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Biofunctional chitosan–biopolymer composites for biomedical applications

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ABSTRACT

In light of escalating biomedical demands across diverse diseases, there arises a pressing need for the development of sophisticated biocompatible materials exhibiting augmented biological functionality. Chitosan, a cationic polyelectrolyte copolymer of natural origin, distinguishes itself through its extraordinary biological properties, positioning it as a promising starting material to develop versatile biomedical materials. Tremendous attention has been directed towards the creation of high-performance biocomposites, achieved through the strategic manipulation of chitosan's structure or its derivative, along with the amalgamation of other biopolymers. This comprehensive review intricately explores recent advancements in chitosan-based biofunctional materials, delving into formulations involving various biopolymers including polysaccharides and proteins. It places specific emphasis on the progress in chitosan chemistry and materials development, encompassing particles, hydrogels, aerogels, membranes, films, and sponges. Also, this review critically evaluates the development and functional properties of biofunctional chitosan–biopolymer composite materials, spotlighting interactions, both dynamic covalent and noncovalent, and their pivotal roles in materials formation. These interactions may either be inherent or realized through chemical modification such as "Click" chemistry, polymer grafts, mussel-inspired chemistry, and selective oxidation. Furthermore, the text illustrates the current and potential biomedical applications of these biofunctional composite materials, spanning from wound dressing to tissue engineering (skin, bone, cartilage, and nerve), the controlled release and targeted delivery of drugs/bioactive compounds, biosensing, and 3D printing. Additionally, it addresses critical challenges within the field, posits potential solutions, and provides a forward-looking perspective on the future directions of functional biomaterials and design strategies.

1. Introduction

As per the report from the World Health Organization [1], health and well-being serve as foundational pillars for many of the other sustainable development goals (SDGs). The SDGs encompass 59 health-related SDG indicators, and the advancements in these indicators have the potential to positively impact other SDGs. In the pursuit of promoting health, there has been a prevailing trend towards the robust development of biomedicines. Given the escalating biomedical requirements associated with diverse diseases, there is a pressing need to innovate and create new biocompatible materials imbued with boosted and novel biological functionalities. This is particularly crucial in light of their interactions with cells, tissues, enzymes, and various physiological conditions within the body.

Natural polymers (or biopolymers), those directly sourced from nature, have garnered considerable attention in biomedical applications

Abbreviations: ADH, Adipic acid dihydrazide; CMCe, Carboxymethyl cellulose; CMCh, Carboxymethyl chitosan; CS, Chondroitin sulfate; DD, Degree of deacetylation; DESs, Deep eutectic solvents; DN, Double network; DS, Degree of substitution; ECH, Epichlorohydrin; ECM, Extracellular matrix; EE, Encapsulation efficiency; EGDE, Ethylene glycol diglycidyl ether; GA, Glutaraldehyde; GAG, Glycosaminoglycan; HA, Hyaluronic acid; HACC, Hydroxypropyltrimethyl ammonium chloride chitosan; IL, Ionic liquid; LbL, Layer by layer; MA, Methacrylamide; OCS, Oxidized chondroitin sulfate; OHA, Oxidized hyaluronic acid; PEC, Polyelectrolyte complex; ROS, Reactive oxygen species; RT, Room temperature; SD-A-SGT, Semi-dissolution acidification sol-gel transition; SF, Silk fibroin; SGF, Simulated gastric fluid; SPI, Soy protein isolate; TG, Transglutaminase; TMC, *N*-trimethyl chitosan; TPP, Sodium tripolyphosphate; WPI, Whey protein isolate.

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owing to their alluring characteristics, including renewability, widespread availability, biodegradability, biocompatibility, and intrinsic functionality. Among the myriad biopolymers, chitin (β-(1,4)-linked polysaccharide of *N*-acetylglucosamine) and chitosan (β-(1,4)-linked polysaccharide of D-glucosamine, the deacetylation form of chitin) stand out for their vast structural potential, amenable to mechanical and chemical modifications that engender novel functions, properties, and applications [2]. Notably, chitin ranks as the second most abundant naturally occurring polysaccharide after cellulose in nature [2,3].

Chitosan has been the subject of extensive investigation for several decades in the realm of biofabrication and bioconjugation, primarily owing to its distinctive characteristics. These include its polymeric cationic nature, antibacterial and mucoadhesive properties, gelation and film-forming abilities, high oxygen barrier property, and the presence of active amino and hydroxyl groups serving as reactive sites [4–6]. While the carbohydrate backbone of chitosan bears a striking resemblance to cellulose, a commonly utilized material in biomedical applications [7,8], chitosan boasts distinctive advantages. Notably, it possesses antibacterial and mucoadhesive properties, setting it apart from cellulose. Besides, chitosan shares a structure similar to glycosaminoglycan (GAG) in the extracellular matrix (ECM) [9], a crucial characteristic for tissue engineering applications. To date, chitosan from shrimp shells [10–20], crab shells [21–28], and fungi [29] has been the focus of extensive investigation, leading to its processing into various materials. Among these derivatives, carboxymethyl chitosan (CMCh) has emerged as one of the most extensively studied due to its favorable water solubility under neutral conditions, without compromising the original excellent characteristics, such as biocompatibility, biodegradability, and biological activity.

Biomedical applications stand out as the paramount and burgeoning domain for chitosan-based materials. However, the robust intramolecular and intermolecular hydrogen bonding within chitosan leads to low water solubility and feeble mechanical properties, imposing limitations on its applications [24,29,30]. While the deficiencies inherent in chitosan can be partially addressed through straightforward modifications of functional groups on the chitosan backbone, materials exclusively reliant on chitosan often struggle to fulfill the comprehensive requirements of various biomedical applications.

Significant endeavors have been dedicated to the formulation of chitosan-based composite materials, encompassing films, membranes, scaffolds, and hydrogels, by integrating chitosan with other natural biopolymers, including polysaccharides and proteins. This collaborative approach results in materials with heightened properties and functionality. The abundance and renewability of different biopolymers on Earth, coupled with the feasibility of their physical or chemical modification to enhance functionality for specific applications, underscore their significance in such composite formulations. Chitosan-based functional composites, boosting desirable properties, can be achieved through the strategic design of molecular structures for chitosan and other natural polymer monomers. This design process relies on chemical strategies such as Schiff base reaction, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/*N*-hydroxysuccinimide (NHS) activation, mussel-inspired chemistry, and Diels-Alder click chemistry, and others. Importantly, these strategies consider not only the chemical interactions but also the inherent functional properties of the polymers themselves.

Chitosan–biopolymer macro-composite materials have garnered attention for their commendable features (e.g., excellent antimicrobial activity, extraordinary conductivity, and the ability to promote cell proliferation and differentiation) and strong application potential (e.g., tissue engineering, wound healing, blood purification, gene delivery, coatings on biomedical implants, 3D-bioprinting, and drug encapsulation) (refer to Fig. 1). It is noteworthy that chitosan-based composites reinforced by nanofillers with varying dimensions are not discussed here and warrant a separate review. Several excellent reviews [7,31–33] have

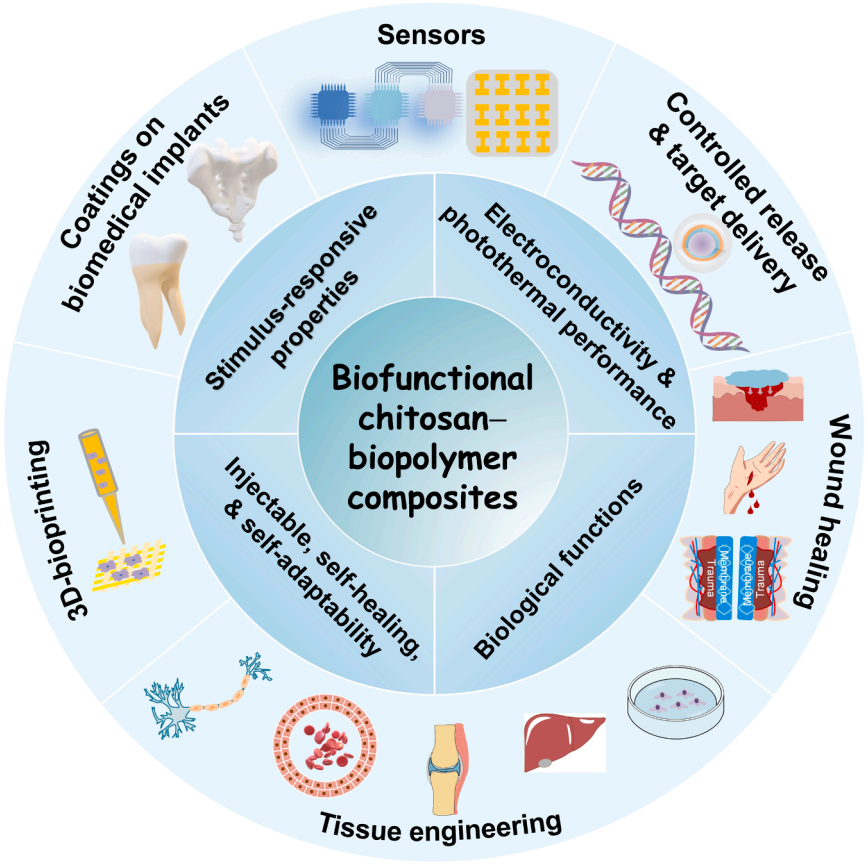


Fig. 1. Overview of the properties and functionality of biofunctional chitosan biopolymer composites and their biomedical applications.

been published on chitosan polymers and their biomedical applications, each with a distinct focus, such as preparation methods and modification chemistry.

Given the swift pace of technological development, novel material forms, functional properties, and polymers combinable with chitosan are continually being unveiled. This review adopts a molecular design perspective, emphasizing the diverse functional properties of chitosan-based composite materials. Given the scope of this article, it is impractical to cover all pertinent aspects of biofunctional chitosan-based composites and all biopolymers utilized in biomedical applications. Instead, this article provides an overview of various representative biofunctional chitosan-based composite systems recently reported, emphasizing their high-value biomedical applications tied to the inherent functions of these biopolymers or those enhanced or introduced through physical/chemical modification. This overview aims to guide both the fundamental research and industrial application of chitosan and other biopolymers.

2. Background of chitosan-based materials

2.1. Structure and properties of chitosan

Chitosan, derived from the partial deacetylation of chitin [2,3], is recognized as a copolymer comprising *N*-acetylglucosamine (2-(acetylamino)− 2-deoxy-D-glucopyranose) and glucosamine (2-deoxy-2-amino-D-glucopyranose) units (Fig. 2). The active primary amino groups at the C-2 position, as well as primary (at the C-6 position) and secondary (at the C-3 position) hydroxyl groups along the chitosan backbone, serve as reactive sites for chemical modification. This allows for the enhancement of both physical and chemical performances, with the hydroxyl group at the C-6 position exhibiting relatively higher reactivity compared to the C-3 position [34]. Further details can be found in **Section 2.2** .

The widespread interest in chitosan for biomedical applications is rooted in its remarkable biological properties (Fig. 3) of chitosan. These include notable biocompatibility [35], a structure akin to GAG with osteoconductive properties [15,36–40], favorable in vitro/in vivo degradation behavior [7,24,41], concentration-dependent antibacterial activity [42–44], outstanding hemostasis activity [45,46], dose-dependent analgesic effects against inflammation [47], antioxidant activity [48], antitumor activity [49,50], and mucoadhesive properties [7]. Among these, the in vitro antimicrobial activity of chitosan is significantly influenced by various extrinsic and intrinsic factors, encompassing both chitosan itself (e.g., molecular mass and degree of deacetylation (DD)) and environmental conditions (e.g., pH, ionic strength, temperature, and metal ions) [51].

The robust mucosal adhesiveness of chitosan is attributed to electrostatic attraction (major driving force), hydrogen bonding, and hydrophobic effects between cationic chitosan and negatively charged mucin [52]. However, it is noteworthy that the tissue adhesion capability of cationic chitosan is limited. This limitation may arise from the weak interaction of chitosan with tissues, primarily through charge interactions, without the formation of mutually entangled chains at contacting interfaces [53].

Under a pH lower than its pKa (typically 6.3 and highly contingent on the DD), the amino groups of chitosan undergo protonation, rendering them positively charged. The deprotonation of these amino groups occurs at a higher pH (about pH 6.5), leading to chitosan's insolubility. The majority of chitosan applications are rooted in its chelating ability and polyelectrolytic nature, primarily governed by $-NH_3^+$ groups (protonated $-NH_2$ groups under acidic conditions) [54]. Additionally, a higher DD generally results in more glucosamine units and a higher linear charge density in an acidic medium [6], indicating increased solubility of chitosan.

Chitosan is insoluble in either organic solvents or water but exhibits solubility in aqueous organic acids and aqueous mineral acids. The solubility of chitosan and the properties (e.g., viscosity, antimicrobial activity, and mechanical properties) of the resulting chitosan solutions are significantly influenced by the type and concentration of the acid. The extent of solubility decreases with increasing acid concentration [27,55–62], attributed to the increased ionic strength that may screen electrostatic repulsions. Other solvents, such as ionic liquids (ILs) [63], LiOH/KOH/urea aqueous solution [64,65], and deep eutectic solvents (DESs) [66] are also available solvents for chitosan processing. Depolymerization techniques, including physical depolymerization, chemical depolymerization, and enzymatic hydrolysis, have gained attention for producing more water-soluble chitosan by controlled reduction of chitosan molecular mass [29,33,67].

2.2. Modification strategies of chitosan

Despite the commendable characteristics of chitosan mentioned earlier, its poor solubility in neutral and basic pH solutions imposes limitations on its applications. To customize chitosan for desired properties (e.g., enhanced solubility, antibacterial activity, and adhesive properties), various chemical modifications (Fig. 4), along with physical modifications such as blending with other polymers, have been explored. Chemical modification plays a pivotal role in mitigating the

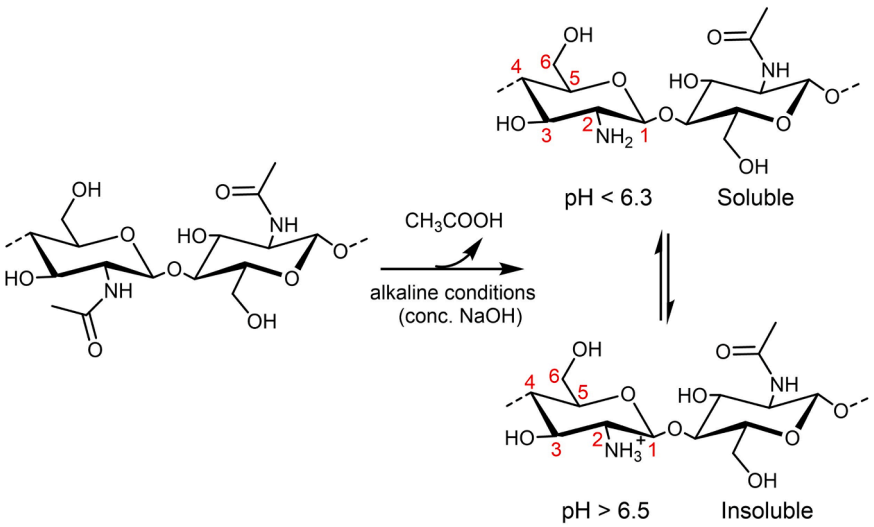


Fig. 2. Deacetylation of chitin and chemical structures of chitin and chitosan.

