

Review Article

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Advancements in Hyaluronic acid-containing Scaffolds in Stem Cell Therapy: Current Trends and Future Aspects

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ABSTRACT

Purpose: Various clinical trials are underway for investigating application of stem cells in the treatment of cancer, degenerative diseases, and repairing tissues. Stem cell transplantation is an established and growing method in regenerative medicine that includes autologous and allogeneic transplantation. HA is a glycosaminoglycan, can be produced naturally via bacterial strains such as *Streptococcus zooepidemicus*, besides using recombinant cells such as *Bacillus subtilis* and *Corynebacterium glutamicum*. HA is present inside the human body and has demonstrated promising attributes in stem cell-based tissue engineering.

Methods: This review investigates the involvement of HA scaffolds in stem cell therapies and discusses several studies focusing on HA applications in regenerative medicine.

Results: HA can have interactions with stem cells by cellular surface receptors inducing cell differentiation, and its hydrophilic nature promotes a hydrated microenvironment that protects the stem cells from desiccation and mechanical stress. HA versatility in hydrogels, nanofibers, and three-dimensional materials resulted in numerous applications of HA-containing scaffolds in medicine which is expanded from bone and cartilage regeneration to dermal fillers and gene expression regulation.

Conclusion: Advanced projects are essential for enhancing our knowledge and discovering new aspects of HA scaffolds in tissue engineering.

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1. Introduction

Mature tissues and organs are derived from stem cells (SC). This cell type can renew itself and undergo division for an extended period.¹ In other words, two designating features of SCs are perpetual self-renewal and the capability of differentiation into a specialized adult cell type.² Concerning the treatment of cancer, the major drawbacks of current therapies are inadequate and nonspecific targets of therapeutics to tumor sites. Stem cell therapy has provided a promising perspective in the treatment of cancer by enhancing its therapeutic effectiveness, improving the target on tumors and therefore decreasing the negative off-target events.³ Stem cell therapy has drawn attention for the treatment of chronic diseases and lifelong disabilities with no specific cure, such as osteoporosis. Usual therapeutics can only prevent the loss of bone mass and recover the bone to some degree. On the other hand the stem cells have shown capacities in regenerating the bone tissue.⁴ SCs are able to move to areas affected by tissue damage, involve in immune modulation, and secrete anti-inflammatory cytokines.⁵

Hyaluronic acid (HA), a glycosaminoglycan (GAG) ubiquitously present in the human body, has attained remarkable attention in regenerative medicine, particularly SC therapy.⁶ The unique physicochemical characteristics of HA, like biodegradability, biocompatibility, and hydrophilicity, has made it a perfect material for the development of scaffolds in stem cell therapy.⁷ HA-containing scaffolds, which serve as three-dimensional (3D) structures, provide a supportive and conducive microenvironment for stem cell growth, differentiation, and regeneration. These scaffolds are engineered for resembling the natural extracellular matrix (ECM) and have a determining role in tissue engineering (TE) and regenerative medicine.^{8,9} They can be customized to fulfill precise requirements including pore size, mechanical strength, and degradation rate, thereby facilitating the optimization of SC behavior and function.¹⁰ Gelation and emulsification capabilities of HA have found applications in food formulations. Inclusion of flavonoids and other healthy compounds with low stability and solubility can be achieved by nano-emulsion gels.¹¹ HA-containing scaffolds are utilized to encapsulate and release growth factors, cytokines, or other bioactive molecules in a controlled manner. This will further support SC survival, proliferation, and differentiation. Moreover, these scaffolds can regulate the immune response, promote tissue repair and regeneration, and reduce inflammation.^{12,13} These attributes make them a promising tool for various applications, mainly the repair and regeneration of damaged tissues in different complaints such as osteoarthritis (OA), cardiovascular disease, and neurodegenerative disorders.^{14,15} HA also has role in promoting angiogenesis, which is critical for the integration and survival of the transplanted stem cells.¹⁵⁻¹⁸

In this review, we will delve into the properties of HA scaffolds and their role in TE, specifically in stem cell therapy. The content includes exploring the types of HA scaffolds, fabrication methods, and their relevance in TE and regenerative medicine. Furthermore, current challenges and future perspectives in the development and optimization of these scaffolds are discussed. Unlike previous review articles that are focused on physicochemical properties or tissue engineering, this review uniquely integrates three key aspects: (1) the connection between HA production methods (microbial fermentation, enzymatic synthesis) and final scaffold performance, (2) a comparative analysis of HA scaffolds across different stem cell types (MSCs, ESCs, umbilical cord-derived cells), and (3) a critical assessment of ongoing and emerging clinical trials. The specific gap which is addressed is the lack of a comprehensive resource covering the entire 'from production to bedside' pathway of HA-containing scaffolds in stem cell therapy.

2. Search strategy

This narrative review was conducted through literature search using PubMed, Scopus, Google Scholar, and Web of Science aiming for articles published between January 2000 and April 2026. Keywords which were used included 'hyaluronic acid scaffold', 'stem cell therapy', 'tissue engineering', 'regenerative medicine', and 'hydrogel'. Original studies, reviews, and clinical trials which evaluated hyaluronic acid-containing scaffolds in stem cell-based applications were added. Articles and studies on synthetic HA derivatives with no stem cell applications were excluded.

Inclusion criteria for studies were: (1) original studies with quantitative evaluation of HA scaffold influences on stem cells behavior, (2) review articles specifically addressing molecular mechanisms, (3) clinical trials with sample size ≥ 10 patients. For commercial products, selection criteria included: (1) FDA or EMA approval, (2) availability of published clinical trial data, (3) variety in applications (medical, cosmetic, drug delivery). Products with unsubstantiated claims lacking scientific documentation were excluded.

3. Biosynthesis of HA

In this section, the production of HA is discussed. First, the early methods for HA extraction are mentioned. Next, its synthesis mechanism in microorganisms is explained and after that various approaches for the biological production of HA are reviewed.

3.1. Background of HA preparation

Since the 1930s, the conventional approach for HA production was the extraction from animal tissues, for example rooster combs or bovine eyes. Human umbilical cords were another source. However, extraction has posed challenges due to its low yield and high cost of purification.¹⁹ In 1937, HA was found in *Streptococcus haemolyticus*, which is a pathogenic bacterium. Afterward, increasing number of microorganisms capable of producing HA including other strains of *Streptococcus* and *Pasteurella multocida* (type A)²⁰ were discovered that led to a shift towards microbial fermentation as the primary method for HA production that replaced the tissue extraction.²¹

Figure 1 illustrates the various sources of HA, including microorganisms, animal tissues, and human-derived umbilical cord. Animal tissues such as rooster combs and bovine eyes represent the conventional extraction method dating back to the 1930s. Microbial fermentation involves bacteria such as *Streptococcus* and *Pasteurella* that represents the modern shift towards more scalable and controlled production. Human-derived materials including the umbilical cord have also been historically used for HA extraction.

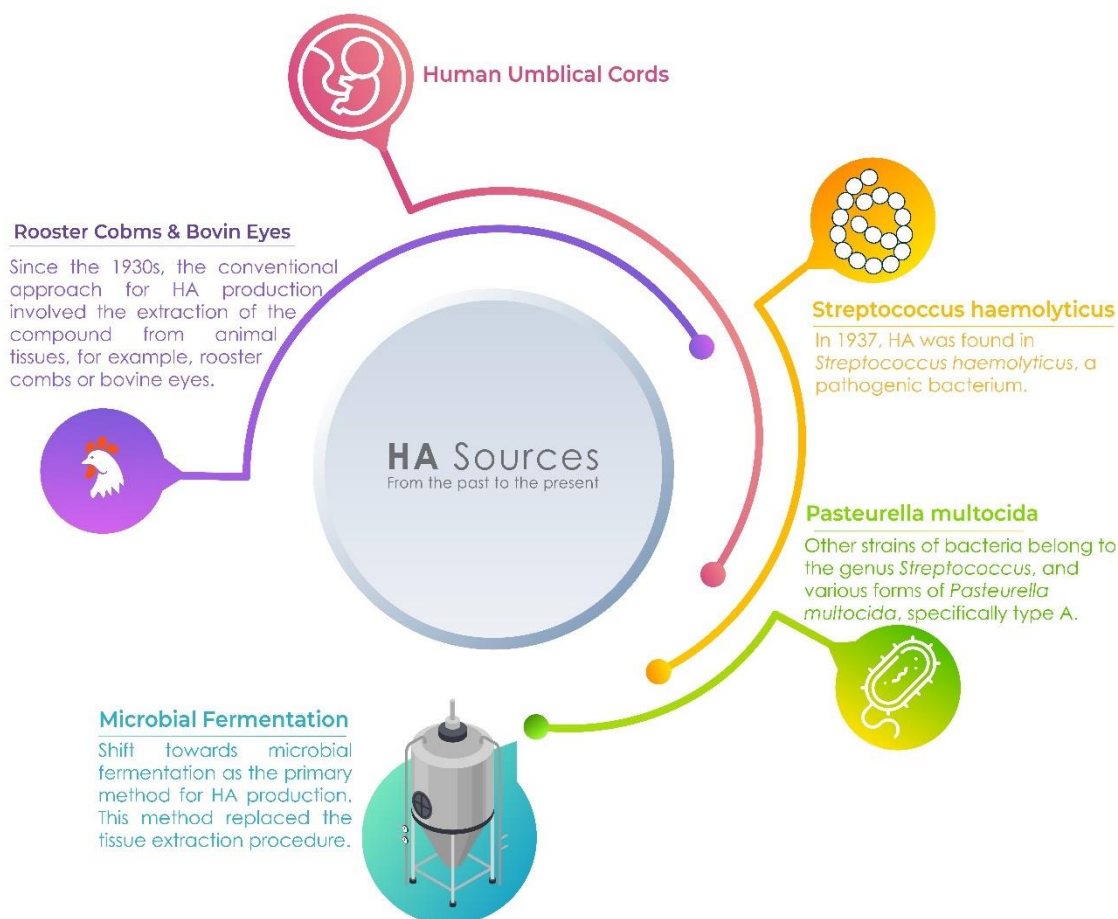


Figure 1. Sources of HA, including microorganisms, animal tissues, and human-derived umbilical cord. Animal tissues: Such as rooster combs and bovine eyes represent the conventional extraction method dating back to the 1930s. Microbial fermentation: Involving bacteria such as *Streptococcus* and *Pasteurella*. This approach represents the modern shift towards more scalable and controlled production. Human-derived materials: Including the umbilical cord. This source has also been historically used for HA extraction.

