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Natural biomaterial composites for tissue engineering: Challenges and opportunities

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ABSTRACT

Tissue engineering has appeared as a promising frontier in regenerative medicine, aiming to restore, maintain, or improve tissue functions. Central to this field are natural biomaterials substances derived from nature that offer biocompatibility and functional mimicry of the body's own tissues. These materials, when combined into composites, hold incredible potential for producing scaffolds that support cell growth and tissue regeneration. This review explores the promising role of natural biomaterial composites in tissue engineering, highlighting their potential to improve regenerative therapies. We begin by discussing the fundamental importance of tissue engineering and the unique advantages offered by natural biomaterials such as collagen, gelatin, and decellularized extracellular matrices. The paper then examines various fabrication techniques, including 3D bioprinting and electrospinning, which enable the creation of complex, functional scaffolds. Emphasis is placed on the biocompatibility and mechanical properties of these composites, critical factors influencing their success in vivo. Additionally, we explore their diverse applications in regenerating skin, bone, and cartilage, showcasing their versatility. Lastly, the review considers future trends and ongoing challenges, aiming to guide the development of innovative, effective, and safe biomaterial-based solutions for tissue regeneration.

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1. Introduction

Tissue engineering is vital for addressing the shortage of donor organs by creating functional biological tissues in the lab, combining insights from biology, materials science, and technology [1, 2]. It has made significant progress over the past two decades, allowing for lab-grown tissues and organs from a patient's own cells, reducing rejection risks [1, 3]. While challenges remain for complex organs like the heart and liver, advancements in stem cell research and biomaterials continue to expand regenerative options [2, 4-6]. Overall, tissue engineering plays a crucial role in developing innovative therapies for organ failure, injuries, and diseases, offering hope for improved patient outcomes [7-9].

Tissue engineering, a key part of regenerative medicine, uses cell biology, materials science, and engineering to create substitutes that mimic natural tissues, aiming to restore function in damaged tissues [7, 10]. It mainly involves two approaches: cell-based [11-13], which combines cells with scaffolds, and scaffold-based [14-16], which relies on the body's natural regeneration using cell-free synthetic or natural scaffolds. These scaffolds degrade over time and are replaced by the body's extracellular matrix (ECM), while cells can also be delivered via injections with carriers like hydrogels or alone [17].

Biomaterials are essential for creating functional genitourinary tissues to replace damaged or malfunctioning ones. They act as a temporary scaffold that directs tissue growth, while also providing bioactive signals such as growth factors that support the maintenance of tissue-specific gene expression [18]. A range of biomaterials, categorized into three groups naturally derived materials (such as collagen), acellular tissue matrices (like small-intestinal submucosa), and synthetic polymers (including polylactic acid) have demonstrated usefulness in reconstructing various genitourinary tissues in animal studies [18, 19].

Natural biomaterials such as collagen and gelatin composites are widely used in tissue engineering due to their interconnected microstructure and inherent bioactivity, closely mimicking the natural ECM [20].

This facilitates cell infiltration, adhesion, differentiation, and nutrient and oxygen transport, ultimately aiding tissue and organ regeneration. Their structural and functional properties are fine-tuned through blending with other natural or synthetic polymers and by physical or chemical crosslinking, ensuring appropriate mechanical strength, degradation rates, and ECM-like environments for supporting cellular activities. Additionally, natural biomaterials play a crucial role in delivering cells, drugs, bioactive molecules, and growth factors [21]. Moreover, the applications of decellularized matrix composites span various tissues, with notable success in skin, bone [22], and cartilage regeneration. Their ability to support growth and integrate seamlessly with host tissues makes them invaluable tools in regenerative therapies [23, 24].

In this review, we explore what tissue engineering entails and why natural biomaterials are vital. Their biodegradability, low immunogenicity, and similarity to native tissues make them ideal candidates for constructing the foundation of engineered tissues. Furthermore, decellularized matrix composites, fabrication techniques i.e., 3D bioprinting and electrospinning and finally applications will be discussed. Finally, the conclusion discusses current trends and future directions, emphasizing innovations such as smart biomaterials and personalized tissue scaffolds.