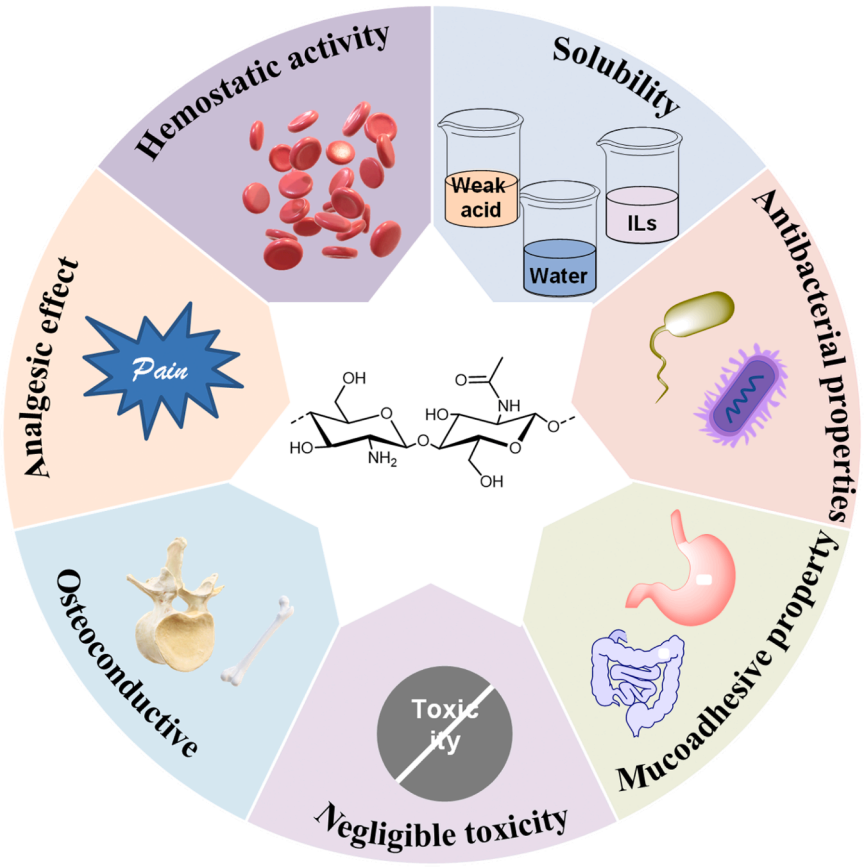


Fig. 3. Functional properties of chitosan.

inherent weaknesses of chitosan, given the presence of the chemically active groups (free amine groups and hydroxyl groups) in the chitosan structure [54,68]. Some instances of chitosan modification reported in the literature are outlined in Table 1. It is noteworthy that certain chitosan derivatives, such as succinylated chitosan, which is negatively charged, lack antibacterial activity due to the loss of the positively charged groups ($-NH_3^+$) [69].

Apart from chemical modification and surface functionality achieved through graft conjugation, molecular design that introduces functional groups and motifs to biopolymer chains facilitates the occurrence of desired molecular interactions and chemical bonding. These interactions encompass noncovalent interactions and covalent molecular assembly (Schiff base linkages, disulfide bond-forming, amidation reaction with EDC/NHS activation, and Diels-Alder addition reaction) (Fig. 5). This strategic molecular design enables the avoidance of crosslinkers in certain applications.

Key chemical modification methods for chitosan are discussed below:

2.2.1. *Carboxymethylation*

CMCh, an amphiprotic ether derivative of chitosan with notable attributes such as water solubility under neutral conditions and in-vivo anti-inflammatory and analgesic activities, can be categorized into *N*-CMCh, *O*-CMCh, and *N*,*O*-CMCh based on carboxymethylation substitution sites. For example, *O*-CMCh, derived from carboxymethyl substitution on the primary hydroxyl site of the chitosan glucosamine unit, demonstrated enhanced anti-inflammatory and analgesic effects on acute edema in rat hind paws compared to pristine chitosan [70].

Due to its negatively charged carboxyl groups, CMCh exhibits a strong affinity for coordinating with metal ions such as Fe^{3+} or Al^{3+}, leading to the rapid formation of a hydrogel [71]. This characteristic has garnered significant interest in the realm of biomaterial preparation. Notably, the degree of substitution (DS) of CMCh plays an important role in the properties of hydrogel. A higher DS may result in localized crosslinked by metal ions, potentially leading to uneven cross-links and a heterogeneous hydrogel system [71].

The conventional synthesis of CMCh involves a two-step reaction process: a) chitosan reacts with a strong alkali in the presence of isopropyl alcohol to facilitate swelling and alkali penetration, and b) alkaline chitosan reacts with monochloroacetic acid [70]. However, the use of organic reagents like isopropyl alcohol and methanol (utilized to terminate the reaction) is environmentally unfriendly and cost-ineffective. In the pursuit of a greener approach inspired by chitosan dissolution in LiOH/KOH/urea aqueous solution, a one-step reaction using LiOH/KOH/urea aqueous solution as a solvent has been employed to produce CMCh with a higher DS [34]. Although this method is laborious and time-consuming, it eliminates the need for organic solvents and yields chitosan derivatives with a high DS.

2.2.2. *Quaternization*

Quaternized chitosan, exemplified by *N*-trimethyl chitosan (*N*,*N*,*N*-trimethyl ammonium chitosan, TMC) and hydroxypropyltrimethyl ammonium chloride chitosan (HACC)), represents water-soluble chitosan derivatives initially documented in 1985, drawing widespread attention for their higher and broader-spectrum antibacterial efficacy [72,73]. The antibacterial potency of quaternized chitosan is contingent on the molecular mass, quaternary chemical structure, and quaternization degree of TMC [74]. The quaternization of free $-NH_2$ positions of chitosan yields a highly charged polyelectrolyte that maintains water-solubility throughout the entire pH range. Besides, this derivative exhibits commendable mucoadhesive properties [3].

Quaternization emerged as the most suitable approach for enhancing the solubility and charge density of chitosan. TMC can be derived from the quaternization of chitosan's amino groups or by the covalent

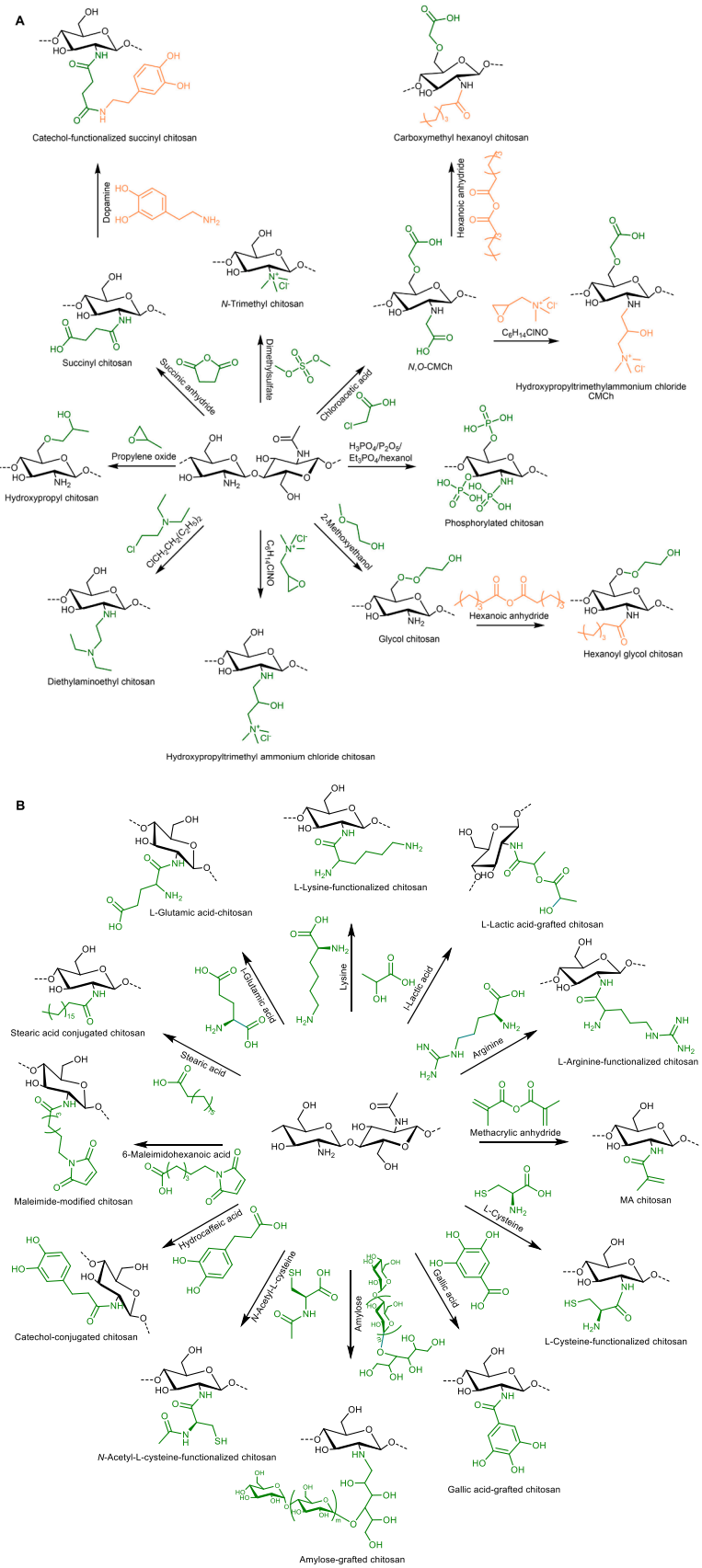


Fig. 4. Chemical modifications of chitosan.

Table 1
Chemical structure and properties of chitosan derivatives.

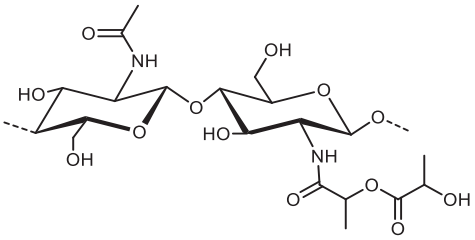
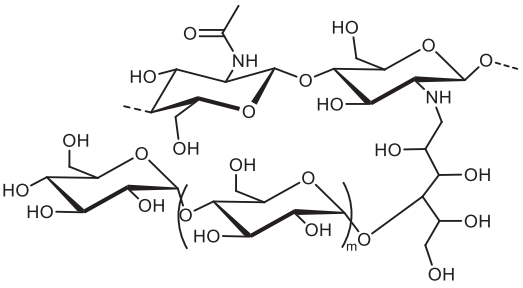
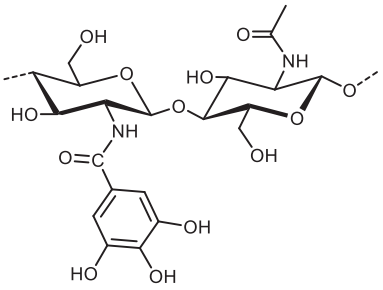
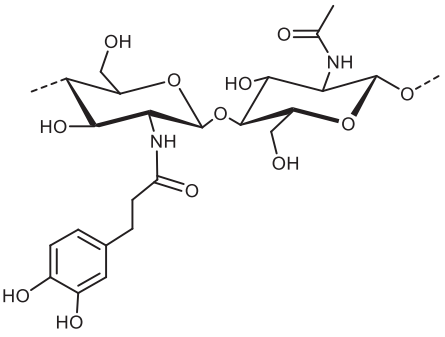
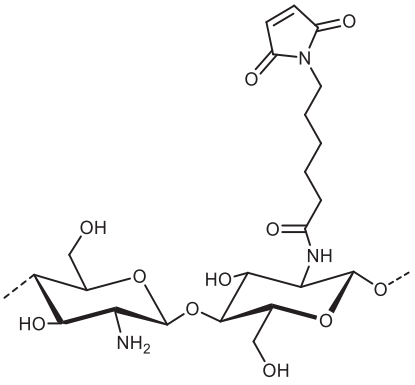
Chitosan derivatives	Chemical structure	Properties (in comparison with pristine chitosan)	Ref.
L-Lactic acid-grafted chitosan		– Mechanical properties ↑; – Thermal properties ↑; – Water absorption ↑	[81]
Amylose-grafted chitosan		– Water-solubility ↑	[311]
Gallic acid-grafted chitosan		– Adhesion capacity ↑ – Near-IR photothermal properties ↑; – Antibacterial activity ↑	[80]
Catechol-conjugated chitosan		– Adhesive properties ↑	[82,83, 248,305]
Maleimide-modified chitosan		– Water-solubility ↑	[85]

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Table 1 (*continued*)

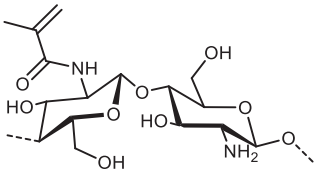
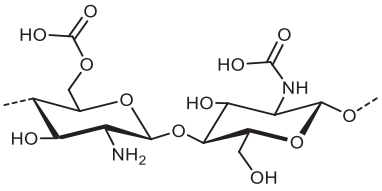
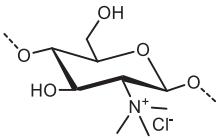
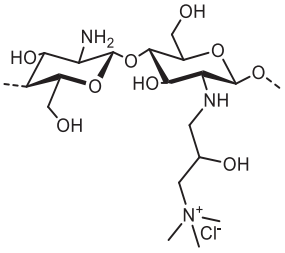
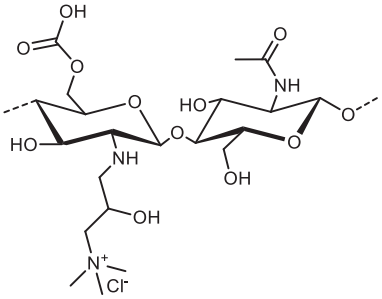
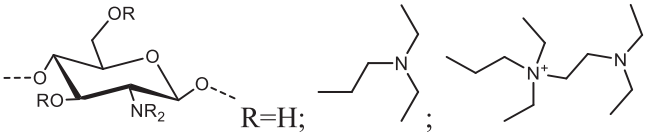
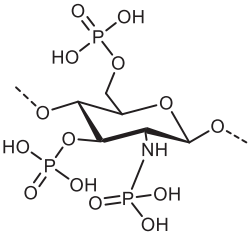
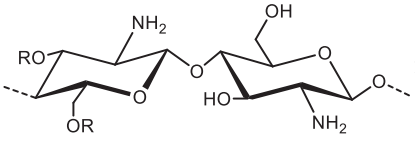
Chitosan derivatives	Chemical structure	Properties (in comparison with pristine chitosan)	Ref.
Methacrylate-modified chitosan		– Water solubility ↑; – UV-crosslinkable capacity ↑; – Injectability ↑, flowability ↑	[90,160, 166]
O-CMCh		– Water solubility ↑; – Antibacterial activity ↑; – Anti-adhesive ability ↑; – Anti-tumor properties; – Promoting fibroblast growth and reducing scar formation; – Osteogenesis-inducing potential	[176,254, 312–315]
TMC		– Water solubility ↑; – Antibacterial activity ↑; – High positive charge	[74,76, 234,312]
HACC		– Water solubility ↑; – Antibacterial activity ↑; – Hemostatic activities ↑	[18,316]
Quaternized CMCh		– Water solubility ↑	[78,317]
Diethylaminoethyl chitosan		– Water solubility ↑	[21]
Phosphorylated chitosan		– Water solubility ↑; – Cation-exchange properties ↑; – Osteoinduction capacity↑; – The ability to recruit signaling biomolecules ↑	[15]
Hydroxypropyl chitosan		– Water-solubility ↑; – Cytocompatibility ↑; hemocompatibility ↑; – Antimicrobial activity ↑; – Film-forming ability↑	[263]

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Table 1 (*continued*)