3.2. Mechanism of HA production in microorganisms

Most studies on HA synthesis in prokaryotes have focused on *S. zooepidemicus*, which utilizes two distinct pathways to generate the precursors of HA. Glucose phosphorylation is the initial step that glucose is converted to glucose-6-P (phosphate) catalyzed by the hexokinase. Glucose-6-P is the primary compound in the HA synthesis. After phosphorylation, the pathway diverges into two separate routes, which eventually create two separate components, glucuronic acid, and N-acetyl glucosamine. The pathways in glucuronic acid production begin by conversion of glucose-6-P to glucose-1-P catalyzed by phosphoglucumutase (PGM). UDP-glucose pyrophosphorylase (*hasC*) catalyzes the transformation of glucose-1-P into UDP-glucose. Following this, UDP-glucose undergoes oxidation by UDP-glucose dehydrogenase (*hasB*) to generate the first precursor of HA, UDP-glucuronic acid. The second pathway that generates N-acetyl glucosamine, starts with the transformation of glucose-6-P into fructose-6-P via phosphoglucoisomerase (*hasE*). Amidotransferase (*glmS*) interacts with fructose-6-P, attaching an amido group to it. After that, glutamine residue is moved to create glucosamine-6-P. Mutase (*glmM*) further catalyzes the transformation of glucosamine-6-P to glucosamine-1-phosphate. The addition of acetyl group and phosphate group to glucosamine-1-P by acetyltransferase and pyrophosphorylase, results in the formation of UDP-N-acetyl glucosamine. Once precursors are formed, hyaluronan synthase (*hasA*)

polymerizes these two components to synthesize the HA polymer chain. This procedure requires energy and various intermediates that are used in the production of biomass, components of the cell wall, and lactate during glycolysis.²²

Classification of *hasA* has been established tentatively based on factors such as molecular size, primary structure, predicted topology of the membrane protein, and enzymological characteristics. Class I involves streptococcal, viral, and vertebrate (3 isoforms, HAS1-3), while Class II consists only of one member, the *P. multocida* enzyme. While the biochemical features and in vivo functional sides of HAS proteins have been thoroughly examined, the process of HA synthesis in bacteria has remained not completely understood.²³

3.3. Bacterial production of HA

Various fermentation methods (batch, fed-batch, repeated batch, continuous) have been studied for HA production using *S. zooepidemicus*. Controlling the specific growth rate via continuous or fed-batch operations lead to increased metabolite production.²⁴ Continuous fermentation allows for longer growth cycles, waste reduction by minimizing fermenter response time, and decrease in molecular weight polydispersity.²⁵ During the initial stage of fermentation, HA continues to extend its chain, while in the later stages, HA accumulation occurs. Therefore, a segmented control strategy for HA production using a two-stage fermentation approach is suggested, which the first phase of fermentation is done at 31°C and pH 8.0 in order to increase the HA molecular weight, while the second phase is conducted at temperature of 37°C and pH 7.0. This suggested dual-phase fermentation leads to elevated levels of produced HA.²⁶ In 1988, a fermentation technique was suggested by Nimrod et al²⁷ that utilized the indigenous HA-producing bacterium *S. zooepidemicus* HA-116 ATCC 39920. The medium contained a consistent sugar concentration of 0.2 to 10 g/l and a magnesium ion concentration of at least 0.05 g/l. A steady pH level of 6.5-7.5 was maintained. The cultivation was with or without aeration. In both instances, it is preferable to conduct fermentation with strong agitation. The aeration rate was recommended around 1-2 vvm (volumes of air per volume of medium per minute). The non-aerated fermenters produced approximately 2-3 g/l of HA with an average MW ranging from 1.5 to 2×10^6 Da. For the aerated fermentation, approximately 4-6 g/l of HA with an average MW of 2.2 to 3.3×10^6 Da was produced. The final fermentation product was sodium hyaluronate which was released into the medium.

The pathogenicity of the natural form of *Streptococcus* impeded its progress, leading to an assessment of nonvirulent mutated strains.¹⁹ Several research studies have focused on improving HA production by regulating its metabolic pathways, engineering precursor supply modules, and genetic modifications.²⁸ Comparative analysis of genome-scale metabolic networks of *Streptococcus zooepidemicus* and *Corynebacterium glutamicum* have been conducted to distinguish the main metabolic targets for increasing the HA production. The reconstructed model of *S. zooepidemicus* was validated using diverse data, including amino acids auxotrophy, carbon sources consumption, and growth rate prediction. Through iterative single-gene deletion analysis, key genes important for HA overproduction in both bacteria were identified. Based on the two models, it was deduced that elimination of the reaction catalyzed by glucose-6-phosphate dehydrogenase in *C. glutamicum* resulted in more similarity of the central carbon metabolisms of these two bacteria which enhanced the HA production.²⁹ Successful development of the HA synthesis pathway has led to high recombinant HA yields in safe microbial hosts,²¹ like *Bacillus subtilis*,³⁰ *Corynebacterium glutamicum*,¹⁹ and *Bacillus amyloliquefaciens*.³¹ Tabasi et al³² have utilized recombinant *Corynebacterium glutamicum* ATCC 13032 for the production of food-grade HA. The most proper fermentation pH, which was neutral, was determined with one factor at a time (OFAT) method. Induction time and the media compositions which included phosphate buffer, glucose, soy protein hydrolysate, urea, and some

other components were optimized using Taguchi method. These optimized conditions resulted in HA concentration of 1.8 g/l after 18 h in a 5-L fermenter. Glucose feeding was examined after the complete consumption of the initial glucose. In this strategy, HA production reached 5.3 g/l after 48 h. Hazaveh et al³³ have investigated the effects of interaction between the key variables on the yield of heterologous HA production in *C. glutamicum*. A 3-level full factorial design was applied and the high significant impact ($p < 0.0001$) of the yeast extract concentration was observed. It has been reported that optimized conditions increased the HA production by 26% compared to baseline.

3.4. Enzymatic synthesis of HA

Enzymatic methods have been developed by Gottschalk et al³⁴ for the synthesis of high-molecular-weight HA with minimal dispersity. In this approach, enzymes were immobilized on magnetic beads to facilitate the production of UDP-N-acetyl glucosamine, UDP-glucuronic acid, and HA. The incorporation of six enzymes in the UDP sugar pathways, along with adenosine-5'-triphosphate renewal, resulted in HA production with 60 to 100% yield over five consecutive batches. This process enabled continuous HA production for three days, reaching a concentration of 0.37 g/L.

Enzymatic production of HA allows for precise control over molecular weight and synthesis of homogeneous HA with low polydispersity, enhancing the safety and reliability of drug formulations. However, this technology is still in the developmental stage and faces economic and technical challenges, including difficulties for large-scale manufacturing.^{35,36}

3.5. Industrial biosynthesis of HA

Current literature cover techniques like simulations and techno-economic assessment to assist industries in producing HA. Ferreira et al³⁷ offered a cost-benefit evaluation of HA manufacturing via *S. zooepidemicus*. The SuperPro Designer program was applied for this analysis. In the standard situation, HA has been manufactured through batch fermentation and reached 2.5 g/L in 24 h. Downstream processing steps were centrifugation, diafiltration, treatment with activated carbon, and finally precipitation with isopropanol. The product was appropriate for topical uses and its manufacturing expense was calculated at 1115 \$/Kg. By applying fed-batch and assuming a HA titer of 5.0 g/L, a comparable situation resulted in a decreased cost equal to 946 \$/kg. Furthermore, in the two other approaches, 10% of the formed HA is redirected to produce a pure HA with high molecular weight, which is appropriate for injectable uses. These trials led to increased expenses for both capital and operational costs but also generated higher profits because of HA's higher selling price for injectable uses that surpasses the higher production costs. The downstream processes (such as tangential flow filtration and polishing) are the main factors contributing to the cost of HA production. High purity HA which is suitable for cosmetics and pharmaceuticals is mainly achieved by modern purification techniques such as size-exclusion chromatography and ultrafiltration. For reducing the costs and decreasing the environmental impacts, it is essential to develop sustainable purification and extraction technologies, specifically those leveraging nanotechnology.³⁸ Additionally, genetically engineered microorganisms have the competency to economically enable the production of HA through batch fermentation using the microbiological pathway.²⁵

4. Applications of HA

In this part, several studies regarding the utilization of HA in different fields such as cosmetics, drug delivery, and TE are reviewed. The methodologies and outcomes of the research studies are investigated and several tables are demonstrated for a more effective comparison.

