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Review

Collagen- and glycosaminoglycan-enriched polymeric scaffolds incorporating perinatal-derived biomaterials for tissue regeneration

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ABSTRACT

This review comprehensively examines the integration of polymeric biomaterials with perinatal-derived extracellular matrix (ECM) components, focusing on their potential for tissue regeneration and clinical applications. The aim of this review is to provide a comprehensive synthesis and critical evaluation of current advancements, existing challenges, and future research directions in the development of biopolymer–perinatal ECM composites for regenerative medicine. The review highlights the unique properties of perinatal tissues, such as the placenta, amniotic membrane, and umbilical cord, which are rich in bioactive molecules like collagen, glycosaminoglycans (GAGs), and growth factors. These properties enable the creation of composite scaffolds that mimic the natural ECM, promoting cell adhesion, proliferation, and differentiation for tissue repair and regeneration. The paper discusses the various applications of these composites in the regeneration of skin, bone, cartilage, and vascular tissues, emphasizing the role of polymeric materials in enhancing the mechanical stability, degradation control, and customization of scaffolds. Moreover, the review addresses key challenges that must be overcome for

Abbreviation: ECM, Extracellular matrix; HAM, Human amniotic membrane; DHAM, Decellularized Human amniotic membrane; MSCs, Mesenchymal stem cells; PCL, Polycaprolactone; sPECM, Solubilized placental extracellular matrix; HUVECs, Human umbilical vein endothelial cells; Gel, Gelatin; HPE, Human placenta extract; PEG, Polyethylene glycol; DPP, Decellularized placenta powder; GAGs, Glycosaminoglycans; G-TA, Tyramine-enriched gel; hpcECM, human placental chorionic extracellular matrix; BTE, Bone Tissue Engineering; PLMS, Placental extracellular matrix sponge; ALP, Alkaline phosphatase; hPMSC, Human placenta-derived mesenchymal stem cells; HMSCs, Human mesenchymal stem cells; PLA, Polylactic acid; PGA, Polyglycolic acid; PLGA, Polylactic-co-glycolic acid; MA, Methacrylate; dHCM, Decellularized human chorion membrane; DWJ, Decellularized Wharton's jelly; ePTFE, Expanded polytetrafluoroethylene; SDVG, Small-diameter vascular grafts; hPM, Human placental matrix; dECM, decellularized extracellular matrix; pECM, Placental extracellular matrix; EV, Extracellular vehicle; PHB, Polyhydroxy butyrate; VEGFR, Vascular endothelial growth factor receptor; SF, Silk fibroin; SA, Sodium alginate; CMF, Craniomaxillofacial bone; pACS, Porcine adipose-derived stem cell; nHAp, Nano hydroxyapatite; Alg, Alginate; PLLA, Poly-l-lactic acid; ASA, Acetylsalicylic acid; EF, Electrospun fibers; SkM, Skeletal muscle cells; CM, Conditioned medium; SPS, Small intestine submucosa-integrated PCL/SF; PVA, Polyvinyl alcohol; RPE, Retinal pigment epithelial; HAMP, Human amniotic membrane powder; PP, Polypropylene; LSCs, Limbal stem cells; FD-HAM, Freeze-dried human amniotic membrane; MoS_2, Molybdenum disulfide; POP, Pelvic organ prolapses; PU, Polyurethane; SB, Sheep bladder; PLCL, Poly-(L-lactide-co-*E*-caprolactone); HA, Hyaluronan; WJ, Wharton's jelly; POC, Poly(1,8-octamethylene-citrate); PEGSA, poly (ethylene glycol)-copoly (glycerol subcategory) acrylate; WJMSC, WJ-derived mesenchymal stem cell; AWJ, Acellular Wharton's jelly; ASCs, Adipose-derived stem cells; VEGF, Vascular endothelial growth factor; bFGF, Basic fibroblast growth factor; ESF, Electrospun nanofibrous silk fibroin; BMP-4, Bone morphogenetic proteins.

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successful clinical translation, including scalability of fabrication techniques, donor eligibility and consent, batch-to-batch variability of perinatal tissues, and regulatory concerns such as the effects of sterilization on ECM integrity. Additionally, this review compares the performance of collagen/GAG-enriched hybrid scaffolds with traditional grafts and decellularized matrices, underscoring their superior regenerative capabilities. The integration of these hybrid scaffolds in clinical trials and their potential to overcome current limitations in personalized medicine are also discussed, providing a roadmap for future research and development in the field of tissue engineering.

1. Introduction

Organ transplants can be lifesaving and greatly improve quality of life for recipients [1]. With over 100,000 individuals on the transplant waiting list in the U.S. alone, organ shortages are a pressing concern, particularly for kidneys, which have the longest wait times of 7–10 years. [2]. In 2023, over 46,000 transplants were performed in the U.S., while over 103,223 people were waiting for an organ [3]. The difference between demand and supply is even worse on a global scale. The Global Observatory on Donation and Transplantation (WHO-ONT) says that less than 10% of the world's real need is met by the more than 150,000 solid organ transplants that happen every year [4]. This huge difference, especially in low- and middle-income countries, shows how important it is to find ways to regenerate tissues instead of traditional transplants.

Another key difficulty in organ transplantation is the body's immunological reactivity to foreign tissues, which can lead graft rejection. To avoid this hazard, transplant recipients must undergo immunosuppressive treatment for the remainder of their lives, but these treatments can have major ill effects, such as increasing susceptibility to infections. Current immunosuppressive regimens have not materially evolved in over two decades, and long-term graft survival rates remain a concern, with many transplants failing within 10 years [5]. Growing new organs from a patient's own cells could eliminate the need for donor organs and lower the danger of rejection in the quickly developing field of regenerative medicine [6]. Synthetic and natural biomaterials play a crucial role in tissue regeneration by serving as scaffolds that mimic the extracellular matrix (ECM), promoting cell adhesion, growth, and differentiation [7]. Biodegradable polymers and other synthetic biomaterials are frequently employed in tissue regeneration, especially for soft tissues like the skin and cardiovascular system. These materials can be altered to have certain properties, such as controlled rates of deterioration and mechanical properties [7]. Biocompatibility, biodegradability, and non-toxicity are only a few benefits of naturally generated biomaterials. Scaffolds enhanced with collagen (COL) and glycosaminoglycans (GAGs), which are essential for simulating the extracellular matrix (ECM) to support cell adhesion, differentiation, and tissue-specific regeneration, are frequently used in the engineering of important tissues like skin, bone, cartilage, and blood vessels. Human perinatal derivatives include the placenta and its annexes, such as the decidua, chorionic membrane, human amniotic membrane (HAM), umbilical cord, and amniotic fluid [8]. A rich source of cells, growth factors, and extracellular matrix proteins, perinatal derivatives have found extensive use in tissue engineering and regenerative medicine [9]. The earliest documented clinical use of perinatal-derived biomaterials dates back to 1910 at Johns Hopkins, where they were employed to support the healing of dermal wounds [10]. Biomaterials derived from perinatal tissue provide substantial immunomodulatory properties crucial for minimising transplant rejection and expediting recovery. These tissues are rich in bioactive chemicals, such as growth factors and cytokines, which facilitate the regulation of immune responses. Due to their unique properties and potential applications, perinatal stem cells derived from the placenta, umbilical cord, and amniotic fluid are emerging as a vital resource in regenerative medicine. This characteristic allows interaction with the immune system without provoking a significant inflammatory response, rendering them suitable for allogeneic applications without the need for substantial immunosuppression [11]. The anti-inflammatory properties of perinatal tissues significantly promote healing and tissue regeneration. These tissues are abundant in anti-inflammatory cytokines and growth factors that assist in alleviating inflammation at the injury site. Placental-derived biomaterials have been shown to reduce pro-inflammatory cytokine levels, fostering a more favorable environment for tissue repair. This is especially crucial in chronic wound healing, since extended inflammation can hinder recovery and lead to fibrosis [12]. Perinatal tissues, including the placenta, umbilical cord, and amniotic membrane, are rich in ECM components like COLs and GAGs, which provide critical structural support and modulate cellular behavior. The COL-GAG matrix facilitates cell attachment, migration, and proliferation, essential for effective tissue regeneration. Combining biomaterials with components obtained from fetuses presents an intriguing chance to develop sophisticated composites that have the potential to greatly influence tissue engineering and regenerative medicine (Fig. 1A). Common methods for fabricating COL and GAGs-enriched perinatal–polymer scaffolds include hydrogel, and 3D printing, coating, and electrospinning for anatomically precise, cell-laden structures. Decellularized perinatal ECM is often integrated with polymeric networks to retain native bioactive cues, and layer-by-layer assembly can be employed to fine-tune surface biofunctionalization (Fig. 1B).

The ECM scaffolds derived from these tissues facilitate cell attachment, migration, and proliferation, which are vital for effective healing and tissue repair. Additionally, perinatal mesenchymal stem cells (MSCs) have a higher differentiation potential compared to adult MSCs, allowing them to contribute to the regeneration of various tissue types, including skin, cartilage, and bone [13]. GAGs represent a diverse group of complex polysaccharides that include heparin (Hep), heparan sulfate (HS), chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS), and hyaluronic acid (HA). Over recent decades, a wide range of GAG-based biomaterials—such as scaffolds, microparticles, and hydrogels—has been developed. As extensively reviewed, these materials have found primary applications in bone, cartilage, and tendon regeneration, as well as in wound healing. The fabrication of GAG-based biomaterials involves various functionalization strategies that allow precise control over their morphology, viscoelastic behavior, cell adhesion capacity [14]. Interestingly, biomaterials constructed from the same GAG type have been successfully employed in engineering different tissue types, demonstrating distinct structural and functional characteristics depending on the specific design and application context [15]. Beyond phenomenological descriptions of angiogenesis and immunomodulation, scaffold performance is governed by two interdependent molecular parameters: (i) GAG chemistry — chain length and sulfation motifs that determine specific growth-factor sequestration and release kinetics, and (ii) COL crosslink density that sets matrix stiffness, exposure rate of bound GFs, and susceptibility to proteolytic remodeling. Highly sulfated HS/heparin-like domains provide multivalent, high-affinity binding sites for FGF2 and VEGF, increasing local GF concentration and potentiating receptor activation (Fig. 1B). Conversely, non-sulfated HA modulates cell behavior primarily via surface receptors (e.g., CD44) rather than ionic GF binding. COL with low crosslink density degrades faster, promoting timed GF release and exposure of matrikines that bias macrophages toward reparative (M2-like) phenotypes; high crosslink density prolongs scaffold persistence and stiffness, which can skew early macrophage responses toward pro-inflammatory phenotypes

unless biochemical cues are present. Blending perinatal ECM with synthetic polymers typically reduces immediate GAG exposure and extends GF presentation windows from weeks to months, trading rapid bioactivity for mechanical stability — a design choice that must be matched to the target tissue's regeneration timeline. A summary of the key characteristics of various GAG types, including their structural properties, GFs they bind, and associated biological outcomes, is presented in Table 1, highlighting the distinct roles of each GAG in modulating tissue regeneration and providing specific bioactive signals that influence cellular behavior.

By using the advantages of both kinds of materials, scientists may create better scaffolds that encourage tissue integration and regeneration. This comprehensive review aims to provide a thorough understanding of the current advancements, challenges, and potential of these materials in the field, synthesizing existing knowledge to highlight gaps in research and inform future developments. One of the biggest problems in tissue engineering has yet to be solved: synthetic polymers and natural perinatal materials can't fully meet the needs of healing on their own. Synthetic polymers have adjustable mechanical and degradation qualities, but they don't have enough bioactivity. On the other hand, perinatal tissues help the immune system and encourage cell growth, but they aren't very strong mechanically. Specifically, this review looks at how these two types of materials can be combined to show how they can work together to help fix tissues and make medicines more widely available.

1.1. Methodology

A comprehensive literature search was conducted to identify studies related to perinatal-derived biomaterials in tissue engineering. Electronic databases including PubMed, Scopus, and Google Scholar were searched up to September 2025. The search used combinations of keywords such as "perinatal-derived biomaterials," "placenta," "amniotic membrane," "Wharton's jelly," "tissue regeneration," "bone," "cartilage," "skin," and "vascularization." Inclusion criteria were peer-reviewed articles, preclinical and clinical studies, and articles published in English. Exclusion criteria included duplicate records, conference abstracts without full texts, and non-English publications. Studies were screened in two stages: initial screening of titles and abstracts followed by full-text review to determine eligibility. A PRISMA-style flow chart to illustrate the screening process and to express the inclusion and exclusion criteria for articles is shown in Fig. 2A. Additionally, the quantity of used studies on the application of composite biomaterials from perinatal sources in regenerative medicine and the percentage of each perinatal based and biopolymer-based usage is shown in Fig. 2B. Perinatal tissue sources, and biopolymer sources, with the number of related studies and their percentage of the total studies are also shown in Fig. 2C,D. The denominators represent the total number of eligible publications identified in the search after removing duplicates and ineligible records. Percentages were calculated based on this final dataset.

Table 2 summarizes the key characteristics of the studies included in this narrative review, detailing biopolymer-perinatal tissue combinations, applications, and outcomes. It includes information on the source of perinatal tissues, the combined polymer used, the specific application, in vitro cell lines, in vivo model/defect model, mechanical properties (tensile strength), decellularization methods, scaffold fabrication methods, degradation rates, and outcomes of each study.

2. Biopolymer-placenta composite for tissue engineering

2.1. Skin

Chronic and acute skin wounds often do not heal properly due to compromised angiogenesis, excessive inflammation, and inadequate extracellular matrix deposition. The combination of placenta-derived materials with polymers generates bioactive substances and structural support that enhance wound healing and tissue regeneration. The skin

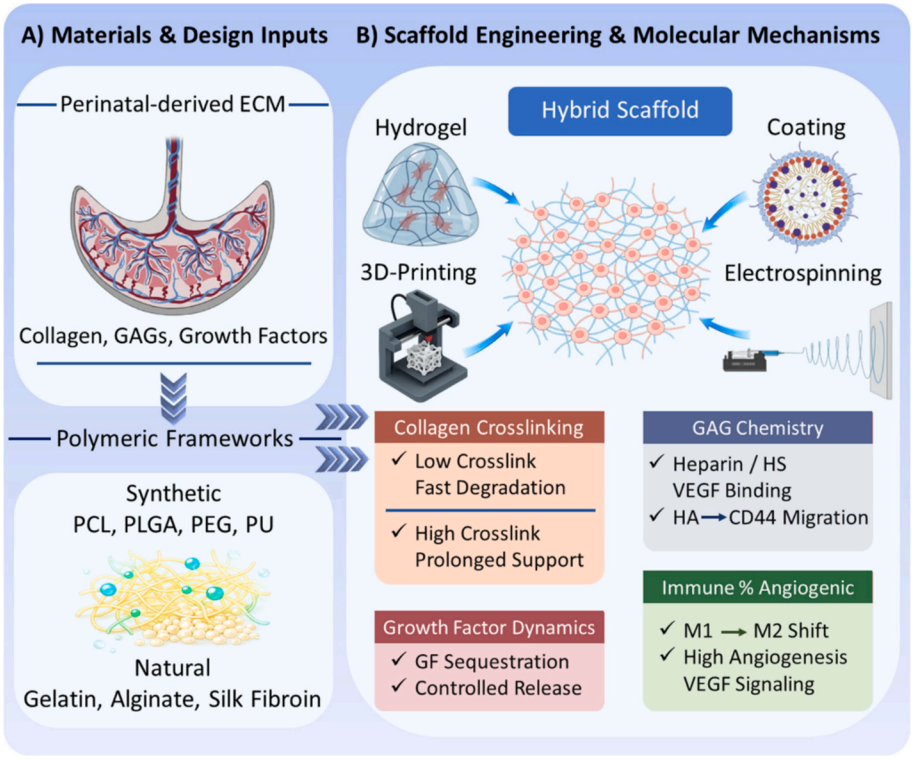

Fig. 1. Design logic and mechanism of action of collagen/GAG-augmented perinatal–polymer scaffolds. A) Material building blocks: perinatal ECM (collagen, GAGs, growth factors) blended with synthetic or natural polymers. B) Fabrication approaches and bioactivity drivers: Design techniques such as hydrogel, 3D-printing, coating, and electrospinning to produce scaffolds which investigate collagen crosslinking and GAG-specific interactions (Created with BioRender).

Table 1
Summary of GAG types, structural features, primary growth factors bound and biological outcomes.

GAG (type / motif)	Chain length / structural note	Primary growth-factor(s) bound	Biological outcome(s)	Ref.
Heparan sulfate (HS)	Variable; specific domain sulfation critical (NS, 2-O, 6-O)	FGF2 (bFGF), VEGF, HGF, PDGF	Potent potentiation of FGF/VEGF signaling → angiogenesis, proliferation; GF protection from proteolysis	[16]
Heparin (highly sulfated HS analog)	Short–long; highly sulfated, high negative charge	FGF2, VEGF, antithrombin interactions	Strong GF sequestration and controlled release; anticoagulant effects (context-dependent)	[17]
Chondroitin sulfate (CS) — CS-A / CS-C	Sulfation pattern matters (4-S vs 6-S)	Less strong for FGF/VEGF; binds BMPs, TGF-β modulators	Modulates chondrogenic signaling, ECM deposition; can influence cell differentiation	[18]
Dermatan sulfate (DS)	IdoA-containing, variable sulfation	Binds growth factors and cytokines (e.g., certain chemokines)	Implicated in collagen fibrillogenesis and modulating inflammation	[19]
Hyaluronic acid (HA) — non-sulfated	High MW vs low MW critical; non-sulfated → no strong GF ionic binding	Indirect: binds CD44, RHAMM; low MW can be pro-inflammatory	Modulates cell migration, inflammation; acts via receptor signaling rather than strong ionic GF sequestration	[20]
Synthetic sulfated polysaccharides / modified GAGs	Tunable sulfation density and position	Designed to bind VEGF/FGF and modulate release	Engineered GF presentation; improved angiogenesis or controlled differentiation depending on design	[14]

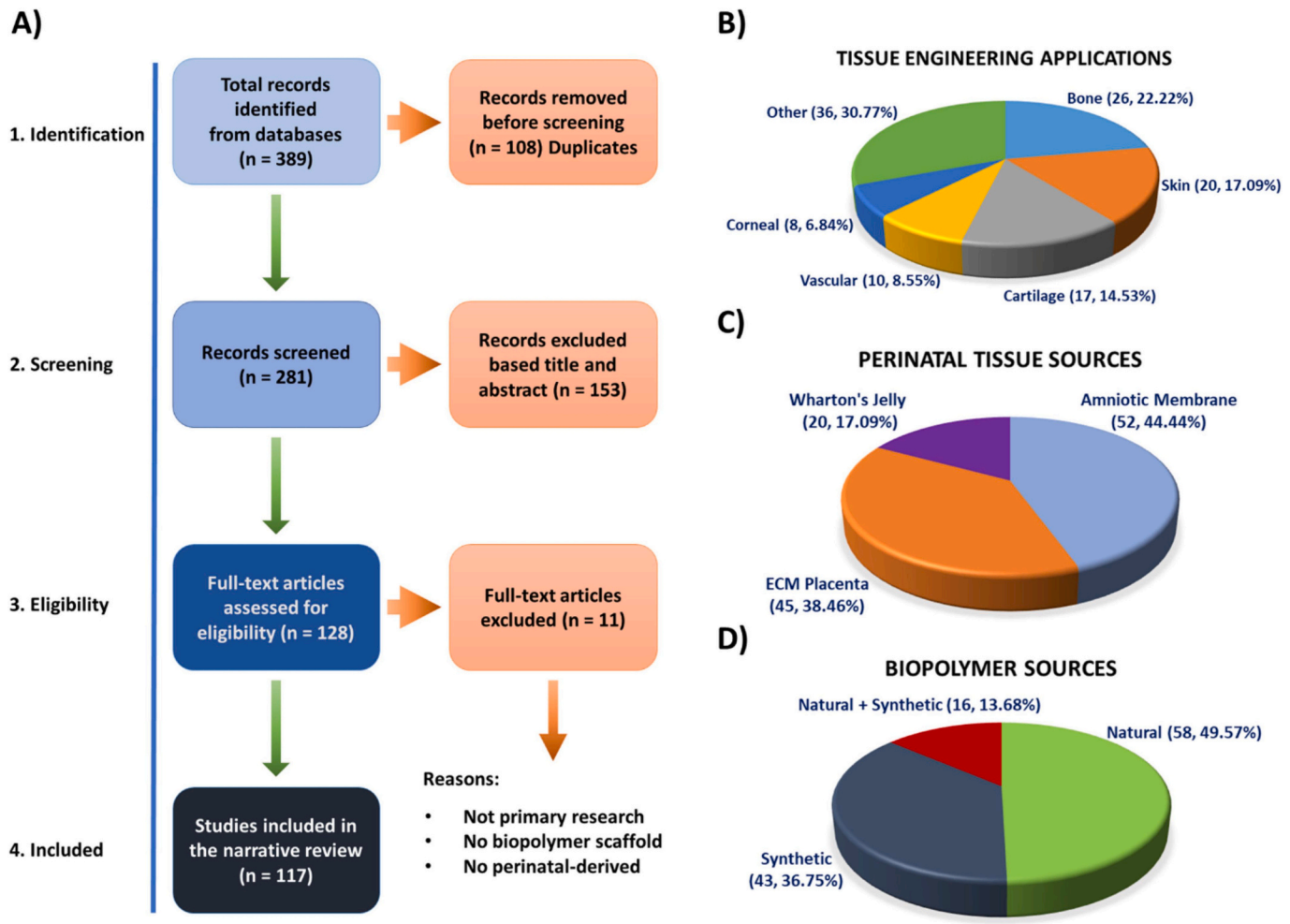

Fig. 2. Publication Trends and Distribution of Biopolymer-Perinatal Tissue Research in Tissue Engineering. A) PRISMA-style flowchart: The selection process for studies included in the narrative review. After full-text assessment, leaving 117 studies included in the final review. This search was last conducted in September 2025. B-D) Distribution of Studies: The distribution of studies across tissue engineering applications, perinatal tissue sources, and biopolymer sources, with the number of related studies and their percentage of the total 117 studies shown in parentheses.

comprises various components, including sweat glands, hair follicles, arteries, nerves, and extracellular matrix (ECM). The primary variables linked to compromised wound healing encompass insufficient angiogenesis, hindered cell migration, inadequate synthesis of growth factors and extracellular matrix components, and modified inflammatory responses in the wound bed. COL, laminin, and elastin exemplify growth factors and filaments that render placental extracellular matrix (pECM) an optimal substrate for the fabrication of skin-like structures applicable in wound healing and transplantation. ECM-based scaffolds have been demonstrated in studies to be effective substrates for facilitating critical cellular activities, including differentiation, migration, and proliferation [83].

