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Composite & Smart Collagen Biomaterials for Multi-Tissue Regeneration: Drug Delivery and Bioactive Composites

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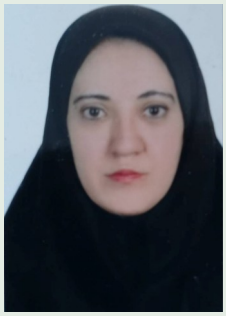

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Abstract

Background: Collagen, the most abundant protein in the extracellular matrix (ECM), provides an ideal platform for designing composite and "smart" biomaterials that simultaneously deliver therapeutic agents and guide tissue regeneration.

Aim: This review critically examines the state of the art in collagen-based composite scaffolds, hydrogels, nanoparticles, and 3D-printed constructs that incorporate bioceramics, synthetic polymers, growth factors, and stimuli-responsive elements.

Result: Emphasis is placed on materials that exhibit bioactivity, controlled drug/growth-factor release, and environmental responsiveness for the repair of bone, cartilage, skin, and vascular tissues. Recent advances in recombinant collagen, macromolecular-crowding-based assembly, and mesoscale mineralization are highlighted.

Discussion: The review concludes with a discussion of current challenges and future directions, including 4D bioprinting and artificial-intelligence-driven material design.

Keywords: Smart Collagen Biomaterials, Tissue Regeneration, Drug Delivery,Bioactive Composites

Introduction

Collagen is the primary structural protein of the extracellular matrix, constituting approximately 30% of total body protein and providing mechanical integrity to skin, bone, cartilage, tendon, and ligament. Its inherent biocompatibility, low immunogenicity, and biodegradability make it a near-ideal biomaterial for tissue engineering and drug delivery. However, native collagen alone suffers from rapid enzymatic degradation, insufficient mechanical strength, and limited osteoinductive or chondroinductive capacity, which restricts its clinical utility (1). Besides,, researchers have developed a range of strategies, including chemical crosslinking using glutaraldehyde or genipin, physical crosslinking (dehydrothermal or UV treatment), and the incorporation of synthetic or inorganic components to form

composite scaffolds. More recently, collagen-based smart systems have emerged that not only provide structural support but also enable controlled spatio-temporal delivery of therapeutic agents (growth factors, anti-inflammatory drugs, or genetic material) directly to the repair site (2). These systems can respond to local physiological cues (pH, temperature, enzymatic activity) or external stimuli (near-infrared light, magnetic fields), thereby enhancing regeneration while minimizing systemic side effects. Furthermore, the combination of collagen with bioactive ceramics (hydroxyapatite, tricalcium phosphate), polymers (chitosan, hyaluronic acid, poly (lactic-co-glycolic acid), and even living cells has yielded constructs with improved mechanical properties, resistance to premature degradation, and tailored bioactivity(1, 3).To overcome these limitations,. This review focuses on collagen-based composite and smart systems that integrate drug delivery and bioactive functionality for the regeneration of multiple tissue types, including bone, cartilage, skin, and vasculature.

Collagen: Structure, Properties, and Modifications

Structure and Biological Functions

Collagen molecules self-assemble into fibrils, fibers, and larger networks that define tissue architecture. Type I collagen is the most abundant form in bone, skin, and tendon, whereas Type II collagen predominates in cartilage and Type III in vascular tissues. The triple-helical structure and the presence of RGD (Arg-Gly-Asp) motifs promote cell adhesion, migration, and differentiation (4).

Limitations of Pure Collagen Scaffolds

Despite its bioactivity, pure collagen scaffolds suffer from several limitations, including low mechanical stiffness (compressive modulus less than 10 kPa for hydrogels), rapid degradation in vivo (occurring over days to weeks), poor osteoinductivity and chondroinductivity, and limited capacity for controlled drug release. These shortcomings motivate the development of composite materials that synergistically combine collagen with reinforcing phases and bioactive agents (5, 6).

Common Modification Strategies

Collagen can be physically blended, chemically cross-linked, or processed into various morphologies. Common fabrication forms include hydrogels prepared by physical or chemical cross-linking, sponges and scaffolds produced by freeze-drying or electrospinning, nanoparticles and microspheres formed through emulsion or desolvation techniques, and 3D-printed constructs made via extrusion or stereolithography (7).