4.1. Applications of HA in cosmetics

HA is widely used in cosmetics coming from its unique properties and versatility. The Resilient HA fillers (RHA[®]) is the first example which are approved by Food and Drug Administration (FDA) for the treatment of dynamic facial lines, adapting uniquely to facial movements for natural results. In addition, combination fillers such as HA/botulinum toxin, HA/poly-L-lactic acid, and HA/calcium hydroxyapatite are employed to accomplish specific cosmetic goals. Combining HA and micro-focused ultrasound with visualization (MFU-V) enhances skin tightness and collagen production.³⁹ Furthermore, a study conducted on improving the cosmetic efficacy of high molecular weight hyaluronic acid (HMWHA) without resorting to chemical alteration, aiming to improve its benefits for skincare applications. Clinical trials and in vitro experiments illustrated the effective augmentation of HMWHA's cosmetic performance, highlighting its promise in skincare without any chemical modifications.⁴⁰ The viscoelastic properties of HA fillers play a crucial role in their clinical effectiveness, and several products exhibit varying viscoelastic behaviors under different conditions. This behavior and cohesion of HA fillers can be affected by multiple variables, for example, chain length, concentration of HA, and the crosslinking method.^{41,42}

4.2. Therapeutic applications of HA

HA is necessary for cellular functions and building physical and immunological barriers, therefore, is useful in modern therapies. HA-based materials mirror the biological processes of their host and are being used in biomedical applications in response to the growing demand for non-toxic and focused therapies. HA has demonstrated versatility in producing nanofibers, hydrogels, and 3D structures, which have found applications in many medical realms, including wound healing, bone and tissue regeneration, and cancer therapy.⁴³ Nanofibers composed of HA-Ag nanocomposites, polyvinyl alcohol, collagen, and chitosan which have been prepared by electrospinning, showed antibacterial activity against *S. aureus*. HA acted as a capping and reducing agent in HA-Ag nanocomposites which caused to avoid the harsh reductants for their preparation. The nanofibers were biocompatible resulting in 70% and 85% L929 fibroblasts viability according to the cytotoxicity assessment.³³ HA supports angiogenesis by promoting vascular endothelial growth factor (VEGF) and other factors aiding blood vessel formation, also it enhances vessel stability, reduce leakage, and has anti-inflammatory effects. In wound healing, HA accelerates recovery by stimulating blood vessel growth, and activating responses in fibroblasts, endothelial cells, and macrophages.^{44,45} The cellular functions of HA are facilitated through various surface receptors including CD44, the receptor for hyaluronic acid-mediated motility (RHAMM), LYVE-1, and toll-like receptors, which have been identified as significant components in the process of wound healing.^{46,47} HA exerts its biological functions through a set of highly regulated interactions with the membrane receptors and the nature of these interactions is strongly dictated by the physicochemical characteristics of the polymer. From a design standpoint, two parameters, molecular weight and crosslinking density play a central role in defining how HA-based scaffolds engage these receptors.⁴⁷ Different molecular weights of HA activate different receptors and lead to different biological responses.¹⁰ HMWHA maintains structural integrity and promotes a quiescent, anti-inflammatory phenotype largely through sustained CD44 ligation, whereas progressive enzymatic degradation and the generation of low-molecular-weight fragments shift signaling toward RHAMM-dependent

pathways associated with injury response, cytoskeletal remodeling, and early stages of tissue repair. Consequently, the controlled adjustment of crosslinking density not only regulates hydrogel stiffness and degradation kinetics but also modulates the temporal profile of receptor-specific cues which cells perceive within the scaffold. In parallel, material chemistry, hydration, and functionalization influence the ligand presentation, receptor clustering, and growth factor retention, thereby integrating the biophysical and biochemical signals that collectively determine osteogenic commitment of the MSCs. These relationships highlight that HA–receptor interactions are inseparable from the scaffold design parameters and can be deliberately tuned to achieve defined regenerative outcomes.⁴⁸

Various studies have reported that HA injections can enhance pain relief and improve function and quality of life in OA patients.^{49–51} HA hydrogels have shown considerable abilities in improving the viscoelastic properties of the synovial fluid and regenerating the degraded cartilage ECM.^{52,53} The other significant utilization of HA is in ophthalmology. High concentrations of HA in eye drops stabilize tear films and increase the number of conjunctival goblet cells. Additionally, HMWHA with anti-inflammatory traits in eye drops, can be strengthened by combination with lower-molecular-weight HA that protects corneal cells from dehydration.^{54,55}

Commercial and candidate HA-based products with documented scientific, clinical, or regulatory support are summarized in **Table 1** to highlight the current translational and therapeutic applications. Selection criteria for the commercial products involved: (1) FDA or EMA approval, (2) availability of published clinical trial data, (3) diversity in application (medical, cosmetics, drug delivery). Products with unsubstantiated claims or lacking scientific documentation were excluded.

Table 1. Selected commercial and candidate hyaluronic acid containing products.

Company	Country	Product Fields	Product Name	Regulatory / Clinical Status	Reference
Contipro AS	Czech Republic	Pharmaceuticals, Cosmetics, and Wound healing	Sorelex	Level II – CE-marked medical device, clinical use	56
			Hyiodine	Level II – CE-marked device, post-market clinical evidence	
			Fascigel HA	Level II – CE-marked injectable medical device	
			Oligo HA	Level IV – Research/industrial-grade ingredient	
Bloomage Biotechnology Corporation Limited	China	Beauty and care, Pharma and aesthetics, Nutrition and health	Hybloom™ Minitru e, miniHA™, Hymagic™-AcHA,	Level III – GMP-certified industrial pharmaceutical-grade HA	57
HTL Biotechnology	France	Pharmaceuticals	Pharmaceutical grade Hyaluronic acid	Level III – GMP/ISO-certified pharmaceutical HA	58
			Oligo HA	Level IV – Preclinical/early-stage material	
Lifecore Biomedical LLC	USA	Pharmaceuticals	Sodium Hyaluronate (NaHy)	Level III – GMP-grade, DMF/EP-certified, clinically translated	59
Baoding Faithful Industry Co. Ltd	China	Industrial supply (Pharmaceuticals, Cosmetic, Food)	Pharmaceutical grade hyaluronic acid, Cosmetic	Level III – Certified industrial HA manufacturing	60

			grade small molecule hyaluronic acid, Food grade hyaluronic acid		
FIDIA Farmaceutici	Italy	Acute wounds and Chronic wounds	Hyalo4 Skin	Level II – CE-marked wound care product with clinical validation	61
MPM Medical	USA	Wound healing	Regenecare HA™	Level II – Commercial HA hydrogel with post-market evidence	62
Medical Instinct® Deutschland GmbH	Germany	Gel membrane and Wound healing liquid	Tissue Support and Flex Barrier	Level II – CE-marked surgical biomaterials	63
Allergan Aesthetics (AbbVie Inc.)	USA	Cosmetics and Injectable gels	SKINVIVE	Level I – FDA-approved dermal injectable with clinical trials	64
REVANCE AESTHETICS	USA	Dermal fillers	RHA® Collection	Level I – FDA-approved, Phase III clinical evidence	65
Merz Pharma	Germany	Dermal filler	BELOTERO BALANCE®	Level I – FDA-approved with clinical + post-market data	66
Galderma	Switzerland	Facial rejuvenation and Volume enhancement	Alastin	Level II – Clinically supported aesthetic dermatology product	67
Sinclair Pharma	UK	Aesthetic treatments	Perfectha® and Ellansé®	Level I–II – CE-marked / clinically used aesthetic injectables	68
BIOPLUS CO., LTD	South Korea	Synovial fluid replacement, Sterile absorbable anti-adhesion barrier	InterBlock, HyalSyno, Blad-Care	Level II – Clinically used medical devices	69
Bioxis Pharmaceuticals	France	Dermal filler	Princess® Filler	Level II – CE-marked aesthetic filler	70
Prollenium Medical Technologies	Canada	Dermal fillers	Revanesse® Versa™	Level I–II – Clinically validated injectable filler	71
Teoxane	Switzerland	Dermal fillers and Dermocosmetics	Teosyal®	Level I–II – Clinically established aesthetic filler portfolio	72

The features and importance of HA in TE are explained in the following sections, focusing on how HA works in concert with other medicinal substances in TE, regenerative medicine, and nanomedicine.

4.2.1. Applications of HA-containing scaffolds in drug delivery

HA has the tumor-targeting capability and binds to cell surface receptors like CD44, LYVE-1, and TSG-6, with CD44 being overexpressed in many cancers. This makes HA a promising candidate for targeted drug delivery in cancer treatment. Modifying HA can alter its interaction with CD44, influencing tumor progression and metastasis.^{73,74} Numerous studies investigated drug delivery strategies based on HA to target tumors through CD44.^{75,76} Development of HA-coated polymeric micelles for the entrapment of Olmesartan medoxomil (OLM), an anti-fibrotic drug, specifically demonstrated in vitro cellular uptake into LX-2 cells (human hepatic stellate cell line), which indicates their potential for targeted drug delivery to hepatic stellate cells. Furthermore, in vivo imaging analysis showed a high accumulation of HA-coated micelles in the liver after intravenous injection in

mice, suggesting their ability to target liver tissue effectively. These results highlighted the potential of these systems in treating liver fibrosis.⁷⁷ HA-coated gold nanoparticles (AuNP-HA) have been studied for their controlled release properties and for demonstrating the drug delivery efficiency, and Sulfasalazine (SSZ) which is a poorly water-soluble drug was used. The AuNP-HA-SSZ system released SSZ slowly over a short period and showed sensitivity to different pH levels. The lowest and highest release rate was under simulated gastric and simulated intestinal conditions respectively, indicating controlled release behavior. These findings suggested that AuNP-HA can be orally administered and used for intestine-targeted drug delivery.⁷⁸ Coating of flurbiprofen-layered double hydroxide (FB-LDH) with HA significantly improved the stability of the LDH when it was exposed to electrolytes. In vitro tests showed that the total release percentages of FB-LDH and HA-FB-LDH within 12 hours were $92.99\% \pm 0.37\%$ and $74.82\% \pm 0.29\%$ respectively, indicating that the HA coating had a specific and sustained impact on the release of the drug. Moreover, in vivo ocular irritation experiments confirmed the safety and non-irritating nature of the ophthalmic formulation which had been examined in this study. These results demonstrated improved corneal permeability and prolonged residence time of HA-FB-LDH, making it such effective ophthalmic drug delivery system.⁷⁹

Since oral medications are given non-specifically over long periods, inflammatory bowel disease (IBD) poses a major drug delivery challenge. Curcumin (CUR) which is widely known for its anti-inflammatory qualities has low bioavailability, therefore, has limited role in the treatment of IBD. Zhang et al⁸⁰ developed a pH-sensitive hyaluronic acid/gelatin (HA/GE) hydrogel drug delivery system, which contains carboxymethyl chitosan (CC) microspheres loaded with CUR, as a potentially effective alternative. With this novel method, CUR can be released selectively and continuously. Through the optimization of the hydrogel's composition and structure, scientists have successfully leveraged this delivery system to offer a more precise and efficacious treatment for IBD. X-ray diffraction and infrared spectroscopy were used to thoroughly examine the physicochemical features of the composite system to comprehend its structural and chemical characteristics. In addition, research on swelling and release behavior has shed light on the regulated release of CUR in gastrointestinal tract segments impacted by IBD.