Table 2
Combination of perinatal-derived cells and polymers in regenerative medicine application.

Source	Combined polymer	Application	In vitro cell lines	In vivo model/ defect model	Mechanics	Decellularization method	Method	Deg rate	Outcome (optimized scaffold compared to polymer only or other controls)	Ref.
hpECM	PCL	Skin	HF, HK	Rat	TS: 1.97 ± 0.39 MPa, YM: 22.88 ± 5.31	Chemical	Electrospinning		92 1% reduction in wound area after 2 weeks	[21]
hpECM	SA + Gel	Skin	Fibroblast cells (L929)	Mouse	Compressive strength: 1.24 ± 0.68–0.67 ± 0.31 MPa	Chemical	3D printing	38.56 ± 2.7% after 30 days	86.66% wound closure on day 21	[22]
hpECM	TCTS	Skin	HF, HUVECs	Mouse		Chemical	Hydrogel	100% after 35 days	No evidence of acute immune response or graft rejection was observed throughout the follow-up period	[23]
hpECM	SA + CMC + CTS + Gel	Skin	L929	Rat	TS: 14.40 ± 0.77 MPa		Freeze-drying	Up to 96.16% after 28 days	Facilitated wound closure, achieving a contraction rate of 95.83 ± 6.3% after 21 days	[24]
hpECM	SF + Gel	Soft tissue	HF	Rat		Chemical	3D bioprinting		Enhanced cell adhesion and proliferation while exhibiting excellent biocompatibility	[25]
hpECM	SF	Bone	HAMSCs	Rabbit	Compressive strength 332 ± 28 kPa	Chemical-physical	Lyophilization		Promoted increased proliferation and markedly improved osteogenic differentiation of HAMSCs in vitro, with a bone volume to total volume (BV/TV) ratio of 90 ± 3% observed after six weeks	[26]
hpECM	PCL	Bone	WJMSCs				Electrospinning	21.647% after 28 days	The peak ALP activity was detected after two weeks	[27]
hpECM	Gel	Bone	AMSCs, HF	Rat	Compressive modulus 0.12 ± 0.05 MPa		3D printing	~9% weight loss at 14 days	Enhanced both bone formation and angiogenesis, exhibiting a pronounced regenerative effect in a rat mastoid defect model	[28]
hpcECM	Fibronectin + expanded polytetrafluorethylene	Vascularization	HUVECs, Human endothelial progenitor cells			Chemical	Coating		Promoted stronger endothelial cell adhesion and attachment, with improved cell retention under flow conditions	[29]
hpECM	PCL	Vascularization	Rat aortic endothelial cells, Rat vascular smooth muscle cells,	Rat	Elastic modulus of hybrid scaffolds was higher than pure PCL	Chemical	Electrospinning	100% after 9 h	Superior hemocompatibility and cytocompatibility, along with enhanced anti-inflammatory effects; a continuous monolayer of vWF^{+} cells was observed covering approximately 89.6 ± 1.9% of the lumen surface	[30]
hpECM	SF	Breast reconstruction	AMSCs			Chemical	Hybrid hydrogel		Higher placenta content enhanced ADSC viability, adhesion, and proliferative expansion	[31]
hpECM	PLGA + PHB	Cardiac muscle	AMSCs		Stress at break 3.34 ± 0.45 MPa		Electrospinning	Scaffolds degraded over 1 month	Enhanced protein adsorption and cell attachment, while promoting greater cardiomyocyte differentiation characterized by elevated expression of GATA4, MyoD, and Troponin T	[32]

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Table 2 (*continued*)

Source	Combined polymer	Application	In vitro cell lines	In vivo model/ defect model	Mechanics	Decellularization method	Method	Deg rate	Outcome (optimized scaffold compared to polymer only or other controls)	Ref.
DHAM	SF	Skin	Mouse embryonic fibroblasts		TS: 25.69 MPa Y: 108.03 MPa	Enzymatic	Electrospinning		Support cell attachment and proliferation	[33]
DHAM	SF	Skin	AMSC		Strain deflection at break (mm): 8.50 ± 0.33	Physical-chemical	Electrospinning	40% in 2 week	Excellent cell adhesion and proliferation accompanied by increased secretion of growth factors	[34]
DHAM	SF + SA + PEO	Skin	MSC			Enzymatic	Electrospinning	67% in 3 week	Increased cell adhesion and proliferation	[35]
DHAM	GelMA	Skin	HUVECs, RAW264.7 cells	Rabbit (diameter 1 cm)		Enzymatic	Photosensitive hydrogel		Wound closure was enhanced by 31.26% relative to the GelMA group	[36]
DHAM	COL	Bone	Porcine AMSCs		Elastic modulus: 2.1 MPa	Enzymatic	Lyophilizing		Enhanced osteogenic activity and mineral deposition even under inflammatory conditions.	[37]
DHAM	PLA	Bone	PC12 cells			Enzymatic, physical-chemical	Non-solvent-induced phase separation	39.48% after 12 weeks	Produced a substantial amount of ALP after 14 days.	[38]
DHAM	CTS	Cartilage			Elastic modulus: 83kpa	Chemical	Hydrogel		Exhibited a higher elastic modulus compared to samples in which collagen was derived from bovine sources	[39]
DHAM	PLGA	Cartilage	Rat MSCs,	Rat osteochondral defect (1.8 mm in diameter, 2 mm in depth)			Cell-derived ECM biotemplating		Significantly better regeneration at 24 weeks	[40]
DHAM	Alg	Vascularization	HUVECs		YM: 32.35 ± 5 kPa	Chemical	Bio printing	51.8 ± 3.8 within 14 days	Enhanced HUVEC viability, proliferation, tube formation capability, and VEGFR-2 expression	[41]
DHAM	PLLA	Vascularization	HUVECs		TS: 1.3 ± 0.35 MPa	Chemical	Electrospinning		Upregulated expression of endothelial-specific genes, including vWF and CD31	[42]
DHAM	PLGA	Vascularization	HUVECs, skeletal muscle cells			Enzymatic	Electrospinning		Markedly increased levels of proangiogenic factors such as angiopoietin-1, IL-8, and VEGF-C	[43]
DHAM	PCL + SF	Vascularization	HUVECs, smooth muscle cells	Rat	TS: 3–4 MPa		Electrospinning	~30% after 4 week	Achieved near-complete endothelialization within four weeks	[44]
DHAM	PVA	Corneal	Rabbit corneal epithelium	Rabbit		Physical-chemical	Hydrogel -immobilization		The expression levels of differentiation markers K3 and connexin closely resembled those found in the native cornea	[45]
DHAM	PCL	Corneal	Retinal pigment epithelial		YM: 25.6 ± 1.6 MPa	Physical	Electrospinning	56% after 28 days	Facilitated the proliferation of RPE cells	[46]
DHAM	PCL	Corneal	Rabbit limbal stem cell	Rabbit	composite membrane exhibited about 4-fold higher ultimate tensile strength	Enzymatic	Electrospinning	42% after 6 days	Enabled the restoration of normal corneal epithelial morphology and structural hierarchy	[47]

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Table 2 (*continued*)

Source	Combined polymer	Application	In vitro cell lines	In vivo model/ defect model	Mechanics	Decellularization method	Method	Deg rate	Outcome (optimized scaffold compared to polymer only or other controls)	Ref.
DHAM	PCL + PLA + PLGA	Corneal	Rabbit limbal stem cell		measured failure forces improved 14.7, 10.5, and 13.2 times by utilizing PCL, PLA, and PLGA nanofiber s respectively	Physical-Chemical	Electrospinning		Increased relative expression of ABCG2 markers within five days, accompanied by a reduction in proinflammatory (M1) marker expression	[48]
DHAM	Fibrin glue	Corneal	Epithelial cells	Rabbit		Physical-Chemical	Lyophilization And coating		The transplanted area was fully covered by epithelial tissue two weeks post-transplantation	[49]
DHAM	PCL + Molybdenum disulfide	Cardiac	Mouse embryonic cardiac cells		TS: 4.33 ± 0.23 MPa	Chemical	Electrospinning		Markedly increased expression of c-TnT, NKX2.5, and α-MHC was detected after seven days	[50]
DHAM	PCL + PLGA	Pelvic organ prolapses	HUMSCs		TS: 2.088 N YM: 36.047 MPa	Enzymatic	Electrospinning	14% after 6 weeks	Improvement the proliferation ability of HUMSCs	[51]
DHAM	PCL	Colon anastomosis		Rat	TS: 4.33 ± 0.23 MPa	Chemical	Electrospinning		*Re*-epithelialization, vascularization, collagen deposition, and muscle tissue regeneration were notably enhanced	[52]
DHAM	PCL	Tendon adhesion	Dermal fibroblasts	Rabbit	TS: 4.08 ± 0.18 MPa		Electrospinning		A significant increase in total flexion angles was observed after three weeks	[53]
DHAM	PU + PP	Uterus tissue repair	Smooth muscle cells	Rabbit		Chemical and Enzymatic	Coating		A 10-month implantation study demonstrated that dHAM/PU exhibited significantly superior biocompatibility compared to PP	[54]
DHAM	PLLA + Sheep bladder-derived ECM	Bladder tissue repair	HAMSCs	Rabbit		Chemical, DNA content: (15 ± 5 ng per mg)	Electrospinning		After 12 weeks, the regeneration of the epithelial layer, muscle fibers, and newly formed blood vessels was observed	[55]
DHAM	PLCL nanofibers	Urinary bladder augmentation	Rat BMSCs	Rat	YM: 4.46 + 1.12 MPa		Electrospinning and grafting		Achieved full re-epithelialization and restoration of the muscular layer within 12 to 14 weeks	[56]
DHAM	PCL fiber	Muscle repair	Rat AMSCs		TS: 0.41 ± 0.107 MPa, YM: 2.48 ± 0.216 MPa	Physical-Chemical	Electrospinning	Biodegradability increased over 2 week	Elevated expression levels of myosin, Mhc2, and myogenin, along with the formation of myotubes averaging 13.261 ± 0.612 μm in diameter	[57]
DHAM	PCL	Nerve regeneration	Schwann cells	Rat			Electrospinning		By the fourth week, a substantial increase in nerve growth factor levels was observed	[58]
DHAM	Poly(1,8-octamethylene-citrate)	Heal cleft palates	BMSCs	Rat	TS: 54.064 ± 1.764 KPa	Chemical	Polymerization graft	58 ± 2% after 14 days	Displayed high BMSC viability and proliferation, while also promoting bone formation, epithelial closure, and palate development	[59]
DHAM	PCL + SF	Abdominal wall	HF	Rat model (20 × 10 mm^2)	TS: ~ 5.8 MPa YM: ~ 12 MPa	Chemical	Electrospinning	~ 30% after 30 days	Exhibited lower adhesion formation, attenuated inflammatory responses, and	[60]

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Table 2 (*continued*)

Source	Combined polymer	Application	In vitro cell lines	In vivo model/ defect model	Mechanics	Decellularization method	Method	Deg rate	Outcome (optimized scaffold compared to polymer only or other controls)	Ref.
									increased deposition of collagen and elastin fibers	
DHAM	PP	Abdominal hernia surgeries		Rabbit model (5 cm abdominal incision)			Coating		Decreased intra-abdominal adhesion formation and promoted superior histological tissue healing	[61]
DWJ	PLLA	Bone	AMSCs				Electrospinning		Enhanced the osteogenic differentiation potential of MSCs, leading to increased cell proliferation and mineralization	[62]
DWJ	GelMA	Bone	BMSCs	Rat skull defect model (5 mm diameter defect)	TS: ~ 7.2 MPa		Hydrogel	100% after 36 days	Stimulated osteogenesis and enhanced bone regeneration in a rat calvarial defect model	[63]
DWJ	Gel methacryloyl	Cartilage	BMSCs		YM: 0.11 MPa	Chemical	3D bioprinting	~ 88% after 50 h	Demonstrated the formation of mature hyaline cartilage with seamless integration into the adjacent native tissue	[64]
DWJ	PCL	Cartilage	AMSCs		YM: 2 MPa	Chemical-physical	Electrospinning	29.3% after 35 days	Improved mechanical properties, biodegradability, and biocompatibility	[65]
DWJ	PCL	Cartilage	Rabbit chondrocyte cells		TS: 16.43 ± 2.51 MPa, YM: 49.72 ± 4.06 MPa	Chemical-physical	Electrospinning	7.72% after 12 weeks	Enhanced bioactivity characterized by calcium-phosphate deposition, along with increased mechanical strength and reduced degradation rate	[66]
DWJ	Alg	Growth of ovarian follicles	Mouse preantral follicles	Mouse		Chemical	Hydrogel	~ 22.14% after 9 days	Promoted the maturation of preantral follicles into the antral stage and upregulated the expression of angiogenic markers	[67]
DWJ	Fibrin + COL + PA	Soft tissue and neural tissue engineering	Human endometrial stem cells			Chemical	Hydrogel		Utilizing PA as a cross-linking agent in fibrin and collagen hydrogels improved their mechanical strength, decreased degradation rates, and enhanced cell adhesion, proliferation, and viability	[68]
DWJ/ECM	PVA + Alg-S	Tympanic membrane perforations	Fibroblast cells	Rat	TS: 0.7 MPa	physical-chemical 50 ± 6.05 ng/ µl	Electrospinning	45% after 21 day	The regeneration rate in the composite group reached 100% after 7 days, whereas the control group exhibited a rate of 80%.	[69]
DHAM	HAM + Gel + PU	Skin	Mouse fibroblast, HF	Rat (1 cm^2)		Chemical	3D printing		100% wound closure after 18 days	[70]
HUCECM + hpECM	Gel methacryloyl + hyaluronic acid	Cartilage and Bone	Rabbit BMSC	Rabbit (5 mm in diameter and 4 mm in depth)	YM; bone layer: 39 kPa Cartilage layer: 10 ± 1.6 kPa	physical-chemical	3D printing	35% after 2 week	Regeneration of both cartilage and subchondral bone tissues, with nearly complete defect closure and well-formed neocartilage observed at 16 weeks	[71]
DHAM	SF	Skin	HK, WJMSCs, HUVECs	Rat	TS: 0.41 ± 1.6 MPa	physical-chemical DNA content (40 ± 1.7 ng/mg tissue)	Lyophilization	70% after 2 week	95.04 ± 1.66% wound closure after 2 week	[72]

(*continued on next page*)

Table 2 (*continued*)

Source	Combined polymer	Application	In vitro cell lines	In vivo model/ defect model	Mechanics	Decellularization method	Method	Deg rate	Outcome (optimized scaffold compared to polymer only or other controls)	Ref.
DHAM	CTS + Alg	Skin	Mouse fibroblast	Rat (2 × 2 cm)	TS: 7.16 ± 0.29 MPa YM: 27.94 ± 0.54 MPa	Chemical	3D printing	94.57% ± 3.18% at 14 days	93.98% wound closure after 20 days	[73]
DHAM	SF + PEO + COL	Bladder	AMSC	Rat	UTS: 0.316 ± 0.09 MPa	Chemical	Lamination		The incorporation of DHAM effectively inhibited the formation of calculi	[74]
hpECM	PCL	Cardiac tissue engineering	Endothelial progenitor cells, H9c2 cardio myoblasts		TS: 3.52 ± 0.57 MPa	Chemical DNA content: (1.00 ± 0.03 ng/mg)	3D printing		The scaffold supported endothelial cell adhesion and proliferation without elevating the expression of inflammatory cytokines such as ICAM-1 and VCAM-1	[75]
hpECM	Alg + SF	Bone	MSC	Rat (8 mm)	TS: 1.289 ± 0.65 MPa YM: 2.643 ± 4.82 MPa	Chemical	3D printing	24.53 ± 2.7 after 30 days	Histological analysis after four weeks revealed the formation and regeneration of bone tissue	[76]
DHAM	CTS + soy lecithin	osteogenic differentiation	HF. BMSC, AMSC			Physical	Ionic gelation method		Osteogenic induction capability was evident after 12 days of cultivation	[77]
DHAM	CTS + Alg	Skin	HF	Rat	TS: 7.16 MPa YM: 27.94 MPa	Chemical	3D printing	~ 100% after 21 day	Facilitating re-epithelialization, stimulating neovascularization, accelerating wound closure, and upregulating the expression of genes linked to the wound healing process	[78]
DHAM	SF	nerve tissue regeneration	PC12			Physical-chemical	Microfluidic devise		Enhanced the expression levels of β-tubulin III and NSE proteins in PC12 cells grown on the nanocomposite scaffold	[79]
DHAM	SF + polycarbonate urethane	Skin	Mouse fibroblast cells		TS: 3.7 ± 0.08 MPa	Physical-chemical DNA content (18.78 ± 3.21)	Spinning	64.33% ± 0.86% after 2 week	Exhibited a higher degree of cell migration compared to the hAM group	[80]
DHAM	CTS	Adipose tissue regeneration	ADSCs	Mouse		Physical-chemical	Microcarrier	~ 30% after 8 week	The integration of an amniotic membrane matrix significantly improves the in vivo adipose tissue regeneration capacity of ADSCs	[81]
hpECM	SF + elastin-like polypeptide	Skin	Human Embryonic Kidney, mouse keratinocytes	Mouse	0.202 ± 0.006 MPa	Chemical	Lyophilization		After only two weeks post-surgery, the SF/hPlacenta 5% ELP group achieved a wound closure rate of approximately 94%, demonstrating a notably rapid healing response.	[82]

Abbreviation: **ECM** - Extracellular matrix, **hpECM** - Human placental extracellular matrix, HF – Human fibroblast, HK – Human keratinocyte, **PCL** - Polycaprolactone, **TS** - Tensile strength, **YM** - Young's modulus, **SA** - Sodium alginate, **Gel** - Gelatin, **sPECM** - Solubilized placental extracellular matrix, **TCTS** - Thermo-responsive chitosan, **SF** - Silk fibroin, **CMC** - Carboxymethyl cellulose, **CTS** - Chitosan, **PLLA** - Poly-l-lactic acid, **PLGA** - Polylactic-*co*-glycolic acid, **WJ** - Wharton's jelly, HAMSCs – Human amniotic mesenchymal stem cells, **MSCs** - Mesenchymal stem cells, **ALP** - Alkaline phosphatase, **PHB** - Polyhydroxybutyrate, **AMSC** - Adipose-derived mesenchymal stem cells, **HUVECs** - Human umbilical vein endothelial cells, **GelMA** - Gelatin methacrylate, **VEGF** - Vascular endothelial growth factor, **HAM** - Human amniotic membrane, **DHAM** - Decellularized human amniotic membrane, **PEO** - Polyethylene oxide, **Alg** - Alginate, **PLA** - Polylactic acid, **PP** - Polypropylene, **PU** - Polyurethane, **DWJ** - Decellularized Wharton's jelly, **PLCL** - Poly-(L-lactide-*co*-ε-caprolactone), **BMSCs** - Bone marrow-derived stem cells, **COL** - Collagen, **PA** - Proanthocyanidin, **HUCECM** - Human umbilical cord extracellular matrix, hpcECM - Human placental chorion extracellular matrix.

