

Review Article**Applications of Natural Polymers in Regenerative Medicine and Tissue Engineering****Abdallah Shabbir Ali, Rabia Gul*, Halima Usman, Faiza Naseer**

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Abstract

Natural polymers, or biopolymers, are widely utilized in regenerative medicine and tissue engineering. These polymers, derived from proteins, polysaccharides, and nucleic acids, serve as biomaterials for scaffolds, drug delivery systems, and bioactive materials that mimic the extracellular matrix. They offer advantages such as biocompatibility, biodegradability, versatility, and integration with gene therapy. Collagen, gelatin, chitosan, hyaluronic acid, fibrin, and alginate are commonly used natural polymers in regenerative medicine. They promote cell growth, tissue formation, wound healing, and tissue regeneration. Natural polymers also play a crucial role in controlled drug and gene delivery systems, providing safe and effective alternatives to synthetic polymers. Moreover, they contribute to developing bioactive and bio-functional materials, including hydrogels, which mimic natural biological processes and have applications in tissue engineering, drug delivery, and wound healing. Overall, natural polymers hold great promise for advancing regenerative medicine and tissue engineering. However, several challenges impede the widespread adoption and utilization of natural polymers in regenerative medicine. These challenges include variations in batch-to-batch composition, limited mechanical strength, rapid degradation rates, immunogenicity concerns, and difficulties achieving precise control over their properties. Overcoming these challenges necessitates a comprehensive understanding of the structure-function relationships of natural polymers and the development of innovative processing techniques to enhance their mechanical properties and stability. The future of natural polymers in regenerative medicine holds immense potential. Ongoing research efforts focus on refining their properties, tailoring their degradation rates, and integrating them with advanced technologies like 3D bioprinting and nanotechnology. By leveraging these advancements, natural polymers can be further optimized for specific tissue engineering applications, enabling the creation of patient-specific scaffolds, enhanced wound healing materials, and personalized drug delivery systems. Additionally, harnessing the innate bioactivity of natural polymers and their interactions with cells and tissues opens new avenues for the development of bioactive materials that promote tissue regeneration and healing.

Keywords: Biodegradable polymers, bone and cartilage repair, scaffolds, regenerative medicine.**1. Introduction**

Natural polymers, also known as biopolymers, are large molecules composed of repeating units found in living organisms. These polymers are derived from natural sources such as proteins, polysaccharides, and nucleic acids (bar, Laurencin, and Deng 2014). In the context of regenerative medicine and tissue engineering, natural polymers are utilized as biomaterials to support the regeneration and

repair of damaged tissues and organs (Dang and Leong 2006). They serve as building blocks for the development of scaffolds, drug delivery systems, and bioactive materials that mimic the extracellular matrix (ECM) and provide a suitable microenvironment for cell growth and tissue regeneration (Dang and Leong 2006). In past decades, the field of regenerative medicine has evolved in terms of

repair, regeneration, and restoration of tissues using various naturally available polymers, including the restoration and repair of skin, bone, cartilage, and blood vessels. In regenerative medicine, guiding cells toward desired behaviors using signals from biopolymeric materials is crucial for tissue restoration and regeneration. The interaction between materials and cells plays a significant role in this process (Iovene and Zhao 2021).

Biopolymers possess several properties and advantages of biocompatibility, biomimicry, biodegradability, versatility, availability, sustainability, bioactivity, and integration with gene therapy, making them highly promising materials for regenerative medicine applications (Abbasian et al. 2019),(Loh and Choong 2013). They are extensively used as scaffold materials, promoting cell growth and guiding tissue formation in various areas such as skin, bone, cartilage, nerves, and blood vessels (Akilbekova et al. 2018). Researchers are focusing on functionalizing natural polymers to incorporate specific cues, including physical, chemical, and biological signals, to guide cellular behavior and tissue development. Efforts are also directed toward improving natural polymers' mechanical properties, degradation rates, and immunomodulatory properties through techniques like blending, crosslinking, and surface modifications. Ongoing research aims to develop more effective and clinically relevant approaches for tissue repair and regeneration using natural polymers (Abbasian et al. 2019).