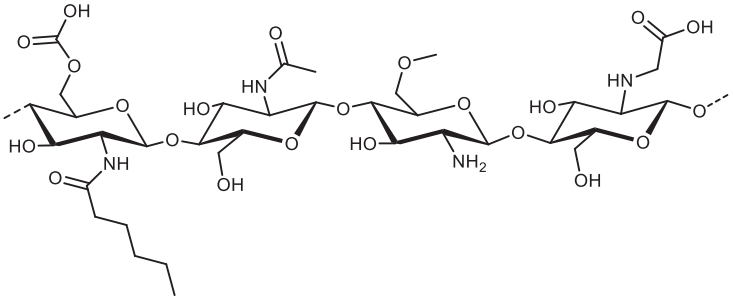
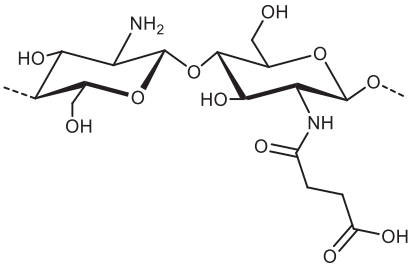
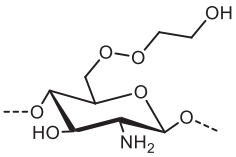
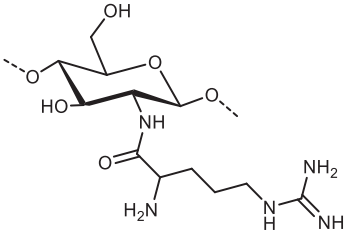
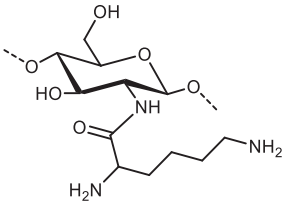
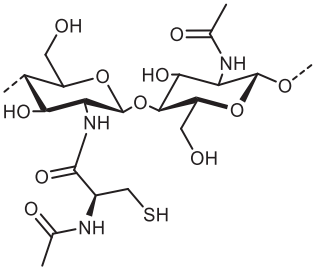
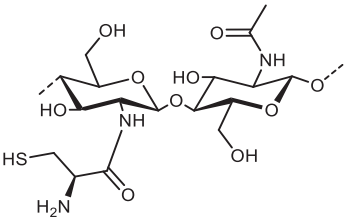
Chitosan derivatives	Chemical structure	Properties (in comparison with pristine chitosan)	Ref.
CMHC		– Water-solubility ↑; – Be capable of forming micelles and hydrogels via electrostatic and hydrophobic-hydrophilic interactions	[219]
Succinyl chitosan		– Water-solubility ↑; – Negatively charged; – Long-term retention in vivo – No antimicrobial activity	[14,69, 178,318]
Glycol chitosan		– Water-solubility ↑; – Specific self-adaptive targeting in the acidic microenvironment (pathologically inflamed tissues, ca. pH 6.3)	[218,238]
L-Arginine-functionalized chitosan		– Water-solubility ↑; – The ability to encapsulate hydrophobic bioactive compounds	[86]
L-Lysine-functionalized chitosan		– Water-solubility ↑; – The ability to encapsulate hydrophobic bioactive compounds	[86]
N-Acetyl-L-cysteine-functionalized chitosan		– Water-solubility ↑	[25]
L-Cysteine-functionalized chitosan		– Water-solubility ↑; – Mucoadhesion combination and permeation-enhancing effects ↑	[25]

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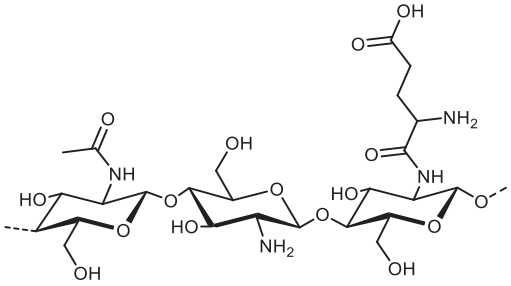
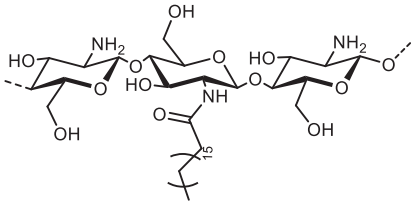
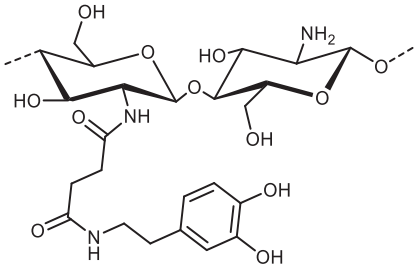
Table 1 (*continued*)

Chitosan derivatives	Chemical structure	Properties (in comparison with pristine chitosan)	Ref.
L-Glutamic acid-chitosan		– Physiological activity ↑	[319]
Stearic acid conjugated (grafted) chitosan		– Water-solubility ↑; – Hydrophobicity (which may facilitate the hydrophobic interaction with amphiphilic biomacromolecules) ↑	[84]
Catechol-functionalized succinyl chitosan		– Adhesive properties ↑	[247]

Abbreviations: carboxymethyl chitosan (CMCh), carboxymethyl hexanoyl chitosan (CMHC), hydroxypropyltrimethyl ammonium chloride chitosan (HACC), *N*,*N*,*N*-Trimethyl ammonium chitosan (TMC)

addition of a substituent containing a quaternary ammonium group, with the former method receiving the most attention [75]. Dimethyl sulfate, owing to its lower toxicity and cost-effectiveness compared to iodomethane, has been the most widely used reactive agent [75–77]. The synthesis of HACC involves the use of 2,3-epoxypropyltrimethyl ammoniumchloride (ETA) or glycidyl trimethylammonium chloride (3-chloro-2-hydroxypropyltrimethylammonium chloride) as a modification agent [64,78,79]. Notably, HACC typically exhibits markedly better solubility than TMC due to the higher DS of the former. A homogeneous etherification method executed in LiOH/KOH/urea aqueous solution with a high DS was developed, utilizing 3-chloro-2-hydroxypropyltrimethylammonium chloride as an etherifying agent. Both amino groups and hydroxyl groups prove sufficient nucleophilic under strong alkaline conditions to instigate the ring-opening of the epoxide hydrolyzed from the etherifying agent [64].

2.2.3. Graft copolymerization

Graft copolymerization of natural and synthetic polymers onto chitosan serves as a crucial method for the functionalization and application of chitosan. Various acids have been investigated as monomers for grafting, such as gallic acid [80], L-lactic acid [81], hydrocaffeic acid [82,83], and stearic acid [84] through free radical-induced grafting [84] and EDC/NHS [25,80,82,85,86]. The incorporation of polymers imparts chitosan with enhanced adhesive properties, water solubility, and other attributes, detailed further in Table 1.

2.2.4. Schiff base interactions

Since its introduction by the German chemist Hugo Schiff in 1864, substantial interest in Schiff Base interactions has burgeoned owing to their mild reaction conditions (yielding only water as a byproduct) and high reaction rates. The interaction between compounds containing amino groups and aldehydes (or ketones) results in a dynamic Schiff base bond (i.e., C═N bonds) characterized by remarkable reversibility, allowing the creation of composites with autofluorescence (Fig. 5). This property is particularly advantageous for drug delivery in biomedicine [87].

2.2.5. Disulfide crosslinking

A reversible disulfide bond, relatively stable in mildly oxidizing conditions (e.g., human blood circulation) and physiological pH, can be derived from the oxidation of two thiols (Fig. 5) [88]. Drawing inspiration from disulfide cleavage triggered by the abundant of cellular free thiols, including glutathione, and the reducing environment of the colon, chitosan-based materials incorporating disulfide crosslinking in their molecular design have been formulated for targeted drug delivery in the realm of biomedicine.

2.2.6. Photo-crosslinking

Photo-crosslinking approaches and techniques, including thiol–ene photo-crosslinking, free-radical chain polymerization, and photo-mediated redox crosslinking, have been largely explored in biomedical applications, particularly in regenerative medicine and in vitro 3D tissue models. The fundamental principles of each approach have been comprehensively discussed by Lim and co-workers [89].

Taking the free-radical chain polymerization reaction as an illustration, this process typically involves three stages: initiation, propagation, and termination. In this sequence, reactive radical species, generated from photo-initiators through photolysis or light-induced cleavage, can react with specific functional groups (e.g., methacrylate, acrylate, and *N*-vinyl amide) on polymer chains, leading to the formation of new covalent bonds. It is noteworthy that these functional groups are commonly pre-grafted onto chitosan chains to endow chitosan with

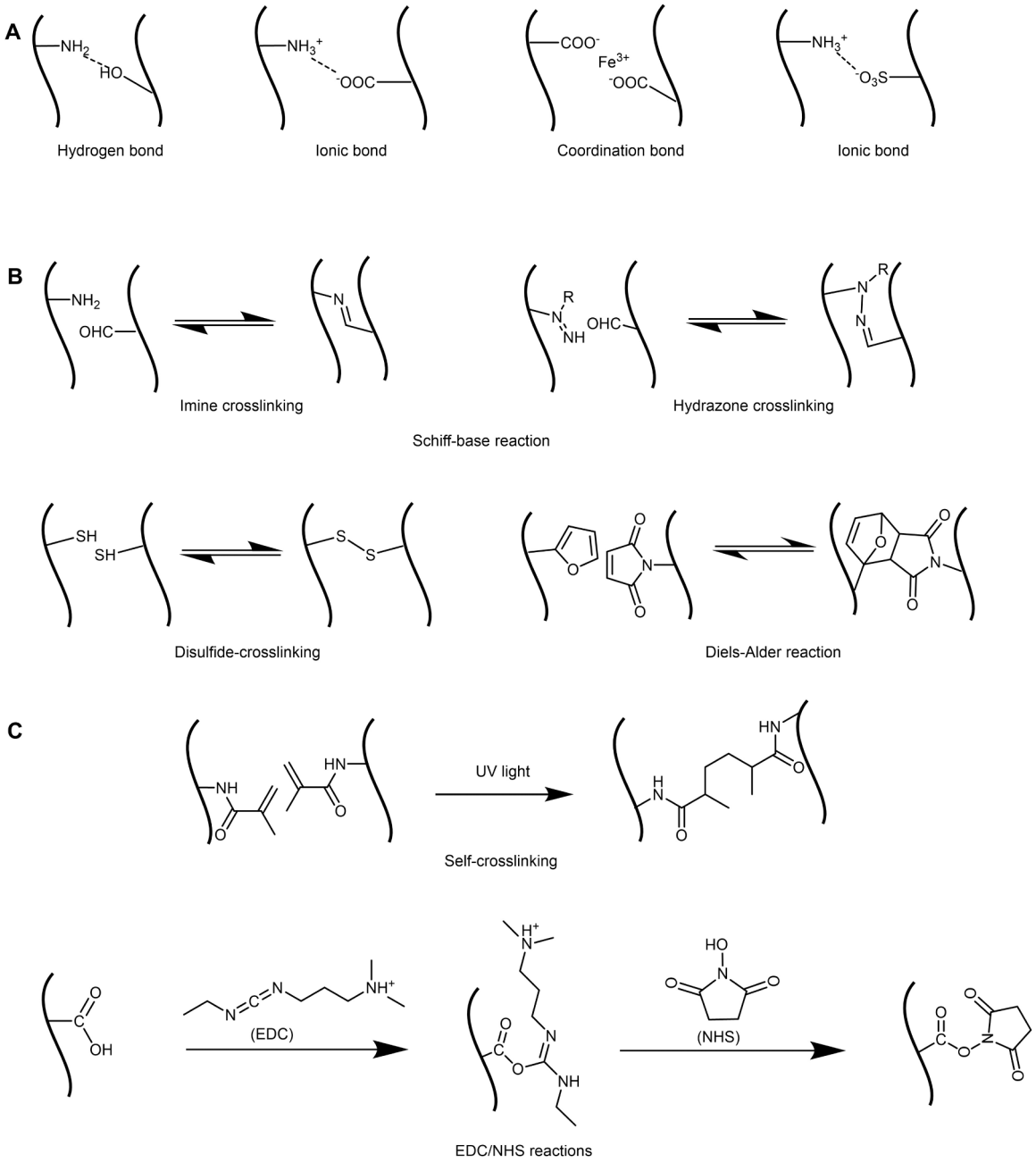


Fig. 5. Common chemical reactions in the synthesis of chitosan-based materials: (A) common interactions to form noncovalent bonds; (B) dynamic covalent crosslinking via Schiff base reaction, disulfide crosslinking, and Diels-Alder reaction; (C) self-crosslinking and EDC/NHS reactions.

UV crosslinking ability [90–93].

2.2.7. *Click chemistry*

Click chemistry, known for its straightforward reaction conditions, high yields, generation of only inoffensive byproducts, and the use of benign solvents, holds promise for addressing various biomedical challenges [94]. Diels–Alder reaction, one subtype of click chemistry, typically involves the coupling of a dienophile and a diene via intra- or intermolecular reactions [95].

2.3. *Polyelectrolyte complexation and complex coacervation*

Because of the positively charged amino groups and the high charge density of chitosan in acidic conditions, it can spontaneously form a polyelectrolyte complex (PEC) with anionic polymers [96]. Polyelectrolyte complexation offers the possibility of combining the physicochemical properties of at least two polyelectrolytes without the need for crosslinking agents, thereby reducing the potential toxicity and undesirable effects of the resulting complexed materials [43,45]. Common chitosan-based PECs are summarized in Table 2. While the formation of PECs is mainly driven by electrostatic attraction (Fig. 6) [97], additional interactions like hydrogen bonding, charge transfer, hydrophobic interaction, and dipole–dipole interaction can also contribute to PEC stabilization [6,84,98]. Polyelectrolyte complexation is a reversible physical crosslinking process without the use of chemical crosslinking agents, organic solvent, or external energy [99] and is governed by Eq. (1):

$$Pol^{+}A^{-}(s) + Pol^{-}B^{+}(s) \rightleftharpoons Pol^{+}Pol^{-}(s) + A^{-}(aq) + B^{+}(aq) \quad (1)$$

In this equation, Pol^{+} and Pol^{-} represent the polycation and

Table 2
Chitosan-based PEC composites.