In order to improve biomechanical qualities and printability, Bashiri et al., [22] combined different amounts of solubilized decellularized placental tissue with sodium alginate (SA) and gelatin (Gel), enhancing the structural integrity and cell interaction of the composite scaffold. The COL in hpECM provides mechanical strength, while GAGs such as HS and CS facilitate growth factor sequestration and release, contributing to improved wound healing and angiogenesis. Specifically, HS's sulfation motifs (2-O, 6-O) allow it to bind and release VEGF and FGF2, promoting capillary growth and tissue integration. The findings demonstrated that the increasing the ECM content enhanced the structural, mechanical, and cell-interaction properties of the scaffolds. Furthermore, it was shown that printed hydrogels based on ECM might stimulate angiogenesis in vivo.

A variety of scaffold types were created to aid in the healing of skin wounds. The electrospinning technique is appealing for use in tissue engineering, medication administration, and other biomedical applications due to its high surface-to-volume ratio and simplicity of use. Because of their nanofibrous topology, which resembles the structure of the extracellular matrix, electrospun nanofiber mats filled with growth factors, peptides, and antibiotics are thought to be promising materials for wound dressings. Electrospinning uses both natural and synthetic polymers [20]. For wound healing applications, PCL's favorable mechanical and biocompatibility properties make it a versatile choice for various tissue engineering applications [84].

By using placental solubilized extracellular matrix (sPECM) and PCL, Rameshbabu et al., [21] created functionalized nanofiber mats as wound dressings (PCL–sPECM). With their desired mechanical properties, the resultant hybrid PCL–sPECM nanofibers may deliver active growth factors to the wound bed and promoting faster healing. Based on the obtained result, the effect of PCL-sPECM on angiogenesis demonstrated in Fig. 3A. Additionally, as demonstrated in Fig. 3B, the PCL-sPECM led to wound healing progress over 21 days compared to other experimental groups (PCL and SHAM). The enhanced healing was attributed to the COL fibers in hpECM, which provided structural support, while GAGs such as HS facilitated the controlled release of growth factors like VEGF, enhancing angiogenesis and tissue integration, as per the structure-function relationship of COL/GAG. In the case of mechanical properties, the elongation at break and Young's modulus of PCL-sPECM was higher than PCL as a synthetic polymer with desirable mechanical characteristic (Fig. 3C).

An analysis of these results highlights an essential design principle: whereas hydrogels offer a natural, interacting milieu, they frequently fall short in mechanical durability necessary for effective dynamic wound healing. In contrast, synthetic polymers such as PCL provide enhanced mechanical support but are intrinsically bioinert. The functionalization of synthetic scaffolds with pECM thus represents a synergistic approach to address this gap, merging the mechanical benefits of synthetic materials with the significant bioactivity of natural ECM. This contrast highlights that the ideal scaffold design is not only a carrier for pECM, but a customised system that harmonises biomechanical stability with regulated bioactivity for particular stages of wound healing.

The science of skin tissue engineering has made extensive use of hydrogel-based wound dressings. Effective wound healing has been shown to be facilitated by hydrogel's ability to provide a moist wound environment. Chitosan (CTS), an FDA-approved polysaccharide, is often used in such applications. Azadbakht et al., [23] created a thermos-responsive chitosan hydrogel (TCTS) by combining CTS, sPECM, and β-glycerol phosphate as a catalyst (Fig. 4A). Both in vitro and in vivo, the resultant composite demonstrated outstanding biocompatibility. Interestingly, fibroblast cells showed better cell adherence to hydrogels with greater concentrations of sPECM. They caused human umbilical vein endothelial cells (HUVECs) to produce the angiogenic factors VEGF and VEGFR. Histological analysis (Fig. 4B) showed progressive tissue integration and cellular infiltration over time, particularly on day 7 and day 21. Hydrogels with higher concentrations of ECM (ECM2.5%-TCTS and ECM5%-TCTS) exhibited enhanced cellular infiltration and tissue regeneration compared to TCTS and ECM1%-TCTS. These findings indicate that increased ECM content promotes better biocompatibility and supports tissue regeneration by providing a conducive microenvironment for cellular activity.

Adhesive films made of absorbent polymers including cellulose, Alg, pectin, and Gel are found in advanced wound dressing materials. Among them, hydrocolloids work especially well for treating wounds that are difficult to heal. When compared to control wounds and hydrocolloid dressings devoid of ECM, the ECM-functionalized hydrocolloid dressing created by Jafari et al. [85] showed a higher capacity for hair follicle regeneration.

A multifunctional bi-layer hydrogel containing human placenta extract (HPE) was reported by Seifi et al., [24] in order to promote cell proliferation, and release HPE continuously, thereby speeding up full-thickness wound healing (Fig. 5). The utilization of biodegradable and biocompatible blend of carboxymethyl cellulose (CMC), for its excellent mechanical properties, fluid adsorption, and Alg for its exudate adsorbing capability, can meet the criteria and used as a dressing layer, which supported cell growth. CTS and Gel made up the underlayer, also known as the regeneration layer, which gave cells a wet, porous, extracellular matrix-like, and antibacterial environment in which to flourish.

The FDA has authorized PEG, a synthetic hydrophilic polymer. To improve cell adherence and provide an ideal environment for cell proliferation, it is crucial to alter hydrogels with bioactive moieties or add active agents, as the majority of synthetic hydrogels are bio-inert. The potential of bioactive PEG hydrogels encapsulated with decellularized placenta powder was investigated by Fan et al., [86]. The findings demonstrated that adding decellularized placenta powder improved the hydrogels' mechanical strength and reduced their swelling ratios.

As summarized in Table 3, various factors like collagen/GAG ratio, crosslinking chemistry, and degradation time are pivotal in determining the scaffold's biological and mechanical properties, influencing tissue-specific applications.

2.2. Bone

Large bone defects are still hard to fix because osteoinduction and angiogenesis don't work very well. The placental ECM is full of growth factors like BMP-4 and VEGF. It has been shown to work well when mixed with polymers to help bone growth and blood vessel growth. Bone is a living thing that has a complicated, hierarchical structure. The body is always changing, which keeps bones strong and prevents them from breaking. The best structure or scaffold for bone tissue engineering (BTE) should have a number of important qualities, including being biocompatible, osteoinductive, angiogenic, cellular adhesion, proliferation, and differentiation potential. In this sense, the hpECM presents itself as a strong candidate for use in BTE. hpECM mixed with SF and pure SF were contrasted by Rameshbabu et al., [28]. However, because of its exceptional mechanical, biocompatible, hemostatic, minimum inflammatory/immunogenic, and progressive degradation qualities, SF was employed. The results of osteogenic differentiation showed that placental extracellular matrix sponge (PIMS) had higher expression of osteogenic genes (COL I, OPN, and OCN) than SF. As mentioned in Table 1, GAGs play a pivotal role by binding and releasing growth factors like BMP-4 and VEGF, which are essential for osteogenesis and vascularization. This suggests that human amniotic mesenchymal stem cells, had a stronger capacity for osteogenic differentiation in PIMS. The PIMS has the ability to draw in host progenitor cells and encourage their development into bone matrix-producing cells by using ECM components and growth factors such as BMP-4, TGF-β1, VEGFA, and PLGF. As a result, it has osteoinductive qualities that promote bone growth. The considerable and uneven dimensions of critical-sized Craniomaxillofacial bone abnormalities hinder the natural healing process. It becomes essential to do surgery, usually with grafts or other techniques, to enable appropriate restoration. The soluble extracts of amnion and

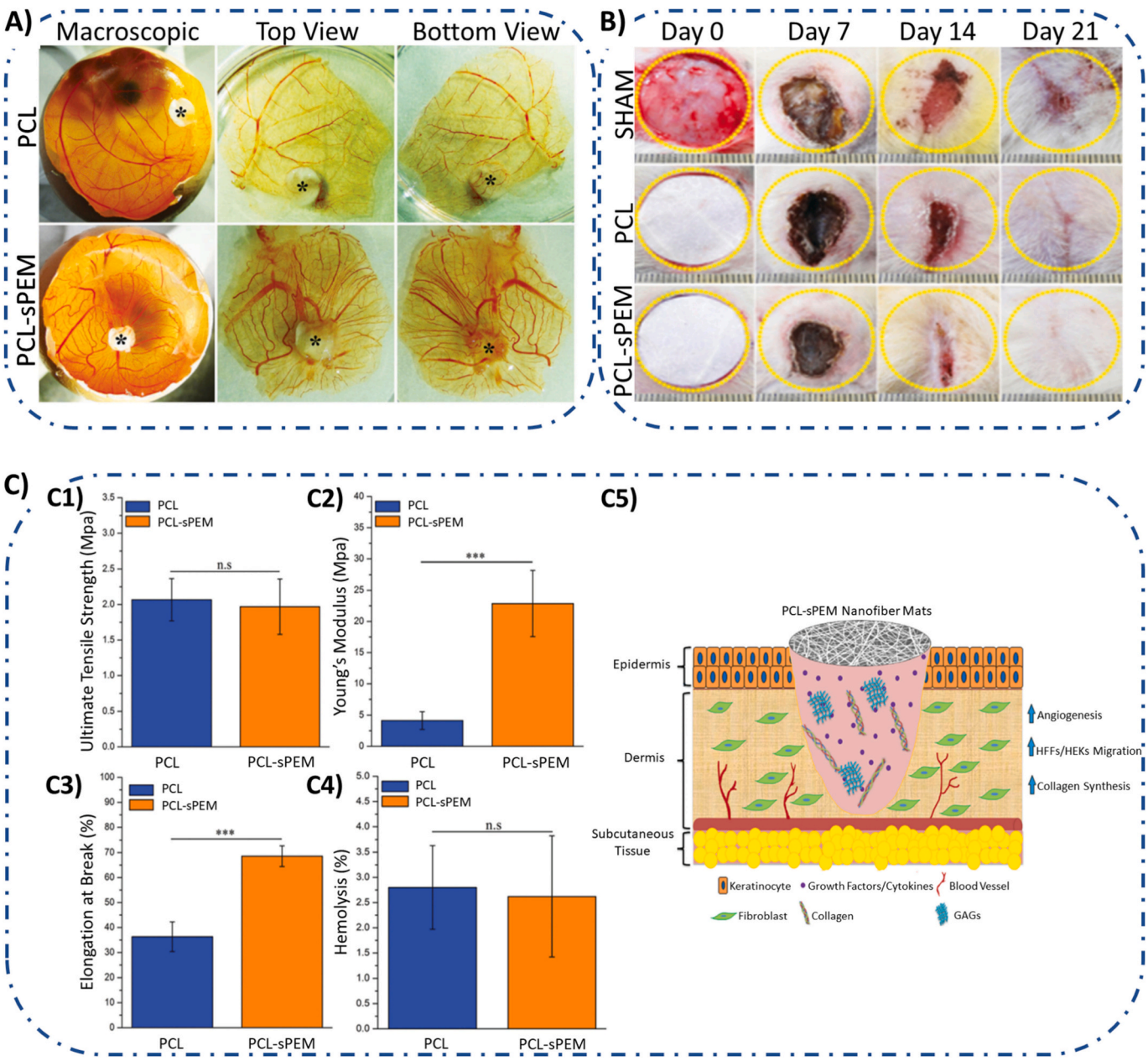

Fig. 3. Characterization and wound-healing performance of polycaprolactone (PCL) and PCL–solubilized placental extracellular matrix (PCL–sPECM) nanofiber mats. A) Representative macroscopic images (top and bottom views) of electrospun PCL and PCL–sPECM mats. B) Representative wound images collected over a 21-day healing period demonstrate accelerated wound closure and improved tissue regeneration in the PCL–sPECM group compared with PCL and sham controls. The enhanced healing is attributed to the bioactive extracellular matrix components, including collagen, glycosaminoglycans, and associated growth factors that promote angiogenesis and tissue integration through sustained biological signaling. (C) Quantitative analysis of the mechanical properties, (C1–C4) shows that incorporation of sPECM increased the elongation at break and Young's modulus of the nanofibers, providing mechanical characteristics closer to those of native granulation tissue, while (C5) summarizes the overall improvement in wound healing. Reprinted with permission from [21].

chorion or matrix-bound components that had a stronger influence on their regeneration capabilities when added to mineralized COL scaffolds were examined by Kolliopoulos et al., [92]. They assessed each component's unique effect on MSCs osteogenic activity in vitro. They found that the scaffold's porosity remained unchanged but its compressive strength was reduced with the addition of amnion or chorion matrix particles. Soluble extracts from the HAM significantly improved MSC viability while maintaining the scaffold's ability to support robust mineral synthesis. The scaffold also contained amnion matrix components, which improved the pro-angiogenic and immunomodulatory qualities of MSCs while maintaining their osteogenic activity. There is a noticeable functional difference between chorion and amnion in terms of promoting tissue regeneration, since scaffolds containing chorion matrix components generated the least amount of osteogenic response. These findings emphasize an important trade-off between mechanics and biology when introducing ECM components into mineralized COL systems. While matrix-bound amnion or chorion reduced compressive modulus without altering porosity, they delivered potent immunomodulatory and angiogenic cues. Conversely, soluble amnion extracts enhanced cell viability and maintained mineral deposition without compromising scaffold strength. Such results align with the broader concept that enriching scaffolds with bioactive ECM signals may soften bulk mechanics but improve regenerative signaling. To mitigate this trade-off, several strategies have been reported, including carbodiimide

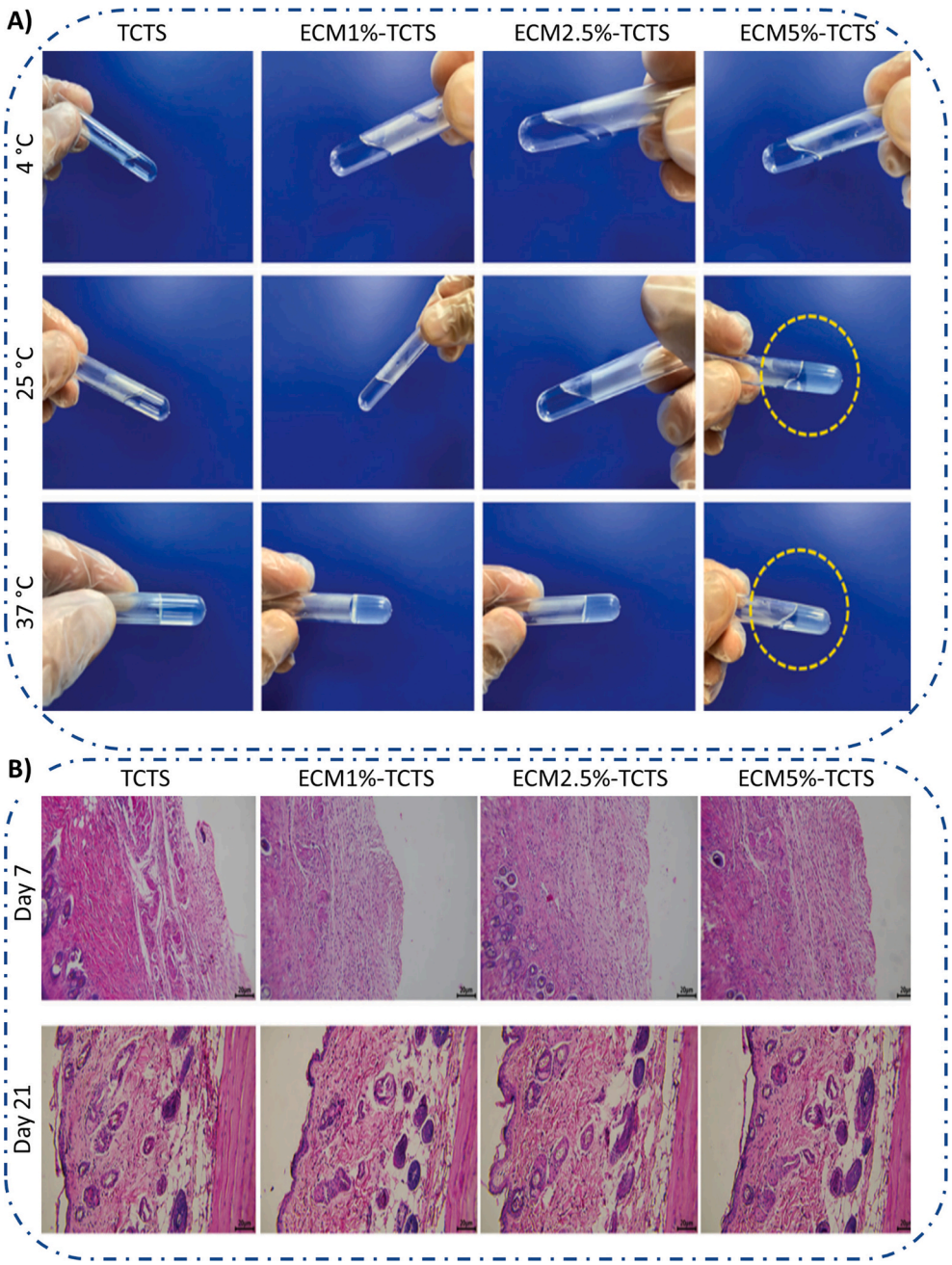

Fig. 4. Temperature-responsive gelation behavior and in vivo biocompatibility of thermosensitive chitosan (TCTS) and extracellular matrix-incorporated TCTS (ECM–TCTS) hydrogels. A) Sol-to-gel transition of TCTS and ECM–TCTS hydrogels at 4 °C, 25 °C, and 37 °C, demonstrating rapid thermally induced gelation at physiological temperature (yellow circles indicate successful gel formation). B) Representative hematoxylin and eosin (H&E)-stained sections of subcutaneous implants containing different ECM concentrations (1%, 2.5%, and 5% *w/v*) after 7 and 21 days. The histological images show progressive cellular infiltration and tissue integration without evident inflammatory response or graft rejection. Increased ECM content enhanced host cell infiltration and tissue remodeling, consistent with the ability of ECM-derived biochemical cues to support cell adhesion, angiogenesis, and tissue regeneration. Reprinted with permission from [23].

crosslinking, adjustment of COL-to-polymer ratios, or incorporation of reinforcing meshes, which can restore mechanical competence while preserving ECM-driven bioactivity. Thus, rational design can balance structural integrity and biological function in perinatal ECM–mineralized COL hybrids.