Naturally occurring polymers found are used in the field of medicine and especially in the field of regenerative medicine. Collagen (structural protein from animal tissues) is used in wound healing, bone repair, and tissue engineering (Cheema, Ananta, and Mudera 2011). Gelatin formed by hydrolysis

polymerization used in pharmaceutical designing and dosage forms is a modified form of collagen (hydrocolloid). Chitosan (a polymer formed due to de-acetylation and is separated from the chitin found in the exoskeleton) also has applications in wound healing, tissue, and cartilage regeneration). Hyaluronic acid (HA) is classified as glycosaminoglycan, synthesized naturally in connective tissues and bacteria; it is used as a bone regenerative agent and also in ocular drug delivery. Fibrin (fibroin silk), discovered thousand years ago, is produced naturally by silkworms and used as a tissue adhesive, tissue regenerative agent as a structural protein. Alginate formed as a result of ionotropic gelation derived from brown algae is also used in tissue repair, regeneration, and restoration (Oliveira and Mano 2014). Natural polymers are enormous, but the given biopolymers, which are of special importance in the field of regenerative medicine and tissue engineering, are summarized in Table 1. This review article aims to highlight the significant role of natural polymers in regenerative medicine and tissue engineering, emphasizing their advantages and applications. Additionally, it aims to address the challenges hindering their widespread adoption, and discuss the potential future developments and advancements that can further enhance their utility in revolutionizing regenerative medicine.

2. Role of Natural Polymers in Regenerative Medicine/Tissue Engineering

2.1. Scaffold Materials

Porous 3D scaffolds play a crucial role in tissue engineering by providing suitable microenvironments for cell growth and function.

Table 1. Natural Polymers in Regenerative Medicine.

Polymer	Chemical Nature	Polymerization Methodology	Medicinal Use	Source	References
Collagen	Protein (Structural protein)	Biosynthesis	Wound and tissue healing, bone repair	Animal tissues (e.g., skin, bones)	(Iovene and Zhao 2021),(Moncal et al. 2019),(Yang et al. 2020)
Gelatin	Partially hydrolyzed collagen (Hydrocolloid)	Hydrolysis	Pharmaceutical coatings, drug delivery, tissue engineering	Collagen derived from animal sources (e.g., porcine or bovine)	(Oliveira and Mano 2014)
Chitosan	Polysaccharide	De-acetylation	Wound healing, drug delivery, tissue engineering, cartilage regeneration	Derived from chitin found in the exoskeleton	(Iovene and Zhao 2021),(Dessi et al. 2013)
Hyaluronic acid	Polysaccharide (Glycosaminoglycan)	Biosynthesis	Ophthalmic solutions, osteoarthritis treatment, tissue engineering	Naturally present in connective tissues and synthesized by bacteria	(Qasim et al. 2019),(Alberts et al. 2015)
Fibrin	Protein (Structural protein)	Polymerization	Tissue adhesives, wound healing, regenerative medicine	Derived from fibrinogen in human or animal plasma	(Kim et al. 2018)
Alginate	Polysaccharide	Ionotropic gelation	Drug delivery, wound healing, tissue engineering, Skin regeneration	Derived from brown algae or bacteria	(Iovene and Zhao 2021),(Venkatesan et al. 2015),(Vowden et al. 2006)

These scaffolds are fabricated using various techniques, depending on the materials and desired pore structures. The structural properties of the scaffolds, such as porosity and pore size, directly impact their functionality in both in-vitro and in-vivo settings. Interconnected porous scaffold networks are essential as they enable nutrient transport and waste removal and facilitate cell proliferation and migration. The porosity and pore size of the scaffolds influences cell behavior and contribute to the final mechanical properties. Measurement techniques and software have been developed for accurate assessment of pore size and porosity. The objective of scaffold fabrication is to produce materials that closely resemble native tissues in terms of performance. However, the current approach of prefabricated scaffolds has various limitations (Loh and Choong 2013). These scaffolds may

not always possess the ideal material properties to support normal cell growth and differentiation, which can lead to their failure. Therefore, a detailed analysis is necessary to determine each scaffold system's optimal porosity and pore size based on the intended tissue engineering application. To mimic the dynamic remodeling and healing processes of the ECM, post-fabrication tunability of scaffolds is crucial. This allows for adjustments that provide a suitable microenvironment for these ongoing changes. By addressing these considerations, scaffolds in tissue engineering can better support cell behavior and contribute to the success of tissue regeneration (Loh and Choong 2013).