PEC combination	PEC forms	Fabrication method
Chitosan–CMCh	Hydrogel	SD-A-SGT[172]
Chitosan–poly(glutamic acid)–alginate	Hydrogel	SD-A-SGT[174]
Chitosan–alginate	Membrane	Solution casting[97]
	Sponge	Freeze-drying[187]
	Three-layered scaffold	Solution mixing + freeze-drying[320]
	Particle	Solution mixing + freeze-drying[321]
HACC–alginate	Hydrogel	Solution mixing + acid treated [175]
Chitosan–CMCe	Hydrogel	Solution mixing[227]
	Film	Thermo-mechanical kneading method[117]
Chitosan–κ-carrageenan	Hydrogel	Solution mixing[322]
	Nanoparticle	LbL assembly deposition[278]
		Self-assembly[323]
		Solution mixing[43,324]
Chitosan–SF	Scaffold	Freeze-drying[189]
Chitosan–silk peptide	Film	Melt processing[325]
Chitosan–gelatin	Hydrogel	Solution mixing[307]
Chitosan–HA	Bilayer coating	LbL assembly[44]
	Multilayer coating	LbL assembly[152,244,326]
	Hydrogel	Solution mixing[106]
	Nanoparticle	Solution mixing[233,327,328]
		Solution mixing+ freeze-drying[236]
	Scaffold	Solution mixing + freeze-drying[12]
Thiolated chitosan–HA	Nanoparticle	LbL + horseradish peroxidase -mediated oxidative crosslinking reaction[229]
Diethylaminoethyl chitosan–HA	Nanoparticle	Solution mixing[21]
Chitosan–xanthan gum	Film	Direct compression[228]
	Particle	Solution mixing[105,329]
TMC–sodium carboxymethyl xanthan gum	Hydrogel	Solution mixing[76]
Chitosan–gellan gum	Scaffold	Solution mixing + freeze-drying[62]
	Nanoparticle	Solution mixing + freeze-drying[281]
Chitosan–methacrylated gellan gum	Hydrogel fibers	Microfluidics technology[210]
Chitosan–katira gum	Nanoparticle	Solution mixing + freeze-drying[280]
Chitosan–gum Arabic	Nanoparticle	Solution mixing + freeze-drying[330]
Chitosan–casein phosphopeptides	Multilayer coating	LbL assembly[266]
Chitosan–casein	Multilayer film	LbL assembly[149]
	Nanofibrous	Self-assembly[45]
	Hydrogel, nanoparticle	Solution mixing[98]
Chitosan–dextran sulfate	Nanoparticle	LbL assembly[193]
		Solution mixing[331]
		Solution mixing + NaOH precipitation[16]
	Hydrogel	Solution mixing[332]
	Multilayer coating	LbL assembly[285]
Chitosan–chondroitin sulfate	Scaffold	Solution mixing + freeze-drying[243,267]
	Membrane	Solution mixing + evaporation compaction[100]
	Nanoparticle	Solution mixing[237,333,334]
		Solution mixing + freeze-drying[222]
Chitosan–pectin	Bilayer coating	Dip-coating LbL assembly [267]
	Membrane	Solution casting[107,335]
Chitosan–pectin–gum Arabic	Membrane	Solution casting[9]
Chitosan–alginate–κ-carrageenan	Microbead	LbL assembly[223]
Chitosan–κ-carrageenan -CMCe	Hydrogel	Solution mixing[336]
Trimethyl chitosan–HA–dextran sulfate–alginate	Nanoparticle	Solution mixing[287]

Abbreviations: carboxymethyl cellulose (CMCe), carboxymethyl chitosan (CMCh), carboxymethyl hexanoyl chitosan (CMHC), hyaluronic acid (HA), hydroxypropyltrimethyl ammonium chloride chitosan (HACC), semi-dissolution acidification sol-gel transition (SD-A-SGT), silk fibroin (SF), *N*,*N*,*N*-Trimethyl ammonium chitosan (TMC)

polyanion, respectively, and A^- and B^+ stand for monovalent salt counterions (e.g., Na^+ and Cl^-), and the subscript "s" refers to components in the complex phase [100–102].

Ionic interaction (i.e., polyelectrolyte complexation) between chitosan and an anionic polymer is only permissible within the pH defined by the pKa values of chitosan and the anionic polymer [96]. Various PEC structures, ranging from nanometer-sized particles to macroscopic forms such as films, membranes, hydrogels, and sponges, can be achieved through various fabrication methods. The formation and properties of PECs are largely affected by the molecular mass, concentration, and charge density of each polymer, the type of pH-adjusting agent, initial pH, order of biopolymers addition, and medium ionic strength [6,9,21,43,55,96,98,99,103–105]. The simplest and most commonly used method for synthesizing PECs is coacervation, achieved by mixing an acidic aqueous solution of chitosan (polycation) with an aqueous solution of a polyanion [96]. However, it is noteworthy that simple mixing of chitosan and a hyaluronic solution results in precipitation rather than gelation [106]. Compact PECs can be obtained using centrifugation or extrusion, forming tough macroscopic hydrogels with high electrostatic crosslink densities [100]. The ionic bonds in compact PECs can be disrupted at high ionic strengths and re-formed at low ionic strengths [100]. Notably, PECs derived from soluble polyelectrolytes with a non-stoichiometric ratio of polycation–polyanion charged groups are generally soluble, whereas stoichiometric combinations of charged groups result in insoluble PEC precipitates [9107]. It is important to mention that precipitated PECs can regain solubility by increasing the ionic strength of the solution [9].

Complex coacervates, often considered as either a subset of, or distinct from, PECs, represent stable, aqueous, and liquid-like phases formed by oppositely charged polyelectrolytes, lacking 'one-to-one' exclusivity between polymer chains [108]. While PECs do not meet all criteria necessary to be a coacervate [108], complex coacervation occurs in solutions containing oppositely charged macromolecular species such as polymers, proteins, and colloids, leading to a coacervate phase (a dense mix of oppositely charged components) and a supernatant phase [109]. Natural polysaccharides are typically neutral or negatively charged, and proteins carry either negative charges above or positive charges below their isoelectric point (pI). Positively charged chitosan logically interacts with oppositely charged macromolecules (polysaccharides or proteins) via electrostatic interactions, with hydrogen bonding, hydrophobic interactions, and entropy gain contributing to the formation of chitosan-based coacervate complexes (see Fig. 6) [110–112].

Controlled external parameters, such as pH, temperature, molecular mass, charge density, ionic strength, biopolymers ratio, and total biopolymer concentration, enable the formation of complex coacervation in chitosan–polysaccharide or chitosan–proteins mixtures [110–115]. The reported chitosan-based coacervate complexes in the literature are listed in Table 3. Among various external factors, pH control, influencing the charge profile and dissolved state of biopolymers, is crucial for chitosan-based coacervate complex formation.

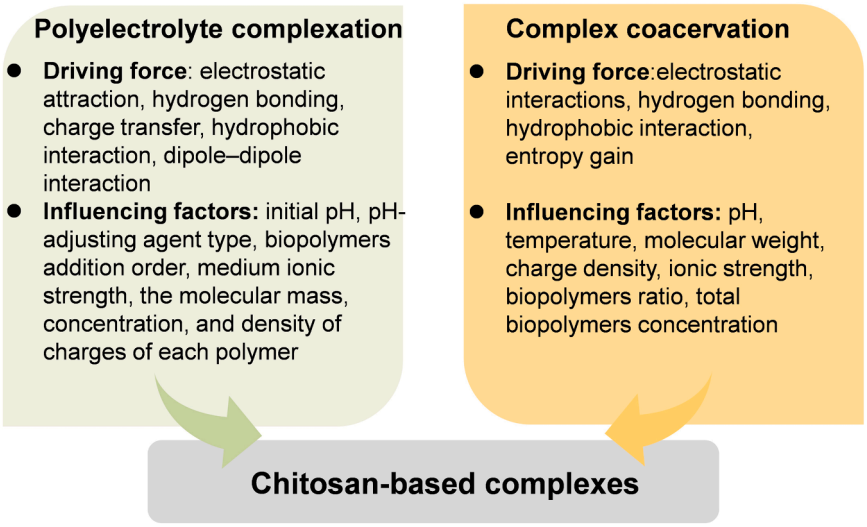


Fig. 6. Chitosan-based complexes.

Table 3
Chitosan-based coacervate complexes.

Combination	Forms	Fabrication method
Chitosan–alginate	Scaffold	Solution mixing + freeze-drying[224]
Chitosan chloride–HA	Scaffolds	Solution mixing + centrifugation[337]
Chitosan–HA	Nanofibers	Electrospinning[338]
	Hydrogel	Solution mixing + dialysisation[339]
		Mixing chitosan hydrogel with HA powder[220]
	Scaffolds	Solution mixing[297]
Lactose-modified chitosan–HA	Colloids	Solution mixing[112]
Chitosan–*Ostrinia furnacalis* cuticular protein hypothetical-1	Gel	Solution mixing[340]
Chitosan–gum Arabic	-	Solution mixing[113]
O-CMCh–gum Arabic	Porous materials	Solution mixing + GA crosslinking + freeze-drying [231]
N,*O*-CMCh–gum Arabic	Porous materials	Solution mixing + freeze drying[115]
Chitosan–type B gelatin	Microparticle	Solution mixing[114]
Chitosan–whey protein	Microparticle	Solution mixing[341]
Chitosan–soy protein	Bulk	Solution mixing[116]

Abbreviations: carboxymethyl chitosan (CMCh), glutaraldehyde (GA), hyaluronic acid (HA)

Moreover, physical treatments like shearing, high pressure, and ultrasound could also influence the formation of chitosan-based complex coacervates [116].

2.4. Processing strategies for chitosan-based materials in various forms

Processing strategies for chitosan-based materials are typically conducted using either solution or melt processing. For the context of chitosan-based materials' application scenarios, we will specifically delve into the discussion of solution processing. Solution processing is the most prevalent method, leveraging the solubility of chitosan in weak acid solutions. This characteristic enables chitosan to be seamlessly processed with other polymers into various material forms, such as particles, hydrogels, aerogels, membranes, films, and sponges. The ensuing subsections will explore the forms and corresponding processing methods of chitosan-based composite materials.

Overall, processing strategies for biopolymers need to effectively disrupt the hydrogen-bonding network in the original chitosan and create a pathway to establish new hydrogen bonds in the post-processed materials [117]. Typically, plasticizers are incorporated into chitosan-based systems to address material brittleness. This is achieved by diminishing inter-chain hydrogen bonding, facilitating molecular chain mobility, thereby enhancing flexibility and reducing material stiffness [14].

Residual acids, such as acetic acid, present in chitosan-based materials, exhibit corrosive properties [7] and may induce cytotoxicity (depending on concentration) [118–120]. These acids may also impede the formation of hydrogen bonds in chitosan induced by the rotational distortion of chitosan chains [121,122], consequently affecting the mechanical properties (e.g., decreased stiffness and strength) of chitosan-based materials. To address this, a subsequent step involving NaOH solution to neutralize the residual acetic acid, followed by rinsing with deionized water, is typically required. In a study [123], an alkaline agarose solution was employed during the production process to neutralize the acidic chitosan solution, eliminating the need for a separate neutralization step. Moreover, when using crosslinking agents such as glutaraldehyde (GA), it is often essential to remove the unreacted crosslinking agents to minimize cytotoxicity.

2.4.1. Biocompatible solvent systems used for chitosan-based materials

Considering the potentially toxic and immunological responses of biomedical materials upon exposure to the body, a judicious selection of solvents is imperative for biomedical applications. Regrettably, a comprehensive solvent guide for guiding the preparation of biomedical applications is currently absent. In response to the growing emphasis on green chemistry, various solvents, including water, renewable solvents (e.g., ethanol, organic acids, and glycerol), ILs, and DESs, have been explored [124,125]. However, it is essential to note that, aside from water, these green solvents should not automatically be deemed nontoxic.

Taking ILs as an example, many ILs exhibit high toxic potential toward bacteria, fungi, and cells by interacting with the cell membrane through the alkyl side chains of the IL cation [126]. Interestingly, there is a lack of uniformity in toxic activities, leading to the exploration of some, potentially less toxic, ILs in constructing drug delivery systems [126] and skin tissue engineering [127]. Typically, additional exhaustive washing with water is conducted to remove the IL from the polymer network [128].

DESs, especially natural ones formed through self-associated intermolecular interactions between hydrogen bond acceptors and donors [129], have recently garnered attention in materials science due to their

favorable properties—being inexpensive, nontoxic, biodegradable, easier to prepare, and highly biocompatible [130]. Combinations of choline chloride (a constituent of vitamin B) as a hydrogen bond acceptor and various natural organic acids, sugars, amino acids, and alcohols as green, renewable hydrogen bond donors are commonly explored for the preparation of natural DESs [129,131]. While pharmaceutical and biomedical applications of DESs have also been discussed [132], reports pointing to their toxicity have also surfaced [130].

Despite accumulating evidence suggesting the vast potential applications of ILs and DESs in biological-related fields, ongoing concerns about their toxicity have made major industries and scientific organizations hesitant to fully embrace these solvents. For the preparation of chitosan-based materials used in biomedical applications, acetic acid remains the most favored solvent. Acetic acid is deemed a relatively less hazardous solvent [120]. Additionally, a post-material preparation alkaline solution treatment process [7] can effectively eliminate any residual acid.

2.4.2. *Membrane/film*

Membrane or film is the most prevalent form of chitosan material, known for its permeability, selectivity, ion conductivity, and control-release capabilities [9133–135]. Various methods, including solution casting (i.e., solvent evaporation) [9,97,133,136,137], spin-coating [135], and freeze-drying followed by compacting [138], are employed for chitosan membrane preparation. When utilizing spin-coating, it is essential to use a support carrier with a smooth surface and a nanometer pore size, such as polyacrylonitrile (PAN) ultrafiltration membranes [135]. Karim et al. [138] demonstrated the creation of a compact membrane through compression molding of a chitosan-based porous material obtained via freeze-drying.

For chitosan-based film preparation, solution casting (Fig. 7A) stands out as the most widely employed method. Drying a chitosan solution, typically using acetic acid as a solvent, yields films with a smoother surface and even thickness. When selecting a solvent system for solution-cast chitosan-based films, consideration should be given to the solubility of chitosan or its derivatives and the nature of solvents. Taking acids as an example, the interactions between chitosan and acid ions vary depending on the nature of the acids. The choice of a proper solvent allows for the design of chitosan-based films with desired properties [58, 59]. It is crucial to ensure sufficient stirring to disintegrate biopolymer particles or aggregates in the film-forming solution [139].

Some researchers [140–148] utilized layer-by-layer (LbL) deposition methods (Fig. 7C) to create multilayer chitosan-based films based on the electrostatic interaction of oppositely charged polymers. LbL methods encompass dip-coating LbL assembly [142,146], spray-assisted LbL assembly [140], LbL drop-casting [147], and LbL electrostatic deposition [148]. In LbL deposition, various substrates (e.g., silicon substrate) are immersed in a layer-forming solution, followed by rinsing and drying steps [142,147]. The primary driving force in LbL self-assembly is electrostatic attraction after each deposition, with other interactions, such as van der Waals forces, potentially contributing to the multilayer formation [149]. Initiation of LbL assembly can stem from diverse driving forces, including electrostatic interaction, covalent and hydrogen bonding, charge transfer, and biological recognition [150]. Altering the immersion sequence and material type enables the construction of multilayer films with distinct structures and compositions, desired properties, and improved functions [151]. In addition, LbL assembly multilayer films typically demonstrate a high level of assembly uniformity, unaffected by the coating cycle [152].

LbL assembly boasts several technical advantages, such as easy operation, mild processing conditions, and cost-effectiveness, making it an increasingly favored method for preparing biomedical materials with desired substrates and biocompatible components [153].

2.4.3. *Hydrogel and ionogel*

The intriguing properties of hydrogels, such as high-water content (or high water-holding capacity (WHC), which differentiates hydrogels from other biomaterials) [28], biodegradability, biocompatibility, interconnected porous structure, adjustable swellability (achieved by varying the crosslinking density of the hydrogel matrix), and appropriate mechanical properties, position them as compelling biomaterials for scaffolds in constructing the ECM [154]. The design and fabrication of hydrogels have garnered significant attention for their applicability as structural platforms in biomedical contexts. The hydrogels in focus can manifest as either bulk hydrogels (Fig. 7A) or hydrogel beads/particles (microparticles, nanoparticles, and microspheres), with the latter elaborated upon in the subsequent section. Ionogels typically result from dissolving chitosan and other polymers in ILs, followed by cooling the composite solutions at room temperature (RT). Ionogels commonly exhibit excellent electrical conductivity [155].