As a polyester, PCL is semi-crystalline and has strong hydrophobic properties that help it break down slowly. It can be used with many different types of materials and breaks down very slowly, which makes it a good choice for many situations. Still, this polymer has some problems, such as not being very wet, breaking down slowly in normal conditions, and not having good cell adhesion on its surface. These problems make it less useful for making scaffolds for tissue engineering. To get around these problems and make the scaffold work better for biology, variables can be added to it. In the work of Abazari et al., [27] the PCL-based scaffold was modified using HPE. HPE contains a wealth of growth factors, cytokines, vitamins, peptides, and ECM remnants that can support cell growth, adhesion, and proliferation. For effective cell binding, the electrospun scaffold's large specific surface area allows for increased surface area. Additionally, there is plenty of room for the growth of new blood vessels due to the electrospun scaffold's high porosity and linked pits. According to their findings, all bone-related markers (including the late osteogenic markers OSC and OSN and the early osteogenic markers

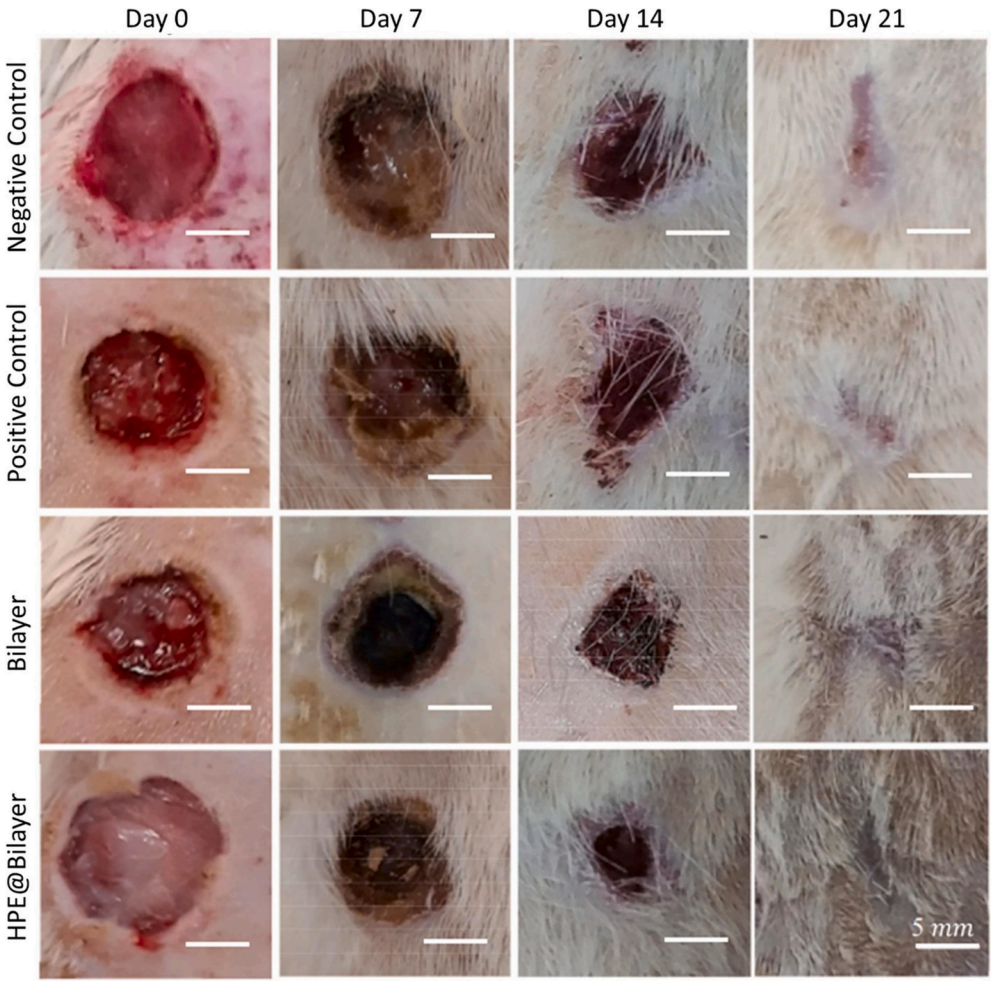

Fig. 5. Wound closure in the negative control, positive control, bilayer, and HPE@Bilayer groups on the 7, 14, and 21 days following surgery. By Day 21, the bilayer and HPE@Bilayer groups exhibited enhanced wound healing, demonstrating accelerated closure and tissue regeneration compared to the negative and positive controls. Reprinted with permission from [24].

Runx2 and Col—I) increased significantly in the presence of the HPE, according to their findings (Fig. 6A). Alkaline phosphatase (ALP) activity and the calcium content, were measured in order to evaluate the osteo-supportive capacity of both PCL and PCL-PE scaffolds (Fig. 6B). Furthermore, this improvement was noticeably increased upon coating PCL nanofibers with HPE, as supports the findings of Table 3, where the incorporation of hpECM in PCL scaffolds significantly improved osteogenic differentiation, with mechanical properties such as tensile strength being a key factor in promoting bone regeneration. In another study a composite containing hydroxyapatite, Gel, and HPE was produced for BTE. Based on the result, HPE due to the presence of bioactive components led to mechanically stable. The final fabricated product showed both osteoinduction and osteoconduction effect with unique elastic recoverable properties [28].

A comparative analysis of these studies reveals a critical and recurring trade-off. While hpECM provides potent osteoinductive, angiogenic, and immunomodulatory signals, its addition can compromise scaffold mechanics. The narrative shifts from simply proving the bioactivity of hpECM to strategically deploying it within engineered constructs. The outcome underscores that the most promising BTE scaffolds are not purely ECM-based nor purely synthetic, but rather intelligently designed hybrids. In these systems, a synthetic or mineralized backbone provides mechanical and architectural support, while the hpECM acts as a critical biological signaling module, thereby overcoming the fundamental trade-off to achieve truly osteoregenerative outcomes.

2.3. Cartilage

For many years, people have tried to fix cartilage damage from injuries, osteochondritis, and other diseases by transplanting chondrocytes, periosteum, osteochondral grafts, or meniscal allografts. Materials from the placenta, such as COL and GAGs-rich ECM, send functional signals that help MSCs make new cartilage and repair damaged cartilage. This is because the sulfation patterns of GAGs, like chondroitin sulphate, help cells differentiate and ECM deposition, which are both very important for making the cartilage matrix solid. It has been shown that scaffolds made from low-concentration PLGA (15–20%) can help chondrocytes grow. To aid MSC chondrogenesis, Hsu et al., [93] created a 3D culture method that combines PLGA and Alg. Alg may help in TGF-β3 presentation to cells and preservation in the microenvironment. The results showed that human placenta-derived mesenchymal stem cells (hPMSCs) were more chondrogenic than human BMSCs. For human MSCs to induce chondrogenic growth, the proper signals are required. The sulfation patterns of GAGs, especially CS, modulate the release of growth factors like TGF-β and bFGF, which are crucial for maintaining chondrocyte phenotype and promoting cartilage regeneration. Using COL and CS, two components of cartilage ECM, Mingchan Du et al., [94] created a porous ECM-based hydrogel with regulated TGF-β and bFGF release. After human MSCs were stimulated to differentiate into chondrocytes by the release of TGF-β, bFGF was released to further promote differentiation and maintain the chondrocyte phenotype. For hPMSCs to differentiate into chondrocytes, the hydrogel

Table 3
Key Parameters in designing collagen/GAG-enriched polymeric scaffolds for tissue regeneration.

Parameter	Typical range / choice	Design rationale & bioactivity	References
Collagen:GAG ratio	10:1–100:1 (*w*/w)	Mimics native ECM composition. Lower ratios increase water retention and growth factor binding, but excessive GAG may compromise mechanical stability.	[87]
Crosslinking chemistry	EDC/NHS (zero-length carbodiimide); Genipin (natural crosslinker)	EDC/NHS preserves bioactivity and provides moderate degradation (≈4–8 weeks). Genipin offers slower degradation (≈8–12 weeks) and superior biocompatibility.	[87]
Porosity & pore size	Total porosity 50–95%; pore size 50–300 μm	High porosity supports cell infiltration and nutrient transport. Larger pores are beneficial for bone/cartilage; smaller pores suit skin or epithelial tissues.	[88]
Degradation timeline	4–12 weeks (tunable)	Degradation should match tissue regeneration rates. Controlled by crosslinking density and polymer blending.	[89]
GAG sulfation patterns	Heparan sulfate, chondroitin sulfate, dermatan sulfate	Sulfation type and density dictate growth factor binding and signaling. Heparan sulfate binds VEGF and FGF2 to enhance angiogenesis; chondroitin/dermatan sulfates support chondrogenesis.	[90]
Blending with synthetic/ natural polymers (PCL, PLGA, PEG, SF)	Typically lower GAG content to avoid phase separation; slower degradation (months); reduced porosity	Enhances mechanical strength and structural stability. May require surface modifications (e.g., heparinization, plasma treatment) to maintain bioactivity.	[91]

scaffolds offered appropriate three-dimensional cell habitats. Numerous ECM-based hydrogels have been developed as a result of this investigation. Notably, the TGF-β family can produce hypertrophy because of prolonged high levels, even though it is commonly employed to stimulate chondrogenesis. Y27632 [1R,4r)-4-((*R*)-1-aminoethyl)-N-(pyridin-4-yl) cyclohexane carboxamide, $C_{14}H_{21}N_3O$, or similar molecular inhibitors may promote tissue renewal without these negative effects. Table 3 emphasizes the importance of the COL/GAG ratio in cartilage tissue regeneration. This is in agreement with this study, where the optimal COL/GAG ratio significantly promoted chondrogenic differentiation of stem cells.

Traditional synthetic biodegradable polymers, such polylactic acid (PLA), polyglycolic acid (PGA), and PLGA, may not have the appropriate elastic qualities to match live tissue, disintegrate at high temperatures, or need organic solvents for 3D printing. In order to improve the differentiation of chondroprogenitors, Hung et al., [95] printed a water-based ink that included polyurethane (PU), hyaluronan (HA), a naturally occurring polymer, and Y27632, a small molecule medication, in place of TGFb3. In comparison to traditional PLGA scaffolds, the elastic recovery capability of PU/HA scaffolds demonstrated exceptional elasticity, and the results demonstrated that Y27632 may inhibit the production of hypertrophic markers. Addressing the intricate demands of osteochondral tissue engineering requires recognizing that the physical characteristics of scaffolds can significantly direct lineage-specific differentiation. A bilayer construct with adjustable stiffness (10–39 kPa) has proven effective in simultaneously promoting chondrogenic and osteogenic processes. In this context, Ouyang et al., [71] engineered a bilayer scaffold composed of GelMA/HA blended with decellularized hpcECM for the cartilage layer and hpECM for the bone layer. This composite configuration offers both mechanical guidance and bioactive signaling to facilitate osteochondral tissue regeneration. Compared to commercial COL sponges, COL fiber orientation analysis after 16 weeks revealed that scaffolds incorporating hpECM supported the formation of a COL network closely resembling the native tissue architecture.

2.4. Vascularization

Every year, about a million vascular grafts are required in clinical practice in the United States alone. The need for small-diameter vascular grafts (SDVGs) (<6 mm) has increased due to the rise in coronary heart disease and arterial occlusive disorders. The majority of arteries in the peripheral, cerebral, and cardiac vasculature have sizes of less than 6 mm (small-diameter vessels), despite the fact that synthetic polymers have proved effective in substituting large-diameter veins (>6 mm). A vascular graft should be able to encourage endothelization of its inner surface and be compatible with endothelial cells. It should also have the right mechanical qualities, infection resistance, and blood compatibility. For this reason, materials made from the human placenta have been investigated. All of these features are present in the decellularized human chorion membrane (dHCM), especially on the reticular layer side, as Laura et al., [95] showed.

Expanded polytetrafluoroethylene (ePTFE) is presently the most sophisticated material for synthetic SDVGs. In therapeutic contexts, patients who cannot undergo autologous vascular grafting due to vascular pathology, limited availability, or unsuitable invasive harvesting techniques are treated with ePTFE grafts. Compared to autologous implants, ePTFE grafts have significantly lower patency rates. The progression of atherosclerosis, intimal hyperplasia, and thrombosis are primary causes of transplant failure, alongside infection; hence, there has been considerable interest in modifying the ePTFE surface to improve endothelial cell adherence. In contrast to ePTFE grafts that are neither coated or coated with fibronectin, Rohringer et al., [29] showed that human placental chorionic extracellular matrix-gel (hpcECM-gel) dramatically increases endothelial cell adhesion. In order to promote endothelialization following implantation, hpECM-gel may therefore be a viable substitute for fibronectin as a surface coating material for ePTFE. The findings in Table 3 suggest that the enhanced endothelial cell adhesion and vascularization can be attributed to the COL/GAG ratio in their scaffolds. A higher COL content relative to GAG promoted better endothelial cell attachment, facilitating vascularization. One possible way to increase the stability of growing angiogenic networks is by controlled release. For the regulated release of certain growth factors, biodegradable polyesters like as PLGA, an FDA-approved polymer, have been widely utilized. Human placental matrix (hPM) was encapsulated using PLGA microparticles by Tonello et al., [96] who also showed that the development of vascular networks depends on the sustained release profile of hPM.

Their ability to promote tissue regeneration is limited by the inertness of synthetic polymer materials and the inadequate mechanical strength of reprocessed decellularized extracellular matrix (dECM). The blood pressure needed for SDVGs cannot be tolerated by pure pECM materials due to their lack of mechanical strength. Liu et al., [30] created hybrid SDVGs made of PCL microfibers and pECM nanofibers using co-electrospinning technique. Active modification sites and biological activity were supplied by the pECM nanofibers. Furthermore, the

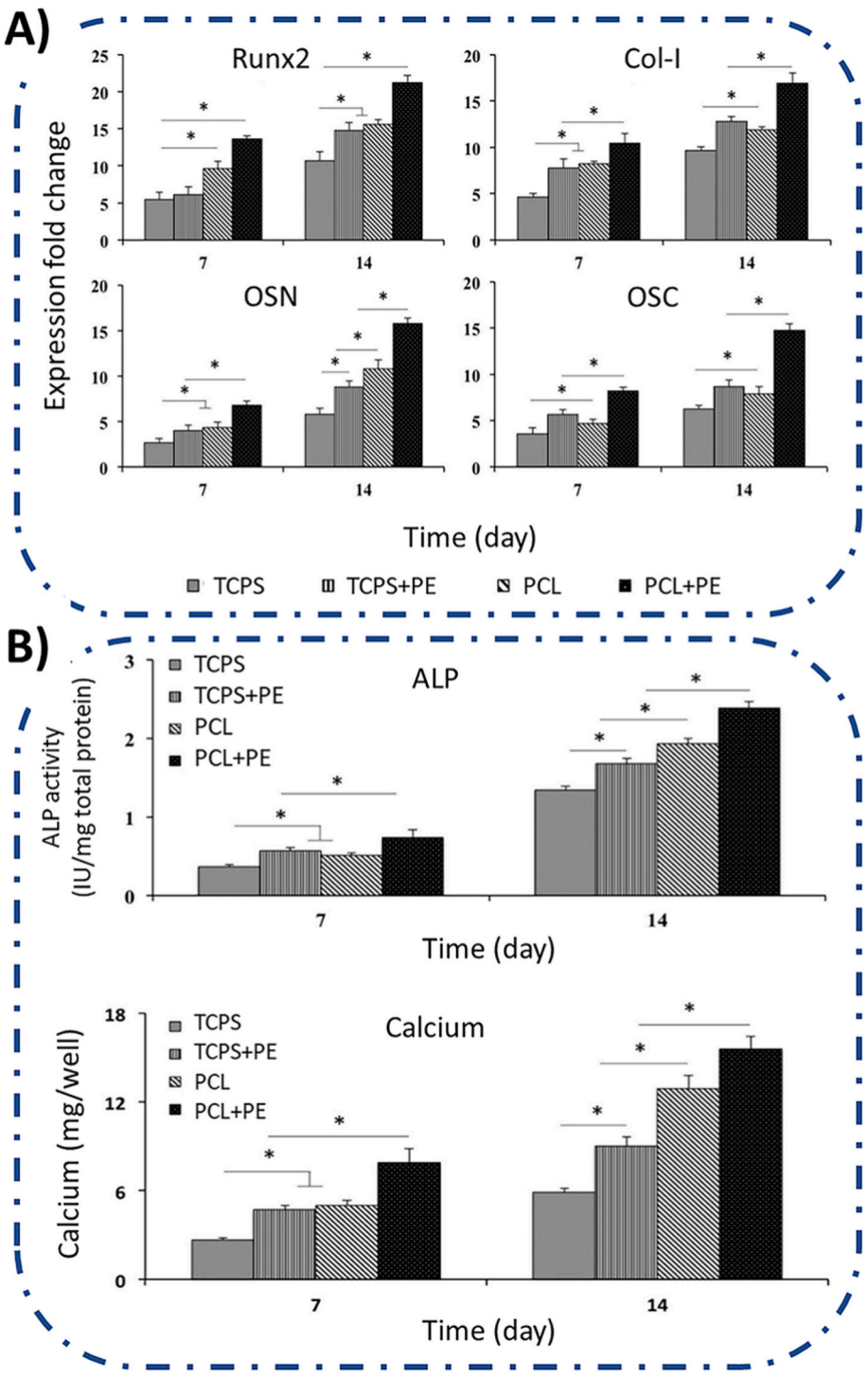

Fig. 6. Effect of placental extract (PE) treatment and substrate type on the osteogenic differentiation and biomineralization of human Wharton's jelly mesenchymal stem cells (WJMSCs). A) Relative expression of osteogenic genes, including early-stage markers (Runx2 and Col—I) and late-stage markers (osteocalcin (OCN) and osteonectin (OSN)), in cells cultured on polycaprolactone (PCL), PCL + PE, tissue culture polystyrene (TCPS), and TCPS + PE after 7 and 14 days. PE supplementation significantly upregulated osteogenic gene expression, indicating enhanced osteogenic differentiation. B) Alkaline phosphatase (ALP) activity and calcium deposition under the same culture conditions at days 7 and 14. Increased ALP activity and mineralized matrix formation in the PE-treated groups demonstrate improved osteo-supportive capacity and biomineralization, consistent with the bioactive factors present in placental extracts that promote osteogenic differentiation. Reprinted with permission from [27].

hybrid scaffolds promoted endothelialization, smooth muscle regeneration, and ECM deposition in a rat model of abdominal artery abnormalities. The natural extracellular space is a dynamic and delicate environment made up of non-cellular components such as soluble factors, non-soluble extracellular matrix, and extracellular vesicles (EVs) [92]. In addition to being rich in lipids, proteins, and RNAs, among other molecular components from their parent cells, EVs have the ability to facilitate cell-to-cell contact [97]. It has been demonstrated that EVs generated from MSCs, especially PMSCs, have the ability to promote angiogenesis [92]. To increase the potential for vascularization and

regeneration, Hao et al., [98] mounted PMSC-EVs onto electrospun ECM-mimicking scaffolds in order to duplicate the EV-ECM complexes [92].

2.5. Others

The creation of affordable, implantable, and sizable bioprostheses, like breast implants, is one of the main issues facing reconstructive surgery. Using dHP and SF at varying ratios, porous hybrid hydrogels were created combinatorically. A 30/70 ratio demonstrated enhanced mechanical qualities and may find use in bioprosthetic such breast implants [31].