Composite Collagen Biomaterials: Reinforcement and Bioactivity

Composite collagen biomaterials combine collagen with bioceramics, synthetic polymers, or natural polymers to improve mechanical properties, degradation profiles, and biological activity. Collagen–bioceramic composites, such as hydroxyapatite/collagen (HAp/Col) nanocomposites with a HAp:Col ratio of approximately 80:20, mimic natural bone and induce rapid vascular invasion and bone remodeling; clinically, porous HAp/Col scaffolds like Refit® serve as bone void fillers (8). Adding keratin enhances osteoinduction, and collagen–bioceramic smart composites enable drug delivery. Collagen–synthetic polymer composites, including those with PLGA, PCL, and PEG, offer tunable mechanics and sustained growth-factor release. Examples include 3D-printed collagen/PLGA scaffolds with TGF-β1 nanoparticles reducing burst release from 38% to 14.5%, collagen/PLGA-PEG-PLGA hydrogels promoting chondrogenesis of human dental pulp stem cells, and mineralized collagen/PCL scaffolds with dual BMP-2 and antimicrobial peptide delivery over 30 days to simultaneously drive osteogenesis and prevent infection. Collagen–natural polymer composites leverage chitosan's antibacterial and hemostatic properties, alginate's mild gelation, and DNA's biofunctionality(9, 10). A collagen–chitosan–hydroxytyrosol composite shows controlled antioxidant release and antibacterial activity against Staphylococcus aureus and Pseudomonas aeruginosa, while DNA–collagen complexes enable gene delivery and stimuli-responsive behavior (11). Finally, these composite scaffolds are applied across multiple tissues: collagen–HAp, collagen–PLGA, and colla-

gen–bioactive glass for bone; recombinant collagen/chitosan/nanoclay/Kartogenin hydrogels for cartilage; collagen–chitosan membranes and hydroxytyrosol composites for skin and wound healing; and electrospun or 3D-bioprinted collagen composites for dental and alveolar bone regeneration (12-14). (Table1)

Smart Collagen Biomaterials: Stimuli-Responsiveness and On-Demand Delivery

Definition and Design Principles

A "smart" collagen biomaterial is one that can sense and respond to internal biological cues (pH, enzymes, redox potential) or external physical stimuli (temperature, light, magnetic field, ultrasound) to trigger drug release, change mechanical properties, or present bioactive signals (25)

. PH-and Temperature-Responsive Systems

Collagen-based hydrogels can be engineered with pH- or thermo-sensitive cross-linkers. For instance, semi-interpenetrating networks of collagen–polyurethane–alginate exhibit pH-dependent swelling and have been explored for soft/hard tissue healing and anticancer drug delivery. Chitosan–collagen composites also display pH-responsive behavior due to the protonation/deprotonation of chitosan's amine groups (26, 27).

.Enzyme-Responsive Systems

Matrix metalloproteinases (MMPs) are overexpressed in wound sites, tumors, and inflamed tissues. Collagen scaffolds incorporating MMP-cleavable peptide sequences allow localized, cell-mediated degradation and release of entrapped therapeutics. This strategy has been employed for on-demand delivery of growth factors in bone and skin regeneration (28).

Externally Triggered Systems

Smart collagen composites can be designed to respond to external stimuli for on-demand drug release or dynamic property changes. Light-responsive systems incorporate photosensitive cross-linkers or gold nanorods into collagen matrices, enabling light-triggered drug release or stiffness modulation. Magnetic-responsive systems embed magnetic nanoparticles such as Fe_3O_4 within collagen scaffolds, allowing magnetically guided cell seeding and hyperthermia-induced drug release. Electro-responsive composites, which are useful for neural and cardiac tissue engineering, can deliver drugs under applied electric fields (29).

Smart Composite Designs with Multiple Biofactors

The sequential delivery of multiple growth factors is crucial for mimicking natural tissue repair cascades, and multizonal collagen scaffolds have been developed to achieve spatiotemporal control. For example, a zonal collagen/Cu-doped mesoporous bioactive glass (Cu-MBG) scaffold system released VEGF and PDGF-BB

with different kinetics to promote angiogenesis and wound healing (30). In another design, a collagen/MSN/VEGF scaffold incorporated VEGF-loaded mesoporous silica nanoparticles (MSNs) into collagen sponges, achieving sustained VEGF release over 28 days and significantly enhanced angiogenesis in a chick chorioallantoic membrane (CAM) model (31).

