposition of mineralized matrices required for bone regeneration. Microcavity-rich scaffolds, for instance, increased the release of BMP-2 and VEGF, enhancing osteogenic activity and alkaline phosphatase expression [31]. These findings highlight the importance of scaffold microarchitecture in optimizing biological activity, particularly in challenging regenerative environments.

The investigation of scaffold-free tissue engineering presented an alternative strategy to traditional membrane-based methods. Scaffold-free constructs, developed from periodontal ligament cells (PDLCs), were capable of self-assembling into organized, multi-tissue structures resembling the native periodontal composition [30]. These constructs exhibited a mineralized cementum-like core surrounded by periodontal ligament-like tissue, maintaining both structural and biochemical integrity in vitro and in vivo [33]. The scaffold-free approach offered unique advantages, such as reduced immunogenicity and improved integration with host tissues, making it particularly beneficial for patients where scaffold implantation may pose challenges due to systemic conditions or immunosuppression.

Preclinical applications of GTR technologies provided additional evidence of their translational potential. Postnatal human organoid units were successfully differentiated into mature colon epithelium within tissue-engineered colon (TEC) constructs [29]. These constructs, created using biodegradable scaffolds and implanted into immunocompromised mouse models, served as a platform for evaluating GTR membrane performance under conditions simulating impaired immune environments [34]. The ability of these constructs to integrate with host tissues and support functional differentiation underscores the potential of GTR technologies to address large-scale tissue deficits in clinical practice.

4. Discussion

The findings from this scoping review highlight the transformative role of GTR membranes in addressing the complex challenges faced by immunocompromised populations. These systemic conditions are often associated with delayed or impaired healing due to factors such as chronic inflammation, reduced angiogenesis, and diminished immune responses [35]. The reviewed studies collectively underscore the promise of GTR technologies, specifically in leveraging stem cells, scaffold designs, and novel engineering approaches to achieve enhanced regenerative outcomes.

4.1. Integration of Stem Cells with GTR Membranes

The integration of stem cells with GTR membranes represents a significant advancement in regenerative medicine [36]. Stem cells, such as OMSFCs and DPSCs, possess self-renewal and multipotency, enabling them to differentiate into multiple cell types and regenerate complex tissues [37]. Abe et al. [27] demonstrated that OMSFCs cultured using the neurosphere technique could regenerate cementum-like structures and ectopic bone in non-hard tissue regions. This aligns with previous findings that stem cells, when embedded in bioengineered constructs, adapt to their microenvironment and respond to regenerative cues, even in compromised conditions [38].

Similarly, Bakopoulou et al. [28] reported that DPSCs embedded in CS/Gel scaffolds pre-treated with BMP-2 significantly enhanced osteogenesis and mineralized matrix deposition. The role of BMP-2 in upregulating osteogenic pathways has been extensively documented, showing promise in promoting bone repair, particularly in diabetic patients where chronic hyperglycemia disrupts osteoblast function [39]. In cancer patients, stem cell

therapies embedded within GTR membranes could mitigate treatment-induced bone loss and accelerate healing following surgical resections or radiotherapy [40].

Collectively, these studies highlight that stem cell integration is not merely additive but foundational for the success of advanced GTR therapies. By embedding stem cells within bioengineered scaffolds and enhancing their activity through growth factors, GTR membranes can overcome significant regenerative deficits observed in immunocompromised populations [41].

4.2. Architectural and Material Innovations in GTR Membranes

The design and material composition of GTR membranes emerged as critical determinants of their efficacy. Graziano et al. [31] demonstrated that microcavity-rich scaffolds enhanced the release of BMP-2 and VEGF, which significantly improved osteogenic activity and alkaline phosphatase expression. VEGF, a potent angiogenic factor, is particularly critical in diabetic wounds, where reduced vascularization impairs tissue repair [31]. Microcavity-rich designs thus provide structural cues that mimic the extracellular matrix, facilitating both angiogenesis and osteogenesis in compromised environments [42].