In hydrogel design, a wide array of noncovalent and covalent dynamic bonds/interactions come into play [85]. Predominant dynamic bonding types encompass hydrogen bonding, ionic interaction, imine bonding, coordination, hydrophobic interaction, and the Diels-Alder addition reaction (see Fig. 5) [85,156]. Chitosan hydrogels frequently materialize through the application of crosslinking agents, including chemical crosslinkers and ionic crosslinkers (Fig. 8), forming covalent and ionic bonds, respectively. To establish enduring chitosan hydrogel

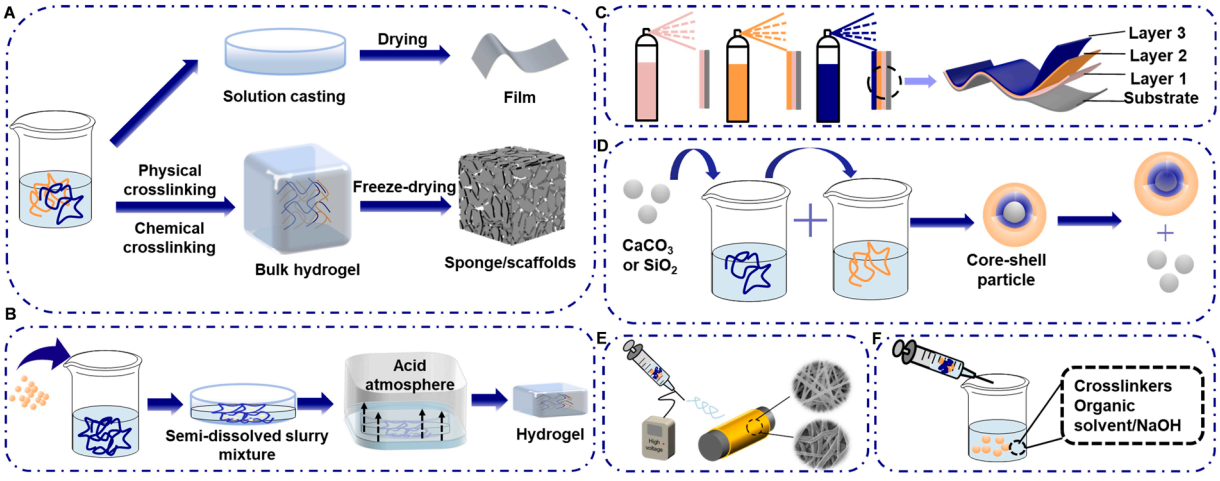


Fig. 7. Processing for chitosan-based materials including: (A) solution-based processing techniques to craft films, hydrogels, sponges, and scaffolds; (B) semi-dissolution acidification sol–gel transition method; (C) layer-by-layer (LbL) deposition methods; (D) sacrificial template method; (E) electrospinning; (F) inverse crosslinking–emulsion method.

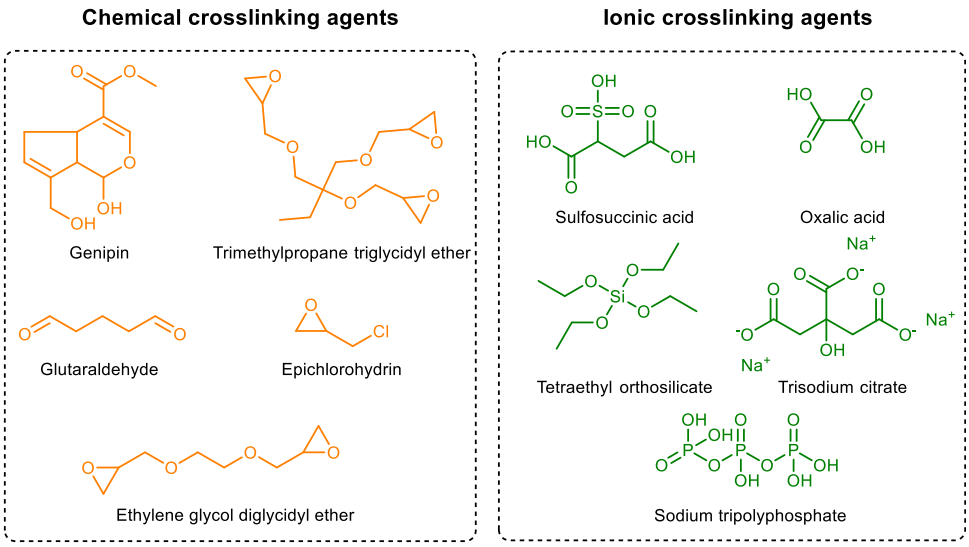


Fig. 8. Crosslinkers for chitosan.

lattices, a direct approach involves using a chemical crosslinking agent (Table 4) to form covalent bonding with chitosan chains. Any compounds with at least two functional groups allowing for a condensation reaction with the polymer may serve as a covalent crosslinking agent [157]. Ionic bonds between chitosan chains and ionic crosslinkers result from the electrostatic attraction of chitosan chains to ionic crosslinkers, with common ionic crosslinkers including citrates and polyphosphates [157]. Jóźwiak et al. [157] demonstrated that ionically crosslinked chitosan displayed a reinforced structure and reduced susceptibility to mechanical damages, while covalently crosslinked chitosan was typically harder but more fragile. Beyond the mentioned crosslinkers, alternatives like transglutaminase (TG, a protein crosslinking agent) can also be employed to develop chitosan-based composite hydrogels with protein (e.g., collagen and casein) by forming amide bonds between a basic amino acid residue and a glutamine residue [158,159].

Table 4
Commonly used crosslinking agents for chitosan-based materials and their crosslinking mechanisms.

Crosslinking agent	Mechanism of crosslinking	Ref.
GA	Schiff-base reaction between the aldehyde groups of GA and the amino groups of chitosan	[206, 342, 343]
Genipin	a) Nucleophilic attack of primary amine groups of chitosan on the dihydropyran ring of genipin; b) Formation of secondary amide based on the nucleophilic substitution between the amino groups of chitosan and the ester group on genipin	[169, 170]
ECH	Formation of covalent bonds between the hydroxyl groups of chitosan and the epoxide functional groups of ECH	[157]
Trimethylpropane triglycidyl ether	Formation of covalent bonds between the hydroxyl groups of chitosan and the epoxide functional groups of trimethylolpropane triglycidyl ether	[157]
EGDE	Formation of covalent bonds between the hydroxyl groups of chitosan and the epoxide functional groups of EGDE	[157]
TPP	Inter- and intra-molecular ionic linkage between the primary amino groups of chitosan and the negatively charged phosphate ions from TPP	[235]
Trisodium citrate	Crosslinking based on the ionic bonds between carboxyl groups of citrate and amino groups of chitosan	[157]
Tetraethyl orthosilicate	Crosslinking based on the Si-O-Si bond between tetraethyl orthosilicate and polymer chain	[276]
Sulfosuccinic acid	Crosslinking based on the ionic bonds between the carboxyl group of sulfosuccinate acid and the amino group of chitosan	[157]
Oxalic acid	Crosslinking based on the ionic bonds between the carboxyl group of oxalic acid and the amino group of chitosan	[157]

Abbreviations: glutaraldehyde (GA); epichlorohydrin (ECH), ethylene glycol diglycidyl ether (EGDE), sodium tripolyphosphate (TPP)

The suboptimal mechanical performance of hydrogels, often attributed to their high water content, intrinsic structural inhomogeneity, and lack of efficient energy dissipation mechanisms [160], can be addressed through effective methodologies aimed at enhancing homogeneity and incorporating energy-dissipation mechanisms [161]. A promising approach involves replacing traditional steady hydrogel networks with noncovalent dynamic linkages, resulting in dynamically crosslinked hydrogels with excellent self-healing ability (i.e., the ability to repair the destroyed network and maintain mechanical properties without external stimuli) and self-adapting capability [71,162].

Double-network (DN) hydrogels are well known for their exceptional mechanical properties, rivaling or even surpassing those of soft load-bearing tissues such as cartilage and tendon. These hydrogels feature two networks—a highly crosslinked, brittle matrix and a loosely crosslinked, ductile network—with heterogeneous structures and complementary properties. The rigid, brittle network effectively dissipates energy through bond scission, while the soft, ductile network maintains hydrogel integrity by withstanding large strain [160,161].

Conjoined-network hydrogels, comprising two or more networks connected by sharing interconnection points, prove effective in promoting toughness. The intertwined networks, featuring similar or equal energy dissipation mechanisms, distribute stress throughout the whole hydrogel system [161]. Physical amino-phytate domains enhance self-recovery and anti-fatigue capacity [161].

Hydrogels with multiple crosslinked networks have garnered tremendous attention for their improved mechanical properties. Engkagul et al. [106] constructed chitosan–hyaluronic acid (HA)-based triple network hydrogel based on a one-pot reaction. The HA was modified with alkyne and azide groups via EDC/NHS reaction to form HA-triazole linkages, forming metal coordination bonds between chitosan and Cu ions and contributing to triple network formation through polyion complexation between chitosan and HA [106].

While hydrogels with robust mechanical properties are crucial, their

utility in diverse applications is further enhanced by multifunctionality. The development of multifunctional hydrogels—possessing properties like injectability, antimicrobial capabilities, self-healing, shape adaptability, on-demand removability, shape memory, adhesive capacity (especially wet adhesiveness), near-infrared photothermal properties, and stimuli-responsiveness properties—has gained favor for practical applications. For example, self-healable hydrogels prove valuable in adapting to deformations caused by frequent body movement, mitigating negative effects (e.g., inflammatory response) associated with damaged hydrogel dressings during tissue repair or regeneration process [163]. The photothermal response of hydrogels can accelerate gelation and degradation in weak acid solutions, achieving timely on-demand gelation and degradation [80]. Various methods for fabricating chitosan-based hydrogel materials are commonly employed.

2.4.3.1. Phase inversion technique (i.e., acid-to-base pH inversion) (Fig. 7F). Pristine physically crosslinked chitosan hydrogel beads can be effortlessly crafted by dropwise addition of chitosan solutions into a NaOH solution (typically 0.1 M), followed by thorough washing with deionized water to eliminate residual solvents [164,165]. In addition, weak bases like β-glycerophosphate and $NaHCO_3$ can induce charge neutralization of chitosan during heating by transferring protons from chitosan to them. This process strengthens the hydrophobic interactions of chitosan chains, leading to the formation of a physical gel [10]. To enhance the mechanical strength of the resulting hydrogel, chemical crosslinkers like genipin and other polymers like carrageenan and chondroitin sulfate (CS) are commonly employed to form covalent and ionic bonds, respectively, with chitosan chains [10,164].

2.4.3.2. Gelation and soaking. Dipping a preformed chitosan-based composite hydrogel in an anionic salt solution can yield an unconventional hydrogel characterized by high modulus and toughness through amino–anion crosslinking. The pivotal factors in this process include the pH and concentration of the anionic salt solution used for soaking, the functionality (i.e., number of crosslinkable sites) of the crosslinker, and the diverse ionic combination [161]. Xu et al. [161] devised conjoined-network hydrogels by immersing a preformed chitosan–gelatin hydrogel into a sodium phytate solution. Phytate ions served as crosslinkers, forming amino–phytate domains through interaction with the amino groups of chitosan and gelatin. This conferred the hydrogel with exceptional anti-fatigue and self-recovery properties [161].

2.4.3.3. Methacrylamide (MA) modification and covalent photo-crosslinking (i.e., exposure to UV light). Exposure to UV light in the presence of a photoinitiator enables the formation of a covalently crosslinked network from the methacrylic groups of chitosan [160]. Commonly employed photoinitiators in the literature include 2-hydroxy-2-methylpro-piophenone photoinitiator [166], 2-hydroxy-4-(2-hydroxyethoxy)− 2-methylpropiophenone [160], and Irgacure D-2959 [90,91]. The resulting covalent photo-crosslinked hydrogels typically exhibited a stable structure over the long term, and their excellence is further highlighted by relatively short gelation times (as low as 60 s) with low-dose UV irradiation. However, hydrogel inks based solely on MA-chitosan for 3D printing face challenges in maintaining the initial geometry of the gel phase and achieving sufficient printing resolutions. This limitation arises because MA chitosan hydrogel inks with lower concentrations (<1.5%) usually possess low viscosity, impeding the formation of a steady flow during extrusion [166]. Chitosan conjugated with phenolic groups, such as catechol groups, can also undergo crosslinking through the Ru-catalyzed photo-crosslinking mechanism with a short gelation time (20 s) [92].

2.4.3.4. Chemical crosslinking. In the presence of chemical crosslinkers such as GA and genipin (an amine-reactive covalent crosslinker), a stable chitosan hydrogel can be achieved. The crosslinking mechanisms are detailed in Table 4. Hu et al. [167] engineered a shape-morphing chitosan hydrogel film through crosslinking via the Schiff-base reaction between the aldehyde groups of GA and the amino groups of chitosan. The resulting hydrogel exhibited distinct swelling and mechanical properties at different thickness levels, affected by the GA concentration gradient across the hydrogel thickness. While chemically crosslinked hydrogels may demonstrate good performance, the associated side effects should not be underestimated. Genipin, a naturally occurring crosslinking agent, with additional anti-inflammatory, anti-fibrotic, and neuroprotective properties, exhibits relatively lower cytotoxicity (3000-fold less cytotoxic) compared to other extensively used crosslinkers such as GA and ethylene glycol diglycidyl ether (EGDE) in bioprostheses development [168–170]. Tissues fixed with genipin even demonstrated mechanical strength and resistance against enzymatic degradation comparable to those fixed by GA [171]. Macaya et al. [169] suggested that the appropriate genipin concentration for in situ scaffold formation capable of delivering cells and therapeutic agents was 0.25–0.5 mM. However, GA remains the most widely used crosslinker due to its high efficiency and cost-effectiveness.

2.4.3.5. Ionic crosslinking. By utilizing negatively charged ions to ionically crosslink the positively charged amine groups of chitosan, a hydrogel could be formed [160]. In addition, the carboxyl groups of CMCh can establish coordination bonds with specific metal ions such as Fe^{3+} and Al^{3+}, resulting in an ultrafast gelation process (within 10 s). This process is notably faster than common chemical crosslinking methods used for hydrogel production (taking over 1 h) [71]. It is worth mentioning that CMCh hydrogels with a high DS (>0.75) exhibit a turbid appearance and an irregular flocculent structure, attributed to excessive crosslinking by Fe^{3+} in local regions [71].

2.4.3.6. Polyelectrolyte complexation. As detailed in **Section 2.3** , a chitosan-based composite hydrogel can be formed through the electrostatic interaction between positively charged chitosan and negatively charged polysaccharides. However, in solutions, the strong electrostatic interaction between cationic chitosan and polyanions often results in the precipitation of polyelectrolyte complexes. While beneficial for preparing microbeads or particles, this poses a challenge in achieving bulk PECs with a homogenous structure. To overcome this challenge, a semi-dissolution acidification sol–gel transition (SD-A-SGT) method was developed for preparing chitosan-based hydrogels (see Fig. 7B) [172–174]. In the semi-dissolution process, chitosan powder is uniformly dispersed in the prepared polyanion (typically alginate) solution to form a slurry-like mixture or suspension, instead of being directly dissolved in acetic acid solution. This mixture is then exposed to an acetic acid atmosphere to achieve the slow protonation of chitosan. As the acidic vapor permeates both the surface and interior of the mixture, a bulk hydrogel with controllable shapes can be obtained within 18–24 h. In addition to the SD-A-SGT method, a stable bulk hydrogel can also be achieved by slowly dropping aliquots of gellan gum aqueous solution into chitosan dilute aqueous HCl solution at 60 °C and then incubation at 25 °C for 2 h followed by soaking in deionized water, with the addition of NaOH to adjust the pH to 5.8 over a period of 6 h [62]. Clearly, the SD-A-SGT method is more straightforward but takes a relatively longer time. Chen et al. [175] reported that by thoroughly mixing HACC with alginate, solidifying for 48 h, immersing in acetic acid for 10 min, and washing until the eluate is neutral, a shapeable and conductive hydrogel can be obtained.