Stimuli-Responsive Nanocomposites for Drug Delivery

A comprehensive review by Zhang et al. summarized stimuli-responsive nanocomposites based on collagen and other biopolymers (chitosan, hyaluronic acid, alginate, silk fibroin). These nanocarriers respond to endogenous stimuli (acidic pH, GSH, enzymes) and exogenous stimuli (temperature, light, magnetic field, ultrasound) to achieve targeted, on-demand drug release (3, 32). Figure 1 summerzed smart collagen composite application.

Processing and Fabrication Technologies

Electrospinning

Electrospun collagen-based nanofibrous mats mimic the nanoscale architecture of native ECM and are idely used for wound dressings and drug delivery. Co-axial electrospinning enables core-sheath structures for sustained release of bioactive molecules (33).

Table 1 Composite Collagen Biomaterials: Reinforcement and Bioactivity

Composite Type	Secondary Phase	Reinforcement / Bioactivity	Applications / Examples	Ref
Collagen–Bioceramic	Hydroxyapatite (HAp)	Biomimetic bone composition (80:20 HAp:Col); induces vascular invasion (3 days) and active remodeling (7 days)	Bone void filler (Refit®); calvarial regeneration	(15)
Keratin	HAp	Enhanced osteoinduction; supports hBMSC colonization	Bone tissue engineering	(16)
Resorbable bioceramics HA, β-TCP	{bioactive glasses)	Smart drug-delivery capabilities	. hard tissue regeneration	(17)
Collagen–Synthetic Polymer	PLGA 3D-printed scaffold with TGF-β1 nanoparticles	Mechanical reinforcement; sustained GF release; reduces burst release (38% → 14.5%)	footprint of human bone tissue	(18)
PLGA-PEG-PLGA	BMSCs	Thermoresponsive nanocomposite hydrogel; upregulates Sox-9, Col II, aggrecan	Cartilage engineering with hDPSCs	(19)
PCL (mineralized collagen)	microspheres	Dual delivery: BMP-2 + antimicrobial peptide Pac-525; two-stage release over 30 days	Bone healing with anti-infection	(20)
Collagen–Natural Polymer	Chitosan	Antibacterial, hemostatic; plus hydroxytyrosol (HT) for antioxidant activity (70% HT release over 10 h)	Wound dressings; antibacterial against *S. aureus* and *P. aeruginosa*	(21)
bioactive glass/ collagen	glycosaminoglycan	Osteogenic differentiation, vascular infiltration	Bone scaffolds	(22)
Recombinant collagen + chitosan	nanoclay + Kartogenin (KGN)	Sustained KGN release; induces chondrogenesis of hBMSCs	Cartilage regeneration	(23)
3D print PLA+	wet Electrospun cellulose nano fiber reinforced chitosan -collagen hydrogel	Migaration of rabbit mesenchymal stem cells into scaffold	meniscus tissue engineering	(24)