By using biologically active scaffolds, tissue engineering has attempted to restore injured cardiac muscle tissues. In a research by Mokhames et al., [32], PLGA-PHB electrospun nanofibers were bioactivated using HPE. By cultivating MSCs on the nanofibers in a cardiomyogenic-induction medium, the manufactured nanofibers' ability to sustain cardiomyocytes was examined. By assessing the expression levels of key genes and a crucial cardiac muscle protein, the cardiomyogenic differentiation capacity of the MSCs was investigated. The results demonstrated that the cultivated MSCs on the PLGA-PHB-HPE nanofibers had the greatest levels of gene and protein expression.

The distinctive repeating protein sequences found in silk fibroin (SF) provide biomaterials remarkable mechanical and structural resilience. However, when the peptides' β-sheet structures build up, SF hydrogels lose their bioactivity and may eventually become brittle. Thus, tyramine-enriched gelatin (G-TA) was added to hpECM by Schneider et al., [25] in order to prevent silk crystallization and improve bioactivity at the same time. hpECM gel was used to enzymatically crosslink the SF and G-TA gels. In a soft silk composite combined with placental extracellular matrix, they noticed elevated metabolic activity and cell proliferation.

3. Biopolymer-amniotic membrane composite for tissue engineering

3.1. Skin

Skin injuries such as burns and chronic ulcers are also characterized by delayed re-epithelialization and poor blood flow. The amniotic membrane, which possesses natural anti-inflammatory and pro-healing properties, has been combined with polymeric supports to promote keratinocytes differentiate and functional skin regeneration. To create a scaffold for skin tissue engineering, HAM and COL scaffold were combined. Inflammation and antigenic qualities were decreased by using HAM [99]. In a study, HAM and SF nanofibers were combined to mimic the extracellular matrix of the skin. SF from *Bombyx mori* cocoons was converted into uniform nanofibers and coated on epithelialized human HAM. Cell attachment and proliferation on scaffolds were shown in in vitro experiments, and cell-matrix interaction was facilitated by scaffolds treated with plasma [33]. In skin tissue engineering, VEGF and bFGF are essential components. They are strong angiogenic agents that encourage the development of new blood vessels, which are necessary to provide oxygen and nutrients to tissues that are just beginning to form. Keratinocytes, fibroblasts, and endothelial cells are among the cell types involved in skin regeneration that are stimulated to proliferate and migrate by VEGF and bFGF. VEGF and bFGF promote angiogenesis and cell proliferation, which speeds up wound healing, tissue regeneration, and the development of functional skin replacements [100].

Gholipourmalekabadi et al., [34] used electrospun nanofibrous silk fibroin (ESF) and DHAM to create a three-dimensional bilayer scaffold. Addressing the unmet clinical need for efficient skin regeneration in burn injuries was the goal of this investigation. Compared to HAM alone, a 7-day cultivation of mesenchymal stem cells from adipose tissue on HAM/ESF enhanced the production of pro-angiogenic factors VEGFa and bFGF. This suggests that HAM/ESF scaffolds may find practical use in skin regeneration. Consistent with these observations, Schwartz et al., [101] conducted a comparative study between placental connective tissue matrix (PCTM), derived from human amnion and chorion, and porcine small intestinal submucosa (SIS) using a diabetic rat wound model. Their results demonstrated that PCTM markedly enhanced fibroblast proliferation and type I COL production, leading to accelerated epithelialization and improved wound closure relative to SIS and untreated controls. Histological evaluations further revealed that PCTM-treated wounds achieved complete re-epithelialization within two weeks, whereas SIS-treated wounds required approximately three weeks to reach comparable coverage. Notably, PCTM promoted COL deposition without inducing excessive inflammation, reflecting its well-balanced pro-regenerative and anti-inflammatory characteristics. Collectively, these findings highlight the superior bioactivity and therapeutic potential of perinatal-derived PCTM compared to xenogeneic SIS.

Ashouri et al., [35] creatively combined SF and SA in a hybrid scaffold on DHAM for chronic wound management. The combination of SF and SA contributed to the scaffold's critical properties, including increased cell adhesion, proliferation, and water wetting, which are critical for effective wound healing.

DHAM can be used as an extracellular matrix, and on the other hand, its properties can be improved by modifying it. Chen et al., [36] introduced a novel solution using DHAM modified with methacrylate (MA) grafting, resulting in photosensitive dECM/MA. By combining it with Gelatin methacryloyl (GelMA) hydrogel, dECM/MA/GelMA, was created that retained bioactivity and supported vital cellular functions such as proliferation, migration, and angiogenesis, while exhibiting significant anti-inflammatory properties. The effectiveness of dECM/MA/GelMA in wound healing and re-epithelialization in rabbit wound defects has been demonstrated. In a comparative investigation by Mahapatra et al., [72] the performance of a commercial wound dressing (DuoDERM) was evaluated against a human amniotic membrane/silk fibroin (HAM/SF) composite for wound healing applications, underscoring the importance of bioactive constituents in regenerative outcomes. After 21 days, wounds treated with DuoDERM exhibited a closure rate of 87.52 ± 2.22%, whereas those treated with HAM/SF scaffolds containing EVs achieved nearly complete healing. By the same time point, HAM/SF–treated wounds showed well-organized, fine reticular COL deposition—characteristic of scarless tissue repair—while DuoDERM-treated sites presented irregular and loosely packed COL fibers, indicative of incomplete ECM remodeling and a greater likelihood of fibrosis. Furthermore, HAM/SF treatment resulted in the lowest levels of IL-6 expression on days 7 and 14, signifying faster resolution of inflammation and an earlier transition into the proliferative phase of wound healing. Although the study acknowledged that a larger sample size could enhance statistical power, the overall findings consistently emphasized the superior therapeutic efficacy of HAM/SF scaffolds in promoting organized, inflammation-controlled, and functionally efficient tissue regeneration.

3.2. Bone

Bone tissue engineering aims to develop implantable bone replacement for abnormalities that are incapable of healing naturally. Traditional methods such as bone grafts and synthetic implants often face limitations, including donor site morbidity, limited availability, and risk of rejection or infection. A study developed a new composite scaffold combining inorganic COL with an AM matrix for craniomaxillofacial bone (CMF) repair. Although the mineralized COL scaffold encourages the production of new bone, the absence of an immune system regulatory component raises the possibility of persistent inflammation, which impedes the healing process. To solve this problem, HAM which has anti-inflammatory qualities—was added to the scaffold. Porcine adipose-derived stem cell culture (pASC) bioactivity was examined to see if the detrimental effects of IL-1β were mitigated by including HAM

matrix into the mineralized COL scaffold. The metabolic activity and total quantity of pASCs within mineralized COL–HAM scaffolds were not adversely affected by IL-1β throughout the 28-day experiment (no significant differences between the groups at any timepoint). Mechanical tests revealed that the generated composite scaffold had better compressive properties and the right porosity structure for cell penetration. Both mineralized COL scaffolds and mineralized COL–HAM scaffolds exhibited equivalent expression of two osteogenic markers, RUNX2 and BGLAP. The results of the study suggest that HAM may be applied to mineralized COL scaffolds to enhance their osteogenic potential and mechanical properties, especially under inflammatory conditions. Additionally, it may be a helpful substance for improving CMF bone repair [37]. The porosity, water absorption, and elastic modulus of a composite scaffold composed of PLA, nHAp, and DHAM were assessed by a group of researchers. Newborn Sprague Dawley rat osteoblasts were used to create the composite in order to assess its biological characteristics. The combination of nHAp and DHAM promoted cell proliferation and ALP secretion, and the scaffolds demonstrated high cell survival and adhesion rates to DHAM. The composite scaffold is appropriate for the creation of solid bone tissue because it promotes osteoblast adhesion, proliferation, and differentiation. Excellent biocompatibility and potential for use as scaffolds in bone tissue engineering were demonstrated by the acellular HAM produced in this study [38].

3.3. Cartilage

Articular cartilage is necessary for bearing loads, lubrication, and friction reduction in joints. Osteoarthritis, a prevalent joint disease that causes considerable physical handicap and economic repercussions, is frequently caused by injury to this tissue because of its poor capability for regeneration. There is an urgent need for efficient therapies to promote cartilage regeneration since the current treatments for cartilage abnormalities have shown inconsistent outcomes. COL and chitosan (2 wt%) were combined with HAM (2.5%, 5.0%, and 10.0% *w*/w) to create hybrid hydrogels. Promising characteristics of these hydrogels included a swelling capacity ranging from 333 ± 19% to 368 ± 28%. They found that there was no discernible variation in the hydrogels' maximum hydration levels. Consequently, the ultimate hydration was unaffected by the COL addition from HAM. According to this work, cartilage tissue engineering may be possible with these hybrid hydrogels containing HAM [39]. For cartilage repair, Nogami et al., [40] concentrated on creating and testing a novel ECM-coated PLGA scaffold (ECM-PLGA) produced from HAM. With its high levels of COL type I, fibronectin, hyaluronic acid, and chondroitin sulfate, the ECM-PLGA scaffold replicates the natural amniotic stroma and promotes superior cell adhesion and proliferation. After three weeks, rat MSCs grown on ECM-PLGA scaffolds increased the expression of type II COL mRNA, according to in vitro tests. ECM-PLGA scaffolds were implanted into osteochondral defects in rat knees as part of in vivo research. In comparison to the blank control group, histological analyses conducted at 4, 12, and 24 weeks demonstrated that ECM-PLGA scaffolds promote progressive tissue regeneration, leading to improved hyaline cartilage repair (Fig. 7 A1). Immunohistochemistry result indicated that regenerated tissue after ECM-PLGA implantation was stained intensely for type II COL, again supporting the hyaline cartilage nature of the surface zone at 24 weeks. On the contrary, staining for type I COL was predominant in the surface layer of empty control and PLGA implanted groups (Fig. 7 A2).

For cartilage tissue engineering, Hussin et al., [102] investigated the development and assessment of a new 3D scaffold made from HAM and fibrin. For the first time, HAM and fibrin were joined in a 3D scaffold, although they had previously been employed independently in other studies. The findings showed that the scaffold has good biodegradation properties and promotes 3D chondrocyte growth. Lacunae containing chondrocytes with round morphological characteristics similar to native cartilage were shown to develop on the HAM-Fibrin scaffold. Proteoglycan staining was somewhat positive, and H&E staining showed resemblance to hyaline cartilage. The scaffold preserved the cells' natural phenotypic while effectively secreting ECM unique to cartilage. The fibrin and HAM-Fibrin constructs were observed to degrade at a tolerable rate by day thirty. Furthermore, the HAM-Fibrin constructions generated a considerable amount of GAGs over the course of a week, suggesting effective biodegradation and support for the creation of cartilage matrix.

The most biomimetic approach seeks to construct a fully natural, 3D ECM environment that recapitulates the native cartilage niche beyond surface coatings. While ECM-coated synthetics (like ECM-PLGA) add bioactivity to a durable backbone, 3D natural matrices (like HAM-Fibrin) offer a more holistic, biomechanically and biochemically authentic environment that may better support the complex 3D cell-ECM interactions essential for mature cartilage formation.

3.4. Vascularization

A sufficient quantity of oxygen and nutrients—both necessary for cell survival and function—are delivered to designed tissues through vascularization. Necrosis and the failure of the designed tissue might result from cells in thick or dense tissues going hypoxic and dying due to an inadequate blood supply. In order to create permeable three-dimensional capillaries for large-scale engineered tissues, Heydari et al., [41] combined DHAM with Alg and HUVECs to create a unique bio-ink. Excellent biocompatibility, porosity, and mechanical stability were demonstrated by the optimized bioink (Alg 4% *w/v* – DHAM 0.6% *w/v*). It also demonstrated considerable and effective tubulogenic expression of VEGFR-2, which is essential for angiogenesis. The high incidence of SDVG occlusion necessitates the development of more biocompatible grafts. To assess HUVEC dispersion and morphology, live-dead staining was performed after 72 h. It is clear in Fig. 7B that in both perfusable 3D bioprinted vasculature (3D netted microchannels and 3D built-in microchannels), vascularization started strikingly as though several vascular lumens (tube-like) structures formed which emulate the paramount aspect of new blood vessel development.

Aslani et al., [42] explored fabricating electrospun polylactic acid (PLLA) scaffolds with random nanofiber configurations, incorporating acetylsalicylic acid (ASA) as an anticoagulant, and coating them with HAM lysates. The results demonstrated that the scaffolds have adequate tensile strength for vascular applications, exhibit excellent cell compatibility and hemocompatibility, and exhibit sustained release of ASA over 7 days. HAM-coated scaffolds significantly improved EC attachment, proliferation, and differentiation and formed an endothelial-like coating. These studies showed that the combining synthetic PLLA and natural HAM components creates a biocompatible surface that mimics the native endothelial basement membrane, reduces the risk of thrombosis, and improves graft function. Because of their procoagulant properties and poor cell attachment rates, traditional synthetic vascular grafts frequently experience problems including stenosis and thrombosis. DHAM and polyacrylamide-Alg gel were combined by researchers to create a composite hydrogel. While keeping a modest swelling ratio, this hydrogel showed exceptional mechanical strength, high elasticity, resistance to enzymatic degradation, and anti-calcification qualities. It also successfully prevented hemolysis, activation, aggregation, and platelet adhesion. Nitric oxide and prostacyclin secretion, which are essential for vascular remodeling and repair, were enhanced by the hydrogel's strong promotion of endothelial cell adhesion, proliferation, and migration to its surface. Immunofluorescence and immunohistology analyses showed enhanced endothelialization and revascularization around the hydrogel, with new blood vessels forming and minimal inflammatory response [103].

In order to increase the paracrine activity of transplanted cells and promote angiogenesis in infarcted hearts, the study aimed to create a cardiac patch (EF-HAM) by covering a HAM with aligned PLGA electrospun fibers. EF-HAM scaffolds with different fiber thicknesses were evaluated for their biocompatibility and angiogenic effects on the

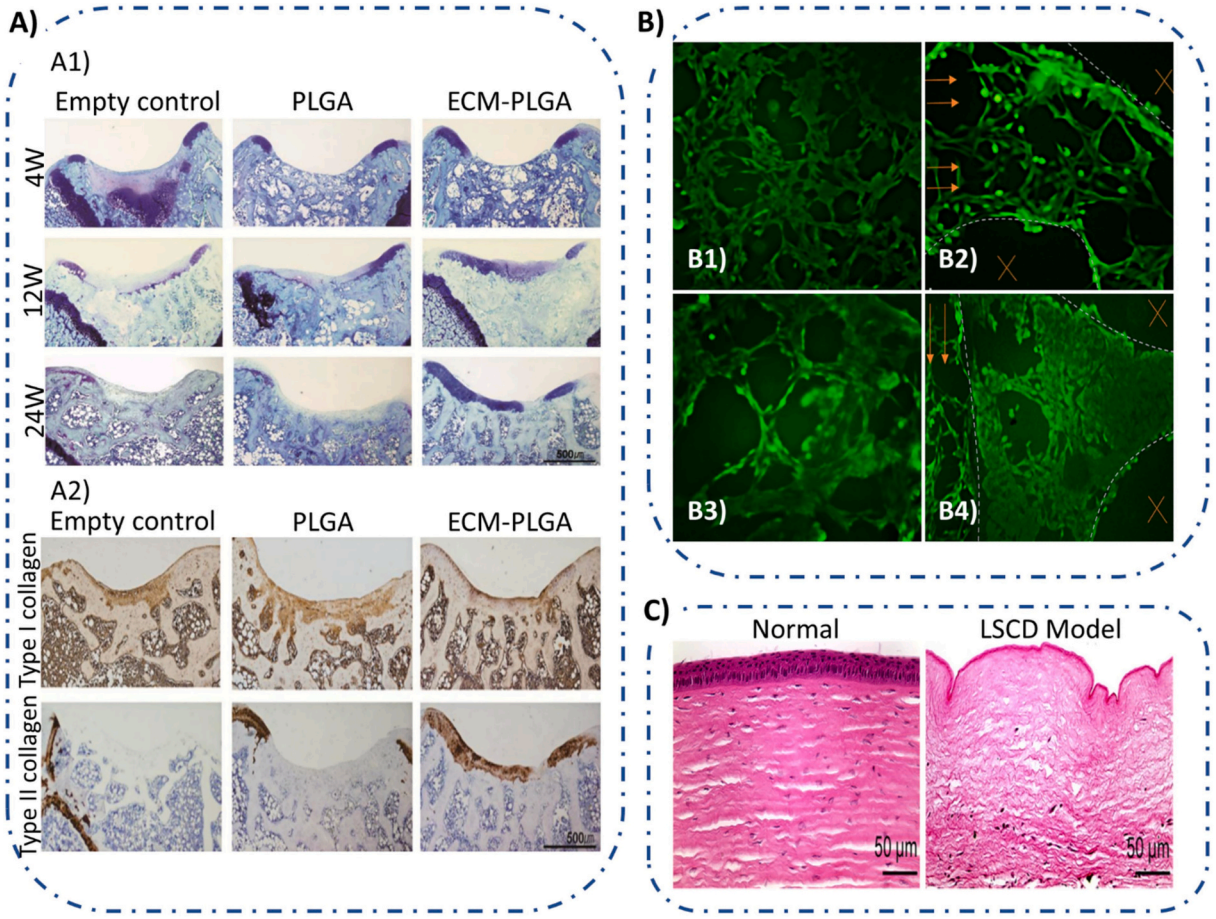

Fig. 7. A) Histological, immunohistochemical, and bioprinting analyses of tissue regeneration. A1: Toluidine blue staining (4, 12, 24 weeks) and type I/II COL staining (24 weeks) show enhanced osteochondral tissue regeneration with ECM–PLGA scaffolds compared to PLGA and control. Reprinted with permission from [40]. B) Live–dead assays and cross-sections of bioprinted "3D netted" and "3D built-in microchannels" constructs reveal increased tubulogenesis and superior vascularization. Reprinted with permission from [41]. (C) H&E staining illustrating normal control epithelium (left) and LSCD model (right), showing significant epithelial damage in the LSCD model two week post-exposure. Reprinted with permission from [47].

paracrine activity of skeletal muscle cells (SkM). On HUVECs, endothelial cell migration, vitality, and tube formation were evaluated, and angiogenic factors were analyzed in the conditioned medium (CM) of SkM-seeded HAM and EF-HAM scaffolds. Based on the findings, every EF-HAM scaffold exhibited exceptional biocompatibility with SkM—CM. Additionally, proangiogenic factors such as VEGF-C, IL-8, and angiopoietin-1 were significantly higher in SkM-seeded EF-HAM scaffolds than in ordinary CM. This CM also significantly increased the migration and survival of HUVECs and enhanced the formation of capillary-like networks on Matrigel. With its rougher surface, bigger PLGA fibers, and reduced wettability, the EF-HAM scaffold exhibited a greater angiogenic potential and promoted the development of skeletal fibroblasts alongside myoblasts. Proangiogenic factor release and endothelial cell activities have been demonstrated to be enhanced by EF-HAM scaffolds [43].

To develop a vascular graft capable of rapid remodeling and degradation while preventing occlusion, researchers engineered a perinatal–polymer hybrid scaffold by combining DHAM with electrospun PCL/SF, referred to as the HPS graft. This construct (1.8 mm in diameter) was benchmarked against a SIS-based hybrid (SPS) and polymer-only counterparts. In vitro assessments demonstrated that the inclusion of HAM imparted dual functionality, promoting endothelial cell proliferation and tube formation while simultaneously inhibiting fibroblast-mediated COL overproduction; features absent in bioinert polymer-only scaffolds. In a rat aortic interposition model, the HPS graft preserved complete patency over 24 weeks, in stark contrast to the 12.5% patency observed for SPS. Moreover, it exhibited accelerated endothelialization, reduced neointimal hyperplasia, and a pronounced polarization toward anti-inflammatory M2 macrophages (M2/M1 ratio ≈ 5.8 compared to 2.9 in SPS). From a mechanical standpoint, the PCL/SF framework provided burst pressure and suture retention comparable to that of the native aorta, while the COL and GAG-rich HAM matrix supplied bioactive cues that promoted angiogenesis and immunomodulation, advantages not present in SIS or synthetic-only scaffolds. Collectively, these results highlight that the synergistic combination of COL/GAG enrichment with perinatal-derived components yields markedly improved vascular regeneration relative to xenogeneic ECM or polymer-only designs [44].