Collagen, gelatin, HA, and fibrin are some of the crosslinked natural polymers used for scaffolding (Abbasian et al. 2019). Collagen used in tendon-tissue engineering forms a spongy scaffold, and gelatin/HA complex

enhances cell adhesion and proliferation, forming a spongy scaffold targeting bone. Fibrin also improves cell attachment, proliferation, and deep artificial tissue

penetration; it forms interconnected and open porous scaffolds, targeting skin in tissue engineering (Abbasian et al. 2019) (Table 2).

Table 2: Biopolymers used as scaffold materials in tissue engineering.

Biopolymer	Target	Type of scaffold	Main findings	Reference
Collagen	Tendon	Soft spongy	-	(Marturano et al. 2014)
Gelatin/HA	Bone	Soft spongy	Improved cell attachment and proliferation	(Rungsiyanont et al. 2011)
Fibrin	Skin	Interconnected, soft porous	Improved cell attachment and proliferation, deep artificial tissue penetration	(Zhang et al. 2017)

2.2. Controlled Drug/Gene Delivery Systems

Polymeric nanomaterials have found wide application in developing targeted and controlled release drug/gene delivery systems. However, using synthetic polymers in these formulations presents challenges, such as the need for toxic solvents and surfactants, which restrict their desirable applications. As a solution, natural biomolecules, including proteins and polysaccharides, offer promising alternatives due to their safety profile (Salatin et al. 2015). Various methods have been demonstrated for producing protein-based nanoparticles aiming for optimal size, morphology, and stability. These methods include crosslinking with cross-linkers, emulsion formation, coacervation, and precipitation.

On the other hand, polysaccharides provide a favorable platform for nanoparticle production due to their biodegradability, biocompatibility, and ease of molecular modification through covalent and ionic interactions. Nanoparticles can be formed from polysaccharides through ionic or covalent crosslinking, ion-complexation, and self-assembly after grafting hydrophobic segments onto the polymer backbone. The selection of the most appropriate technique for nanoparticle fabrication depends on factors

such as the materials' charges and polymer chain lengths (Nitta and Numata 2013).

Nanoparticles have garnered significant attention as biomaterials for delivering therapeutic molecules, including drugs and genes, as well as for tissue engineering applications. Biopolymers, in particular, exhibit desirable characteristics, such as biocompatibility, biodegradability, and low immunogenicity, making them suitable for clinical use. These versatile traits make biopolymers a favorable choice as nanoparticle-based delivery systems for various medical applications (Nitta and Numata 2013). Tissue engineering represents a unique approach to controlled drug delivery, specifically focusing on delivering cells in a controlled manner. The effectiveness of tissue engineering can be enhanced by precisely regulating the release of therapeutic factors. By designing biomaterials with controlled nano-scale structures, the biological functions of encapsulated drugs and cells can be significantly improved. Integrating gene delivery components into scaffolds offers the potential to enhance the interaction between cells and their surrounding environment. Spatially and temporally delivering genes to specific sites provides signals and cues for tissue growth and maintenance, thereby enhancing tissue incorporation, growth, and

integration with neighboring tissues. Biopolymers used for gene delivery serve as DNA carriers and act as structural scaffolds for tissue engineering applications. This integration of gene therapy and tissue engineering in a single system represents a promising approach to regenerative medicine. The utilization of a localized gene delivery system, known as a gene-activated matrix, combines these strategies by acting as a local bioreactor with therapeutic gene expression and as a structural template to fill lesion defects, promoting cell adhesion, proliferation, and synthesis of the ECM (Nitta and Numata 2013).