4.2.2. Applications of HA-containing scaffolds in tissue engineering

HA has gained attention in TE, coming from its biocompatibility and extensive distribution in vertebrate tissues and controlling cell activities.⁸¹

Scaffolds employed in TE must remain structurally stable for months before cells may deposit extracellular matrix. Limitation of nutrient and gas transport to a depth of 150-250 μm , necessitates the formation of a blood capillary network for sustaining the cells. HA can be chemically changed to stimulate capillary development while maintaining its biocompatibility. In vivo, hyaluronidase may break down HA into oligomers with high biological activity which can alter the cell behavior, including angiogenesis. These oligomers bind to host cells and stimulate the growth of new blood vessels.⁸²

Scaffolds can be synthetic or natural. Synthetic materials like poly(lactide-co-glycolide) (PLG) are FDA-approved and have good mechanical properties, however, they are hydrophobic and struggle with cell entrapment. On the other hand, hydrogels, which are made of hydrophilic polymer chains, are gaining popularity. Hydrogels are biodegradable, easily processed, minimally invasive, and have controllable structural properties similar to what tissues have. For TE scaffolds, HA is frequently applied in modified forms or together with other substances such as fibrin, chitosan, platelet-rich plasma (PRP), tricalcium phosphate, collagen, and alginate. Better mechanical

qualities can be obtained from crosslinked HA than the linear HA. Besides, composites can integrate the benefits of several materials.⁸³

Researchers have manufactured diverse composite HA hydrogels by modifying HA and incorporating covalent binding materials which are significant for bone and cartilage tissue engineering (CTE).⁸⁴ HA has also shown promise in bioengineered scaffolds for cartilage, nerve, and skin tissues.⁸⁵

In **Table 2** numerous HA-contained composite hydrogels and their applications have been named. In vitro / in vivo tests and techniques for the preparation of these composites have been mentioned.

Table 2. Hyaluronic acid-based composite hydrogels, their fabrication techniques, and biomedical applications.

Natural biopolymers	Copolymer	Technique	Cell type or drug	Application	In vitro / In vivo	Animal / Tissue	Reference
	Collagen	Injectable hydrogels	L929 fibroblast cells	Cartilage tissue	Histological staining	Mice	86
		Cryogelation	3T3 fibroblast and SAOS-2 cells	Tissue engineering	-		87
		Enzymatic crosslinking reaction	MSCs	Cartilage tissue	-		88
		Freeze-drying	3T3-L1 preadipocytes	Adipose tissue engineering	-		89
		Extrusion-based bioprinting	Patient-derived cancer cells	Disease models	-		90
	Gelatine	Oxidative coupling reaction	Human dermal fibroblast (hDFB)	Tissue engineering	-		91
		Electrospinning	Glioblastoma cells (U251)	Glioblastoma (GBM)	-		92
		Injectable hydrogel	H9c2 cells	Damaged myocardium	Computer tomography	Freshly harvested pig heart (ex vivo)	93
		H ₂ O ₂ -mediated crosslinking	Mouse myoblast C2C12 cells	Muscle cell sheet fabrication	-		94
		Crosslinked	L929 fibroblasts	Wound healing	Digital planimetry	C57BL/6 J mice	95
		Freeze-drying	Rat fibroblasts	Soft tissue engineering	-		96
		Microspheres, Drug delivery system	CUR	Inflammatory bowel disease (IBD)	Pharmacokinetics	Mice	80
		Core/shell, Bio-inspired, 3D printing	Doxycycline	Local drug delivery and Bone regeneration	Confocal laser scanning microscopy, Cone beam computed tomography, Histological and histomorphometric analyses	Rabbit	97

		3D printing	Human bone marrow-derived mesenchymal stem cells (hBMSCs)	Bone tissue engineering	-		98
		3D printing	Homologous auricular chondrocytes	Nasal septal cartilage	Computed tomography, Magnetic resonance imaging, Histological evaluations	Rabbit	99
	Silk fibroin	Freeze-drying	Mouse fibroblast cell (NIH/3T3)	Soft tissue engineering	-		100
		Freezing-annealed	-	Soft tissue engineering	-		101
	Corn silk extract	Mixing	Mouse C34/An (L929 cells)	Bone tissue regeneration	-		102
	Alginate	3D Printing	Human chondrocytes	Cartilage	-		103
		Chemical cross-linking	-	Skin diseases	-		104
		3D bioprinting	Chondrocytes cells	Cartilage tissue	-		105
		Mixing	Human bone marrow mesenchymal stem cells	Tympanic membrane (TM)	Ear endoscopy	Rats	106
	Gelatin methacrylamide (GelMA)	3D bioprinting	Bone marrow-derived human mesenchymal stem cells (BM-MSCs)	Cartilage tissue	-		107
		Stereolithography (SLA)-based bioprinting	Chondrocytes cells	cartilage tissue	-		108
		Injectable and In situ gelating biomimetic hybrid	MG-63 cells	Bone tissue regeneration	--		109
	Chitosan	Extrusion-based bioprinting	Vancomycin	Drug delivery	-		110
		Electrospinning	MC3T3-E1 pre-osteoblasts cells	Bone tissue regeneration	-		111
	Polycaprolactone (PCL)	3D printed	-	Bone tissue	Micro-computed tomography,	Rats	112

Synthetic biopolymers					Histology analyses		
		Electrospinning	Human vocal fold fibroblasts	Wound repair	-		113
	polyethylene glycol diacrylate (PEGDA)	Suspension mix	Human mesenchymal stem cells (hMSCs)	Bone and cartilage			114
	Polyethylene glycol (PEG)	Injectable composite hydrogel	Dhuha-7 cells	Chronic low back pain (CLBP)	-		115
		Injectable composite hydrogel	Mouse fibroblasts (L929)	Central nervous system tissue engineering	-		116

4.2.2.1. Applications of HA-containing scaffolds in bone and cartilage tissue engineering

Bone defects can be result of trauma, cancer, congenital issues, or surgery. The healing process involves inflammation, cell growth, and calcification. Healing can be affected by factors like infection and blood supply. The body's natural healing abilities are limited, so external intervention is often necessary. Autologous bone grafts are the current "gold standard", but they are limited by inadequate bone stock, especially for extensive defects.¹¹⁷ In orthopedics, meniscus and articular cartilage injuries pose major hurdles because of few options available for viable regeneration therapy. Bone diseases which affect joints can lead to cartilage damage resulting from lack of blood vessels, nerves, and lymph. Cartilage is sustained by chondrocytes and plasmids in its ECM which is composed of collagen, proteoglycans, and HA. The mechanical properties of cartilage vary based on collagen and GAG compositions. With chondrocytes making up only 1-5% of cartilage, its low cell density and absence of blood vessels limit the tissue regeneration. Consequently, fibrous cartilage with reduced performance will be formed during healing.¹¹⁸

In order to improve the joint function, formation of natural joint or hyaline cartilage over fibrous cartilage needs to be promoted. Autogenous chondrocyte grafts have their own limitations, including long harvest time, lack of cell sources, and poor effects in elderly. TE using stem cells combined with biological materials is being explored as a solution, which involves culturing and amplifying autologous osteoblasts, chondrocytes, or bone marrow stroma stem cells, and implanting them into a compatible scaffold or extracellular matrix for effective degradation.¹¹⁹ Bone Tissue Engineering (BTE) relies on osteoconductivity, osseointegration, and osteoinductivity. Development of 3D printing has revolutionized TE by making it possible to manufacture customized tissue replacements that improve and encourage regeneration in regions of tissue defect.¹⁰⁷ The materials of scaffolds used in BTE or CTE should possess biocompatibility, natural ecology, ability to seed osteoprogenitor cells, differentiation and proliferation capabilities, and natural ECM and morphogenesis signals. A major barrier in BTE 3D printing is selecting the materials that possess the best rheological characteristics and the consistent cell integration capabilities.