2.4.3.7. Schiff base crosslinking. Chitosan-based hydrogels can be formed through dynamic crosslinking via imine bonds, specifically the Schiff base reaction. Notably, the GA crosslinking process is a type of Schiff base reaction. However, to mitigate potential cytotoxicity associated with additional crosslinkers and avoid side effects induced by

radiant light sources, some studies opt to combine chitosan with aldehyde-modified polysaccharides to establish covalent and physical bonds, which are much more stable than electrostatic interaction. These polysaccharides, including HA, pectin [156], CS [176], gellan gum [177], and dextran [69,178], typically undergo modification through an alcohol phase reaction using sodium periodate as an oxidizing agent [179]. This results in aldehyde-modified derivatives that can undergo the Schiff base reaction when reacting with chitosan. By controlling the amount of sodium periodate, products with varying degrees of oxidation can be obtained [179]. Pectin with a higher aldehyde content (degrees of oxidation (DO): 33.56%) can form a stable three-dimensional network structure [156]. However, Nguyen et al. [180] reported that a lower oxidation degree (DO: 40%) of HA supported cell proliferation, cell attachment, and the wound healing process more effectively. Similar findings were reported by Chan et al. [69], who observed that chitosan-oxidized dextran aldehyde (DO: 25%) was non-cytotoxic (no overall impairment of cell migration) to mammalian cell lines, while the counterpart with 80% DO showed moderate in vitro cytotoxicity. However, the low-DO hydrogel exhibited decreased antimicrobial efficacy and anti-fibroblast activity [69].

2.4.4. Aerogel, cryogel, and sponge

Polymer aerogels are typically created through sol–gel chemistry, followed by either supercritical drying or freeze-drying [181]. Supercritical carbon dioxide ($scCO_2$) is employed in the drying process, yielding aerogels, whereas drying chitosan hydrogels in the air produces xerogels, lacking the fibrous structure or functional groups [182]. Another method involves crafting a chitosan-based hybrid aerogel through electrostatic self-assembly, followed by freeze-drying, with the resulting porous aerogel ideal for controlled drug delivery applications [183].

Apart from aerogel, chitosan-based porous materials encompass cryogels and sponges, albeit without the ultralow density and lightweight features of aerogel. Porous cryogels are easily obtained through cryogelation, a straightforward method typically employing an aqueous reaction mixture without the need for organic solvents [184]. Notably, the pore size and geometry of cryogels can easily be tailored by adjusting freezing conditions such as cooling rate and time.

Chitosan-based sponges are commonly prepared using freeze-drying [36–38,40,185–190] and freeze-gelation [191]. For chitosan–biopolymer composite sponges, a freeze-dried chitosan sponge can undergo in-situ polyelectrolyte complexation by immersion into a polymer solution followed by freeze-drying [187]. Alternatively, frozen chitosan-based mixtures can be freeze-dried [36–38,40,185,186,188–190].

Beyond these methods, there are alternative approaches to crafting porous materials. For example, the freeze-gelation method relies on thermally induced phase separation (TIPS) and immersion precipitation, primarily employed in the fabrication of porous scaffolds [191]. Additionally, a freeze-dried porous scaffold based on a single biopolymer, such as silk fibroin (SF), can be coated with chitosan [192].

2.4.5. Particles and fibers

Cationic chitosan can spontaneously interact with anionic polysaccharides in aqueous solutions, forming beads or microspheres through coacervation. The addition of a polyanion (e.g., alginate) solution into a solution of cationic chitosan under high-shear conditions results in the formation of core-shell structure PEC particles. The particle size is influenced by the net charge ratio between chitosan and the other polymers, as well as their molecular masses [103]. Electrostatic interaction enables the creation of nanoparticles coated with PEC multilayer films through LbL deposition [193].

Various methods, such as inverse crosslinking-emulsion (Fig. 7F) [194], sacrificial template (Fig. 7D) [195], nanoprecipitation [196,197], and sol-gel [198], have been employed to prepare chitosan-based nanoparticles [196–198], hollow nanocapsules [195], or composite microspheres [194]. Nanocapsules are achieved through the alternate deposition of oppositely charged polyelectrolytes onto micro/nanoscale templates (e.g., $CaCO_3$ microparticle), followed by removal under treatment by a chelating agent (e.g., ethylenediaminetetraacetic acid (EDTA)) or dissolution in an acidic medium [195]. Shu et al. [199] successfully synthesized chitosan–gelatin complex beads by utilizing the low-temperature coagulation of gelatin and the electrostatic interaction-induced crosslinking between chitosan and sodium tripolyphosphate (TPP, polyanion). The resulting complex beads exhibited homogeneous crosslinked structure and enhanced mechanical strength, with a chitosan–alginate PEC complex film on the bead surface improving sustained-drug-release performance.

For hydrogel particles, ionic crosslinking, exemplified by TPP (a small ion crosslinker with triple-negative charges), influences the size of TPP-crosslinked chitosan–HA nanoparticles with an interpenetrating polymer network (IPN) [104]. Also, it is possible to create porous microspheres based on biopolymers without using crosslinkers. For example, chitosan sponge microspheres, serving as a protein adsorbent with a hierarchical porous structure, were synthesized by Qiao et al. [200] using agarose involved forming chitosan–agarose microspheres via a simplified water-in-oil (W/O) emulsion from an alkaline/urea aqueous system. Subsequently, agarose was removed through heat treatment to create nanopores or nanochannels.

Chitosan-based nanofibers can be prepared through electrospinning or self-assembly via polyelectrolyte complexation [45,201–204]. Electrospinning, conducted in a high-voltage electrostatic field, is effective for producing nanofibers in the nanometer diameter range. Electrically charged jets move toward the collector, and nanofibers form on the collector with solvent evaporation (Fig. 7E). Nanofibers exhibit a high surface area, sufficient mechanical stability, and high fluid absorption capacity [45]. Those prepared through self-assembly via polyelectrolyte complexation generally have a smaller fiber diameter, higher surface area, more uniform distribution, and greater cost-effectiveness compared to electrospinning [45].

A recent paper reported the preparation of nanofibrous membranes (or mats) through multi-biopolymer (SF and chitosan) self-assembly and co-electrospinning [205]. Alternately depositing polyelectrolytes with opposite charges on a substrate surface through electrostatic force yielded multi-biopolymer self-assembled nanofibers. The resulting nanofibrous membranes exhibited excellent antibacterial activity and the ability to promote cell attachment, proliferation, migration, and wound healing.

3. Development and functional properties of biofunctional chitosan–biopolymer composite materials

3.1. Natural biopolymers used for chitosan–biopolymer composite materials

Chitosan can be combined with various other polymers to create macro-composite materials. While most synthetic polymers remain inert to degradation in a cellular environment [180], biopolymers offer additional advantages, including non-toxicity, bioabsorbability, and structural similarity to the natural ECM [180]. Additionally, these biopolymers possess intrinsic biocompatibility and biodegradability [206]. Similar to chitosan, other biopolymers contain polar groups (e.g., hydroxyl, carboxyl, and amino groups) in their molecular structures, facilitating strong interactions with chitosan.

A range of biopolymers, including polysaccharides (e.g., cellulose, starch, pectin, alginate, carrageenan, agarose, natural gums, dextran, HA, and CS), proteins (e.g., SF, collagen, gelatin, casein, keratin, whey protein, and soy protein), and lignin can be blended with chitosan. The chemical structure and properties of these biopolymers are detailed in Table 5. Macro-composites based on chitosan can exhibit combined characteristics or even synergistically enhanced properties derived from each polymer component, providing benefits for various applications.

Table 5
Chemical structure and properties of biopolymers for hybridization with chitosan.

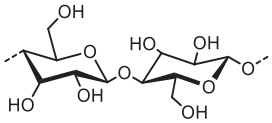
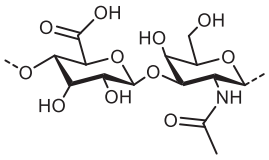
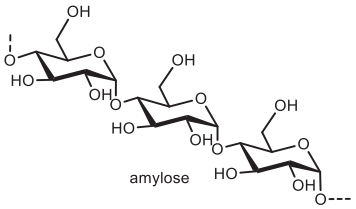
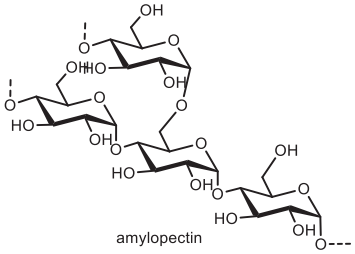
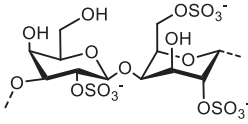
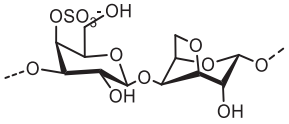
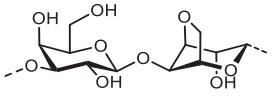
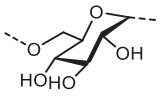
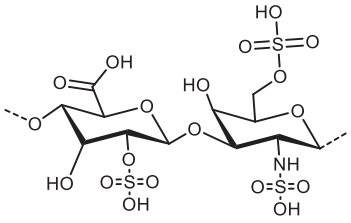
Biopolymer	Common source	Structure	Functional properties	Ref.
Polysaccharide				
Cellulose Derivatives: CMCe, carboxymethylated methylcellulose, oxidized cellulose	Wood, plant, tunicate, algae, and bacteria		-	[207,344, 345]
HA Derivatives: HA dialdehyde	Rooster combs, *Streptococcus equi*		– Mimic the ECM and articular cartilage environment – CD44-targeting property; – Free radical scavenging and antioxidant activities	[12,21,44, 179,219, 235,291]
Starch Derivatives: Microporous starch, ball-milling modified starch, dialdehyde starch, enzyme hydrolyzed starch	Roots, seeds, and tubers of different origins (e.g., corn (maize), potato, rice, and others)	 	–	[22,245, 252,277, 346–349]
λ-Carrageenan	Red algae *Chondrus armatus* (Gigartinaceae)		– Anticoagulant, antiviral, antitumor, and immunomodulatory activities	[23,43, 322]
κ-Carrageenan	*Eucheuma cottonii,* red algae *Chondrus armatus* (*Gigartinaceae*)			
Agarose Derivatives: oxidized agarose	Marine red algae		– Film-forming ability – Strong gelling power under mild conditions similar to the ECM	[123,155, 206,350, 351]
Dextran (pKa = 2) Derivatives: Dextran sulfate, oxidized dextran aldehyde	*Leuconostoc mesenteroides*		– Ease of chemical modification; – Soluble in polar solvents	[69,195]
Heparin sulfate	Cell surface and ECM		– Enhancing the affinity of antithrombin III to thrombin; – Accelerating the inactivation of thrombin and inhibiting adhesion aggregation of platelets; – Inhibiting bacterial adhesion and biofilm formation; – Repairing and regenerating various tissues	[8,74,241, 293,309, 352]

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Table 5 (*continued*)

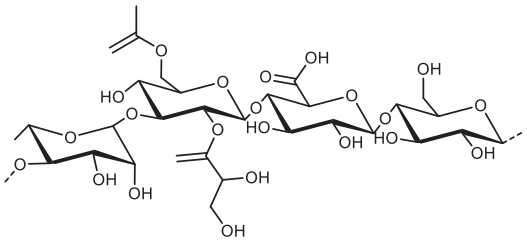
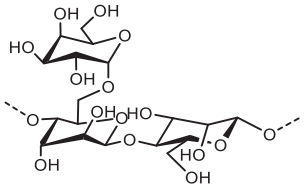
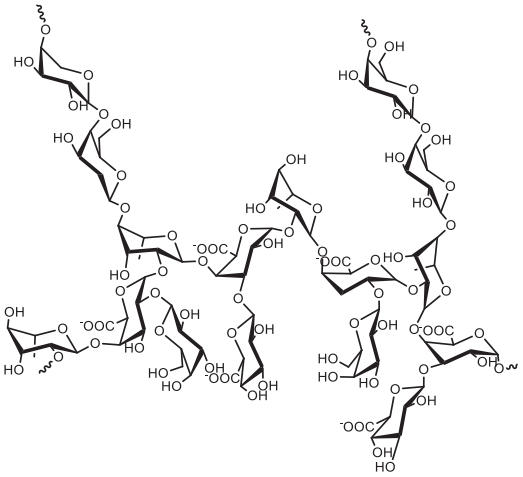
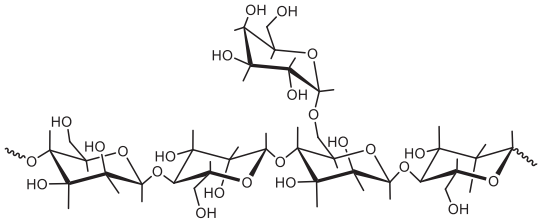
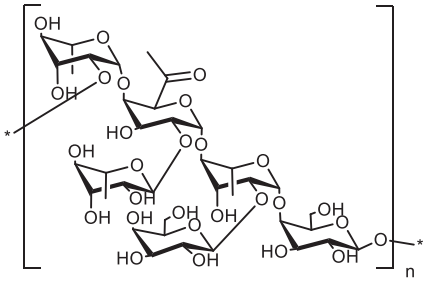
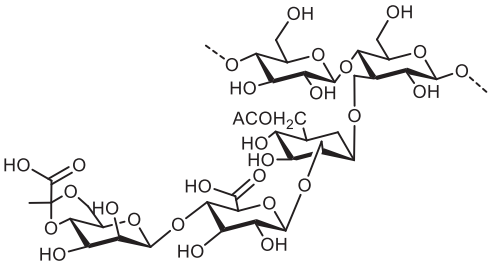
Biopolymer	Common source	Structure	Functional properties	Ref.
Gellan gum Derivatives: Oxidized gellan gum, methacrylated gellan gum	*Pseudomonas elodea*		– Forming strong gels at low concentrations (0.2% w/v)	[62,148, 177,210, 281]
Guar gum Derivatives: Cation guar gum	Endosperm of *Cyamopsis tetragonolobus* or *Cyamopsis psoraloides*		– Film-forming ability	[306,353, 354]
Karaya gum	*Sterculia urens*		-	[355]
Locust bean gum	Seeds of the carob tree (*Ceratonia siliqua*)		-	[279]
Katira gum	*Cochlospermum religiosum*		– Resistant to acidic pH in the stomach; – Susceptible to degradation by colonic bacterial enzymes	[280]
Xanthan gum (pKa = 3.1) Derivatives: Dialdehyde xanthan gum, sodium carboxymethyl xanthan gum	*Xanthomonas campestris*		-	[68,76, 356–358]

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Table 5 (*continued*)

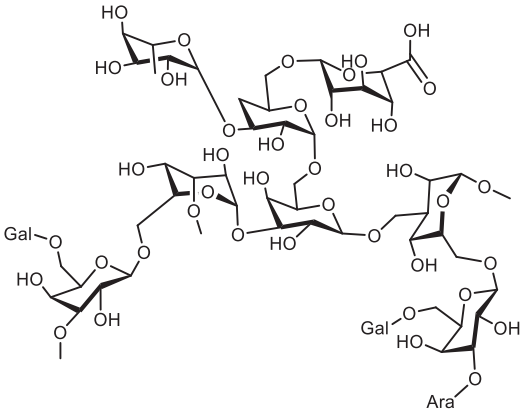
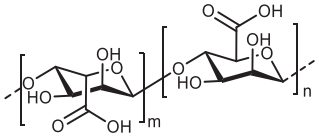
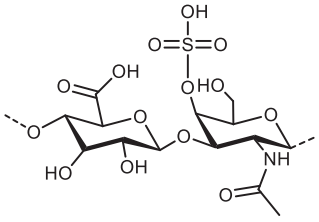
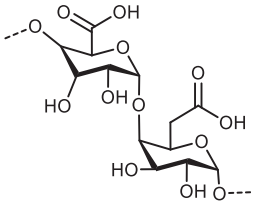
Biopolymer	Common source	Structure	Functional properties	Ref.
Gum Arabic	Stems and branches of acacia trees		– Stable in wide acid-base, high temperature, and high ionic strength environments	[9330, 359]
Alginate Derivatives: Oxidized alginate	Brown seaweed		– pH-sensitive; – Bio-adhesive; – Easy gelation when exposed to divalent cations such as Ca^{2+}	[318, 360–362]
Chondroitin sulfate Derivatives: Oxidized chondroitin sulfate	Bovine trachea		– Regulating immune response involved in chondrogenesis and bone formation; – Antioxidant and antiapoptotic activities, anti-inflammatory; – Triggering key mechanisms involved in cell migration and vascular repair	[10,100]
Pectin (pKa = 3.5) Derivatives: Oxidized pectin, furan-modified pectin	Citrus, sugar beet, apple, fruit peel extract		– Anti-inflammatory	[85,107, 246,272, 363]
Silk fibroin	*Bombyx mori* silkworms	Gly-Ser-Gly-Ala-Gly-Ala	– High permeability to oxygen and water; – Low inflammatory response – Relatively low thrombogenicity; – Protease susceptibility; – High tensile strength with flexibility; – Supporting cell adhesion and growth, promoting cell proliferation	[40,201, 205]
Collagen Derivatives: collagen peptide	Rat tail tendons, unicorn leatherjacket skin, fish skin and scales, bovine tendon, goat Achilles tendon	Gly-X-Y	– The main component of the ECM; – Excellent cell adhesion and biological activity; – Low immunogenicity; – Supporting cell attachment, migration, and proliferation	[24,276, 288,315, 364]
Gelatin	Bovine skin, porcine skin	Ala-Gly-Pro-Arg-Gly-Glu-4Hyp-Gly-Pro	– Low-temperature coagulation	[199,365, 366]
Casein (pI = 4.5) Derivatives: caseinate and casein phosphopeptides	Bovine milk	α_{S1}-, α_{S2}-, β-, and κ-casein (4:1:4:1, w/w)	– Promoting epithelial proliferation; – Restoring the epithelial barrier integrity; – Enhancing the hemostatic agent's wound-healing activity	[6,45,98]