Although challenges like scalability and long-term stability exist, ongoing research promises a future where natural biomaterial composites revolutionize tissue repair and regenerative medicine.

2. Types of natural biomaterial composites

Natural biomaterials can be divided into two categories: non-ECM component mimics (such as cellulose, alginate, chitin, chitosan, dextran, silk fibroin) and ECM component mimics (like collagen, gelatin, laminins, fibronectin, elastin, glycosaminoglycans, and dECM) [21]. Naturally derived polymers like cellulose, chitosan, alginate, and agarose are promising due to their biocompatibility and low cost [25]. Some of these materials are already in clinical use for genitourinary applications. Ultimately, selecting or developing suitable biomaterials could enable the engineering of multiple functional genitourinary tissue types [18]. In a study, Ko et al. [25] explored natural polymers cellulose, chitosan, alginate, and agarose and their composites as scaffolds for tissue engineering. Using lyophilization, sponge-like, porous scaffolds were created. Moreover, HeLa cells successfully attached and grew on cellulose, chitosan, and alginate scaffolds.

2.1. Collagen and gelatin composites

Collagen, a primary structural protein present in the ECM, is known for its high biocompatibility and minimal immunogenic response [20]. Additionally, collagen contains specific cell-binding sites that promote cell attachment, interaction, and spreading, which helps sustain cell survival and encourages proliferation. Recently, researchers have increasingly focused on collagen-based hydrogels to address the limited mechanical strength of collagen. In particular, collagen-alginate composite hydrogels have garnered significant interest because of their superb biocompatibility, ability to gel under gentle conditions, low toxicity to cells, tunable mechanical properties, broad availability, and ease of integrating other biomaterials and bioactive substances [26].

2.2. Decellularized matrix composites

Despite progress in polymeric scaffolds for tissue engineering, clinical translation remains challenging due to difficulty replicating native tissue microenvironments. Decellularized extracellular matrix (dECM) scaffolds, deriving from natural tissues, offer biomimetic properties that promote cell growth and differentiation, but often face issues like weak mechanical strength. Researchers have developed composite dECM platforms, combining natural or synthetic polymers and bioactive factors, to better mimic tissue environments. This review covers recent advances in dECM preparation, its applications in regenerative medicine, and emerging uses beyond tissue engineering, highlighting its potential as a crucial biomaterial in medical science [27-29].

In research, Kort-Mascort et al. [30] developed a reinforced dECM-based hydrogel by integrating alginate and gelatin to enhance its mechanical stability for bioprinting tumor models. This composite could mimic tumor stiffness, support cell proliferation, and maintains high viability for weeks. The model effectively replicates key features of the tumor microenvironment, enabling more accurate evaluation of chemotherapeutics like cisplatin and 5-fluorouracil, which showed increased IC50 compared to traditional cultures, providing a valuable tool for cancer research. Moreover, in another research by Lee et al. [31], a biomimetic hydroxyapatite-gelatin-calcium silicate (HGCS) scaffold was developed for bone regeneration, evaluating its potential in a rat calvarial critical-sized defect model. They compared it to decellularized bone matrix (DECBM) and controls, with some groups seeded with multipotent adult progenitor cells (MAPCs). After 12 weeks, results showed that the HGCS+MAPCs group

achieved the highest new bone formation, outperforming DECBM, which had limited osteoinductivity. The study suggested that the HGCS scaffold enhances bone regeneration and serves as a promising stem cell delivery platform. Moreover, Xu et al. [28] developed a dECM/Gel/CS scaffold with strong mechanical strength, antibacterial activity, and biocompatibility via a one-pot method. It effectively removed immune components, had high porosity for cell growth, suitable elasticity, and controlled degradability. Chitosan added antibacterial and moisture-retention properties. In vitro tests confirmed enhanced cell proliferation, making it promising for skin tissue engineering. Fig. 1 illustrates materials, technologies, and applications related to decellularized matrix composites in tissue engineering [27].