Hydrogels have been emerged as viable options for 3D bioprinting because they offer adequate printability, which enables cell encapsulation and formation of scaffolds with uniform cell distribution.¹⁰⁷ These conditions are crucial for ensuring the success of the healing phase.¹²⁰ Hydrogels are being extensively studied as representative

materials with the potential for streamlining the BTE or CTE. They should maintain cell phenotype, rebuild tissue interfaces, mimic the natural environment, support vascularization, degrade safely, and deliver growth factors and drugs.¹²¹

Advancements in material manufacturing have led to increased use of HA-based hydrogels in both BTE and CTE. In these scaffolds, HA undergoes chemical modification and crosslinking, commonly targeting its hydroxyl and carboxylic acid groups. Modification of the hydroxyl group can be done with an ester bond, while the carboxylic acid group is altered by hydrazide and then crosslinking with an ester bond. Addition of other functional groups can enhance the physicochemical properties. Partial deacetalization of HA through treatment with acidic or alkaline substances, results in free amino groups that can be crosslinked by amides, or secondary amine bonds, thus recovering the bond energy.¹²² Previous studies have demonstrated that the down-regulation of cartilage gene expression can be restored with the use of HA and PRP. HA has been employed for the engineering of the nucleus pulposus, vocal cords, intervertebral discs, and other structures.⁸³ HA has also promoted chondrocyte metabolism by increasing the production of essential components for cartilage tissue such as chondroitin-6-sulfate, collagen II, and GAG.¹²³

The following studies emphasize the potential of HA in various medical applications, but additional research is required to comprehend the exact mechanisms of its interactions.⁷³

Costantini et al¹⁰⁷ developed a 3D-printed hydrogel scaffold using hyaluronic acid methacrylate (HAMA), GelMA, and chondroitin sulfate amino ethyl methacrylate (CS-AEMA) and used a two-coaxial-needle bio-printing system to achieve high cell density, high printing resolution, and improved cell viability. This innovative approach has great potential for applying in TE and regenerative medicine. Silk fibroin (SF)/HA composite hydrogel has demonstrated encouraging capability in promoting bone tissue regeneration. The HA content inside this matrix can be easier distributed by the surface modification of HA nanoparticles. To encourage cell attachment, proliferation, and eventually the shaping of a new bone tissue, a homogeneous dispersion is crucial. In a work by Kim et al¹²⁴ surface-modified hydroxyapatite nanoparticles and HA-dopamine were used. This novel technique produced a material with exceptional cell proliferation and great prospect for implementation in BTE. Injectable HA-based hydrogels are effective in repairing small-scale bone and cartilage defects. However, its use is limited by natural degradation processes in the body.¹²³ The HA-containing hydrogels provide a low-oxygen environment, which stimulates chondrocyte proliferation. Glucosamine is essential for controlling chondrocyte activity and HA is also appropriate for osteochondral TE since it can be used in bone regeneration as well. Huang et al¹²⁵ fabricated an injectable nano-hydroxyapatite/glycol chitosan/HA composite hydrogel for BTE. The porosity, pore size, and swelling ratio reduced with increasing HA concentration. After four weeks, hydrogels totally broke down and were safe for cells with good cell adhesion and dispersion.

HA can also be utilized to change bio-inert artificial materials in a physiologically active way. HA can form a scaffold for the regenerated matrix when it matches with polyethylene glycol (PEG) or tiny intestine submucosa. Studies have demonstrated the potential of biodegradable PEG hydrogel modified by high concentrations of HA, as it considerably enhanced chondrocyte proliferation and extracellular matrix deposition.¹²⁶

4.2.2.2. Applications of HA-containing scaffolds in skin tissue engineering

In typical skin TE, skin substitutes are used, which are created by seeding keratinocytes and fibroblasts into a non-human matrix such as type I bovine collagen.¹²⁷ Scientists have shown that HA can enhance the survival and maintenance of early fat transplantation. HA-based scaffolds can promote the in vivo and in vitro development of adipose tissue. Recent studies have investigated the effects of HA on cell formation, wound repair, and

inflammation.¹²⁸ HA-based hydrogels have the ability to provide a moist environment that encourages wound healing and protects against microbial infections. Furthermore, HA has the capacity to communicate with tissues and cells which speeds up the healing.¹²⁹ Human amnion membranes are considered for treating wounds although they are expensive and difficult to handle. HA hydrogel in combination with solubilized amnion membrane (SAM) is a novel cell-free solution with simple production, storage, and application to wounds. HA-SAM dramatically accelerated the wound closure in a model mouse. The results showed the wound that had been treated with HA-SAM had thicker regenerated skin, more blood vessels, and more proliferating keratinocytes. This illustrates the efficacy of amnion membrane, circumventing the drawbacks associated with utilizing fresh, cryopreserved, or dried tissue.¹³⁰

From topical formulations to skin substitutes, the integration of HA in wound dressings has highlighted promising results. Wound dressings can address several facets of the wound healing process by mixing HA with various medicines, which improve the results, and hasten the recovery.¹³¹ De Angelis et al¹³² evaluated a bio-functionalized scaffold made of PRP and HA in 182 patients with chronic ulcers (vascular and diabetic) in vitro and in vivo. The outcomes were compared with the ones from 182 patients cured with conventional dressings (HA alone) as the control group. After thirty days, the patients who received PRP + HA showed $96.8\% \pm 1.5\%$ re-epithelialization, whereas the control group (HA alone) showed $78.4\% \pm 4.4\%$. As opposed to $87.8\% \pm 4.1\%$ re-epithelialization in the control group (HA alone; $p < 0.05$) in 80 days, the target group experienced $98.4\% \pm 1.3\%$. During the follow-up period, no local recurrence was noted. PRP with HA demonstrated more regeneration capacity than HA alone in terms of skin renewal and epidermal proliferation.

Davidenko et al⁸⁹ created a 3D porous collagen-HA scaffold, offering a robust and freely permeable matrix for mimicking the complex microenvironment of the mammary gland. Development of 3D in vitro models of the mammary gland offers significant capacity for enhancing our understanding of breast tissue biology and diseases. For manufacturing the 3D porous collagen-HA scaffolds, a carefully monitored freeze-drying and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride crosslinking were applied. The pore structure was intended to be consistent and interconnected, with a total porosity of around 85%. Crucially, no indications of collagen denaturation throughout the construction process were observed which emphasizes that these scaffolds can maintain the extracellular matrix's structural and functional integrity, which is essential for accurately portraying mammary gland tissue.

Injectable hydrogels have the capacity to fill irregularly shaped defects and administer therapeutic substances in a less invasive way. This is especially helpful where encouraging tissue regeneration and repair requires precise delivery of cells, growth factors, and other bioactive substances. Novel hydrogel's cytocompatibility makes it a desirable option for encasing and conveying different kinds of cells, offering an environment that is favorable for their survival and function inside the body. Nejati & Mongeau¹³³ have shown a new injectable double network hydrogel made of two derivatives of HA: HAMA and dopamine-grafted HA (DAHA). Its novel composition and structure enabled the extraordinary characteristics of this hydrogel.

The role of HA in enormous fields of regenerative medicine is presented in **Table 3**. In each field, the HA function has been specifically described.

Table 3. Applications of HA in regenerative medicine.

Application	Description	Reference
Stem Cell Therapy	HA is used with stem cells to improve therapeutic results. Its characteristics encourage the proliferation, differentiation, and migration of cells, all essential for successful treatment.	¹³⁴
Tissue Engineering	HA acts as a scaffold, creating an environment that is conducive to cell adhesion and proliferation. It is frequently mixed with other substances, such as alginate, to make hydrogels that resemble the extracellular matrix.	⁴⁷
3D Bioprinting	Bioinks based on HA are under development for use in 3D bioprinting. These bioinks allow for the encapsulation of stem cells while preserving their vitality, which makes it easier to print intricate tissue architectures.	^{135,136}
Wound Healing	Due to its ability to promote tissue creation and remodeling, HA is essential for wound healing. Because of its capacity to enclose moisture, it is an important ingredient in therapeutic formulations for skin restoration, which promotes healing.	¹³⁷
Immune Modulation	HA can help to promote immunological tolerance In cell therapy, which lowers the risk of rejection and improves transplanted cells' incorporation into host tissues.	¹³⁵
Gene Expression Regulation	In order to preserve stem cells' pluripotency and therapeutic potential, HA hydrogels improve the expression of genes linked to stemness.	¹³⁸
Bone Regeneration	To improve bone repair, HA is mixed with other biomaterials such as collagen and alginate. It enhances the mechanical characteristics of scaffolds used in bone tissue engineering and promotes osteogenic differentiation.	¹³⁹
Cartilage Regeneration	HA-based hydrogels are used in cartilage repair for enhancing chondrocyte proliferation and encouraging the production of cartilage matrix components.	¹⁴⁰
Nanomedicine	To improve the bioavailability and therapeutic effectiveness of medications, HA is added to nanocarriers for targeted drug delivery. It can be used in a variety of applications due to its biocompatibility and capacity to alter immune responses.	¹⁴¹
Tendon and Ligament Healing	Tendons and ligaments can rehabilitate faster after injury when HA is applied.	¹⁴²
Cardiovascular Repair	Heart-related tissue engineering and repair processes may find use for HA.	¹⁴³
Nerve Regeneration	The potential of HA to stimulate nerve regeneration after damage is being studied.	¹⁴⁴
Ocular Applications	HA is used in the treatment of dry eye conditions and eye surgery.	¹⁴⁵
Dermal Fillers	HA is a typical component of face rejuvenation cosmetic fillers.	¹⁴⁶

Osteoarthritis Treatment	Injections of HA intraarticularly can assist individuals with osteoarthritis by lubricating their joints and feeling less pain.	¹⁴⁷

5. HA in stem cell therapy

HA is crucial in enhancing the efficacy of stem cell therapy. One of the early challenges is ensuring the survival of transplanted cells. Different studies have confirmed the potential of HA-based hydrogels in stem cell therapies.¹⁴⁸⁻¹⁵⁰ HA hydrophilic nature creates a hydrated microenvironment that protects stem cells from desiccation and mechanical stress. This hydration not only increases cell viability but also promotes cell proliferation and differentiation. HA-containing hydrogels also support the differentiation of stem cells, aiding in cartilage tissue regeneration and in providing lubrication for synovial fluid.¹²³ HA reinstitutes the production of cartilage by stimulating stem and cartilage progenitor cells to develop into chondrocytes, preserving chondrocyte phenotype, and promoting the deposition of extracellular matrix necessary for CTE.¹²³ HA accumulates in wounded cartilage. It also serves as a cell carrier, encasing chondrocytes and stem cells in the injected location and allowing them to develop and alter in place. In both laboratory and animal studies, HAMA has shown that it promoted the differentiation of mesenchymal stem cells into cartilage and addition of certain cytokines, for example transforming growth factor- β 3, might increase this impact.¹⁵¹