3.5. Corneal

Artificial cornea is a promising approach to address corneal transplantation limitation such as limited donor availability and high costs. In a study, an advanced artificial cornea was fabricated using PCL and PVA with a bioactive macromolecule obtained from HAM coating. Based on characterization tests, the modified artificial cornea showed better biocompatibility compared to its unmodified counterpart. The anti-angiogenic qualities of artificial cornea were markedly improved by the sustained release of anti-angiogenic substances from nanoparticles, such as endostatin and thrombospondin-1. Vascular inhibition was demonstrated by decreased von Willebrand factor and CD31 expression, which was confirmed by real-time PCR and flow cytometry. This study

concluded that this fabricated artificial cornea had great potential for use in corneal transplantation [104]. The creation of a PVA-HAM hybrid scaffold for usage in artificial corneas was investigated in a study. To improve epithelialization, human HAM was crosslinked to PVA. On PVA-HAM, rabbit corneal epithelial cells developed a stratified epithelium with enhanced organization and differentiation. Up to four weeks after implantation, the PVA-HAM scaffold preserved transparency, decreased inflammation, and accelerated corneal epithelialization. Although stabilising HAM to stop degradation is a challenge, this hybrid scaffold shown encouraging outcomes for upcoming keratoprosthetics applications [45]. Another study observed the management of retinitis pigmentosa and age-related macular degeneration (AMD), which were linked to Bruch's membrane breakdown and dysfunctional retinal pigment epithelial (RPE) cells. In order to facilitate RPE cell transplantation for vision restoration, the researchers set out to create an ultrathin porous fibrous film that mimicked natural Bruch's membrane. They created an electrospun scaffold with varying amounts of PCL and HAM powder (HAMP). Larger fiber diameter, enhanced hydrophilicity (contact angle dropped from 119° to 92°), and quicker disintegration (from 14% to 56% over 28 days in PBS) were the outcomes of increasing HAMP content, according to the results. It is a potential option for treating AMD because of these qualities [46].

Although DHAM shows considerable potential for regenerative applications, its inherent thinness and fragility present major handling and processing challenges. To render DHAM clinically viable, two critical aspects must be addressed simultaneously: (1) enhancing its mechanical strength to achieve suitable performance across different implantation environments and facilitate easier manipulation, and (2) preserving the biological activity of native growth factors and cytokines naturally present in the amniotic membrane. While several strategies—such as chemical or enzymatic crosslinking and the incorporation of amniotic extracts into hydrogels—have been investigated to mitigate these issues, these methods often disrupt the structural integrity of the native ECM.

A promising alternative involves creating interfacial bonding between surface-carboxylated PCL nanofiber meshes and dehydrated amnion sheets. This approach effectively minimizes the loss of AM bioactivity commonly associated with stratification, delamination, or repeated crosslinking during processing, while substantially improving mechanical strength (approximately 4–10 times greater than that of decellularized AM alone). The resulting PCL–DHAM composite membrane successfully retained the intrinsic pro-regenerative and anti-inflammatory characteristics of DHAM in vivo. Furthermore, the composite maintained its shape, position, and structural integrity for at least two weeks following implantation, whereas both the DHAM-only and DHAM-supported limbal stem cell (LSC) transplantation groups showed complete degradation and membrane displacement within a week. H&E staining verified the depletion of the central corneal epithelium and the deformation of the limbal epithelium at two weeks post-exposure (Fig. 7C). A more stable environment for cellular adhesion and differentiation during healing was made possible by the composite membrane's enhanced mechanical qualities and longevity. The study's findings of decreased corneal opacity and neovascularization, as well as improved epithelial development, were probably influenced by this stability. Furthermore, the PCL-DHAM composite membrane promoted polymorphonuclear leukocyte death, which further decreased local inflammation [47]. In order to address LSC deficiency, which can result in severe ocular surface damage, visual loss, and other issues, Liu et al., [48] investigated the constraints of utilizing HAM for LSC transplantation. Despite its effectiveness, the classic AM has poor mechanical strength and significant preservation costs. In order to get over these problems, scientists created a composite membrane by using interfacial conjugation to join electrospun bioabsorbable polymer fiber mesh to a DHAM sheet. The resultant nanofiber-DHAM composite membrane retained the bioactivity required for LSC attachment, growth, and maintenance while demonstrating noticeably increased tensile strength and toughness. Additionally, it preserved DHAM's anti-inflammatory qualities. Compared to conventional AM, this increased mechanical strength makes handling and suturing simpler, which makes it more appropriate for clinical settings. To sum up, the new electrospun fiber-DHAM composite membrane combines the advantages of electrospun fiber mesh and DHAM, providing superior suture retention, mechanical characteristics, and bioactivity. Compared to fresh and lyophilized DHAM, its lyophilization and rehydration qualities make it simple to store and transport, significantly lowering expenses. By addressing soft tissue injury and LSC deficit, this composite membrane offers a viable treatment option that might increase clinical application potential and enhance patient outcomes. Comparative studies conducted by Naasani et al., [105] further highlighted the superior biological performance of HAM compared to xenogeneic SIS matrices. Both scaffolds supported limbal mesenchymal stem cell (LMSC) viability, adhesion, and cytoskeletal organization; however, the transparent nature and biocompatible ECM of HAM enabled improved visualization and preservation of cellular morphology and phenotype. Conversely, cells cultured on SIS exhibited a modest upregulation of negative mesenchymal markers ($CD34^-$, $CD45^-$, $CD14^-$) following prolonged culture, indicating a slight phenotypic shift. Taken together with its inherent anti-inflammatory and low-immunogenic characteristics, these findings suggest that perinatal HAM provides a more favorable and stable microenvironment for stem cell maintenance and regenerative applications than porcine-derived SIS.

Sekiyama et al., [49] used a bio adhesive-coated, freeze-dried HAM (FCFD-HAM) to assess the safety and effectiveness of a new suture-less technique for reconstructing the ocular surface. The FCFD-HAM is produced by sterilizing the chorionic side of freeze-dried, denuded HAM with γ-radiation and attaching a small amount of fibrin glue. Electron microscopy and immunohistochemical analyses verified that the fibrin glue had no effect on the HAM's morphological or biological characteristics. When the HAM was transplanted into rabbit scleral surfaces without sutures, it adhered right away and remained there for at least 12 weeks. Within two weeks, the FCFD-HAM encouraged epithelialization. According to the study, the FCFD-HAM's fibrin glue, which is made up of thrombin and fibrinogen, maintained its adhesive properties for at least six months at room temperature, guaranteeing its usefulness. The HAM offered durability and long-term coverage, but the adhesive biodegraded in two weeks. The results of the study indicated that FCFD-HAM may be a useful instrument for reconstructing the ocular surface.

However, a critical comparative analysis shows that simple blending or coating may not suffice for applications demanding significant mechanical integrity and sustained physical support, such as treating LSCD or large corneal defects. This identifies a key translational gap: the need for a construct that does not merely borrow bioactivity from HAM but structurally reinforces the HAM itself to create a durable, yet fully bioactive, graft. The work on creating composite membranes via interfacial conjugation of electrospun PCL nanofibers to dehydrated HAM directly addresses this gap [52,53]. These composites produce a synergistic result that neither component could produce on its own. This is in stark contrast to techniques like hydrogel inclusion or chemical crosslinking, which frequently sacrifice biological activity in order to achieve mechanics. A parallel breakthrough aimed at clinical applicability is the creation of freeze-dried HAM with bioadhesive (FCFD-HAM). By providing instant adhesion and encouraging quick epithelialization, it resolves handling and surgical application issues and bridges the gap between a bioactive material and an approachable surgical implant. Additive biofunctionalization (coatings/blends), structural biohybridization (interfacial composites), and surgical optimisation are the next steps in the development of ocular HAM-based engineering. This progression represents a holistic design philosophy: the ideal build must be a biologically pure, mechanically capable, and medically friendly carrier that takes use of HAM's natural regenerative signals while offering the handling and durability needed for clinical success.

3.6. Others

In order to build a scaffold for cardiac tissue engineering, Nazari et al., [50] synthesized molybdenum disulfide (MoS_2) nanosheets and integrated them into PCL that was electrospun onto the surface of DHAM. The goal of this hybrid scaffold was to increase the mechanical properties and electrical conductivity of DHAM in order to make it more suitable for cardiac tissue regeneration. In contrast to DHAM and DHAM/PCL scaffolds, the MTT assay, which confirmed the scaffolds' biocompatibility, showed that DHAM/PCL-MoS2 scaffolds enhanced cell adhesion and aggregation. Cells grown on DHAM/PCL-MoS_2 scaffolds produced more cardiac genes, including as GATA-4, c-TnT, NKX 2.5, and alpha-myosin heavy chain, according to studies employing real-time PCR and immunostaining. To improve cell adhesion, plasma treatment was used to modify the DHAM/PCL-MoS_2 scaffold, which showed higher hydrophobicity. The scaffolds' mechanical properties were suitable, which are essential for cardiac elasticity and blood flow. PCL and PCL/MoS_2 were electrospun onto the DHAM surface, increasing the ultimate strength from 1.87 ± 0.16 MPa to 3.14 ± 0.11 and 4.33 ± 0.23 MPa. The fracture point of DHAM also rose from 4.87% to 9.39% and 6.46%. The results also shown that when PCL-MoS_2 nanofibers were applied to DHAM, the Young's modulus increased from 45.95 to 49.87. The increase in mechanical properties of the scaffolds was therefore attributed to the addition of PCL and PCL-MoS_2 nanofibers to the bare DHAM, as established by statistical comparison.

Pelvic organ prolapse (POP) has a significant influence on women's quality of life, necessitating effective treatment options. To explore their potential for treating POP, a study developed electrospun composite scaffolds using DHAM in combination with PCL and PLGA. The physicochemical properties of the scaffolds were assessed; they showed suitable hydrophilicity, a suitable degradation time, and suitable mechanical properties for pelvic floor restoration. Human umbilical cord mesenchymal stem cells were used in cell compatibility testing, which showed biocompatibility and non-cytotoxicity. This study showed that combining PCL and PLGA with DHAM through electrospinning provides the necessary physical, chemical and biological properties for pelvic floor repair. The scaffolds demonstrated good stability after 6 weeks of in vitro degradation, supporting tissue regeneration while preventing long-term foreign body reactions associated with nondegradable meshes. They also support the proliferation of MSCs better than synthetic scaffolds alone, and this shows its potential as a new strategy for pelvic floor tissue repair [51].

According to Table 3, in vitro degradability, scaffold stability, and improved MSC proliferation, can likely be attributed to the COL/GAG ratio in DHAM. The optimal COL/GAG ratio in DHAM-based scaffolds enhances tissue regeneration by promoting cellular adhesion and ECM production, supporting the regeneration process and preventing inflammation, as seen in other tissue engineering applications.

Anastomosis, a critical surgical technique for conditions like obstruction and tumors, often faces complications such as leakage and adhesion. To enhance healing and reduce postoperative risks, A study investigated a hybrid scaffold comprising HAM and polycaprolactone-molybdenum disulfide nanosheets (PCL-MoS_2) was developed for colon anastomosis. PCL provided mechanical support, and MoS2 facilitated electrical conductivity, crucial for maintaining gastrointestinal motility post-surgery. In a rat model study, the scaffold significantly improved histopathologic scores and burst pressure at the anastomosis site. Notably, no mortality or anastomosis leakage occurred in the scaffold-treated group. Additionally, inflammatory markers expression was reduced, and anti-inflammatory cytokines expression increased, indicating decreased inflammation and accelerated healing. The presence of HAM in the scaffold composition led to reepithelization, vascularization, and COL deposition, enhancing tissue integrity [52].

Excessive inflammatory reactions during recovery frequently worsen tendon adhesion, a typical problem after tendon surgery. A study investigated the utilization of an electrostatically spun HAM and a PCL membrane loaded with celecoxib, a selective COX-2 inhibitor. The membrane's improved anti-adhesion qualities were validated in vivo on a rabbit tendon repair model without sacrificing tendon tensile strength. By suppressing COL synthesis (COL I and COL III) and downregulating pro-inflammatory factors (COX-2, IL-1β, TNF-α), the PCL/HAM decreased peritendinous inflammation and created a favorable microenvironment for tendon healing. It is essential to include the HAM since it provides growth hormones that promote endogenous tendon healing. In order to balance anti-inflammatory effects and promote tissue regeneration, the PCL/HAM composite membrane showed continuous drug release over a three-week period, coinciding with the crucial time of tendon healing [53].

A study examined the possibility of using DHAM as an implantable biological scaffold to repair uterine tissue. In vitro cytocompatibility was evaluated with primary smooth muscle cells grown on DHAM showing high cell growth and differentiation. For in vivo evaluation, DHAM/PU composite mesh and polypropylene (PP) mesh (control) were implanted in rabbit uterus. After two months, it was concluded in the study that DHAM/PU mesh demonstrated outstanding biocompatibility with good integration with surrounding tissues and no symptoms of inflammation. On the other hand, the PP mesh induced adherence to the viscera and prolonged irritation. Histological assessment showed tissue ingrowth into the DHAM/PU mesh which favoured regeneration and organized tissue remodeling, whereas PP mesh resulted in disorganised tissue arrangement and persistent inflammation. At 10 months, the DHAM was totally destroyed and well-organized tissue remained, whereas the PP mesh still showed symptoms of inflammation and poor tissue integration. The study concludes that the biocompatibility and tissue healing efficacy of DHAM/PU composite meshes is better than regular PP meshes [54].

The small intestine (ileum segment) is used in modern bladder reconstruction techniques to restore injured bladder tissue. The significant absorption of urea and metabolic wastes from the urine by the ileum epithelium transplanted into the bladder might result in metabolic disorders or kidney failure over time, even though this approach is successful in restoring bladder function. In addition, this process takes a long time and may make intestinal fistulas more prone to infection. Gholami et al., [55] created scaffolds of PLLA covered with HAM or sheep bladder (SB)-derived ECM proteins, taking into consideration the benefits of nanofibrous scaffolds and dECM in tissue engineering. Following 12 weeks of transplanting PLLA scaffolds coated with HAM/SB-derived ECM and uncoated PLLA, the surface of the PLLA scaffolds coated with HAM/SB-derived ECM proteins showed the development of an epithelial layer, muscular fibers, and neovascularization, whereas the PLLA scaffold alone only showed the formation of a layer of urothelial cells. However, in order to effectively remove cells from bladder-derived tissues, more intricate decellularization techniques are needed than in HAM, which might lead to the elimination of growth factors and bioactive proteins. According to the data, HAM ECMs could be a superior option than SB-ECMs for producing ECMs for bladder repair. This is because HAMs have less preparation restrictions and a shorter processing time for decellularization. Furthermore, in this work, SB-ECMs did not outperform AM ECMs in terms of bio functionalizing the PLLA scaffold's nanofibers.

In order to improve the mechanical qualities of HAM while maintaining its bioactivity, Adamowicz et al., [56] investigated the usage of a biocomposite material combining HAM with electrospun nanofibers for urinary bladder augmentation in a rat model. Following hemicystectomy, the biocomposite—which was composed of frozen Am and poly-(L-lactide-*co*-*E*-caprolactone) (PLCL) nanofibers was utilized to strengthen the bladder in Wistar rats. Effective regeneration of the urothelial and smooth muscle layers was shown by histological and immunohistochemical investigations (H&E, anti-smoothelin, and Masson's trichrome staining); anti-smoothelin staining confirmed the existence of contractile smooth muscle in the rebuilt bladder wall. Normal bladder tension, contraction, elasticity, and compliance were all

sustained by the biocomposite structure. The intact HAM provided by the biocomposite enabled the effective histological remodeling of the increased bladder portion, according to mechanical tests. The mechanical properties of HAM were improved by the PLCL nanofibers, which did not impede the regeneration process. This work demonstrated that the biocomposite material offers a viable approach for reconstructive urology by fusing the mechanical strength of electrospun nanofibers with the healing qualities of HAM.

A study aimed to create a permanent scaffold to support aligned myotube formation and enhance the myogenic differentiation of selected stem cells. Researchers engineered a scaffold by combining DHAM with electrospun PCL fibers, arranged in randomized and aligned patterns. Adipose-derived stem cells (ADSCs) from adult Wistar rats were cultured on these scaffolds and induced to differentiate into myotubes. The aligned PCL fibers on DHAM were particularly effective in promoting cell alignment, growth, and differentiation, leading to high expression of myogenic markers such as myosin and myogenin. This indicates that the PCL-DHAM biocomposite can enhance the formation and alignment of myotubes. The PCL-DHAM biocomposite scaffold designed in this study demonstrated promising potential for muscle repair and myogenic differentiation [57].

Adhesion and scarring after neurological surgery inhibit nerve regeneration and functional recovery. In a study, rats with a sciatic nerve compression were treated with an electrospun PCL-HAM nanofibrous membrane. The membrane's capacity to inhibit adhesion and promote nerve regeneration was examined using electrophysiological and histological examinations. The PCL-HAM significantly reduced the adhesion of peripheral nerve and accelerated nerve conduction recovery as compared with the medical chitosan hydrogel dressings. Immunohistochemical study showed that PCL-HAM group had more Schwann cells and fewer pro-inflammatory M1 macrophages. Western blot and RT-PCR studies indicated that the expression levels of type-I and type-III COL were half as high in PCL treated rats compared to control group, whereas the expression of nerve growth factor (NGF) was around 3.5 times more than in rats treated with CTC. It shows that PCL-HAM can promote nerve regeneration and repair and can effectively reduce adhesion and inflammation and invasion of scar tissue [58].

A new tissue-engineered graft made of poly(1,8-octamethylene-citrate) (POC) combined with DHAM was used in a study by Li et al., [59] to heal cleft palates. For applications in the oral environment, the DHAM-POC scaffold's structural stability and enzyme resistance were essential. MSCs grown on DHAM-POC showed increased alkaline phosphatase activity and great vitality in vitro. Promising findings were obtained from in vivo testing conducted on a juvenile rat model with surgically induced palate abnormalities. Within eight weeks, the DHAM-POC scaffold enabled almost complete healing of both soft and hard tissues, demonstrating its biocompatibility and efficiency in directing tissue regeneration without obstructing spontaneous development. By supporting tissue development, the DHAM-POC scaffolds provide a less intrusive surgical approach, improving the treatment of cleft palate and lowering related problems.

Although electrospun meshes are being created for the repair of defects in the abdominal wall, it is difficult to create a mesh that is appropriate for intraperitoneal application. Using electrospinning, Liu et al., [60] created a functional mesh by mixing PCL, SF, and HAM. The PCL/SF/HAM mesh decreased TGF-β1 expression and COL production under inflammatory circumstances, while promoting cell proliferation and vasculature creation in a rat model with a full-thickness abdominal lesion, according to in vitro and in vivo studies. Compared to PCL and PCL/SF meshes, this mesh exhibited a lesser inflammatory response and less strong adhesion. It demonstrated improved neovascularization and COL and elastin fiber integration after 90 days, attaining physiological stiffness and mechanical strength comparable to genuine tissues.

HAM has been explored as a covering for PP mesh to reduce adhesions and improve histological outcomes in abdominal hernia operations. A study included ten rabbits allocated randomly to two groups: Group II was given a PP mesh with a HAM coating and Group I was given a PP mesh alone. Each rabbit was made an abdominal incision of 5 cm in length. In group I, a PP mesh of 2 × 3 cm was placed adjacent to the viscera under the abdominal wall. In Group II the same method was followed but a 4 × 6 cm layer of HAM was also added to the mesh. The rabbits were killed after three weeks for macroscopic and histological examination. Tissue samples were studied for adhesions and histological changes of the abdominal wall and adjacent viscera. From the data no microscopic difference between the two groups could be identified. However, histological investigation demonstrated greater healing score in the group covered with HAM. At the macroscopic level, the HAM-coated group revealed reduced adhesions and inflammatory signs in comparison to the mesh-only group. Specifically, 3 animals in the non-HAM group had inflammation, while only 1 animal in the HAM group exhibited inflammation. The study states that HAM application as a cover on PP mesh may improve abdominal wound healing and reduce adhesions [61].