Polysaccharide-based natural polymers are suitable agents in drug/gene delivery and tissue engineering due to their ability to form colloids, hydrogels, and films and their ability to modify surfaces to enhance controlled release and specific tissue/cell targeting (Salatin and Jelvehgari 2017). Alginate, chitosan, HA, dextran, and pullulan are major polysaccharides used in the nanoparticles for targeted drug delivery of gene/drug (Salatin and Jelvehgari 2017). Protein-based natural polymers are either plant-derived or animal-derived. The most commonly used plant-derived proteins for the preparation of natural polymers for gene/drug delivery are gliadin, zein, soy protein, legumin, and vicilin. They are cheap, and processing is easier compared to that of animal protein-derived polymers. Animal-derived protein biopolymers exhibit a balanced composition of essential amino acids. Among a lot of animal protein-based natural polymers, albumin, gelatin, elastin, collagen, casein, whey, silk, and fibrin are most commonly used in the targeted delivery of drugs/genes (Salatin et al. 2015).

Incorporating drugs or genes into polymers involves combining therapeutic molecules with polymeric materials to form a drug/gene

delivery system. This process can be achieved through various techniques, including encapsulation, conjugation, or complexation (Tagami et al. 2019). The choice of the specific method for incorporating drugs or genes into polymers depends on factors such as the nature of the therapeutic molecules, desired release kinetics, and the properties of the polymer. These techniques enable the development of effective drug/gene delivery systems, allowing for precise control over the release and localization of therapeutic agents (Tagami et al. 2019). The incorporation of the drug/gene in the polymer is shown in Figure 1.

2.3. Bioactive and Bio-Functional Materials

Bioactive and bio-functional materials are substances or structures that interact with biological systems and elicit specific biological responses. These materials are designed to mimic or enhance natural biological processes and functionalities. Hydrogels are bio-inspired, bioactive, and bio-functional materials. They are three-dimensional networks of polymer chains that are highly hydrophilic, allowing them to absorb and retain large amounts of water. The polymer chains in hydrogels can be either naturally derived (such as proteins or polysaccharides) or synthetic (such as polyacrylates or polyethylene glycol). They can be tailored in terms of chemistry, structure, and functionality to be utilized in various applications, including drug delivery, shape morphing, artificial muscles, and tissue engineering. Hydrogels with responsive behavior, conductivity, and bioactivity have been developed by incorporating diverse functional groups or bioactive components (Fu 2019). Natural polymers with abundant functional groups and hydrogen bonding capabilities are significant in developing hydrogels for various biomedical uses. Multifunctional cellulose-based hydrogels are

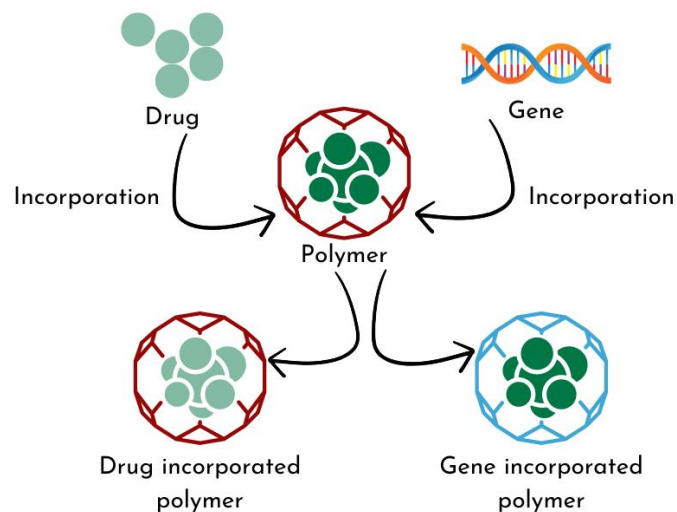


Figure 1. The incorporation of drugs and genes into protein-based nanoparticles.

discussed for applications in biomedicine, including drug delivery, tissue engineering, wound dressing, bio-imaging, and as wearable sensors (Fu et al. 2019).