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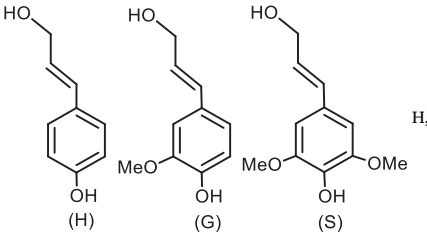
Table 5 (*continued*)

Biopolymer	Common source	Structure	Functional properties	Ref.
Keratin Derivatives: MA keratin	Chicken feather, wool, human hair	A (Cys-Cys-X-Pro-X) B (Cys-Cys-X-SerTher-SerTher)	– Good cellular interaction activity; does not elicit an immune reaction; – Supporting cell adhesion and proliferation	[17,26,93, 262,264, 367]
Whey protein Derivatives: whey protein isolate	Bovine, caprine, or ovine milk, and whey	α-lactalbumin, β-lactoglobulins, bovine serum albumin, lactoferrin, several immunoglobulins	– Excellent barrier performance against gases, lipids, and aromas; – Moderate mechanical characteristic	[18, 368–371]
Soy protein isolate	Soybean seeds	Albumins, globulins	– Good film-forming ability; – Hemostatic; – Hypoimmunogenic	[18,263, 372]
Rice protein hydrolysates	Rice protein	–	– High nutritional value, low water-vapor permeability	[139]
Egg yolk high-density lipoprotein	Egg yolk	α-lipovitellins, β-lipovitellins	– High protein content	[84]
Lignin Derivatives: alkali lignin	Sugar cane (*Saccharum munja*), a by-product from paper and wood mills	 H, G, and S refer to three primary lignin monomers: *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol, respectively	– High thermal stability; high adsorption capacity (higher than activated carbon in some cases); – Antimicrobial, antioxidant	[5,259, 373–376]

Abbreviations: extracellular matrix (ECM), glycosaminoglycan (GAG), hyaluronic acid (HA).

3.2. Modification of natural biopolymers

Merely blending chitosan or its derivatives with pristine natural biopolymers falls short of meeting the demands for the multi-function properties required in biomedical applications. Therefore, researchers often propose obtaining modified biopolymers through the rational functional design based on additional chemical or physical modifications. Among various chemical modification methods, carboxymethylation, methylation, methacrylation, acetylation, and selective oxidation have been extensively utilized to create biopolymer derivatives.

3.2.1. Carboxymethylation

Similar to chitosan, the carboxymethylation of polysaccharides, such as cellulose, enhances the water solubility of some water-insoluble polysaccharides. Carboxymethyl cellulose (CMCe), sharing a similar structure but possessing an opposite electric charge to chitosan, can form PECs with chitosan. In addition, carboxymethyl xanthan gum has been combined with trimethyl chitosan to prepare drug delivery systems [76].

3.2.2. Methylation

The methylation of polysaccharides like cellulose could yield derivatives with thermo-responsive behavior [207], as the hydrophobic interaction between methoxide groups may induce chain association under the lower critical solution temperature [208].

3.2.3. Methacrylation

Methacrylation involves the reaction of biopolymers with methacrylic anhydride at a certain temperature (varies by biopolymer type), followed by dialyzing against distilled water and lyophilization [166, 209,210]. Biopolymers such as gelatin and gellan gum, when methacrylated, provide additional stability to chitosan-based composites through photo-crosslinking. Compared to native gelatin, methacrylated gelatin, for instance, exhibits thermal sensitivity and photo-crosslinking ability, forming hydrogels below gelation temperature (25 °C) or upon exposure to UV light [166].

3.2.4. Acetylation

Acetylation usually enhances biopolymers' physiochemical properties. Acetylated HA, for example, exhibits increased bioavailability and improved anti-inflammatory activity compared to the short half-life, quick degradation in vivo, and poor bioavailability of non-acetylated HA [154,211]. The acetylation process involves dissolving biopolymers in formamide through vigorous stirring at a specific temperature, sometimes followed by the addition of pyridine. Subsequently, acetic anhydride is introduced for further reaction, and the final product is obtained through dialysis and lyophilization [154].

3.2.5. Selective oxidation

The oxidation of natural polysaccharides involves periodate oxidation and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)-mediated oxidation [212]. The latter is normally used for the selective conversion of hydroxyl groups of cellulose to carboxyl groups of oxidized cellulose [213,214]. The resulting products from TEMPO-mediated oxidation usually have a nanoscale presence. Hence, in this review, we focus on periodate oxidation, widely used for the preparation of oxidized polysaccharides.

Polysaccharides can be conveniently oxidized by sodium periodate ($NaIO_4$) to form an oxidized product, enabling a Schiff base reaction with chitosan or its derivatives. The oxidization, usually conducted in the dark by continuously stirring the mixture solutions of polysaccharides and $NaIO_4$ for 2–24 h, is followed by terminating the reaction using ethylene glycol/diethylene glycol and subsequent dialysis purification. This process results in the cleavage of C2—C3 bonds, forming dialdehyde functions per ring. Chitosan-based composites with favorable physiochemical properties are obtained through dynamic covalent imine bonds formed in the Schiff base reaction, eliminating the

need for chemical crosslinkers. Table 6 lists some common chitosan–oxidized polysaccharide combinations reported in the literature.

3.3. Functional properties of chitosan–biopolymer composite materials for biomedical applications

Chitosan-based composite materials are pivotal in advanced biomedical applications. The synergy of chitosan and other biopolymers is anticipated to showcase outstanding biomedically related functional properties such as injectable and self-healing capabilities, stimuli-responsiveness, targeted effects, antimicrobial activity, and hemostatic activity. These different functional properties are outlined below.

3.3.1. Injectable, self-healing, and self-adaptability

Injectable and self-healing properties are two important qualities of chitosan-based composite hydrogels used for biomedical applications such as implanted biomaterials in minimally invasive surgery [163,215]. The self-healing feature not only enhances fault tolerance but also reduces material waste [85]. Even when subjected to external tensile strength after healing over time, hydrogel materials with self-healing ability could maintain the integrity of the healing surface (Fig. 9A) [163]. Some highly adhesive hydrogel materials enable instant reconnection [80]. The self-adaptability of hydrogel materials is a valuable trait for applications such as wound dressing, ensuring automatic adaptation to irregular regions and optimal response to limb movements.

The combination of chitosan and other biopolymers, facilitated by dynamic bonds, including dynamic covalent and noncovalent interactions, has garnered considerable attention. This pairing results in hydrogels with injectable and self-healing abilities. The reversible nature of the dynamic bonds in a sliced hydrogel allows for dissociation and subsequent re-formation once the damaged surface comes into contact [176]. More details can be seen as follows.

3.3.1.1. Covalent interaction. Harnessing dynamic covalent bonds, established through Schiff-base crosslinking between amino groups of chitosan or hydrazide groups of adipic acid dihydrazide (ADH) and aldehyde groups of oxidized polysaccharides (e.g., oxidized chondroitin sulfate (OCS), oxidized hyaluronic acid (OHA), and oxidized pectin), along with Diels-Alder reactions, extensive investigations have delve into the injectable and self-healing attributes of chitosan-based composite materials [85,176,216–218]. For instance, an *N*,*O*-CMCh–OCS hydrogel, formed by Schiff base interactions, including imine and acylhydrazone bonds, seamlessly merged after 0.5 h without external intervention [176]. The self-healing prowess of a glycol chitosan-oxidized HA–ADH hydrogel, featuring two types of covalent interaction (imine and acylhydrazone bonds), enabled the creation of 3D constructs using 3D extrusion printing, eliminating the need for post-gelation or additional crosslinking processes [217,218]. Furthermore, the Diels-Alder reaction between maleimide-modified chitosan and furan-modified pectin resulted in a hydrogel capable of self-healing after contacting at 37 °C for 5 h and bearing a 500 g weight without sustaining damage [85].

Table 6
Periodate oxidation of natural polysaccharides.

Combination	Forms of composite materials
Chitosan–dialdehyde chitosan	Film with good mechanical strength [377]
N-succinyl chitosan–oxidized alginate	Biodegradable hydrogel [318]
Chitosan–oxidized alginate	Multilayered film [362]
Chitosan–oxidized agarose	Film [351]
CMCh–oxidized chondroitin sulfate	Injectable hydrogel [275,296], biocompatible hydrogel [293]
N,*O*-CMCh–oxidized chondroitin sulfate	Injectable, self-healing, antibacterial, and hemostatic hydrogel [176]
Succinyl chitosan–dextran aldehyde	Hydrogel [69,178], injectable hydrogel [292]
Hydroxypropyl chitosan–dextran aldehyde	Nanoparticle [378]
CMCh–oxidized gellan gum	Biodegradable hydrogel [177]
Chitosan–cationic guar gum	Hydrogel [354]
Chitosan–oxidized xanthan gum	Hydrogel [68]
Chitosan–hyaluronic acid dialdehyde	Hydrogel [269,379,380], nanoparticle [179]
N,*O*-CMCh–hyaluronic acid dialdehyde	Hydrogel [180,216]
Glycol chitosan–hyaluronic acid dialdehyde	Self-healing hydrogel [218]
CMCh–collagen peptide–oxidized konjac gulcomannnan	Hydrogel [315]
Chitosan–oxidized pectin	Injectable and self-healing hydrogel [156], nanofiber membrane [246]
Chitosan–collagen–hyaluronic acid–dialdehyde starch	Scaffold [381], sponge [349]

Abbreviations: carboxymethyl chitosan (CMCh).

3.3.1.2. Noncovalent interactions. The self-healing ability of chitosan-based hydrogels can also be realized with reversible noncovalent interactions, encompassing electrostatic interaction (i.e., ionic interaction), hydrogen bonding, and hydrophobic interactions. The significant resemblance and compatibility, along with hydrogen bonds and polyelectrolyte complexation between chitosan and its derivatives CMCh, played a crucial role in the self-healing ability of a chitosan–CMCh hydrogel (Fig. 9C) [172]. In a study by Lu et al. [219], electrostatic interaction between amphiphilic carboxymethyl hexanoyl chitosan and HA (M_w: 15–30 kDa) was harnessed to induce carboxymethyl hexanoyl chitosan to form colloidal particles. Stir-induced shear stress overcame the repulsion barrier of carboxymethyl hexanoyl chitosan colloidal particles, resulting in the formation of an injectable hydrogel. Notably, while high- and medium-molecular-mass (1000 kDa and 200 kDa) HA led to flocculation, it did not result in gel formation.

In addition, a thermo-irreversible injectable *N*-hexanoyl glycol chitosan–acetylated HA, developed through ionic interaction, hydrogen bonding, and hydrophobic interaction, exhibited sol-gel transition behavior. This property renders it suitable as an injectable scaffold system for cartilage regeneration [154]. However, it is essential to highlight that certain hydrogels, like the chitosan–HA hydrogel based on complex coacervation, may lose injectability once under specific pH conditions (pH 6–7) due to coacervation between chitosan and HA [220].

3.3.1.3. Multiple crosslinking. Some hydrogel systems exhibit a combination of covalent bonding and noncovalent interactions, particularly when chitosan is paired with oxidized polysaccharides like oxidized pectin. This pairing allows for the formation of polyelectrolyte complexation and Schiff base reaction [156]. An injectable, self-healing, and shape adaptability glycol chitosan–catechol-modified oxidized HA–guar gum hydrogel, enhanced with borax, was achieved through multiple-dynamic-bond crosslinking. This involved imine bonds between glycol chitosan and catechol-modified oxidized HA, borate/didiol interactions between guar gum and borax, and hydrogen bonding between guar gum or catechol-modified OHA (Fig. 9A, B) [163]. The hydrogel formed by the Schiff base between gallic acid-grafted chitosan–oxidized *Bletilla striata* polysaccharide and the pyrogallol–Fe^{3+} coordination bond displayed remarkable self-healing properties. It successfully lifted a weight of 20 g after being cut and allowed for self-healing (Fig. 9D) [80].