CS/Gel composites further exemplify the importance of material properties in creating an optimal regenerative microenvironment [28,43]. These scaffolds not only promoted cellular adhesion and polarization but also supported the controlled release of BMP-2, providing sustained osteogenic signaling [44]. Previous studies have corroborated that biocompatible and biodegradable materials such as chitosan enhance regenerative outcomes by integrating seamlessly with host tissues and minimizing inflammatory responses [45].

These findings highlight the pivotal role of scaffold architecture and materials in amplifying biological activity, particularly in immunocompromised settings where natural regenerative signals are often insufficient. Advanced designs that mimic the extracellular matrix while releasing bioactive factors could bridge the gap between experimental efficacy and clinical application [46].

4.3. Scaffold-Free Tissue Engineering

Scaffold-free tissue engineering offers a novel approach to tissue regeneration, particularly for patients at higher risk of scaffold-related complications [47]. Basu et al. [30] demonstrated that scaffold-free constructs derived from PDLCs could self-assemble into organized, multi-tissue structures, mimicking the composition and functionality of native periodontal tissue. This approach is particularly relevant for immunocompromised patients, as synthetic scaffolds may increase the risk of immune rejection or foreign body reactions [48].

Scaffold-free constructs align with the body's natural healing processes by leveraging the innate organizational capabilities of cells [49]. This approach is supported by other studies demonstrating that scaffold-free tissue engineering reduces immunogenicity while maintaining functional tissue integrity [50]. These advantages make scaffold-free constructs an attractive option for addressing complex tissue defects in vulnerable populations.

4.4. Preclinical Models and Translational Potential

Preclinical models provide valuable insights into the translational potential of GTR technologies [51]. Barthel et al. [29] demonstrated that TEC constructs successfully differentiated into mature colon epithelium when implanted in immunocompromised mice. These findings align with research indicating that biodegradable scaffolds can support the functional differentiation and integration of tissue-engineered constructs in vivo [29,52].

While preclinical models highlight the feasibility of applying GTR technologies to complex tissues, they also underscore the challenges of translating these findings to human populations. Differences in immune system dynamics and tissue-specific responses

between animal models and humans necessitate rigorous clinical trials to validate efficacy and scalability.

4.5. Gaps and Challenges

Several gaps in the current literature were identified. First, the predominant reliance on preclinical models limits the generalizability of findings to human populations. While these models simulate immunocompromised environments, they do not fully replicate the complexities of human physiology, particularly in chronic conditions like diabetes and cancer.

Second, the heterogeneity within immunocompromised populations remains underexplored. Variations in glycemic control among diabetic patients or differences in cancer treatment regimens likely influence GTR membrane performance but were not adequately stratified in the reviewed studies. Future studies should account for these variables to develop personalized regenerative solutions.

Finally, the long-term outcomes and potential adverse effects of GTR membranes are poorly understood. Chronic conditions may introduce systemic factors that affect the performance and longevity of these technologies, necessitating longitudinal studies to assess sustained efficacy and identify delayed complications.

4.6. Clinical Implications

The findings from this review underscore the transformative potential of GTR membranes in addressing the unique challenges of tissue repair and regeneration in immunocompromised populations. These systemic conditions often impair the body's natural healing processes due to chronic inflammation, reduced angiogenesis, and immune system suppression [29,53]. The advancements highlighted in the reviewed studies provide a foundation for incorporating GTR membranes into clinical practice to improve outcomes in these high-risk populations. However, a better understanding of their clinical implications is essential for maximizing their therapeutic potential.

4.6.1. Personalized Approaches to Regeneration

One of the most significant clinical implications is the necessity for personalized approaches when applying GTR membranes in immunocompromised patients. The reviewed studies revealed that variations in systemic conditions could influence the performance of GTR membranes. For instance, diabetic patients often experience impaired bone repair and chronic wound healing due to diminished angiogenic and osteogenic responses [54]. The use of biomimetic scaffolds pre-treated with BMP-2 has shown potential in overcoming these deficits by enhancing osteogenesis and angiogenesis [55]. These findings suggest that integrating patient-specific factors into GTR membrane design, such as incorporating growth factors or antimicrobial properties tailored to an individual's physiological needs, could significantly improve clinical outcomes.