Murakami et al¹⁵² observed that a 900 kDa HA facilitated the proliferation of meniscus cells derived from patients, probably through the PI3K/MAPK signaling pathway. Oligosaccharide hyaluronic acid (oHA) with a molecular weight of approximately 1.6-8.0 kDa (4-20 mers) provoked the proliferation of human umbilical vein endothelial cells (hUVECs) via the oHA-ezrin signaling pathway.¹⁵³ Moreover, a 300 kDa HA expedited the proliferation of human amniotic mesenchymal stem cells (hAMSCs) through the Wnt/ β -catenin signaling pathway.¹⁵⁴ Notably, HA preserved the phenotypic characters and differentiation potential of human amniotic epithelial cells (hAECs) and enhanced the release of anti-inflammatory cytokines, such as interleukin-10 (IL-10), and the transforming growth factor beta 1 (TGF- β 1).¹⁵⁵ Combination of HA and multipotent stromal cells (MSCs) secretome demonstrated synergistic effects. This has promoted MSCs viability, differentiation into Alveolar type II (ATII) cells, and exhibition of an anti-inflammatory profile which indicates the potential for lung tissue repair and inflammation reduction.¹⁵⁶

5.1. Applications of HA-containing scaffolds in stem cell therapy

HA-containing scaffolds enhance cell proliferation, differentiation, and survival by improving scaffolds' distinctive physicochemical properties and the interactions with cellular receptors.^{9,157} HA interacts with stem cells and induces the process of differentiation.⁹ Recent clinical trials have explored the combination of stem cells and HA, demonstrating the potential of this approach in translational medicine.¹³⁴ Overall, HA-containing scaffolds have shown great promise in enhancing stem cell function and promoting tissue repair and regeneration.¹⁵⁸⁻¹⁶⁰ The synergistic interplay between these scaffolds and stem cells has been found to significantly enhance the regenerative processes in a wide range of tissues, such as cartilage, bone, and dental pulp. This promising approach has opened up new gates, offering innovative solutions for the repair and restoration of damaged or diseased tissues.¹⁶¹ HA treated with photoreactive methacrylates has attracted a lot of interest due to its potential for creating microstructures that can serve as functional parts of microfabricated devices. Through

the synthesis and use of this modified HA, microstructures with great potential for a range of biological applications can be fabricated. By displaying the flexibility and versatility of micropatterning hydrogels, new courses of action for technological advancement and biological research have become accessible.

Khademhosseini et al¹⁶² have forged the cell-laden HA microgels by micro-molding in a ground-breaking work. This novel strategy for the development of innovative biomaterials might completely alter the medical care, with important ramifications for regenerative medicine and TE. A trio of photoinitiators, ESCs, and methacrylated HA were used. Their technique was precisely placing the materials on a polydimethylsiloxane master mold with patterns. By following this rigorous procedure an astounding 82% cell viability rate in ESCs was achieved. There are available research studies which have employed human MSCs (hMSCs) and methacrylated HA for the cartilage repair. They have discovered that cultivation of MSC-laden HA hydrogels facilitated chondrogenesis in vitro and in vivo, as evidenced by early gene expression and the formation of cartilage-specific matrix proteins. Yazdani et al¹⁵⁷ comprehensively reviewed the potential of HA-based hydrogel scaffolds for treating limbal stem cell deficiency owing to the association between HA and limbal stem cell function in preclinical studies. MSCs seeded on a hyaluronan-based scaffold (HYAFF®11) were transplanted into the knee joints of rabbits with surgically induced OA. It was found that the implants with MSCs have shown statistically significant improvements in the quality of the regenerated tissue compared to the scaffold alone and untreated controls, particularly after 6 months.¹⁵⁹ HYAFF®11's highly porous structure facilitated robust rat MSC growth and function in static culture. The scaffold promoted cell adhesion, migration, proliferation, and ECM production, including fibronectin, decorin, and versican without compromising stemness. MSCs readily adhered, demonstrated high viability, proliferated consistently, and migrated throughout the scaffold, formed a subconfluent monolayer, and interacted with the material by enveloping individual fibers and depositing ECM.¹⁶³

HA-serum hydrogels have rapidly restored the metabolism and promoted the viability of encapsulated stem cells within 1 hour, in vitro and in vivo. HA/Serine hydrogels acted as synthetic stem cell niche, and significantly improved the retention, proliferation, viability, and engraftment of the encapsulated stem cells in the myocardium, and promoted angiogenesis as well.¹⁶⁴

Gojgini et al¹⁶⁵ have found that gene transfer to the stem cells encapsulated within the hydrogels is significantly influenced by hydrogel mechanical properties and arginylglycylaspartic acid (RGD). Softer hydrogels (100-260 Pa) resulted in higher gene transfer compared to stiffer hydrogels (839-1730 Pa). The highest gene transfer was observed in the intermediate RGD clustering (0.4 RGD/HA molecule), not in the homogeneous distribution (0.2 RGD/HA) or high clustering (4.7 RGD/HA). MSCs encapsulated in HA hydrogels have shown increased expression of chondrogenic genes like type II collagen, aggrecan, and sox 9 than the initial cell population, even without adding the growth factors. Moreover, addition of transforming growth factor beta 3 (TGF-β3) or pre-culturing the MSCs in chondrogenic media has further intensified the expression of chondrogenic genes. HA hydrogel provided a more promising environment compared to the inert PEG hydrogel for the chondrogenic differentiation of MSCs, suggesting the importance of cell-scaffold interactions.¹⁶⁶ Prestwich¹⁶⁷ reported that development of a HA-based synthetic ECM (sECM) can be used as a vehicle for delivering, retaining, growing, and differentiating stem cells for regenerative medicine such as cancer-related applications. A bioinspired, tissue-adhesive hydrogel which comprised of HA and catechol (HA-CA), has demonstrated superior biocompatibility and functionality for human adipose-derived stem cells and hepatocytes in comparison with standard HA hydrogels. The HA-CA hydrogel's strong adhesive properties enabled effective cell delivery to organs like liver and heart without invasive injection. This hydrogel promoted angiogenesis which enhanced the stem cell therapeutic efficacy in ischemic disease models. Transplanted hepatocytes within the HA-CA hydrogel have also

exhibited improved liver function.¹⁶⁸ Radice et al¹⁶⁹ have demonstrated the safety and efficacy of a hyaluronan-based scaffold for delivering mesenchymal progenitor cells (MPCs) to repair articular cartilage defects. MPCs seeded on the scaffold produced key cartilage matrix components, including type II collagen. Implanted in rabbits, the scaffold with or without MPCs, was biocompatible, degraded completely within four months, and caused no inflammation. Moreover, both scaffold groups facilitated faster and more effective healing of osteochondral lesions compared to untreated controls. 3D HA hydrogel scaffolds supported liver cancer spheroid formation and potentially enhanced stemness, thereby improving tumor modeling.¹⁷⁰

Comparison of representative HA-based scaffold systems suggests that physicochemical characteristics directly determine cellular behavior and regenerative outcomes. Higher porosity generally promotes nutrient diffusion, cell infiltration, and extracellular matrix deposition, whereas excessive porosity may reduce mechanical stability. Scaffold stiffness and compressive modulus influence lineage specification, with intermediate mechanical environments often supporting balanced proliferation and differentiation, while highly rigid matrices favor structural maintenance but may restrict remodeling. Similarly, degradation kinetics regulate the duration of cell–matrix interactions; rapidly degrading scaffolds facilitate early tissue integration but may compromise long-term support, whereas slower degradation improves structural persistence at the expense of cellular migration. Viscoelastic properties also influence stem cell mechanotransduction and retention within the regenerative niche. Collectively, these observations indicate that biological performance is governed by coordinated optimization of scaffold architecture rather than maximization of any single material parameter.

Table 4 presents a direct comparison of porosity, compressive modulus, degradation rate, and viscoelasticity (G') from representative key studies. HAMA/GelMA 3D-bioprinted scaffolds exhibit high porosity (85–92%) and intermediate compressive modulus (15–25 kPa), while HA/PEGDA photo-crosslinked scaffolds offer the highest compressive modulus (30–45 kPa) and longest degradation time (42–56 days), making them suitable for load-bearing applications. Conversely, injectable HA-SH scaffolds show lower modulus (1–5 kPa) and faster degradation (14–21 days), which may be advantageous for minimally invasive delivery and rapid cell infiltration.

Table 4. Comparison of physicochemical properties of HA scaffolds in key studies.

Scaffold type	Porosity (%)	Compressive modulus (kPa)	Degradation rate (days)	Viscoelasticity (G', Pa)	Reference
HAMA/GelMA (3D bioprinted)	85-92	15-25	28-35	1200-1800	¹⁰⁷
HA/Collagen (freeze-dried)	80-88	5-12	21-28	400-800	⁸⁹
HA-SH (injectable)	70-78	1-5	14-21	100-300	¹⁴⁹
HA/PEGDA (photo-crosslinked)	75-82	30-45	42-56	2500-3500	¹¹⁴

Overall, HAMA/GelMA systems demonstrated a favorable balance between structural support and biological permissiveness, whereas HA/PEGDA scaffolds favored mechanical durability and injectable HA systems facilitated rapid cellular integration.

Although HA-containing scaffolds consistently demonstrate favorable regenerative effects, comparison across studies suggests that scaffold performance depends more strongly on design strategy than on HA incorporation alone. Variations in molecular weight, crosslinking degree, degradation kinetics, and mechanical properties produce substantially different biological responses even within similar therapeutic indications. Studies employing softer and rapidly remodeling matrices generally reported enhanced cell migration and integration, whereas mechanically reinforced systems more effectively preserved structural support and lineage commitment. Importantly, outcomes observed under in vitro conditions were not always reproduced in animal or translational studies, highlighting the influence of immune response, tissue mechanics, and scaffold–host interactions. Collectively, current evidence indicates that successful clinical translation will likely require application-specific optimization rather than adoption of a universal HA scaffold design, emphasizing the need for standardized reporting and direct comparative studies.