Hydrogels, renowned for their biocompatibility and biomimetic nature, have long been used as tissue engineering scaffolds. The wide range of tissues and organs, each with unique mechanical properties, structures, and biological functions, necessitates manipulating scaffold materials in terms of structure, properties, and functionalities. Hydrogels offer significant advantages due to their ability to tailor chemical, physical, and biological characteristics to meet diverse requirements. Injectable hydrogels, which can contain biomolecules, drugs, and cells, provide a minimally invasive approach by directly injecting them into target tissues (Fu 2019). Load-bearing tissues require sufficient strength and toughness to match the properties of the surrounding host tissues. One such example is articular cartilage tissue engineering, which is particularly challenging

due to the avascular nature and load-bearing requirements. Traditional hydrogel scaffolds often lack adequate mechanical support, despite their ability to promote chondrogenesis of stem cells and the formation of cartilage-like tissues (Fu 2019). Recently, novel approaches have been adopted to enhance the strength and toughness of bio-functional hydrogels. Chondrocytes, essential for cartilage tissue engineering, are encapsulated in gelatin methacryloyl hydrogels that are reinforced with microfiber scaffolds (Pahoff et al. 2019).

A moist microenvironment around wounds increases the susceptibility to bacterial infections and inflammation (Wang et al. 2018),(Shan et al. 2019). Furthermore, the combination of oxidative stress damage caused by free radicals and the disruption of the body's immune system due to various external factors further hampers the wound-healing process. Various antibacterial strategies have been devised to address bacterial infections, and inflammation, and

promote wound healing. These include the use of antibiotics (Lei et al. 2018), antimicrobial coatings (Gu et al. 2017), antibacterial band-aids (Sun et al. 2022), metal-based nanoparticles (Shan et al. 2019), photo-thermal and photocatalytic sterilization techniques (Xu et al. 2019), and antibacterial hydrogels (regenerative wound healing dressings) (Sun et al. 2022),(Liu et al. 2020),(Zhang et al. 2021). Regenerative wound healing dressings are designed to promote the regeneration of damaged tissue and facilitate wound healing. These dressings aim to restore normal tissue function and accelerate skin tissue regeneration at the wound site. The key goals of regenerative wound healing dressings include tissue regeneration, accelerated healing, and restoration of normal function of the damaged organ. A careful balance between material functionality, degradation, safety, and tissue regrowth is necessary (Sun et al. 2022).

For these goals, regenerative wound healing dressings often incorporate advanced materials with specific properties, such as biocompatibility, biodegradability, and the ability to interact with the wound microenvironment. These dressings may also contain bioactive molecules, growth factors, or nanoparticles that can enhance cellular responses, modulate inflammation, and support tissue regeneration. A new approach involves the development of an "all-in-one" chitosan-based hydrogel that incorporates self-assembled cinnamaldehyde-tannic acid-zinc acetate nanospheres (CA-TA-ZA-NSs) of drug-food small molecules into the three-dimensional network structure of the hydrogel. This integration results in a multifunctional hydrogel with excellent antibacterial, antioxidant, anti-inflammatory, and oxidative stress-reducing properties. Moreover, the hydrogel exhibits rapid in situ

gelation at wound sites and effectively covers irregular wounds. These advantageous features enable the chitosan-nanoparticles-based hydrogel to create a conducive microenvironment for stimulating skin tissue remodeling, blood vessel repair, hair follicle regeneration, restoring normal immune system activity, and accelerating the wound healing process (Sun et al. 2022).

3. Tissue Engineering Applications of Natural Polymers

3.1. Skin Tissue Engineering

Due to their excellent biocompatibility, biodegradability, and low cytotoxicity, as compared to synthetic polymers, natural polymers find extensive application in skin tissue engineering (Sundaramurthi, Krishnan, and Sethuraman 2014) (Moon et al. 2023). Polysaccharides and protein-based materials are the two primary categories of natural polymers employed in hydrogels for this purpose (Gomes et al. 2013). Dermal substitutes comprising collagen or HA serve as scaffolds for cellular growth (Biswal 2021). On the other hand, epidermal substitutes, consisting of keratinocytes and fibroblasts, are utilized to replace the outermost layer of the skin (Gomes et al. 2013).