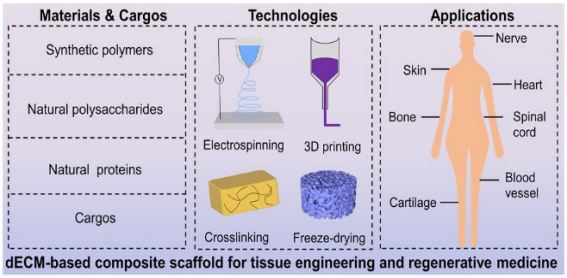

Fig. 1. Materials, technologies, and applications related to decellularized matrix composites in tissue engineering [27].

3. Fabrication techniques

Methods like 3D bioprinting enable precise spatial control over scaffold architecture, while electrospinning produces nanofibrous structures that closely resemble natural tissue matrices. These techniques are critical in designing functional, tissue-specific scaffolds.

3.1. 3D bioprinting

3D bioprinting is an advanced form of additive manufacturing that creates complex, living tissue constructs through precise layer by layer deposition of bioinks i.e., mixtures of biomaterials and living cells [32-34]. It involves using a bioprinter to deposit bioinks composed of natural or synthetic biomaterials, cells, and growth factors into desired tissue shapes. The bioinks can be stabilized during or after printing to form functional tissues. The process allows precise placement of various biological components to mimic natural tissue architecture [35, 36].

3D bioprinting aims to produce tissues and organs for transplantation, drug testing, tissue research, and disease modeling. It offers high reproducibility, customization, and potential for high-throughput tissue manufacturing, significantly advancing regenerative medicine and pharmaceutical development [32, 33]. The applications of 3D printing extend to various industries, including significant uses in the pharmaceutical sector [34]. Fig. 2. displays some applications of 3D printing technology within the pharmaceutical field.

3.2. Electrospinning

Electrospinning is a cost-effective technique to produce ultrafine fibers, ranging from nanometers to micrometers in diameter, by applying an electrostatic field to polymer solutions or melts, resulting in highly porous, high-surface-area materials [37].

The process uses an electric charge to draw thin fibers from a liquid polymer solution through a specialized spinneret. By controlling parameters like voltage, flow rate, and collector design, precise fiber dimensions and shapes are achieved. Material composition and additives can be tailored to modify fiber properties [38].

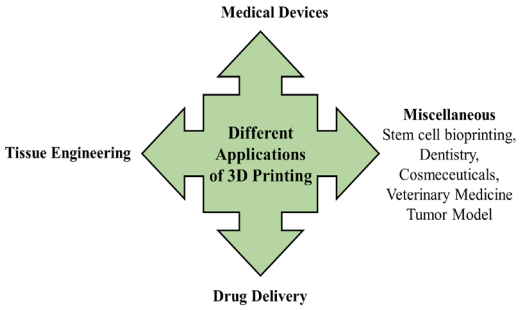

Fig. 2. Applications of 3D printing technology within the pharmaceutical field.

Electrospinning is used across numerous fields, including tissue engineering, drug delivery, filtration, sensors, wound healing, and environmental applications. Its ability to create fibers with unique morphologies and high porosity makes it ideal for advanced biomedical, industrial, and environmental uses [39].

Recent advances focus on scaling up production, developing complex 3D structures, and enhancing fiber functionalities through material modifications. Despite challenges, electrospinning remains a versatile, scalable, and cost-effective method for fabricating nanofibrous materials with diverse applications[40].

4. Biocompatibility and mechanical properties

Recent tissue engineering mainly uses 3D scaffolds to support tissue repair and regeneration. Ideal biomaterials should be biocompatible, porous, mechanically suitable, and biodegradable [25].

Gelatin and collagen are highly regarded in tissue engineering owing to their biocompatibility and similarity to the ECM [41, 42]. However, their main drawbacks include weak mechanical strength, lack of osteoconductivity, limited capacity to promote stem cell differentiation, and fast degradation [43]. Therefore, optimizing gelatin and collagen hydrogels for applications like bone tissue and cartilage regeneration is essential. To overcome these issues, efforts are underway to enhance gelatin and collagen hydrogels by incorporating inorganic materials and bioactive agents, aiming to boost their mechanical stability and functionality for improved bone and cartilage regeneration therapies [43].