4.6.2. Enhanced Material Design for Clinical Applications

The architectural and material innovations in GTR membranes, such as CS/Gel scaffolds and microcavity-rich designs, offer promising solutions for creating tissue-specific regenerative environments [56]. These biomimetic scaffolds not only mimic the extracellular matrix but also promote cell adhesion, polarization, and growth factor release, essential for successful tissue integration and repair [57]. For cancer patients undergoing radiotherapy or chemotherapy, who may face significant tissue loss and delayed healing, these materials could provide critical support for reconstruction and regeneration [4]. The ability to incorporate bioactive molecules that counteract the immunosuppressive effects of cancer treatments further enhances the applicability of GTR membranes in oncology [34].

The development of multifunctional GTR membranes that combine regenerative, antibacterial, and anti-inflammatory properties could address multiple challenges simultaneously in clinical settings [58]. For example, diabetic patients with chronic wounds are at a heightened risk of infection [59], making antibacterial membranes a crucial innovation. Similarly, anti-inflammatory membranes could modulate chronic inflammation in cancer patients or those with poorly controlled diabetes, fostering a more conducive environment for tissue repair [60].

4.6.3. Scaffold-Free Constructs for Immunocompromised Patients

Scaffold-free tissue engineering represents an alternative approach with specific clinical advantages for immunocompromised patients. By leveraging the self-organizing capabilities of cells, such as PDLCs, scaffold-free constructs eliminate the risks associated with synthetic scaffold implantation, such as foreign body reactions and delayed integration [61]. For patients at higher risk of immune-related complications, this approach aligns closely with the body's natural healing mechanisms and offers a viable pathway for complex tissue regeneration.

In clinical practice, scaffold-free constructs could be particularly beneficial in reconstructive surgeries or periodontal repair, where maintaining native tissue compatibility and minimizing the immune response are critical [62]. These constructs also have the potential to reduce the procedural complexity of scaffold placement, offering streamlined regenerative solutions [47].

4.6.4. Preclinical Findings and Translational Potential

The preclinical studies reviewed in this study demonstrate the potential for GTR membranes to support the regeneration of large-scale tissue defects and even complex organ systems [63]. These findings highlight the scalability and adaptability of GTR technologies for clinical applications. However, translating these preclinical successes to human populations requires rigorous clinical trials to evaluate efficacy, safety, and long-term outcomes [64,65]. Clinicians must consider patient-specific variables, such as the degree of immunosuppression, comorbid conditions, and potential interactions with concurrent treatments, when implementing GTR-based therapies.

4.6.5. Addressing Challenges and Building on Current Innovations

Despite the promising advancements, the successful clinical implementation of GTR membranes in immunocompromised populations requires addressing several challenges. The lack of human studies and limited understanding of long-term outcomes necessitate extensive clinical trials. Additionally, the heterogeneity of systemic conditions in immunocompromised patients requires stratified research that accounts for variations in disease severity and treatment regimens. Developing standardized protocols for membrane selection, application techniques, and monitoring could enhance consistency and effectiveness in clinical settings.

4.7. Limitations of This Review

The review process has several limitations. Restricting the included studies to those published in English introduced a language bias, potentially excluding relevant research from non-English sources. Additionally, while the selected databases offer broad coverage, studies in less commonly indexed journals or newer repositories might have been overlooked. The exclusion of meta-analyses, review articles, and studies with insufficient methodological details limited the scope of evidence and broader context. Reviewer bias may have influenced study selection, as resolving disagreements involved subjective judgment. Heterogeneity in study designs, populations, and outcome measures complicated

comparisons and reduced generalizability. The reliance on preclinical models further limits the applicability of the findings to clinical settings. Furthermore, the search period cut-off might have excluded recent advancements in GTR technologies. Lastly, the focus on healing outcomes and membrane efficacy may have overlooked critical factors such as patient variability, long-term impacts, and economic considerations. These limitations underscore the need for more comprehensive and inclusive future research in this field.