4. Biopolymer-Wharton's jelly composite for tissue engineering

4.1. Bone

Bone defects larger than critical size require scaffolds that mimic the natural extracellular microenvironment to support bone formation. Wharton's jelly, rich in mesenchymal stem cells and ECM proteins, has been combined with biopolymers to improve the potential for osteogenesis, mineralization, and structural stability in bone tissue engineering [106]. Combining these scaffolds with biopolymers strengthens bone production by providing an environment that is conducive to mesenchymal stem cell attachment, proliferation, and differentiation to osteoblasts [107]. Ahmadi et al., [62] created a novel technique for covering electrospun PLLA nanofibrous scaffolds with WJ to increase their osteogenic capacity for bone tissue creation. WJ-PLLA scaffolds outperformed tissue culture plates and PLLA scaffolds in terms of MSC proliferation. WJ-PLLA scaffolds showed significantly higher ALP activity and calcium mineralization, which indicates increased osteogenic differentiation potential. MSC derived from WJ showed low immunogenicity and reduce the risk of rejection when implanted in the body [108]. The combination of WJ with biopolymers increases the biocompatibility of the scaffold and ensures compatibility with the host tissue and minimizes adverse reactions [65]. Another group presented the development of polycaprolactone/nanohydroxyapatite (PCL/nHA) hybrid nanofibrous scaffolds for BTE. PCL/nHA composite scaffolds were prepared through electrospinning. Biocompatibility was confirmed by MTT method and WJMSC cultured on scaffolds showed more adhesion and proliferation compared to PCL alone, which indicates their superior osteogenic potential [109]. When these scaffolds are combined with WJ, they create a biomimetic microenvironment that supports cell adhesion, migration and proliferation, which is very similar to native bone tissue architecture [65]. Biopolymers, such as hydrogels or nanofibers, can improve the mechanical strength and stability of scaffolds and provide structural support during tissue regeneration [110]. WJ helps the flexibility and elasticity of the scaffold and ensures optimal transport and compatibility with irregular bone defects [65]. In addition to the mentioned cases, the use of scaffolds containing WJ and biopolymers for animal analyzes has also brought positive results.

Zhang et al., [63] introduced an artificial periosteum composed of GelMA, E7 peptide, and WJ for bone repair (G-*E*-W). The resulting hydrogel membrane promoted bone tissue healing by simulating the biological activity of the normal periosteum. When G-E-W membranes were implanted in rat skull defects, the bone healed better than in the control group at 4 and 8 weeks, demonstrating the membrane's efficacy in repairing fractures. The mechanical characteristics and biocompatibility of the G-E-W membrane were preserved. WJMSC cultivated on electrospun PLA/carbon nanotube (PLA/CNT) scaffolds were examined in a different investigation for their capacity to repair significant bone

lesions in mice calvaria. The scaffold's capacity to improve bone healing was demonstrated by the noticeably greater volumes of newly created bone seen in the cell-containing scaffold group as opposed to the scaffold alone. MSCs flourished in the PLA/CNT scaffold's 3D structure, which resembled the natural bone matrix and promoted bone formation [111].

Chen et al., [112] introduced a novel method of treating critical size bone defects by mixing bioactive hydrogels for BTE with 3D printed bone scaffolds. Curable resins for 3D printing were created by combining hydroxyapatite nanoparticles with the biodegradable polymer poly (ethylene glycol)-copoly (glycerol subcategory) acrylate (PEGSA). This produced scaffolds with good permeability and biomimetic qualities. To improve the effectiveness of cell administration, these scaffolds were refined and mixed with bioactive hydrogels that included WJMSC. Evaluations conducted in vivo verified that 3D printed scaffolds promote osteogenesis.

While all studies report improved osteogenic outcomes, the spatial organization and presentation of the WJ component—whether as a coating, a blended component, or a discrete layer—fundamentally influence the scaffold's degradation kinetics, the release profile of bioactive factors, and its long-term mechanical performance. For instance, a surface coating may offer a rapid, initial burst of signals but could be quickly degraded, whereas WJ integrated into the bulk may provide more sustained cues but potentially at the cost of initial mechanical strength. The progression is from simple additive combinations (WJ + polymer) to functionally and structurally stratified designs. The overarching design principle is no longer mere biocompatibility but the orchestration of a regenerative microenvironment that provides: (a) immediate mechanical sufficiency, (b) topographic cues for cell adhesion, (c) sustained presentation of osteoinductive signals from the WJ ECM, and (d) a supportive niche for delivered or host MSCs. The identified gap moving forward is the precise spatiotemporal control over the WJ's bioactive factor release within these engineered constructs to sequentially guide the complex stages of bone healing—inflammation, osteoprogenitor recruitment, differentiation, and ultimately, remodeling—within a mechanically stable scaffold architecture.

4.2. Cartilage

Articular cartilage regeneration requires scaffolds that closely mimic the microenvironment of natural cartilage. Wharton's Jelly, with its abundance of ECM components and chondrogenic stem cells, could be a promising option in polymer composites to create a biomimetic niche that supports stem cell differentiation. Researchers have created a unique 3D bioprinted cartilage-mimicking alternative for full-thickness articular cartilage lesions. Methacryloyl-modified AWJ(AWJMA) and GelMA were used to generate a hybrid hydrogel that has appropriate physicochemical qualities, bioactivity, and outstanding biocompatibility. WJ, which is made from human tissue, is perfect for this use since it is hypoimmunogenic and high in chondrogenic components. For 3D bioprinting, the AWJMA/GelMA hydrogel showed the right mechanical strength, swelling ratios, and degradation rates. In a rabbit investigation, cartilage abnormalities were repaired using scaffolds loaded with BMSC. The findings, which demonstrated improved BMSC survival, proliferation, and chondrogenic differentiation, were encouraging. In six weeks, the BMSC-loaded constructions developed into mature hyaline cartilage. This success is attributed to the scaffold's ability to enrich local stem cells, facilitate nutrient transport, and provide a conducive microenvironment for stem cell differentiation and cartilage regeneration [64]. For cartilage tissue engineering, Lin et al., [65] investigated the possibilities of a scaffold made of electrospun nanofibers from a decellularized WJ matrix (DWJ) reinforced with PCL. The umbilical cord is used to make WJ, which is structurally and compositionally similar to cartilage and hence an ideal scaffolding material. The DWJ/PCL scaffold that was created showed excellent mechanical properties, appropriate biodegradation rates, and high hydrophilicity. It also demonstrated enhanced cell adhesion, decreased immunological reactivity, and superior biocompatibility when compared to pure DWJ or PCL scaffolds. Adipose-derived stem cells (ASCs), which are well-known for their simplicity in separation and capacity to develop into chondrogenic cells, were used to assess the scaffold. The findings demonstrated that ASCs stuck to the DWJ/PCL scaffold more readily, most likely as a result of the DWJ components' ability to anchor. The DWJ/PCL scaffold's biocompatibility and minimal cytotoxicity were demonstrated by the successful survival, attachment, and proliferation of ASCs, as demonstrated by live and dead staining and cell proliferation tests. ASC chondrogenesis was stimulated by the DWJ/PCL scaffold throughout the course of a 4-week in vitro culture period.

In a different work, PCL and DWJ nanofibrous scaffolds were created using electrospinning for articular cartilage tissue engineering. Tensile strength (7.68 ± 2.35 MPa), water contact angle (46.85° ± 3.09°), porosity (>80%), and fiber diameter (283.90 ± 49.07 nm) were all adequate for the ideal scaffold with 2% DWJ. To enhance the scaffold's mechanical qualities, 0.5% carboxyl-functionalized multi-walled carbon nanotubes (MWCNTs) were added. This led to improved wettability (water contact angle of 38.96° ± 3.49°), a greater tensile strength (16.43 ± 2.51 MPa), and a reduced fiber diameter (193.134 ± 36.69 nm). The addition of MWCNTs enhanced the scaffold's bioactivity, thermal stability, and cell survival while maintaining the appropriate cell shape. Because of the physicochemical interactions between the carboxyl groups of MWCNTs and the functional groups in DWJ, the scaffolds demonstrated increased mechanical strength. By improving the solution's electrical conductivity, MWCNTs also enhanced the electrospinning process, resulting in superior mechanical qualities and lower fiber diameters. The PCL-DWJ-MWCNTs scaffold facilitated cell attachment, growth, and proliferation, simulating the extracellular matrix of cartilage. Following 24 h and 7 days of cell seeding on the scaffolds, Fig. 8A displays SEM images pertaining to the chondrocyte morphology. A tissue engineering scaffold's ability to proliferate and be cytocompatibility are critical components. After 1 day, the cells are firmly affixed to the scaffolds as they attempt to disperse across the surface with the help of their pseudopods. They multiplied on both scaffolds after 7 days, and secreted ECM was observed surrounding them. A suitable level of cytocompatibility for both scaffolds was indicated by the gradual rise in cell stretch and ECM deposition on both scaffolds. Additionally, both scaffolds' cells may be seen to be circular and somewhat stretched next to their pseudopods. By combining DWJ with substances that resemble cartilage ECM, the scaffold can produce a desired biomimicry of genuine tissue, preserving cell shape in its healthy state and promoting proper cell attachment. The composite scaffold's adequate porosity and fiber diameter encouraged chondrocytes to take on a spherical shape, which is essential for their development and multiplication [66].

4.3. Others

Human WJ Hydrogel (WJH) was studied by Zand et al., [67] as a framework for the in vitro cultivation and auto-transplantation of mice ovarian follicles. DWJ combined with Alg to create a composite hydrogel (WJH + Alg) after being removed from the umbilical cord. This material demonstrated optimal rheological properties and biocompatibility. Mouse preantral follicles were encapsulated in WJH + Alg hydrogel and either transplanted into mice or cultured for 14 days. In contrast to Alg alone, which was unable to sustain follicle life, the results demonstrated that the WJH + Alg hydrogel considerably aided antral follicle production. Furthermore, the WJH + Alg hydrogel enhanced vascularization and follicle growth by promoting the production of angiogenic factors VEGF and CD34. They demonstrated how WJH and Alg together offer a favorable milieu for the growth of ovarian follicles both in vitro and in vivo.

A study incorporated DWJ extract into fibrin and COL hydrogels and used pro anthocyanidins (PA), extracted from grape seeds, as a crosslinker to improve hydrogel's suitability for tissue engineering

applications. The findings showed that PA considerably improved the hydrogels' stability and mechanical characteristics. Hydrogels containing DWJ extract and PA showed superior cell proliferation and mechanical strength compared to those without these modifications. Human endometrial stem cells seeded on these hydrogels exhibited good attachment, morphology, and proliferation, as observed through SEM and optical microscopy. The study concludes that modifying hydrogel compositions with agents like PA can effectively improve their biocompatibility and mechanical properties, making them more suitable for tissue engineering applications [68].

A novel composite scaffold for tissue engineering tympanic membrane perforations (TMPs) was developed in another study employing DWJ extracellular matrix (DWJ/ECM), PVA, and Alg sulfate (Alg—S). Initially, a variety of electrospun PVA/ALG-S scaffold mix ratios were developed to assess their mechanical, biological, and surface morphological properties. Afterwards, this nanofiber scaffold was combined with DWJ/ECM to form a three-layer composite. When 25 mg/cm^2 DWJ/ECM was added, the composite's mechanical properties, rate of degradation, swelling behavior, and biological activities were all significantly enhanced. Although the MTT findings demonstrated a considerable improvement in cell viability over the course of 7 days, PVA/ALG-S 50 nanofibers exhibited higher levels of cell proliferation and viability than other groups. According to the findings, ALG-S in the electrospun nanofibers can be regarded as a component that considerably improves cell survival and responsiveness (Fig. 8 B1). A rat model of TMP was used in vivo investigations to show that the composite scaffold not only promoted TMP healing but also sped up the healing process. The composite group outperformed the control group, achieving a 70% regeneration rate in 5 days and full healing in 7 days. The efficiency of the scaffold was shown by auditory brainstem response

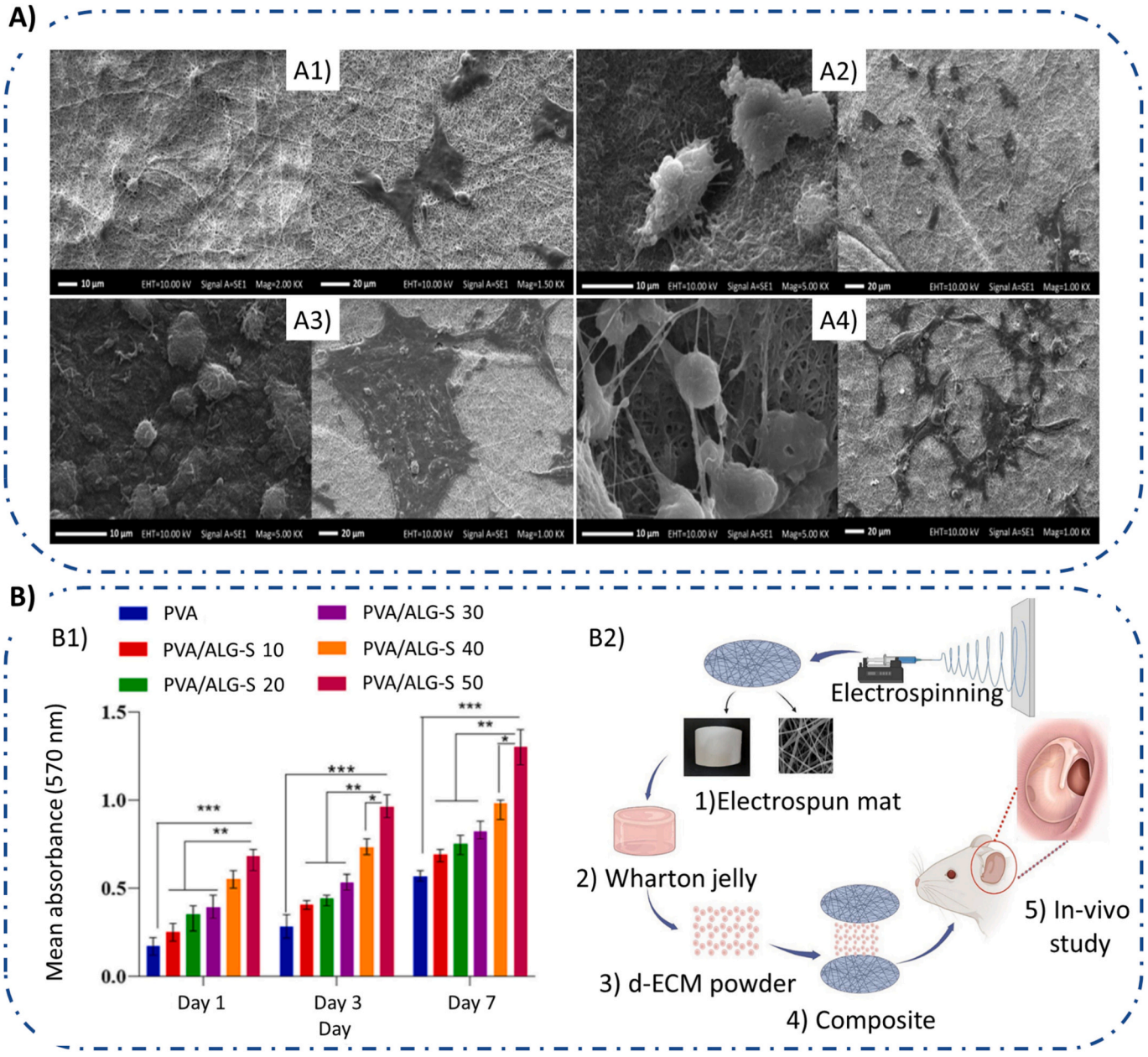

Fig. 8. Morphology, cell proliferation, and fabrication schematic. A) SEM images of chondrocytes on PCL-DWJ and PCL-DWJ/MWCNTs scaffolds at 24 h and 7 days. Reprinted with permission from [66]. Characterization of electrospun PVA/ALG-S scaffolds: B) (B1) MTT assay shows significantly higher proliferation and viability on PVA/ALG-S 50 nanofibers over 7 days, highlighting the role of ALG-S in enhancing cell responses (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). (B2) Schematic of tympanic membrane regeneration using multilayer sulfated Alg nanofiber/WJ ECM composites. Reprinted with permission from [69].

thresholds, which showed that the composite-treated TMPs had almost normal hearing function. In summary, the PVA/ALG-S and DWJ/ECM composite scaffold demonstrated enhanced cell survival, mechanical strength, and TMP healing speed, indicating that it is a viable substitute for traditional surgical TMP therapies (Fig. 8 B2) [69].

5. Biopolymer-perinatal-derived cells for tissue engineering

Perinatal tissues (e.g., placenta, umbilical cord, and HAM) are increasingly recognized as rich sources of stem cells and ECM components that possess remarkable immunomodulatory and regenerative properties. These tissues are particularly valuable in regenerative medicine and tissue engineering due to their unique biological characteristics, such as being angiogenic, anti-inflammatory, and immune privileged [113]. The therapeutic potential of these perinatal-derived cells is significantly enhanced when they are combined with advanced biomaterials that mimic the ECM, providing structural support essential for tissue repair and regeneration [114]. Table 4 lists the combinations of perinatal-derived cells and biopolymer reported in the literature.

6. Clinical applications of scaffolds in medicine

Recent advances in the use of perinatal-derived biomaterials have led to significant breakthroughs in clinical applications, particularly in skin regeneration and wound healing. However, despite these successes, challenges remain in translating these innovations into widespread clinical use, particularly in more complex tissues such as bone and cartilage. This section will analyze the current clinical applications, discussing both successful cases and limitations in the field.