5.2. Balancing mechanical properties and biological responses in HA-based scaffolds

5.2.1. Balancing mechanical stability and dynamic remodeling

Based on the literature, it has been proposed to utilize dynamic/evolving networks instead of static scaffolds in tissue engineering. By controlling the degradation rate of these scaffolds, natural tissue remodeling and replacement can be facilitated while maintaining the necessary mechanical stability to support the cells. This approach has shown superior performance compared to static scaffolds, leading to increased expression of ECM markers and improved mechanical properties.¹⁷¹ Achieving the optimal mechanical stability is crucial through precise control of cross-link density. This is accomplished by adjusting parameters such as degree of methacrylation and component concentrations.^{172,173}

5.2.2. Optimal stiffness and crosslinking range

The presented research has indicated the existence of an optimal stiffness range for supporting desirable stem cell behavior. For instance, phenolated HA (HA-Ph) hydrogels with moderate stiffness (Young's modulus of 6.0 kPa) demonstrated the highest osteogenic differentiation induction in bone marrow-derived stem cells (bMSCs).¹⁷² Furthermore, an appropriate balance between initial stiffness and degradability/remodeling is essential for an enhanced cell function. ECM production and remodeling can be impeded by excessively rapid degradation or an overly rigid scaffold.¹⁷¹ Optimized polymer compositions with specific crosslinking degrees can lead to higher cellular metabolic activity and viability.¹⁷³

5.2.3. Necessity of in vivo validation

According to the literature, considerable differences existed between laboratory settings (in vitro) and the actual physiological environment (in vivo). Scaffold properties and cell behavior vary across these two environments. Therefore, while in vitro studies are useful for screening, generalizing those findings to real physiological conditions requires further validation in animal models or clinical studies.¹⁷⁴

5.3. Clinical applications of HA-stem cell scaffolds

To improve interpretation of the current evidence, findings related to HA-containing scaffolds should be considered according to their experimental level. In vitro studies primarily provide mechanistic insights and demonstrate how scaffold properties influence stem cell viability, proliferation, differentiation, and receptor-

mediated signaling under controlled conditions. In vivo investigations extend these observations by evaluating scaffold degradation, immune interactions, vascularization, and functional tissue repair within complex biological environments. Clinical and translational studies provide the highest level of evidence by assessing safety, feasibility, and therapeutic effectiveness in patients; however, these studies remain relatively limited compared with preclinical research. Consequently, positive outcomes observed in laboratory settings should be interpreted as supportive rather than directly predictive of clinical performance, emphasizing the need for progressive validation across evidence levels.

HA-based hydrogels boost the survival and therapeutic effectiveness of stem cells in treating myocardial infarction (MI). In a research study, sulfated hyaluronic acid (SHA) hydrogel was designed to deliver two therapeutics, Kartogenin (KGN) and TGF- β 1, to enhance chondrogenesis and facilitate articular cartilage restoration. The researchers found that injection of SHA hydrogels remarkably demoted cartilage abrasion as well as hypertrophy in the animal model. The hydrogel's ability to delay degradation and to enhance the retention of the growth factor has promoted human MSCs chondrogenesis and has maintained articular cartilage integrity. This injectable dual-drug-loaded SHA hydrogel has demonstrated promising potential for stem cell therapy in articular cartilage repair, as it promoted chondrogenesis and restored damaged cartilage which was a synergistic drug delivery approach.¹⁷⁵ Moreover, the potential of extracellular vesicles (EVs) derived from MSCs induced with HA (HA-iMSC-EVs) has been studied in enhancing cardiac repair following MI. The results have shown that HA-iMSC-EVs exhibited superior abilities in promoting tube formation and enhancing endothelial cells survival under oxidative stress conditions compared to iMSC-EVs (without HA). On the other hand, a decrease in reactive oxygen species (ROS) production in cardiomyocytes was also detected. The study confirmed that HA-iMSC-EVs which were localized within the heart tissue after administration via intravenous or intramyocardial routes, had higher intensity after intramyocardial injections. Echocardiography revealed that intramyocardial injections reduced adverse cardiac remodeling, improved cardiac function, and decreased necrotic areas in the heart affected by MI. These findings suggested that HA-iMSC-EVs have contributed to an improved cardiac function by promoting the growth of blood vessels and simultaneously reducing fibrosis and inflammation.¹⁷⁶ For enhancing the efficiency of cell-based injections, direct intra-articular administration of bone marrow-derived stem or stromal cells (BMSCs) and the supplementary function of HA in promoting the cartilage repair in rabbits have been investigated. In vivo analysis showed chondral defects that were treated with a combination of BMSCs and HA, exhibited superior therapeutic results than treatments with BMSCs or HA alone in terms of the overall assessment and histological scores. The results confirmed that HA has played a crucial role in facilitating cartilage healing not only by protecting chondrocytes but also by enhancing the ability of BMSCs to differentiate into chondrocytes.¹⁷⁷ A combination of umbilical cord mesenchymal stem cells (UC-MSCs) and auto-crosslinked HA has been investigated in mice with premature ovarian insufficiency (POI) as well as naturally aging mice for examining its potential to save ovarian reserve and fertility. To track the cell activity, Jiao et al¹⁷⁸ used PCR and immunofluorescence to monitor cell behavior on day 1, 3, 7, and 14 after transplantation. It was observed that HA had positive effects both in extending the presence of UC-MSCs in the ovary, and in enhancing their ability to secrete factors. Additionally, UC-MSCs had a role in promoting follicular survival via activation of the PI3K-AKT pathway through a paracrine mechanism, both in vitro and in vivo.

Thiol-functionalized HA (HA-SH) hydrogel has been designed by Lee et al¹⁴⁹ to enhance the effectiveness of MSCs for treating inflammatory lesions associated with atopic dermatitis (AD). The SH hydrogels which contained HA and MSCs have contributed to this outcome that over 80 percent of the cells remained viable and survived after one week, and exhibited promising in vivo biocompatibility upon implantation under the skin of

mice. HA-SH hydrogel along with MSCs in an AD animal model decreased epidermal thickness and lowered mast cell infiltration, which has shown a promising potential for the management of inflammatory conditions such as AD. A controlled-release hydrogel microsphere from acrylated hyaluronic acid (AHA) has been developed by Hamilton et al¹⁷⁹ for stem cell delivery. AHA microspheres had higher cell viability compared to polyethylene glycol diacrylate (PEGDA) microspheres, with superior biocompatibility in vivo, less foreign body response, and no cellular infiltration into the microsphere. A novel delivery system for glioma therapy has been examined in Wang et al¹⁸⁰ study. MSCs that are filled with paclitaxel (PTX)-encapsulated within hyaluronic acid-poly (D, L-lactide-co-glycolide) (PTX/HA-PLGA) micelles were used for targeting and managing glioma tumors. The findings have proven that the overexpression of CD44 on the surface of MSCs and cancer cells improved the loading of PTX/HA-PLGA micelles in the MSCs and facilitated the transfer of medication between MSCs and the neighboring cancer cells. CD44-mediated transcytosis has been found to be crucial for the deep penetration of a substance into glioma tissue. Furthermore, this substance has significantly prolonged the survival rate of rats with orthotopic glioma.

Figure 2 illustrates the multilevel framework through which HA scaffolds contribute to tissue engineering and regenerative medicine. At the core, HA provides a bioactive extracellular matrix–mimicking platform that interacts with various cell types, including stem cells, primary cells, and established cell lines, through specific receptor-mediated pathways. These interactions regulate key cellular processes such as adhesion, proliferation, migration, and differentiation. HA-based scaffolds can also serve as carriers for bioactive molecules, including growth factors and cytokines, enabling controlled delivery and modulation of the local microenvironment. Different engineering strategies including natural, synthetic, and composite scaffolds, as well as hydrogels, electrospun matrices, and 3D-printed structures are employed to tailor the physicochemical and mechanical properties of HA-based materials. Collectively, these features support a broad range of biomedical and translational applications, such as wound healing, cartilage repair, osteoarthritis treatment, ophthalmic drug delivery, intra-articular therapies, tumor targeting, and liver fibrosis treatment. The schematic highlights the interconnected relationship between scaffold design, cellular interactions, and therapeutic outcomes in HA-based biomaterials.