4.8. Future Integration into Standard Care

As the field of regenerative medicine evolves, GTR membranes have the potential to become a standard component of care for high-risk patient populations. By integrating these technologies into multidisciplinary treatment plans that include wound care specialists, surgeons, and oncologists, GTR membranes can address a wide range of clinical needs, from managing chronic wounds to supporting reconstructive surgeries. The ability to customize GTR membranes for individual patients further enhances their versatility and positions them as a cornerstone of future regenerative therapies.

5. Conclusions

GTR membranes show immense potential in addressing the complex challenges of tissue repair in immunocompromised populations. The integration of stem cells with advanced scaffolds, enriched with growth factors like BMP-2, significantly enhances regenerative outcomes, particularly in environments compromised by systemic conditions. Innovations in scaffold design, including biomimetic and microcavity-rich structures, as well as scaffold-free tissue engineering, further highlight the versatility of GTR technologies. While preclinical studies demonstrate promising translational potential, challenges remain regarding clinical validation, personalized applications, and long-term efficacy. With continued research and development, GTR membranes could transform regenerative medicine, offering effective and sustainable solutions for high-risk patients.

Author Contributions: Conceptualization, M.H. and K.S.; methodology, M.H., C.S. and A.M.; software, M.H., C.S. and A.M.; validation, M.H., C.S. and A.M.; formal analysis, M.H., K.S., A.D., R.T. and A.M.; investigation, M.H., K.S., A.D., R.T., C.S. and A.M.; resources, M.H.; data curation, M.H., K.S., A.D., R.T., C.S. and A.M.; writing—original draft preparation, M.H., K.S., A.D., R.T. and A.M.; writing—review and editing, M.H., K.S., A.D., R.T., C.S. and A.M.; visualization, M.H., K.S., A.D., C.S. and A.M.; supervision, M.H.; project administration, M.H.; funding acquisition, M.H. All authors have read and agreed to the published version of the manuscript.

Funding: This study did not receive any external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Fort Collins. Key Benefits of Guided Tissue Regeneration. Available online: https://www.fortcollinsperio.com/benefits-of-guided-tissue-regeneration (accessed on 5 December 2024).
2. Wang, D.; Zhou, X.; Cao, H.; Zhang, H.; Wang, D.; Guo, J.; Wang, J. Barrier membranes for periodontal guided bone regeneration: A potential therapeutic strategy. *Front. Mater.* **2023**, *10*, 1220420. [CrossRef]
3. Liu, W.-S.; Liu, Y.; Gao, J.; Zheng, H.; Lu, Z.-M.; Li, M. Biomembrane-Based Nanostructure- and Microstructure-Loaded Hydrogels for Promoting Chronic Wound Healing. *Int. J. Nanomed.* **2023**, *18*, 385–411. [CrossRef] [PubMed]
4. Abtahi, S.; Chen, X.; Shahabi, S.; Nasiri, N. Resorbable Membranes for Guided Bone Regeneration: Critical Features, Potentials, and Limitations. *ACS Mater. Au* **2023**, *3*, 394–417. [CrossRef]