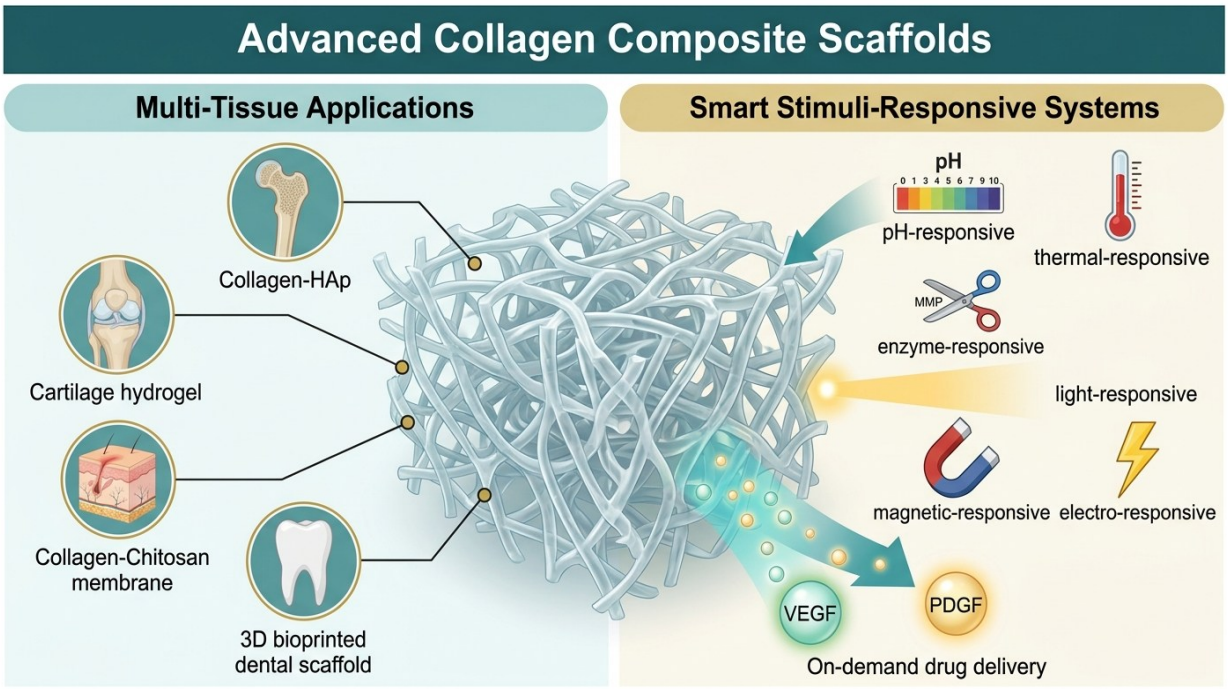

Figure1.Advanced Collagen Composite scaffods: application and bioactivity function

3D Bioprinting

3D bioprinting allows precise spatial deposition of collagen-based bioinks, cells, and growth factors. Zhang et al. 3D-printed recombinant collagen/chitosan methacrylate/nanoclay hydrogels loaded with KGN nanoparticles, achieving continuous drug release and chondrogenic differentiation of hBMSCs. A recent breakthrough in collagen biofabrication, termed Tunable Rapid Assembly of Collagenous Elements (TRACE), uses macromolecular crowding to achieve instant collagen gelation, enabling high-throughput bioprinting of cellular tissues with structural complexity and biofunctionality (23).

Freeze-Drying and Particulate Leaching

These traditional methods produce porous collagen sponges and scaffolds with interconnected pore networks suitable for cell infiltration and nutrient transport. They are often combined with cross-linking to modulate degradation kinetics (34, 35).

. Self-Assembly and Mineralization

Collagen's intrinsic self-assembly properties can be harnessed to create hierarchical structures. A recent Nature Communications article elucidated the mesoscale orchestration of collagen mineralization by phosvitin, which templates the formation of mineralized spherules and guides intrafibrillar mineralization. This mechanistic insight enables the design of highly biomimetic collagen–mineral composites for bone regeneration (36).

Synthetic Collagen Design

To overcome safety and purity concerns of animal-derived collagen, synthetic collagens that self-assemble into banded fibers have been developed. These synthetic collagens recapitulate the morphology and biological properties of natural collagen, stimulating osteoblast differentiation at levels comparable to native collagen (37).

Drug Delivery from Collagen-Based Smart Composites

Growth Factor Delivery

Growth factors (GFs) are potent regulators of cell behavior but have short half-lives in vivo. Collagen composites protect GFs from degradation and provide sustained, localized release. For instance, BMP-2 has been delivered from collagen/PLGA microsphere scaffolds for bone regeneration, TGF-β1 has been encapsulated in PLGA-PEG-PLGA nanoparticles within collagen hydrogels for cartilage repair, and VEGF has been released from collagen/MSN scaffolds to stimulate angiogenesis.(38)

Small-Molecule Drug Delivery

Several small-molecule drugs have been successfully incorporated into collagen-based systems. Kartogenin (KGN), a chondro-inductive small molecule, has been loaded into collagen/chitosan/nanoclay hydrogels for cartilage regeneration. Hydroxytyrosol (HT), an antioxidant, has been incorporated into collagen–chitosan wound dressings for controlled release. Additionally, antimicrobial peptides such as Pac-525 have been co-delivered with BMP-2 from mineralized collagen/PCL scaffolds to prevent infection during bone healing.(39 ,23)