3.2. Bone Tissue Engineering

Natural polymers, including alginates, collagens, HA, and gelatin, are commonly used in bone tissue engineering (Szczepańczyk et al. 2021). These polymers are employed in three primary forms: nanofibrous scaffolds, hydrogels, and microspheres (Guo et al. 2021). Biocomposites, combining natural polymers with hydroxyapatite, have also been developed for bone tissue engineering (Swetha et al. 2010). Bone scaffolds serve as a crucial application of natural polymers and provide a supportive structure for cellular growth. Osteogenic differentiation, involving the

transformation of mesenchymal stem cells into bone-forming osteoblasts, is another important aspect of natural polymer utilization (Szczepańczyk et al. 2021). Additionally, natural polymers are used in bone regeneration strategies, acting as scaffolds or carriers for growth factors to promote the restoration of damaged or lost bone tissue (Koons, Diba, and Mikos 2020).

3.3. Cartilage Tissue Engineering

Natural polymers, such as chitosan, collagen, alginate, silk fibroin, hyaluronan, and gelatin, have extensive applications in cartilage tissue engineering (Balasundaram, Storey, and Webster 2014),(Zhao et al. 2021). Cartilage scaffolds serve as primary natural polymers in cartilage tissue engineering, providing a supportive structure for cellular growth (Gomes et al. 2008). Various materials, including chitosan, collagen, alginate, silk fibroin, hyaluronan, and gelatin, can be utilized in the fabrication of these scaffolds (Biswal 2021). Chondrogenic differentiation is another significant application of natural polymers involving the transformation of mesenchymal stem cells into chondrocytes, which contribute to cartilage formation (Balasundaram, Storey, and Webster 2014). Furthermore, natural polymers are being investigated for repair and regeneration techniques to promote the restoration of damaged or lost cartilage tissue (Gomes et al. 2008). These techniques often employ natural polymers as scaffolds or carriers for growth factors (Zhao et al. 2021).

3.4. Vascular Tissue Engineering

Tissue engineering is a promising field that focuses on creating functional tissues and organs using natural or synthetic materials. Within tissue engineering, vascular tissue engineering presents significant challenges (Abdul Sisak, Louis, and Matsusaki 2020).

Various approaches have been explored in this field:

3.4.1. Vascular Scaffolds: Synthetic polymers, including polycaprolactone, poly-l-lactic acid, and polyglycolic acid, and their blends have been utilized to fabricate vascular scaffolds (Abdul Sisak, Louis, and Matsusaki 2020) (Devillard and Marquette 2021).

3.4.2. Endothelial Cell-Based Approaches: These approaches involve seeding endothelial cells onto scaffold surfaces to establish functional blood vessels. Endothelial cells play a vital role in vascular homeostasis (Abdul Sisak, Louis, and Matsusaki 2020).

3.4.3. Blood Vessel Regeneration Strategies: These strategies aim to stimulate a body's innate repair mechanisms for regenerating damaged blood vessels. Growth factors, cytokines, or signaling molecules that promote angiogenesis are employed (Chen et al. 2021). Natural polymers like collagen and chitosan have also been employed in the development of vascular grafts. These materials offer advantages over synthetic polymers, including biocompatibility and biodegradability (Leal et al. 2021).

3.5. Nerve Tissue Engineering

Nerve tissue engineering has emerged as a prominent field of research in recent years (Boni et al. 2018b). Several approaches have been employed in this area:

3.5.1. Neural Scaffolds: These three-dimensional structures provide a supportive environment for the growth and differentiation of nerve cells. Natural polymers like collagen, alginate, chitosan, and silk have been utilized to fabricate neural scaffolds (Boni et al. 2018b).