5. Huang, T.-H.; Chen, J.-Y.; Suo, W.-H.; Shao, W.-R.; Huang, C.-Y.; Li, M.-T.; Li, Y.-Y.; Li, Y.-H.; Liang, E.-L.; Chen, Y.-H.; et al. Unlocking the Future of Periodontal Regeneration: An Interdisciplinary Approach to Tissue Engineering and Advanced Therapeutics. *Biomedicines* **2024**, *12*, 1090. [CrossRef]
6. Pandit, N.; Malik, R.; Philips, D. Tissue engineering: A new vista in periodontal regeneration. *J. Indian Soc. Periodontol.* **2011**, *15*, 328–337. [CrossRef]
7. Jiamset, I.; Hanprasertpong, J. Impact of diabetes mellitus on oncological outcomes after radical hysterectomy for early stage cervical cancer. *J. Gynecol. Oncol.* **2016**, *27*, e28. [CrossRef]
8. Burgess, J.L.; Wyant, W.A.; Abujamra, B.A.; Kirsner, R.S.; Jozic, I. Diabetic Wound-Healing Science. *Medicina* **2021**, *57*, 1072. [CrossRef]
9. Buranasin, P.; Mizutani, K.; Iwasaki, K.; Mahasarakham, C.P.N.; Kido, D.; Takeda, K.; Izumi, Y. High glucose-induced oxidative stress impairs proliferation and migration of human gingival fibroblasts. *PLoS ONE* **2018**, *13*, e0201855. [CrossRef]
10. Yadav, J.P.; Verma, A.; Pathak, P.; Dwivedi, A.R.; Singh, A.K.; Kumar, P.; Khalilullah, H.; Jaremko, M.; Emwas, A.-H.; Patel, D.K. Phytoconstituents as modulators of NF-κB signalling: Investigating therapeutic potential for diabetic wound healing. *Biomed. Pharmacother.* **2024**, *177*, 117058. [CrossRef]
11. Wolf, S.J.; Melvin, W.J.; Gallagher, K. Macrophage-mediated inflammation in diabetic wound repair. *Semin. Cell Dev. Biol.* **2021**, *119*, 111–118. [CrossRef]
12. Deptuła, M.; Zieliński, J.; Wardowska, A.; Pikuła, M. Wound healing complications in oncological patients: Perspectives for cellular therapy. *Postep. Dermatol. Alergol.* **2019**, *36*, 139–146. [CrossRef] [PubMed]
13. Słonimska, P.; Sachadyn, P.; Zieliński, J.; Skrzypski, M.; Pikuła, M. Chemotherapy-Mediated Complications of Wound Healing: An Understudied Side Effect. *Adv. Wound Care* **2024**, *13*, 187–199. [CrossRef] [PubMed]
14. Kolimi, P.; Narala, S.; Nyavanandi, D.; Youssef, A.A.A.; Dudhipala, N. Innovative Treatment Strategies to Accelerate Wound Healing: Trajectory and Recent Advancements. *Cells* **2022**, *11*, 2439. [CrossRef]
15. Bajpai, D.; Rajasekar, A. Recent advances in GTR scaffolds. *Bioinformation* **2022**, *18*, 1181–1185. [CrossRef]
16. Aryal, R.; Chen, X.p.; Fang, C.; Hu, Y.c. Bone Morphogenetic Protein-2 and Vascular Endothelial Growth Factor in Bone Tissue Regeneration: New Insight and Perspectives. *Orthop. Surg.* **2014**, *6*, 171–178. [CrossRef]
17. Hassan, S.U.; Bilal, B.; Nazir, M.S.; Naqvi, S.A.R.; Ali, Z.; Nadeem, S.; Muhammad, N.; Palvasha, B.A.; Mohyuddin, A. Recent progress in materials development and biological properties of GTR membranes for periodontal regeneration. *Chem. Biol. Drug Des.* **2021**, *98*, 1007–1024. [CrossRef]
18. Bruna, T.; Maldonado-Bravo, F.; Jara, P.; Caro, N. Silver Nanoparticles and Their Antibacterial Applications. *Int. J. Mol. Sci.* **2021**, *22*, 7202. [CrossRef]
19. Quteish, D.; Dolby, A.E. The use of irradiated-crosslinked human collagen membrane in guided tissue regeneration. *J. Clin. Periodontol.* **1992**, *19*, 476–484. [CrossRef]
20. Solomon, S.-M.; Sufaru, I.-G.; Teslaru, S.; Ghiciuc, C.; Stafie, C. Finding the Perfect Membrane: Current Knowledge on Barrier Membranes in Regenerative Procedures: A Descriptive Review. *Appl. Sci.* **2022**, *12*, 1042. [CrossRef]
21. Choi, J.F.; Chang, P. *Oral Surgery, Extraction of Unerupted Teeth*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
22. International Diabetes Federation. Facts & Figures. Available online: https://idf.org/about-diabetes/diabetes-facts-figures/ (accessed on 5 December 2024).
23. International Agency for Research on Cancer. Latest Global Cancer Data: Cancer Burden Rises to 19.3 Million New Cases and 10.0 Million Cancer Deaths in 2020. Available online: https://www.iarc.who.int/news-events/latest-global-cancer-data-cancer-burden-rises-to-19-3-million-new-cases-and-10-0-million-cancer-deaths-in-2020/ (accessed on 5 December 2024).
24. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef]
25. Sasaki, J.-I.; Abe, G.L.; Li, A.; Thongthai, P.; Tsuboi, R.; Kohno, T.; Imazato, S. Barrier membranes for tissue regeneration in dentistry. *Biomater. Investig. Dent.* **2021**, *8*, 54–63. [CrossRef] [PubMed]
26. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
27. Abe, S.; Yamaguchi, S.; Sato, Y.; Harada, K. Sphere-Derived Multipotent Progenitor Cells Obtained From Human Oral Mucosa Are Enriched in Neural Crest Cells. *Stem Cells Transl. Med.* **2015**, *5*, 117–128. [CrossRef]
28. Bakopoulou, A.; Georgopoulou, A.; Grivas, I.; Bekiari, C.; Prymak, O.; Loza, K.; Epple, M.; Papadopoulos, G.C.; Koidis, P.; Chatzinikolaidou, M. Dental pulp stem cells in chitosan/gelatin scaffolds for enhanced orofacial bone regeneration. *Dent. Mater.* **2019**, *35*, 310–327. [CrossRef]
29. Barthel, E.R.; Levin, D.E.; Speer, A.L.; Sala, F.G.; Torashima, Y.; Hou, X.; Grikscheit, T.C. Human tissue-engineered colon forms from postnatal progenitor cells: An in vivo murine model. *Regen. Med.* **2012**, *7*, 807–818. [CrossRef]