. Gene and Nucleic Acid Delivery

Collagen-DNA complexes enable the delivery of siRNA, antisense oligonucleotides, and DNA origami nanostructures. These complexes form without external stimuli, provide stability against enzymatic degradation, and can be tailored for targeted gene therapy in regenerative medicine.(40)

Stimuli-Responsive Drug Release

Smart collagen composites are designed to respond to various triggers for on-demand drug release. An acidic pH in wound or tumor microenvironments triggers drug release from pH-responsive systems. Enzyme-responsive composites utilize MMP-cleavable linkers to enable on-site release. Thermo-responsive polymers such as PNIPAAm grafted onto collagen allow temperature-dependent drug elution. Finally, external stimuli such as light or a magnetic field provide on-demand release profiles.(42 ,41)

Multi-Tissue Regeneration Applications

Figure 2 illustrates advanced collagen scaffolds enabling bone regeneration via mineralized HAp-collagen nanocomposites with active remodeling, skin wound healing through fibrous collagen-chitosan membranes acting as antibacterial barriers, and cartilage regeneration using 3D-printed collagen/chitosan hydrogels that support chondrocyte alignment.

Bone Regeneration

Collagen–HAp and collagen–PLGA composites are the most studied systems for bone regeneration. Key advances include HAp/Col nanocomposites that undergo rapid vascular infiltration and bone remodeling, mineralized collagen/PCL scaffolds with dual BMP-2/antimicrobial peptide delivery, studied by Todd et al. covering collagen-based scaffolds, sponges, microspheres, and films for bone and cartilage regeneration (43).

. Cartilage Regeneration

For cartilage repair, 3D-printed collagen/chitosan/nanoclay/KGN hydrogels have been shown to promote cartilage repair in vivo. Additionally, PLGA-collagen/PLGA-PEG-PLGA-TGF-β1 nanocomposite hydrogels support chondrogenic differentiation of human dental pulp stem cells (hDPSCs) (23).

. Wound Healing and Skin Regeneration

In wound healing applications, collagen–chitosan fibrous membranes accelerate full-thickness wound closure. Collagen–chitosan–HT composites exhibit controlled hydroxytyrosol release, cytocompatibility, and antibacterial efficacy. Furthermore, collagen/MSN/VEGF scaffolds enhance angiogenesis and overall tissue repair (44).

Dental and Periodontal Regeneration

Collagen-composite scaffolds fabricated by electrospinning and 3D bioprinting have shown progress in restoring dentin, gingival tissue, and alveolar bone. Nevertheless, challenges remain regarding scaffold stability and long-term efficacy in dental applications (45).