3.5.2. Neuronal Differentiation: By utilizing growth factors or signaling molecules, neuronal differentiation aims to promote the transformation of stem cells into

functional neurons. This approach shows promise in regenerating damaged nerve tissue (Boni et al. 2018a).

3.5.3. Nerve Regeneration

Techniques: These techniques stimulate the body's intrinsic repair mechanisms for nerve regeneration. Growth factors, cytokines, or signaling molecules that foster nerve growth are employed (Jiang et al. 2020). Natural polymers possess advantages over synthetic polymers for nerve tissue engineering, including biocompatibility and biodegradability (Boni et al. 2018b).

4. Challenges and Future Perspectives

Natural polymers have found extensive application in tissue engineering scaffolds owing to their exceptional biocompatibility, biodegradability, and reduced cytotoxicity in comparison to synthetic polymers (Moon et al. 2023),(Phutane et al. 2023). However, utilizing natural polymers in tissue engineering presents certain limitations and challenges. For instance, these polymers often exhibit inadequate mechanical properties or limited processability, impeding their suitability as natural tissue substitutes (Moon et al. 2023). Moreover, natural polymers may demonstrate variations in their characteristics across different batches and sources(Phutane et al. 2023).

Various strategies have been suggested to address the limitations of natural polymers in tissue engineering. One approach involves blending natural polymers with synthetic counterparts to enhance mechanical properties and processability (Ciolacu and Nicu 2022) (Abbasian et al. 2019). Another strategy involves modifying natural polymers to augment their properties through chemical or physical means (Ciolacu and Nicu 2022). For instance, the development of photo cross-linkable natural polymers has been explored

for tissue engineering purposes (Moon et al. 2023).

Natural polymer-based hydrogels offer a promising strategy for scaffold development in tissue engineering. They provide valuable cues for cellular interactions, scaffold formation, and tissue regeneration (Singh, Patel, and Singh 2016). Another emerging approach is the use of decellularized ECM scaffolds, which mimic the in-vivo microenvironment and exhibit mechanical and biochemical properties similar to native tissues. These approaches help overcome limitations associated with natural and synthetic polymer-based scaffolds (Zhang et al. 2022). Additionally, novel polymeric biomaterials, both natural and synthetic, have demonstrated potential in manufacturing-based tissue engineering. They replicate the ECM and facilitate the growth of various cell types, thereby improving biological behavior in-vitro and in-vivo (Akhtar et al. 2023).

Furthermore, Future advancements will focus on enhancing the properties of natural polymers and exploring their synergistic potential with other materials like synthetic polymers and ceramics. These approaches have wide-ranging applications, including the regeneration of bone, cartilage, skin, and various other tissues.

5. Conclusions

Natural polymers hold significant promise for various applications in regenerative medicine, owing to properties and advantages like biocompatibility, biomimicry, biodegradability, versatility, availability, sustainability, bioactivity, and integration with gene therapy. Crosslinking these polymers can enhance their properties, facilitating optimal cell attachment, proliferation, and tissue formation. Natural polymers also find application in the

development of controlled drug and gene delivery systems. Techniques such as encapsulation, conjugation, or complexation enable incorporating drugs or genes into polymers, granting precise control over the release and localization of therapeutic agents. Moreover, natural polymers are employed to develop bioactive and bio-functional materials. They can be customized in chemistry, structure, and functionality, making them suitable for drug delivery, tissue engineering, and shape-morphing applications. Natural polymers can also play a crucial role in the development of hydrogels for wound healing and regenerative wound dressing materials incorporating natural polymers. They promote tissue regeneration, expedite healing, restore normal function, and prevent infections. Overall, natural polymers offer a wide range of advantages and functionalities in regenerative medicine and tissue engineering. Ongoing research aims to enhance their properties further, develop novel fabrication techniques, and explore their potential in various medical applications.

Conflict of Interest

The authors declare no conflict of interest.

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Authors Contribution

FN and RG conceptualized the study and wrote the final manuscript, AS & HU helped in the analysis and writing the first draft, FN, AS, and HU did the literature search and

analysis, and RG supervised the whole project.

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