30. Basu, A.; Rothermund, K.; Ahmed, M.N.; Syed-Picard, F.N. Self-Assembly of an Organized Cementum-Periodontal Ligament-Like Complex Using Scaffold-Free Tissue Engineering. *Front. Physiol.* **2019**, *10*, 422. [CrossRef]
31. Graziano, A.; d'Aquino, R.; Angelis, M.G.C.-D.; Laino, G.; Piattelli, A.; Pacifici, M.; De Rosa, A.; Papaccio, G. Concave pit-containing scaffold surfaces improve stem cell-derived osteoblast performance and lead to significant bone tissue formation. *PLoS ONE* **2007**, *2*, e496. [CrossRef]
32. Liu, P.; Zhang, Y.; Ma, Y.; Tan, S.; Ren, B.; Liu, S.; Dai, H.; Xu, Z. Application of dental pulp stem cells in oral maxillofacial tissue engineering. *Int. J. Med. Sci.* **2022**, *19*, 310–320. [CrossRef]
33. Woo, H.N.; Cho, Y.J.; Tarafder, S.; Lee, C.H. The recent advances in scaffolds for integrated periodontal regeneration. *Bioact. Mater.* **2021**, *6*, 3328–3342. [CrossRef]
34. Alqahtani, A.M. Guided Tissue and Bone Regeneration Membranes: A Review of Biomaterials and Techniques for Periodontal Treatments. *Polymers* **2023**, *15*, 3355. [CrossRef]
35. Gao, P.; Kajiya, M.; Motoike, S.; Ikeya, M.; Yang, J. Application of mesenchymal stem/stromal cells in periodontal regeneration: Opportunities and challenges. *Jpn. Dent. Sci. Rev.* **2024**, *60*, 95–108. [CrossRef] [PubMed]
36. Angjelova, A.; Jovanova, E.; Polizzi, A.; Annunziata, M.; Laganà, L.; Santonocito, S.; Isola, G. Insights and Advancements in Periodontal Tissue Engineering and Bone Regeneration. *Medicina* **2024**, *60*, 773. [CrossRef] [PubMed]
37. Huang, G.T.-J.; Gronthos, S.; Shi, S. Mesenchymal stem cells derived from dental tissues vs. those from other sources: Their biology and role in regenerative medicine. *J. Dent. Res.* **2009**, *88*, 792–806. [CrossRef] [PubMed]
38. Velikic, G.; Maric, D.M.; Maric, D.L.; Supic, G.; Puletic, M.; Dulic, O.; Vojvodic, D. Harnessing the Stem Cell Niche in Regenerative Medicine: Innovative Avenue to Combat Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2024**, *25*, 993. [CrossRef]
39. Halloran, D.; Durbano, H.W.; Nohe, A. Bone Morphogenetic Protein-2 in Development and Bone Homeostasis. *J. Dev. Biol.* **2020**, *8*, 19. [CrossRef]
40. Chu, D.-T.; Nguyen, T.T.; Tien, N.L.B.; Tran, D.-K.; Jeong, J.-H.; Anh, P.G.; Thanh, V.V.; Truong, D.T.; Dinh, T.C. Recent Progress of Stem Cell Therapy in Cancer Treatment: Molecular Mechanisms and Potential Applications. *Cells* **2020**, *9*, 563. [CrossRef]
41. Latimer, J.M.; Maekawa, S.; Yao, Y.; Wu, D.T.; Chen, M.; Giannobile, W.V. Regenerative Medicine Technologies to Treat Dental, Oral, and Craniofacial Defects. *Front. Bioeng. Biotechnol.* **2021**, *9*, 704048. [CrossRef]