Vascular and Multi-Tissue Interfaces

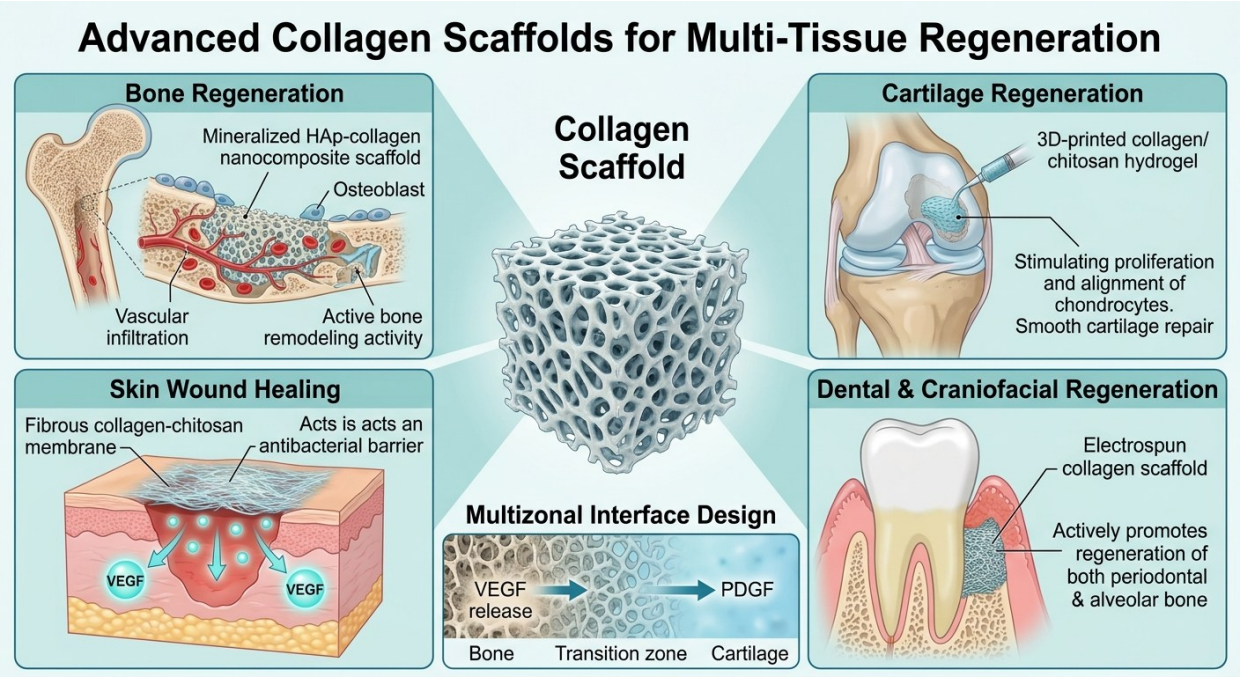

Figure 2. Multi-tissue regeneration applications of advanced collagen scaffolds. Schematic overview of collagen-based scaffolds tailored for bone (mineralized HAp-collagen with osteoblast activity and vascular infiltration), skin (fibrous collagen-chitosan antibacterial membrane), cartilage (3D-printed collagen/ chitosan hydrogel stimulating chondrocyte proliferation and alignment), and dental/craniofacial tissues (electrospun collagen scaffold for periodontal and alveolar bone repair).

Multizonal collagen scaffolds with spatially controlled growth-factor release are being developed for complex tissue interfaces such as osteochondral and periodontal defects. A notable example is the zonal COL-MBG scaffold system with dual VEGF/PDGF release, which enables region-specific regeneration (46). Figure2.

Challenges and Future Directions

Current Limitations

Despite the promise of advanced collagen scaffolds, several limitations remain. Mechanically, even reinforced collagen composites rarely match the demands of load-bearing bone. Degradation kinetics are difficult to control, as balancing scaffold breakdown with new tissue formation remains challenging. Immunogenicity is a concern with animal-derived collagen, which carries risks of immune responses and pathogen transmission. Scalability and reproducibility are problematic, since many fabrication methods such as electrospinning, 3D printing are hard to scale for clinical manufacturing. Finally, long-term efficacy is not yet fully achieved, as controlled release over clinically relevant time frames of months to years remains unknown (47).

Remaining Challenges and Opportunities

Future strategies for collagen-based scaffolds focus on overcoming current limitations through innovative approaches. Recombinant human collagen, particularly Type III, eliminates immunogenicity and enables precise sequence engineering, making it promising for skin and soft tissue repair. 4D bioprinting introduces time-dependent shape-morphing of printed constructs, allowing dynamic tissue maturation. AI-driven material design leverages machine learning to predict optimal composite formulations, cross-linking densities, and drug release

profiles. Bio-hybrid systems integrate living cells, growth factors, and smart materials into a single construct, paving the way for true "living" implants. Finally, mesoscale mineralization control—inspired by biomolecules such as phosvitin—offers new routes for biomimetic composite design in collagen mineralization.(49 ,48)

Conclusion

Collagen-based composite and smart biomaterials represent a paradigm shift in regenerative medicine, moving from passive scaffolds to bioactive, stimuli-responsive platforms that actively orchestrate tissue repair. The integration of bioceramics, synthetic polymers, growth factors, and responsive elements has yielded materials capable of controlled, multi-modal drug delivery and multi-tissue regeneration. Advances in 3D bioprinting, recombinant collagen technology, and mesoscale mineralization are driving the field toward truly biomimetic constructs. Overcoming remaining challenges in mechanical performance, immunogenicity, and scalable manufacturing will pave the way for the widespread clinical adoption of these next-generation biomaterials.

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