In recent years, several products based on placental components have been developed for therapeutic purposes and have been explored and researched in a variety of fields. Over 10,000 research studies and clinical trials have been conducted on umbilical cord blood cells, with significant applications in treating hematological malignancies and traumatic brain injuries. As of 2017, there were over 351 clinical trials involving cord blood cells, highlighting their application in treating hematological malignancies and traumatic brain injuries. After pre-transplant conditioning, 120 million human placental mesenchymal stem cells (hpMSC) were injected intravenously into a 20-year-old male patient with acute myeloid leukemia in second remission. Two cord blood units were used for hematopoietic stem cell transplantation after the hpMSC were infused without any negative side effects. The receiver and the cord units did not match the MSC, and the infusion itself did not cause any problems. However, a number of treatments were used to manage the patient's post-transplant problems, which included viral reactivation, bacterial infections, and graft-versus-host disease (GVHD). Despite these interventions, he developed respiratory distress and died of interstitial pneumonitis on day 68 post-transplant. The clinicians did not attribute his death to the MSC infusion. The trial marked the first known human use of placental MSC, demonstrating the need for more efficient, large-scale closed systems for future trials [144]. The COVID-19 pandemic, with its high morbidity and mortality rates, particularly from acute respiratory distress syndrome (ARDS), has spurred global health efforts to find effective treatments. Because of their regenerative, anti-inflammatory, and immunomodulatory qualities, MSC have become attractive options. The safety of intravenous allogeneic placenta-derived MSCs (PL-MSCs) in the treatment of COVID-19-induced acute respiratory distress syndrome (ARDS) was the focus of another investigation. Twenty critically ill patients with COVID-19-induced ARDS were included in the study. The treatment group (10 patients) received a single intravenous dose of PL-MSCs in addition to standard care, while the control group (10 patients) received only standard treatment. PL-MSCs were prepared using a GMP-compliant, xeno-free protocol. Laboratory results and clinical complaints were tracked both at baseline and during a 28-day follow-up. There were no documented side effects in the PL-MSC group. The length of hospital stays, oxygen saturation levels, and other clinical and laboratory indicators did not significantly differ between the treatment and control groups. PL-MSCs are safe and practical for intravenous usage in patients with COVID-19-related ARDS, according to the study's findings. To investigate any therapeutic advantages, more studies using larger cell dosages and repeated injections are advised [145]. When WJMSCs were planted on an acellular HAM scaffold, Hashemi et al., [146] examined the healing benefits on patients with chronic diabetic ulcers. This randomized clinical trial included five participants between the ages of 30 and 60. WJMSC-seeded HAMs were applied to the wounds every three days for nine days, followed by a follow-up one month later. Records were kept on the wound's size, healing duration, and healing %. It is well recognized that stem cells, including WJMSCs, may develop into important cell types that aid in wound healing, including fibroblasts, endothelial cells, and keratinocytes, which hasten the healing process. A randomized, double-blind, crossover, placebo-controlled trial with 10 patients (7 men and 3 women, aged 25–47) with chronic complete spinal cord injury (SCI) at the thoracic level was examined by Albu et al., [147]. After 6 months, patients switched to the alternative treatment after receiving a single intrathecal dosage of WJMSCs. Clinical assessments included motor and sensory function, pain, spasticity, and bladder and bowel function. Urodynamic studies and quality-of-life measures were also recorded. The results demonstrated that WJMSC infusion was safe, with no significant adverse effects. Improvements were noted in pinprick sensation below the injury level compared to placebo, and some patients showed individual improvements in bladder capacity, compliance, and reduced neurogenic hyperactivity. Studies on WJMSCs for diabetic ulcers and spinal cord injury report safety and hints of efficacy in sensory or bladder function. Conversely, trials of PL-MSCs for systemic conditions like AML or COVID-19-associated ARDS, while confirming safety, failed to demonstrate clear therapeutic superiority over controls in primary endpoints. This apparent contradiction is not effectively analyzed in the current literature. It likely stems from critical variables that lack comparative standardization: cell source (WJ vs. placenta), dosage, route of administration (local vs. systemic), target pathophysiology (localized tissue repair vs. systemic immunomodulation), and trial endpoints.

The use of HAMs in clinical settings has also seen significant growth, with 114 trials focused on various ocular and dermatological conditions. For example, Zelen et al., [148] conducted a clinical study on 65 participants in 2014, utilizing two commercial placenta-based treatments, EpiFix® and Apligraf®. In this study, they compared the efficacy of these two products in diabetic wound care using COL-Alg dressings. The results revealed that using the EpiFix® product in diabetic wound healing at 4–6 weeks is preferable to using Apligraf® and COL-Alg dressings. Furthermore, the cost and quantity of EpiFix® were lower than those in the other groups.

Another clinical research by Bianchi et al., [149] used the EpiFix® product for 16 weeks to treat and mend 109 individuals with full-thickness, non-healing venous leg ulcers. When compared to particular wound care, the method produced improved wound treatment outcomes for the patients. After 12 weeks, the EpiFix® product showed a 60% improvement, whereas special wound care showed a 35% improvement throughout the same time frame. Its remarkable efficacy was demonstrated by the 16-week healing rates of 71% and 44% for EpiFix® and special wound care, respectively.

The necessity for treatments that speed up wound closure is increased since diabetes patients' lower limb amputations are significantly influenced by the delayed healing of foot ulcers. The study, which is filed under ClinicalTrials.gov Identifier NCT02209051, compared DAMA (dehydrated HAM allograft) (AMNIOEXCEL, Derma Sciences Inc.) in combination with standard of care (SOC) with SOC alone in the treatment of chronic diabetic foot ulcers (DFUs). Until the incision was fully healed or up to six weeks of therapy had elapsed, individuals were randomly assigned to receive either SOC alone (14 participants) or DAMA plus SOC (15 participants). The main goal was to determine the

Table 4
Combination of perinatal-derived cells and polymers in regenerative medicine application.

Cell type	Source	Combined polymer	Application	Ref.
MSCs, Epithelial cells	HAM	Polyvinylidene difluoride	Tissue engineering	[115]
MSCs	HAM	PLLA + PEG	Urethral Epithelium Repair	[116]
MSCs	HAM	PLCL	Vascularization	[117]
MSCs	HAM Epithelial	Gel	Spinal Cord Injury	[118]
MSCs	HAM	CTS + Xantan	Cartilage	[119]
MSCs	HAM	SF- hpECM	Bone	[26]
Epithelial stem cell	HAM	GelMA	Corneal	[120]
MSCs	Umbilical Cord	PCL + Fibronectin	Cardiac Function	[121]
MSCs	Umbilical Cord	PCL + Alg	Mastoid Obliteration	[122]
MSCs	Umbilical Cord	Fibrin	Muscle Tissue	[123]
MSCs	Umbilical Cord	COL	Endometrial Regeneration	[124]
MSCs	Umbilical Cord	PCL + COL	Cardiac Regeneration	[125]
MSCs	Umbilical Cord	Gel	Endometrial Repair, Fertility Recovery	[126]
MSCs	Umbilical Cord	COL	Ovarian Function	[127]
MSCs	Umbilical Cord	COL	Tracheal	[128]
MSCs	Umbilical Cord	COL	Endometrial Repair, Fertility Recovery	[129]
MSCs	Umbilical cord- HAM- Chorion	PCL diacrylate- polydopamine	Bone	[130]
MSCs	WJ	Gel	Cardiomyocytes	[131]
MSCs	WJ	P(LLA-CL) + COL	Tracheal cartilage	[132]
MSCs	WJ	PCL + COL	Skin	[133]
MSCs	WJ	Alg	Cartilage	[134]
MSCs	WJ	SF	Skin	[135]
MSCs	WJ	PCL	Bone	[109]
MSCs	WJ	PLA	Bone	[111]
MSCs	WJ	Gel	Bone	[63]
MSCs	WJ	Alg	Osteoarthritis	[136]
MSCs	WJ	PEGSA	Bone	[112]
MSCs	WJ	PCL	Bone	[27]
MSCs	AM- chorionic plate- WJ	COL + Elastin	Skin	[137]
MSCs + Endothelial cells	WJ + Human umbilical vein	SF	Skin	[72]
MSCs	Placenta	Gel	Skin	[138]
MSCs	Placenta	COL	Bone	[139]
MSCs	Placenta	PLA- PLGA	Bone	[140]
MSCs	Placenta	PLA	Bone	[141]
MSCs	Placenta	PLGA- Alg	Cartilage	[93]
MSCs	Placenta	Chondroitin sulfate- COL	Cartilage	[94]
MSCs	Placenta	SA + Gel + decellularized porcine corneal extracellular matrix	Corneal	[142]
MSCs	Placenta	Polyethylene butylene adipate diol- PCL	Cartilage	[143]
Endothelial cells	Human umbilical vein	hpECM- PLGA	Vascularization	[96]
Endothelial cells	Human umbilical vein	PCL + hpECM	Cardiac Regeneration	[75]
Endothelial cells	Human umbilical vein	hpECM- Expanded polytetrafluorethylene	Vascularization	[29]
Endothelial cells	Human umbilical vein	CTS + DEX + PCL + PVA	Corneal	[104]
Endothelial cells	Human umbilical vein	Alg + PAA	Vascularization	[103]

Abbreviation: **MSCs** - Mesenchymal stem cells, **HAM** - Human amniotic membrane, **COL** - Collagen, **PLLA** – Poly-l-lactic acid, **PEG** - Polyethylene glycol, **PLCL** - Poly-(L-lactide-co-ε-caprolactone), **Gel** - Gelatin, **CTS** - Chitosan, PAA - Polyacrylic Acid, DEX - Dextran, **SF** - Silk fibroin, **hpECM** - Human placental extracellular matrix, **PHBV** - Polyhydroxybutyrate valerate, **PCL** - Polycaprolactone, **Alg** - Alginate, **WJ** - Wharton's jelly, **PLA** - Polylactic acid, **PEGSA** - Polyethylene glycol-co-glycerol sub-category acrylate, **PU** - Polyurethane, **PLGA** - Polylactic-*co*-glycolic acid, **SA** - Sodium alginate, **PVA** - Polyvinyl alcohol, **GelMA** - Gelatin methacryloyl.

percentage of individuals who completely re-epithelialized their wounds without the need for drainage or dressings, a process known as full wound closure. In contrast to 0% in the SOC-only group, 35% of patients treated with DAMA+SOC had complete closure by week 6 ($P = 0.017$). Subsequent analysis revealed that none of the SOC-only patients achieved complete closure, but 45.5% of the DAMA+SOC group did ($P = 0.0083$) [150]. Human clinical studies on placental membrane have provided valuable insights into its diverse applications across various medical specialties.

Despite promising preclinical data, there is a stark absence of robust clinical evidence supporting the efficacy of perinatal biomaterials in regenerating load-bearing skeletal tissues (bone and articular cartilage) in humans. This represents one of the most significant translational gaps in the field. Beyond wound care, there is a scarcity of large, multicenter randomized controlled trials comparing next-generation biomaterial scaffolds (e.g., ECM-polymer hybrids) against current surgical standards (e.g., autografts, synthetic implants) for orthopedic or cardiovascular applications. Long-term data on safety, functional integration, and graft durability are also lacking. The clinical translation of perinatal biomaterials presents a bifurcated reality: decellularized structural allografts (like DHAM) have achieved validated success in wound healing, serving as a model for successful product development. In contrast, cell-based therapies and applications for complex tissue regeneration remain in earlier translational phases, constrained by challenges in standardization, manufacturing, and the generation of conclusive comparative efficacy data. The current clinical evidence base is overwhelmingly dominated by studies utilizing relatively unprocessed or minimally manipulated perinatal tissues. There is a conspicuous scarcity of human clinical trials evaluating the safety and efficacy of engineered, composite scaffolds. This gap indicates that the most innovative design strategies from the laboratory have yet to transition meaningfully into clinical testing. Furthermore, the existing clinical literature on perinatal biomaterials often suffers from qualitative limitations that hinder robust conclusions. Many reports consist of small-scale case series or pilot studies lacking rigorous control groups, standardized protocols, or long-term follow-up. There is a distinct lack of head-to-head comparative clinical trials pitting next-generation composite scaffolds against the current clinical gold standards. Consequently, while biological safety is frequently demonstrated, conclusive evidence of superior therapeutic efficacy and functional improvement for complex tissue regeneration remains largely anecdotal or insufficiently powered.

6.1. Limitations in clinical translation and regulatory considerations

A primary translational barrier is the intrinsic batch-to-batch heterogeneity of biological source materials. Unlike synthetic polymers, the biochemical composition (e.g., COL/GAG ratios, growth factor concentrations) of amniotic membrane, Wharton's jelly, or placental ECM varies significantly with donor age, health, and obstetric history. This variability directly contradicts the pharmaceutical imperative for product consistency and predictability. Compounding this, essential sterilization processes (e.g., gamma irradiation, ethylene oxide) necessary to ensure safety can unpredictably alter the very bioactive and structural properties (e.g., growth factor integrity, COL cross-linking) that define the material's therapeutic value. Current Good Manufacturing Practice (GMP) guidelines provide a framework for process control but do not solve the fundamental biological inconsistency of the starting material.

Many advanced scaffold designs reported in the literature—such as co-electrospun bilayers or 3D-bioprinted ECM-hydrogel composites—are fabricated using bespoke, small-scale laboratory techniques. Scaling these processes to produce consistent, GMP-compliant lots large enough for multi-center clinical trials presents a formidable engineering challenge. Key gaps include the development of in-line quality control metrics for complex structural features and the establishment of validated, non-destructive methods to confirm the retention and distribution of bioactive factors in the final product. Without solving these scale-up challenges, promising technologies risk remaining confined to academic publications.

7. Challenges and future perspectives

Recent advancements in the field of biomaterials have led to significant progress in integrating both synthetic and naturally derived perinatal materials. Perinatal-derived biomaterials, including amniotic membrane, umbilical cord tissue, and placenta, offer unique regenerative potential due to their biocompatibility, biodegradability, and ability to promote cellular growth and differentiation. These features have made them promising candidates for a wide range of regenerative medicine applications, particularly in skin regeneration, bone repair, cartilage regeneration, and vascularization. Although the collective body of research on perinatal–polymer hybrid biomaterials demonstrate encouraging progress, several limitations must be acknowledged when interpreting the reported outcomes. Many studies showing enhanced angiogenesis, osteogenesis, or wound closure rely on small sample sizes, short-term follow-ups (typically $\leq$4 weeks), and rodent models, which may not accurately predict long-term performance or human physiological responses. In most cases, mechanical testing under dynamic or physiological loading conditions is limited or absent, leaving uncertainties regarding scaffold durability and compliance in vivo—particularly for vascular and musculoskeletal applications. Likewise, few investigations include large-animal models or comparative controls against clinically used grafts such as SIS or dermal matrices, making it difficult to benchmark performance objectively.

Furthermore, heterogeneity among perinatal tissues, donor variability, and differences in decellularization or solubilization protocols can lead to inconsistent biochemical composition and mechanical behavior across studies. While extensive knowledge exists regarding the target tissue, it is essential to thoroughly characterize perinatal-derived biomaterials to fully harness their multipotential properties and optimize their application in tissue engineering. Addressing these limitations will require systematic, standardized investigations that combine quantitative biomechanical assessment with longitudinal in vivo studies. Future work should include (i) comparative evaluation of hybrid scaffolds against established clinical matrices, (ii) testing under relevant mechanical loading and perfusion conditions, and (iii) expanded preclinical trials in large animals with extended observation periods. Establishing harmonized protocols for decellularization, sterilization, and biochemical characterization will be essential to minimize variability and facilitate regulatory approval. Ultimately, integrating robust mechanical design with rigorous biological validation will be key to translating perinatal-derived hybrid biomaterials from proof-of-concept to reliable clinical therapies.

7.1. Skin tissue engineering

While significant advances have been made in skin tissue engineering using composite biomaterials, challenges remain in optimizing biomechanical properties and ensuring adequate vascularization for full-thickness skin regeneration. For instance, the incorporation of perinatal-derived ECMs, such as from the placenta and amniotic membrane, has demonstrated significant promise in promoting angiogenesis and wound healing. However, the main challenges lie in the variability of tissue response due to the heterogeneous nature of these materials, and difficulties in achieving consistent skin regeneration outcomes in chronic wounds. Future research should focus on optimizing the mechanical properties of skin scaffolds to enhance the strength and elasticity needed for functional skin regeneration. Additionally, incorporating growth factors and exploring bioactive surface coatings could promote faster wound closure and reduce scar formation. Understanding the interaction between different bioactive components in scaffolds will also be essential in optimizing long-term outcomes in skin regeneration.

7.2. Bone tissue engineering

Bone regeneration is particularly challenging due to the need for scaffolds that not only provide mechanical strength but also promote osteogenesis and vascularization. COL-based scaffolds enriched with GAGs enhance osteogenic differentiation by binding key growth factors such as BMP-4, VEGF, and FGF2. These GAGs, when incorporated into scaffolds, provide controlled release of bioactive molecules, fostering angiogenesis and osteogenesis, which are crucial for successful bone healing. Perinatal-derived biomaterials, such as hpECM, as a source of COL/GAG material, hold great promise due to their osteoinductive properties, but their limited mechanical strength under physiological conditions remains a barrier. Future directions should focus on improving scaffold materials through better material design, such as the incorporation of mineralized ECM components, or the use of 3D bioprinting technologies to customize scaffold architecture. Moreover, enhancing angiogenesis through the controlled release of growth factors could facilitate bone regeneration in larger defects.

7.3. Cartilage tissue engineering

Cartilage regeneration, particularly articular cartilage, remains a difficult challenge due to the tissue's avascular nature and limited intrinsic healing capacity. Despite the promising results with scaffolds incorporating placental-derived ECM and WJ, achieving long-term integration and hyaline cartilage formation remains a challenge. The mechanical properties of scaffolds for cartilage tissue engineering need to better mimic the stiffness and resilience of natural cartilage to ensure effective functional recovery. Additionally, optimizing the chondrogenic potential of stem cells and ensuring that the scaffold allows for adequate nutrient exchange and vascularization remain key areas for improvement. Future research should investigate more robust 3D-printed or electrospun scaffolds that enhance chondrogenesis and prevent hypertrophic differentiation of stem cells. Moreover, strategies to enhance matrix production, through the use of bioactive signals or co-culture systems, could improve outcomes in cartilage regeneration.

7.4. Vascularization and vascular graft engineering

Achieving effective vascularization in engineered tissues is a critical

issue across various tissue types, particularly for large tissue constructs that require a robust blood supply. While scaffolds incorporating placental-derived ECM, such as human chorion membrane or amniotic membrane, have shown potential in promoting endothelial cell attachment and angiogenesis, the challenge lies in replicating the complexity and functionality of natural vasculature. The scalability of vascular grafts for small-diameter arteries, which are commonly required for coronary and peripheral artery disease treatments, remains limited due to inadequate strength and endothelialization. Future research should focus on developing hybrid scaffolds that combine synthetic polymers with bioactive materials to create highly porous, mechanically stable structures capable of supporting the growth of functional blood vessels. Additionally, the integration of cellular components, such as endothelial cells or pericytes, could improve the functionality of these vascular grafts.

7.5. Other tissue types

Regenerative medicine for other tissue types, including muscle, nerve, and corneal tissues, also faces specific challenges. For instance, in nerve tissue engineering, the main hurdles are related to the alignment of axons and the promotion of neuronal growth over long distances. The use of scaffolds based on AM or WJ has demonstrated promise in reducing scar tissue formation and promoting nerve regeneration. However, achieving consistent functional recovery remains a challenge, particularly in large nerve injuries. Similarly, for muscle and corneal tissue regeneration, the main challenges are related to optimizing scaffold properties to promote appropriate cell alignment, differentiation, and long-term integration into the native tissue. The future of these tissue types relies on the development of scaffolds that can more effectively guide cellular behavior, along with the incorporation of specific growth factors to drive tissue-specific regeneration.

8. Conclusion

In conclusion, the combination of perinatal-derived biomaterials with synthetic polymers represents a significant advancement in tissue engineering, particularly for the regeneration of skin, bone, cartilage, and vascular tissues. The unique characteristics of perinatal tissues, including their high content of collagen (COL) and glycosaminoglycans (GAGs), contribute to their exceptional biocompatibility, immunomodulatory effects, and regenerative capacity. COL and GAGs play pivotal roles in ECM structure and function, where COL provides mechanical strength and structural integrity, while GAGs, through their sulfation motifs and growth factor binding capabilities, enhance bioactivity by promoting angiogenesis, cell adhesion, and differentiation. These properties make perinatal-derived materials optimal candidates for improving the efficacy of tissue engineering scaffolds. Despite considerable progress in the development of composite biomaterials, several challenges remain. The variability in donor-derived materials, the need for enhanced mechanical properties, and the scalability of these materials for clinical applications must be addressed. Moreover, the structural properties of COL and GAGs, including their ratio, crosslinking chemistry, and sulfation patterns, must be further optimized to improve scaffold performance. Standardizing decellularization, sterilization, and fabrication methods of these biomaterials will be essential for ensuring consistency and reproducibility across studies.

CRediT authorship contribution statement

Mohammadamin Momeny: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Amirreza Hafezi:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Seyedehfargol Afzal:** Writing – original draft, Methodology, Investigation, Data curation. **Masoumeh Nouri:** Writing – review & editing. **Morteza Zarrabi:** Writing – review & editing. **Mazaher Gholipourmalekabadi:** Writing – review & editing. **Sasha H. Shafikhani:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Conceptualization. **Sanaz Alizadeh:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors state that none of the work described in this study could have been influenced by any known competing financial interests or personal relationships.

Data availability

Data will be made available on request.

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