In a study, Pottathara and Kokol [44] developed a GCH hydrogel for 3D bone scaffolds, optimizing printability with different needle sizes. After crosslinking, they tested the scaffolds' structure and mechanics before and after incubation. Smaller nozzles produced thinner walls and larger pores, while longer crosslinking improved strength. The scaffolds retained high stiffness, making them suitable for bone and cartilage regeneration. Furthermore, Monavari et al. [45] showed that the addition of astaxanthin and borate bioactive glass microparticles into alginate dialdehyde gelatin hydrogel enhanced the stiffness and slowed degradation, likely due to hydrogen bonding with the hydrogel.

5. Applications in tissue engineering

Tissue engineering has diverse applications, including regeneration of bone, cartilage, skeletal muscle, blood vessels, skin, neural tissues, spinal cord, heart, liver, pancreatic islets, trachea, and lungs [19, 34].

5.1. Skin

The skin serves as a vital protective barrier against infections, injuries, and burns while regulating moisture and temperature. It contributes to healing by repairing damaged tissue. The skin's immune defenses are divided into the epidermis and dermis, supporting immune cell activity and tissue regeneration. Key cells like fibroblasts help maintain and repair connective tissues by producing collagen and renewing the ECM [45].

In a study by Kaka et al. [46], keratin–chitosan–gelatin composite scaffold for soft tissue engineering was developed. The structure of the composite scaffold demonstrated favorable porosity and interconnected pores. An MTT assay with NIH3T3 fibroblast cells verified that the scaffold supported effective cell viability.In another study, Monavari et al. [45] developed a 3D-printed wound dressing made of an alginate dialdehyde gelatin (ADA-GEL) hydrogel infused with astaxanthin (ASX) and borate bioactive glass (70B), which consists of 70:30 B_2O_3/CaO mol%. The composite effectively sustained and delivered ASX and released beneficial ions (Ca and B), promoting wound healing. In vitro, the material supported fibroblast adhesion, proliferation, VEGF expression, and keratinocyte migration, driven by ASX's antioxidant properties and the biocompatibility of the components.

5.2. Bone

Bone naturally undergoes continuous repair and remodeling, but traditional methods like autografts and allografts often face limitations. Tissue engineering offers an alternative approach by using biomaterials that mimic the ECM. Collagen, a chief organic component of bone ECM, has been widely used as a scaffold in bone tissue engineering due to its biocompatibility and ability to support new tissue growth. Its versatility makes it a promising material for repairing and regenerating damaged bone tissue [47]. Additionally, gelatin is often utilized in bone tissue engineering alongside various natural, synthetic polymers, and inorganic substances to achieve synergistic properties that support the intricate biological processes involved in bone healing. In a research, Kazemzadeh Narbat et al. [48] fabricated porous hydroxyapatite-gelatin composite scaffolds for bone tissue engineering.

The biological response of the scaffolds, assessed with L929 fibroblast cell culture, indicated that fibroblast cells partially proliferated and began to cover the scaffold surface 48 hours after seeding. In another study, Begines et al. [49] investigated the fabrication of biphasic composite implants, using porous Ti as a cortical bone substitute and a polymer blends of gelatin and alginate with bioactive glass as a soft tissue layer. Their analysis of microstructure, degradation, biofunctionality, and wear showed optimal micromechanical performance in the 200–355 μm pore size range. The alginate coating exhibited lower mass loss, while a 50/50 alginate/gelatin composite showed higher elastic recovery, simulating soft tissue functions in joints. The result suggest that porous Ti combined with alginate/gelatin/45S5 BG composites could be promising for osteochondral repair and other conditions affecting both hard and soft tissues.