42. Hashemi-Afzal, F.; Fallahi, H.; Bagheri, F.; Collins, M.N.; Eslaminejad, M.B.; Seitz, H. Advancements in hydrogel design for articular cartilage regeneration: A comprehensive review. *Bioact. Mater.* **2024**, *43*, 1–31. [CrossRef]
43. Bee, S.-L.; Hamid, Z.A.A. Asymmetric resorbable-based dental barrier membrane for periodontal guided tissue regeneration and guided bone regeneration: A review. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2022**, *110*, 2157–2182. [CrossRef]
44. Zhu, L.; Liu, Y.; Wang, A.; Zhu, Z.; Li, Y.; Zhu, C.; Che, Z.; Liu, T.; Liu, H.; Huang, L. Application of BMP in Bone Tissue Engineering. *Front. Bioeng. Biotechnol.* **2022**, *10*, 810880. [CrossRef]
45. Pramanik, S.; Aggarwal, A.; Kadi, A.; Alhomrani, M.; Alamri, A.S.; Alsanie, W.F.; Koul, K.; Deepak, A.; Bellucci, S. Chitosan alchemy: Transforming tissue engineering and wound healing. *RSC Adv.* **2024**, *14*, 19219–19256. [CrossRef] [PubMed]
46. Khanna, A.; Zamani, M.; Huang, N.F. Extracellular Matrix-Based Biomaterials for Cardiovascular Tissue Engineering. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 137. [CrossRef] [PubMed]
47. De Pieri, A.; Rochev, Y.; Zeugolis, D.I. Scaffold-free cell-based tissue engineering therapies: Advances, shortfalls and forecast. *NPJ Regen. Med.* **2021**, *6*, 18. [CrossRef]
48. Mariani, E.; Lisignoli, G.; Borzì, R.M.; Pulsatelli, L. Biomaterials: Foreign Bodies or Tuners for the Immune Response? *Int. J. Mol. Sci.* **2019**, *20*, 636. [CrossRef]
49. Mao, A.S.; Mooney, D.J. Regenerative medicine: Current therapies and future directions. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 14452–14459. [CrossRef]
50. Chan, B.P.; Leong, K.W. Scaffolding in tissue engineering: General approaches and tissue-specific considerations. *Eur. Spine J.* **2008**, *17*, 467–479. [CrossRef]
51. Murphy, K.G.; Gunsolley, J.C. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. *Ann. Periodontol.* **2003**, *8*, 266–302. [CrossRef]
52. Hamdy, T.M. Dental Biomaterial Scaffolds in Tooth Tissue Engineering: A Review. *Curr. Oral. Health Rep.* **2023**, *10*, 14–21. [CrossRef]
53. Schilrreff, P.; Alexiev, U. Chronic Inflammation in Non-Healing Skin Wounds and Promising Natural Bioactive Compounds Treatment. *Int. J. Mol. Sci.* **2022**, *23*, 4928. [CrossRef]
54. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget* **2017**, *9*, 7204–7218. [CrossRef]
55. Chen, Y.; Zhou, Y.; Lin, J.; Zhang, S. Challenges to Improve Bone Healing Under Diabetic Conditions. *Front. Endocrinol.* **2022**, *13*, 861878. [CrossRef]
56. Wang, J.; Guo, J.; Liu, J.; Wei, L.; Wu, G. BMP-functionalised coatings to promote osteogenesis for orthopaedic implants. *Int. J. Mol. Sci.* **2014**, *15*, 10150–10168. [CrossRef] [PubMed]