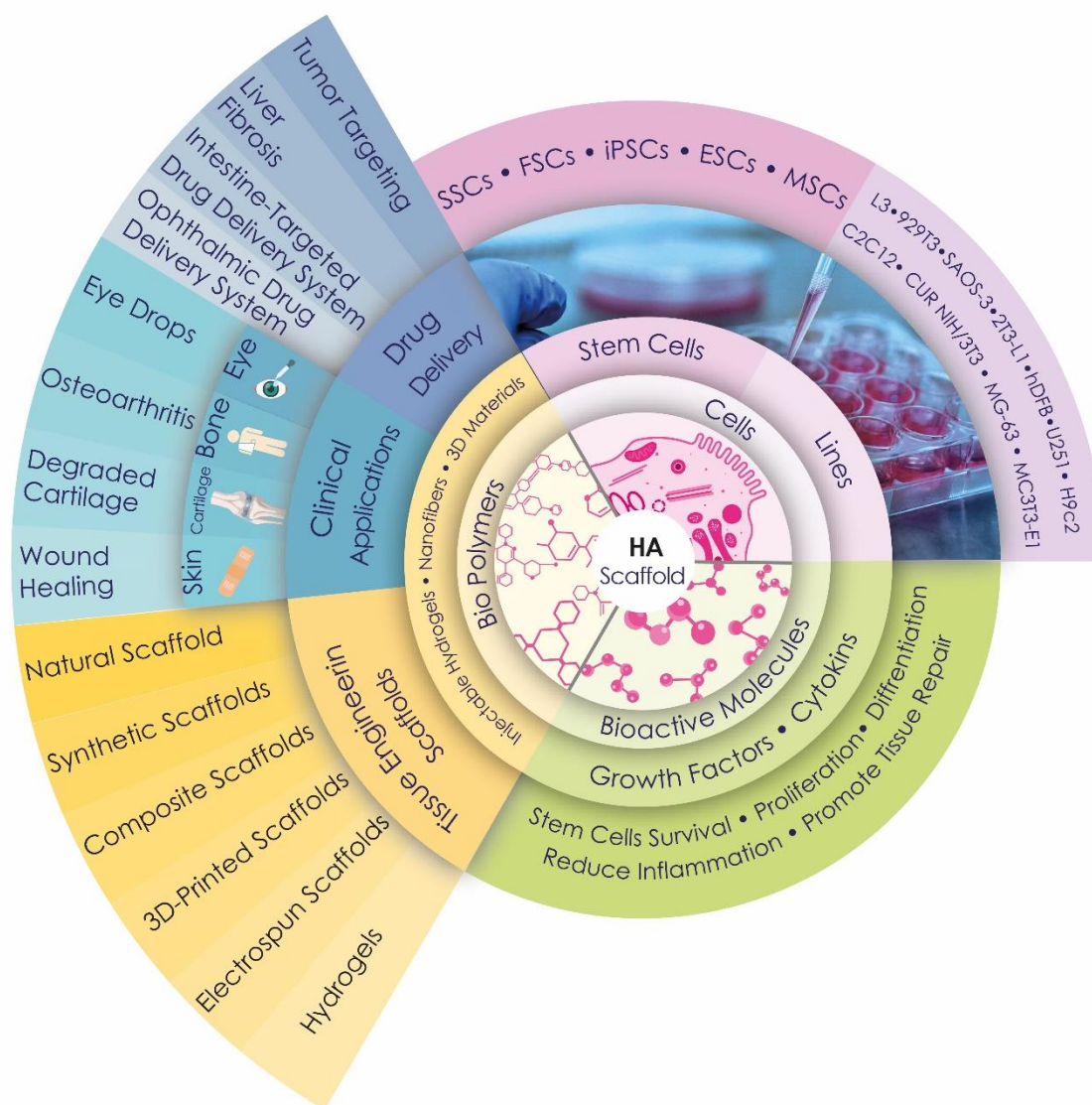


Figure 2. This schematic illustrates the multilevel framework through which hyaluronic acid (HA) scaffolds contribute to tissue engineering and regenerative medicine. At the core, HA provides a bioactive extracellular matrix–mimicking platform that interacts with various cell types, including stem cells, primary cells, and established cell lines, through specific receptor-mediated pathways. These interactions regulate key cellular processes such as adhesion, proliferation, migration, and differentiation. HA-based scaffolds can also serve as carriers for bioactive molecules, including growth factors and cytokines, enabling controlled delivery and modulation of the local microenvironment. Different engineering strategies including natural, synthetic, and composite scaffolds, as well as hydrogels, electrospun matrices, and 3D-printed structures are employed to tailor the physicochemical and mechanical properties of HA-based materials. Collectively, these features support a broad range of biomedical and translational applications, such as wound healing, cartilage repair, osteoarthritis treatment, ophthalmic drug delivery, intra-articular therapies, tumor targeting, and liver fibrosis treatment. The schematic highlights the interconnected relationship between scaffold design, cellular interactions, and therapeutic outcomes in HA-based biomaterials.

5.4. Rational standardization of HA scaffold design

Despite the substantial variability reported in HA-based systems across studies, emerging evidence suggests that a standardized descriptor framework is feasible at the level of core material parameters, rather than as a universal formulation applicable to all scaffold types. Differences in HA molecular weight, chemical modification routes, crosslinking chemistries, and intended biomedical applications inherently limit the development of a single, universally applicable metric system. However, these challenges do not prohibit the establishment of a harmonized set of key descriptors capable of enabling predictive correlations between material composition and functional performance.^{181,182}

In this context, quality-by-design (QbD) principles, supported by design-of-experiments (DoE) methodologies, provide a robust and systematic framework for identifying critical material attributes and linking them quantitatively to performance outcomes. These approaches allow the delineation of multidimensional design spaces in which variations in input parameters such as polymer molecular weight, degree of substitution, and crosslinking density can be directly associated with measurable outputs, including rheological behavior, mechanical properties, and biological responses.^{183,184} Such strategies move the field beyond empirical optimization toward predictive and reproducible scaffold design, as outlined by Ranamalla et al¹⁸⁵ which provides a detailed implementation protocol for integrating QbD and DoE in biomaterial development.

Within HA-based biomaterials, several parameters consistently emerge as core descriptors governing scaffold performance. These include molecular weight, polymer concentration, degree of chemical modification, and crosslinking density, all of which collectively regulate network formation, viscoelasticity, and degradation behavior.¹⁸⁶ In parallel, rheological properties, particularly storage modulus (G'), loss modulus (G''), and viscosity, serve as functional data that directly relate to injectability and mechanical compatibility with target tissues.¹⁸⁷

To facilitate reproducibility, we propose that both input parameters (e.g., molecular weight, concentration, degree of substitution, crosslinker type) and output metrics (e.g., viscosity, swelling ratio, degradation rate, pore size) be systematically reported and linked within a unified framework. This approach enables more reliable prediction of scaffold performance.

6. Conclusion, limitations, and future perspectives

Development of HA-based scaffolds for stem cell therapy is a multidisciplinary endeavor involving materials science, biology, and engineering. These scaffolds hold substantial potential for advancing regenerative medicine by providing a supportive microenvironment which facilitates stem cell-mediated tissue repair and regeneration. Current research focus is on improving scaffold design, material properties, and biological performance to enhance their clinical applicability and therapeutic success. Integrating HA-based scaffolds with complementary therapeutic approaches such as gene therapy or immunotherapy may lead to more effective strategies for treating complex diseases. Moreover, the emergence of smart HA scaffolds capable of responding to environmental cues and adapting to tissue dynamic conditions is expected to further enhance their therapeutic efficacy. Engineering the injectable HA hydrogels with appropriate mechanical and biochemical properties, may lead to more precise and site-specific stem cell delivery in regenerative applications such as cartilage, cardiac, and neural tissue repair. Rather than biocompatibility, natural polymer-based biomaterials, like HA, can offer 3D network hydrogels which resemble extracellular environment for stem cell culture.¹⁸⁸ The shift from 3D to 4D-bioprinting has indicated a noteworthy progression in tissue engineering and drug delivery.¹⁸⁹ 5D bioprinting includes 3-D, temporal, besides informational dimensions, promoting pioneering prospects in biomedical applications, advancing intelligent scaffolds and construction of adaptive biomaterials, which transform regenerative medicine as well as personalized healthcare. 5D printing distinctively integrates coded and transmitted information straight into the objects.¹⁹⁰ Dissimilar to static HA scaffolds, dynamic systems are engineered to undergo controlled changes in their physical and chemical characteristics in response to external or internal stimuli, such as pH, temperature, enzymatic activity, or specific biomolecules. This dynamic quality is achieved through various crosslinking strategies, including reversible covalent bonds, host-cell-mediated degradation, and incorporation of stimuli-responsive polymer chains. For stem cell therapy, these dynamic HA scaffolds offer significant advantages. They facilitate controlled release of encapsulated stem cells or therapeutic factors, adapt their mechanical properties to match tissue remodeling, and provide a more biomimetic microenvironment which promotes stem cell survival,

proliferation, and directed differentiation. Injectable dynamic HA hydrogels can gelate in situ and respond to localized cues to precisely release cells, or modulate their stiffness to direct the tissue regeneration. Future research aims to further refine the responsiveness and tailor the degradation kinetics of these systems for more precise therapeutic interventions in areas like regenerative medicine and drug delivery.¹⁹¹⁻¹⁹⁴ Incorporating nanoscale features or bioelectronic components into these scaffolds could strengthen cellular interactions and even enable real-time monitoring of cell behavior and scaffold performance. Artificial intelligence and machine learning also offer promising tools for optimizing scaffold design and predicting therapeutic outcomes, thereby accelerating the development of HA-based regenerative strategies.

Although preclinical findings remain encouraging, broader clinical validation is necessary to establish reproducibility, long-term safety, and therapeutic effectiveness. At the same time, this field still provides ample opportunities for further investigation. Conducting more extensive studies on refining scaffold fabrication techniques, achieving more detailed assessments of biological performance, and elucidating cell–scaffold interactions can contribute to a deeper understanding of the effectiveness of HA-based biomaterials. Additionally, further research on clinical translation, long-term safety, and combined therapeutic approaches may help facilitate the transition of these technologies from the laboratory to clinical applications. Overall, continued advancements in the design and development of HA-based biomaterials are expected to play a significant role in expanding the scope of regenerative medicine and improving the treatment of various diseases.

This review has some limitations. First, as a narrative review, formal meta-analytic methods were not applied. Second, publication and selection bias may have influenced study inclusion despite predefined search criteria. Third, heterogeneity in scaffold formulations and outcome reporting limited direct quantitative comparison. Future investigations should prioritize head-to-head comparisons and standardized characterization methods to establish predictive relationships between scaffold properties and therapeutic outcomes.

Disclosure of the use of generative AI and AI-assisted technologies

During manuscript preparation, the authors used ChatGPT Plus and Perplexity exclusively for English language editing and refinement of grammar, readability, and sentence structure. No AI-assisted tools were used to generate, modify, or interpret figures, data, scientific conclusions, or references. All scientific content, critical analysis, figure preparation, and final manuscript approval were conducted entirely by the authors.

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Declaration of Competing Interests

The authors declare that they have no competing interests.

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