5.3. Cartilage regeneration

Osteoarthritis (OA) affects millions globally, causing significant disability and economic burden. Since cartilage injuries often lead to OA, effective regenerative strategies are essential. Currently, no surgical, material, cell, or drug therapies reliably restore hyaline cartilage, mainly due to limited understanding of why cartilage fails to regenerate spontaneously. Early diagnosis using advanced biosensing technologies has the potential to identify degenerative changes at their onset, thus enabling timely intervention and improved outcomes in cartilage repair strategies. Research into these mechanisms is vital for advancing next-generation treatments [50, 51]. Cartilage's avascular nature hampers its healing after injury, with common causes including trauma and OA. Traditional treatments like drugs and joint replacement have limitations. Tissue engineering using cells, scaffolds, and growth factors is a promising approach, with ongoing advances in seed cells, biomaterials, and stimulatory agents [52, 53].

Mesenchymal stem cells (MSCs) show potential, but variability among MSCs affects outcomes. Understanding MSC heterogeneity at the donor and cell level can improve therapeutic precision and repair efficiency [54]. Fig. 3 shows a summary of the three fundamental components involved in tissue engineering for cartilage regeneration [52].

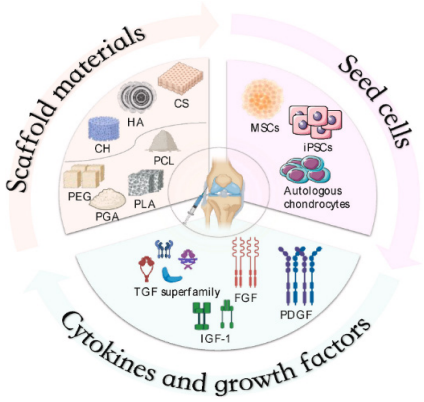

Fig. 3. A summary of the three fundamental components involved in tissue engineering for cartilage regeneration [52].

6. Future trends

Tissue engineering aims to repair or replace diseased tissues and organs, with advances driven by fields like cell biology and cutting-edge technologies such as bioprinting. While lab-grown simple structures like tubular tissues have seen clinical success, creating complex solid organs like the heart or liver remains a major challenge [55-57]. Critical hurdles include establishing vascularization to sustain large cell populations, sourcing suitable cells, and developing cost-effective, scalable scaffolds. Overcoming these obstacles is essential to commercialize human organs [58, 59].

In the near term, applications such as drug testing [60, 61] and treating minor tissue disorders [8, 62] are expected to expand. Long-term goals remain focused on fabricating fully functional human solid organs [63, 64]. Scaffold-based strategies using biodegradable polymers face regulatory and toxicity barriers, limiting widespread use, while scaffold-free methods which influence cells' ability to produce their own ECM show promise but are not yet mainstream due to clinical and manufacturing challenges [65-67].

Moreover, techniques like cell sheet engineering preserve cell contacts and ECM, enabling more natural tissue transplants with fewer complications. However, high manufacturing costs, strict regulatory frameworks, and reimbursement issues hinder commercialization, with therapies costing hundreds of thousands per patient and limited evidence of long-term benefits. Moving forward, automation, xeno-free materials, and improved regulatory pathways are expected to drive down costs and accelerate the translation of tissue engineering into broader clinical practice [2, 13].

7. Conclusion

Tissue engineering is progressing towards overcoming major barrier like vascularization and scaffold development to enable the construction of complex organs. While current successes are mostly in simpler structures and certain applications like drug testing, efforts are continuing to refine biomaterials and manufacturing techniques such as natural, decellularized matrices and biofabrication methods to develop clinical viability. Future advances, driven by innovations such as smart materials and personalized scaffolds, aim to address existing challenges, potentially transforming regenerative medicine and expanding treatment options for organ failure and tissue damage.

Author contributions

Ali Shirbacheh: Resources, Writing – original draft, Writing – review & editing. **Kimiya Shirbacheh:** Conceptualization, Writing – original draft, Writing – review & editing. **Kamran Shirbache:** Writing – original draft, Writing – review & editing. **Mojtaba Karbalaee:** Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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