57. Gao, Y.; Wang, S.; Shi, B.; Wang, Y.; Chen, Y.; Wang, X.; Lee, E.-S.; Jiang, H.-B. Advances in Modification Methods Based on Biodegradable Membranes in Guided Bone/Tissue Regeneration: A Review. *Polymers* **2022**, *14*, 871. [CrossRef] [PubMed]
58. Bender, E.C.; Kraynak, C.A.; Huang, W.; Suggs, L.J. Cell-Inspired Biomaterials for Modulating Inflammation. *Tissue Eng. Part. B Rev.* **2022**, *28*, 279–294. [CrossRef] [PubMed]
59. Anjum, S.; Rahman, F.; Pandey, P.; Arya, D.K.; Alam, M.; Rajinikanth, P.S.; Ao, Q. Electrospun Biomimetic Nanofibrous Scaffolds: A Promising Prospect for Bone Tissue Engineering and Regenerative Medicine. *Int. J. Mol. Sci.* **2022**, *23*, 9206. [CrossRef]
60. Coussens, L.M.; Werb, Z. Inflammation and cancer. *Nature* **2002**, *420*, 860–867. [CrossRef]
61. Diban, F.; Di Lodovico, S.; Di Fermo, P.; D'Ercole, S.; D'Arcangelo, S.; Di Giulio, M.; Cellini, L. Biofilms in Chronic Wound Infections: Innovative Antimicrobial Approaches Using the In Vitro Lubbock Chronic Wound Biofilm Model. *Int. J. Mol. Sci.* **2023**, *24*, 1004. [CrossRef]
62. DuRaine, G.D.; Brown, W.E.; Hu, J.C.; Athanasiou, K.A. Emergence of Scaffold-free Approaches for Tissue Engineering Musculoskeletal Cartilages. *Ann. Biomed. Eng.* **2014**, *43*, 543–554. [CrossRef]
63. Liu, J.; Ruan, J.; Weir, M.D.; Ren, K.; Schneider, A.; Wang, P.; Oates, T.W.; Chang, X.; Xu, H.H.K. Periodontal Bone-Ligament-Cementum Regeneration via Scaffolds and Stem Cells. *Cells* **2019**, *8*, 537. [CrossRef]
64. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Regenerative Medicine. *Emerging Technologies and Innovation in Manufacturing Regenerative Medicine Therapies: Proceedings of a Workshop—In Brief*; National Academies Press (US): Washington, DC, USA, 2024.
65. Yang, Z.; Wu, C.; Shi, H.; Luo, X.; Sun, H.; Wang, Q.; Zhang, D. Advances in Barrier Membranes for Guided Bone Regeneration Techniques. *Front. Bioeng. Biotechnol.* **2022**, *10*, 921576. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.