3.3.2. Stimulus-responsive properties

Stimulus-responsive material systems, capable of undergoing phase transitions in response to changes in the application environment, such as variations in pH, temperature, light, ionic strength, electric field, magnetic field, and even Redox, have garnered considerable attention.

pH-responsive properties play a pivotal role in the controlled release

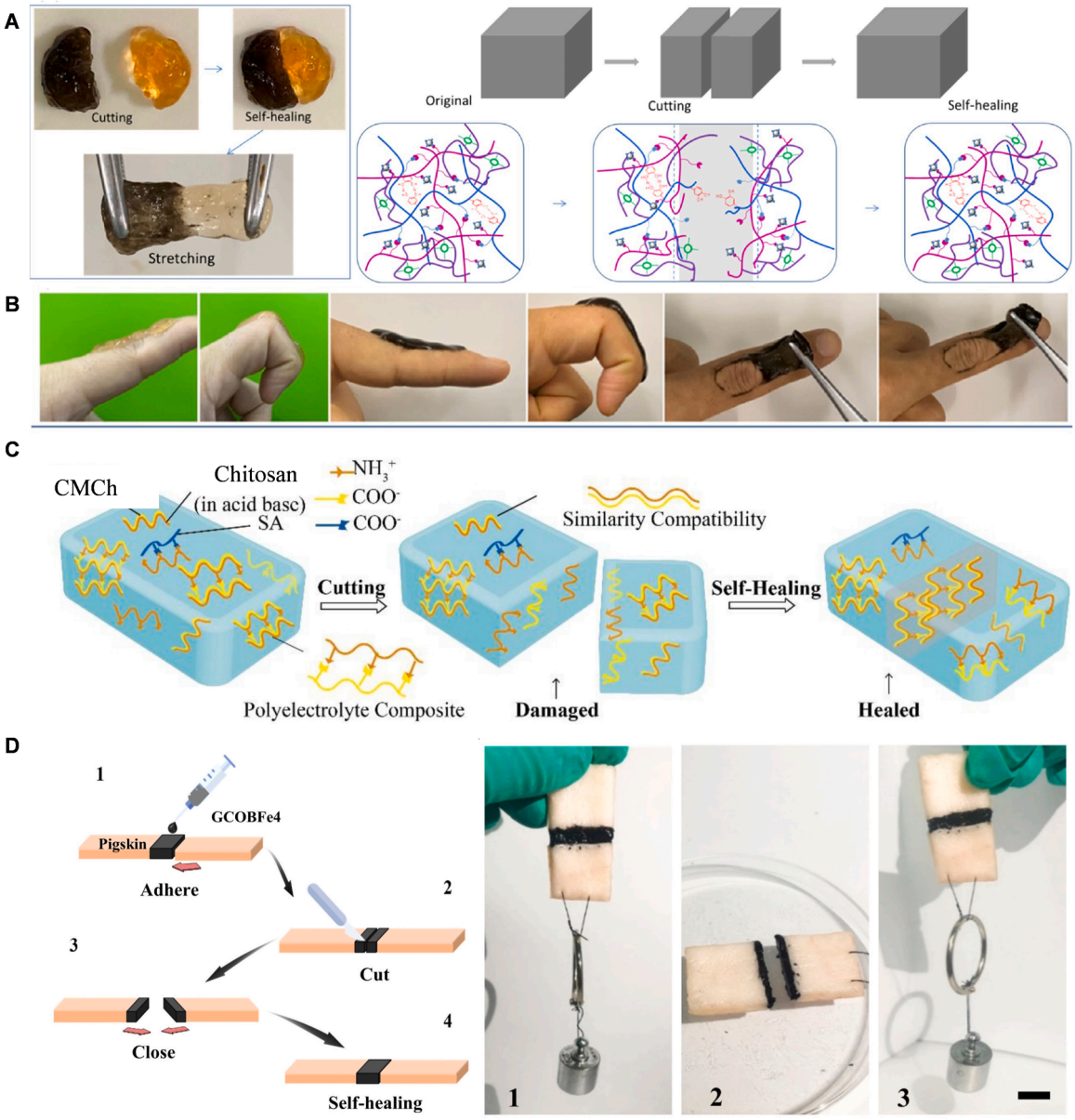


Fig. 9. Self-healing ability (A) and self-adaptability (B) of the glycol chitosan–catechol-modified oxidized hyaluronic acid–guar gum hydrogel [163]. Copyright 2022. (C) Self-healing mechanism of the chitosan–carboxymethyl chitosan hydrogel [172]. Copyright 2020. (D) Self-healing property of the gallic acid-grafted chitosan–oxidized *Bletilla striata* polysaccharide hydrogel [80]. Copyright 2021.
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behavior of chitosan-based composites used for drug delivery. The pH-dependent swelling behavior hinges on the ionization (depending on the pKa) of the $-NH_2$ (pKa 6.5) and —COOH (pKa 4.57)/$-OSO_3H$ (pKa 2.6) groups of chitosan and other polysaccharides (e.g., pectin, cellulose, CMCe, CMCh, alginate, HA, and CS) at different pH conditions. The $-NH_2$, $-OSO_3H$ and —COOH groups exist as $-NH_3^+$, $-OSO_3H$, and $-COOH_2^+$, respectively, with pH < pKa but change to be $-NH_2$, $-OSO_3^-$, and $-COO^-$ group under pH > pKa [85,128,221]. The electrostatic repulsion of negatively charged groups at high pH values (pH > pKa) reduces interactions (either polyelectrolyte complexation or complex coacervation) between chitosan and other polysaccharides, destabilizing the polymer network and cause expansion [128,222,223].

Drawing inspiration from the distinct swelling behaviors of a chitosan hydrogel and a cellulose–CMCe hydrogel at the same pH, a bilayer chitosan/cellulose–CMCe hydrogel with self-rolling deformation ability was developed. This attribute resulted from tight interfacial adhesion caused by the strong electrostatic attraction between the positively charged chitosan and the negatively charged cellulose or CMCe layers, was developed (Fig. 10A). The deformation speed of the hydrogel could be increased by elevating the medium temperature [221]. However, excessive swelling behavior is undesirable in tissue engineering applications, as continuous swelling may compromise the mechanical integrity of materials and exert compressive stress on surrounding tissue [224]. A scaffold with a stable structure, without excessive swelling, could be obtained through complexation between chitosan and alginate, thereby preventing the protonation of $-NH_2$ of chitosan [224].

Besides pH, ionic strength stands out as another crucial factor influencing the swelling behavior of chitosan-based composite materials. Ionic bonds, breakable at high ionic strength but reformable at low ionic strength [100], play a role in shaping polyelectrolyte complexation and complex coacervation between chitosan and other biopolymers. Adding 0.4 M NaCl into phosphate-buffered saline (PBS) notably increased the release behavior of chitosan–xanthan gum PEC film-coated tablets compared to PBS alone [228].

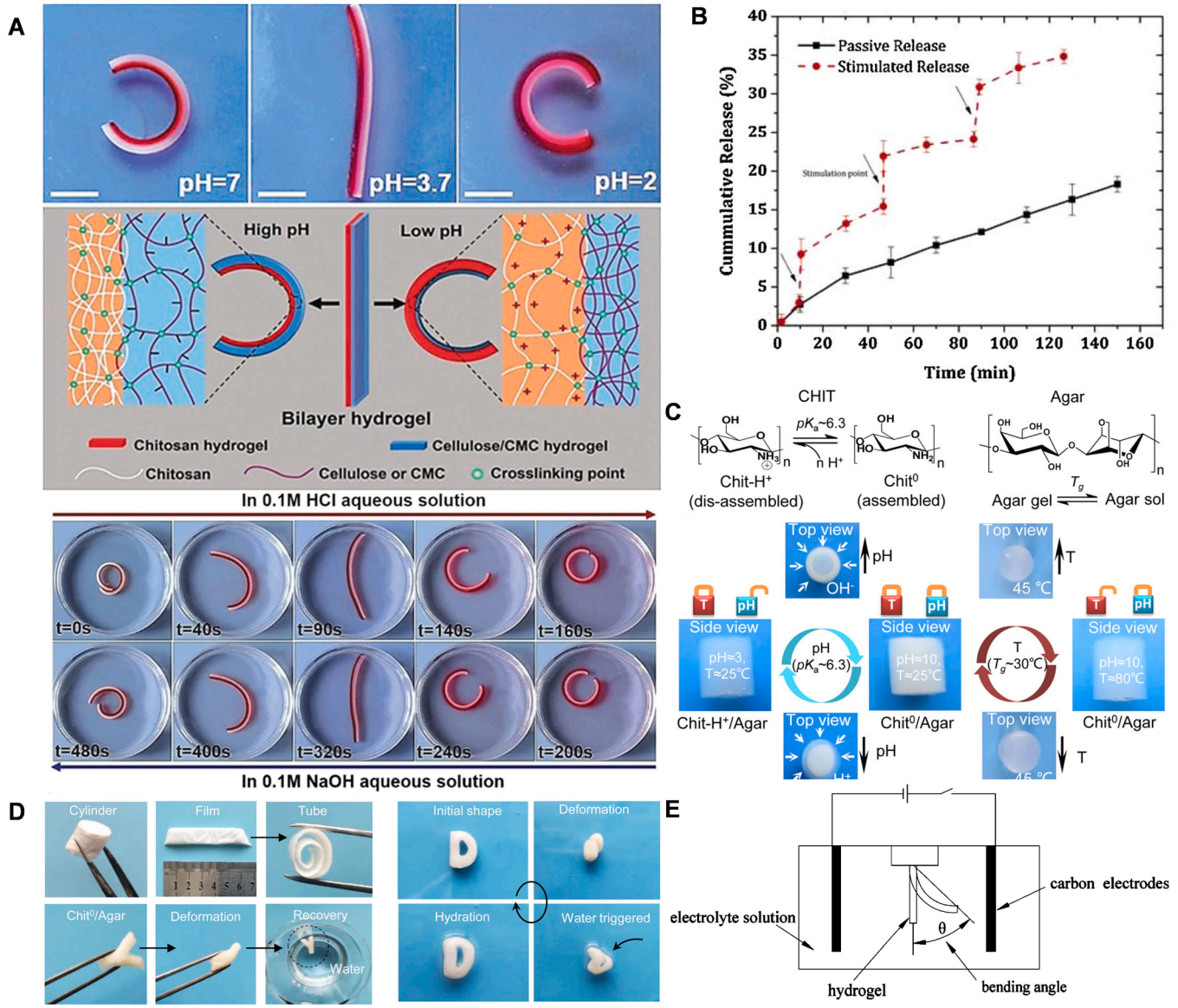

Fig. 10. (A) Schematic representation of the self-deformation of the chitosan–(cellulose–carboxymethyl cellulose) bilayered hydrogel [221]. Copyright 2017. (B) On-demand drug release patterns of the chitosan–alginate–agarose hydrogel [225]. Copyright 2019. (C) Dual responsiveness properties and (D) shape-memory performance of the chitosan–agarose hydrogel [226]. Copyright 2020. (E) Schematic representation of the bending behavior of the chitosan–carboxymethyl cellulose polyelectrolyte complex hydrogel under an electric field [227]. Copyright 2008.
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Thermosensitive materials, especially injectable hydrogels (in a liquid state at physiological pH at RT), could be delivered in vivo to a targeted site through simple injection and form a gel based on a thermal gelation mechanism, which does not need any surgical procedures and can minimize damage to surrounding tissue [10]. An injectable chitosan-CS thermosensitive hydrogel was developed in the presence of a gelling agent (β-glycerophosphate and $NaHCO_3$). The transfer of protons from chitosan to β-glycerophosphate and $NaHCO_3$ during heating (37 °C) facilitated attractive interchain forces (hydrophobic interactions) between chitosan molecules, resulting in the formation of a physical gel. This renders it a promising material for the delivery of therapeutic cells [10].

Electrical stimulation, capable of inducing chain rupture or polarity changes, offers a means to finely regulate drug release [225]. The introduction of electroconductive oligomers, such as aniline pentamer, into a chitosan–alginate–agarose hydrogel enabled on-demand drug release under external electrical current stimulations (Fig. 10B) [225]. Shang et al. [227] devised a chitosan–CMCe PEC hydrogel with reversible bending behavior under an electric field (Fig. 10E). The bending behavior was also affected by pH and ionic strength, with the maximum equilibrium bending angle achieved at pH 5–6 with 0.2 M ionic strength.

Apart from the aforementioned stimulus-responsiveness, another intriguing property is redox-sensitivity. Disulfide-crosslinked thiolated chitosan–HA microparticles can be degraded in the presence of dithiothreitol, a disulfide-cleaving agent, due to the cleavage of disulfide crosslinkages [229].

Materials with single responsiveness often fall short of the demands in biomedical applications. The combination of chitosan with pH-responsiveness and agar with thermal responsiveness results in a composite material with dual responsiveness. The resulting materials, featuring various shapes, also exhibited shape memory performance

(Fig. 10C, D) [226]. According to Chen et al. [230], the reversible formation and disassociation of hydrogen bonding between amino groups of chitosan and amide groups of SF allowed a chitosan–SF hydrogel to exhibit reversible pH-sensitivity and ion-sensitivity, making it suitable for use as an artificial muscle.

3.3.3. Biological functions

3.3.3.1. Targeting properties. Targeting properties play a vital role in biomedical applications, as they enhance the delivery of drugs, bioactive compounds, and even RNA, significantly improving their bioavailability. The targeting mechanisms of chitosan-based composites discussed here fall into three main categories: i) mechanisms akin to the stimulus-responsive properties of chitosan-based composites, primarily based on polyelectrolyte complexation or complex coacervation between chitosan and other biopolymers; ii) ligand–receptor-mediated targeting mechanism; and iii) contributions from the charge conversion of chitosan.

The encapsulation by chitosan-based composite materials serves to protect drugs or bioactive compounds against the harsh environment of the gastrointestinal tract, allowing them to function only at target locations [223,231]. It is crucial to note that the "targeted delivery" mediated by polyelectrolyte complexation and complex coacervation is more accurately described as controlled release behavior rather than truly targeted delivery.

Apart from utilizing interactions between chitosan and other biopolymers, targeting properties can also be achieved through the coupling of specific ligands. Conjugating specific ligands (e.g., cetuximab [232], HA [179,233–236], and folate [237]) to the surface of chitosan-based materials imparts the capability to recognize relevant moieties (epidermal growth factor receptors (EGFRs), CD44, and folate receptors (FRs)) on the target tissue through a ligand–receptor-mediated targeting mechanism, enabling the selective delivery of the active cargo. For example, FA-conjugated chitosan-based materials could enhance drug uptake in colorectal cancer cell lines, relying on folate receptor-mediated endocytosis [237].

Glycol chitosan has been reported to exhibit a specific self-adaptive targeting ability toward pathologically inflamed tissues in an acidic microenvironment (about pH 6.3) without causing harm to normal and healthy tissues (around pH 7.4) [238]. The charge-conversion property of glycol chitosan enables it to boost the accumulation of glycol chitosan-coated nanoparticles in lesion regions, leveraging electrostatic attractions between negatively charged cell membrane surfaces and positively charged nanoparticles.

3.3.3.2. Antimicrobial activity. Chitosan-based composites stand out as exceptional materials for wound healing, blood purification, tissue engineering, and coatings in biomedical implant applications, thanks to their potent broad-spectrum antibacterial activity. The primary antimicrobial mechanisms of these composites encompass contact-killing, photothermal antibacterial action, and the prevention of bacterial adhesion by enhancing the material surface's hydrophilicity. The anti-adhesive capability of the materials plays a pivotal role in combating bacteria, as the initial adhesion of bacteria may swiftly evolve into biofilm [239].

To assess the antimicrobial effectiveness of chitosan-based composite materials, a commonly employed method is inhibition zone tests. Biopolymer cationic charges attract bacterial cells electrostatically, with the biopolymer inserted into the bacterial membrane, leading to lysis and bacterial death [18]. Notably, not all bacteria with damaged membranes die immediately. Wang et al. [18] found some damaged bacteria treated with quaternized chitosan–soy protein isolate (SPI) sponge could survive and form new bacterial communities. Additionally, Wu et al. [205] reported that protuberances of chitosan–type I collagen nanofibers could enhance bacterial contact, contributing to improved antibacterial capacity.

Despite OCS having the minimal antibacterial ability, an *N*,*O*-CMCh-OCS hydrogel demonstrated enhanced antibacterial efficacy against both S. aureus and E. coli, possibly due to the Schiff base formed between *N*,*O*-CMCh, and OCS [176]. Similarly, a chitosan–rapeseed protein hydrolysate film exhibited superior antimicrobial activity compared to its individual components, with bioactive peptides generated by rapeseed protein isolate hydrolysis suspected to contribute to this activity [240]. Generally, the antibacterial activity of chitosan-based materials correlates positively with the content of antibacterial substances. However, Zhang et al. research [241] indicated that CMCh–heparin one-bilayer coatings exhibited superior antibacterial activities compared to three-bilayer coatings and five-bilayer coatings, possibly due to easier diffusion of CMCh from the one-bilayer, leading to enhanced contact with bacteria.

Another approach to exploring antimicrobial materials involves combining biopolymers with antibacterial properties. Chitosan–lignin composites displayed increasing antibacterial activity with a higher amount of added lignin (1–5 wt%) [242]. The inherent antibacterial activity of both chitosan and CS resulted in a chitosan–CS PEC scaffold demonstrating robust antimicrobial activity [243]. Certain chitosan-based composites, like a gallic acid-grafted chitosan–oxidized *Bletilla striata* polysaccharide–Fe^{3+} hydrogel with a photothermal effect, exhibited a rapid bactericidal effect against *S. aureus* after 5 min of pure NIR radiation [80]. Introducing exogenous substances like quercetin and triclosan (an antibacterial molecule with proven efficacy) further enhanced the antimicrobial activity of chitosan-based composites. Quercetin-impregnated chitosan–fibrin scaffolds demonstrated better bacterial inhibitory effects than chitosan–fibrin scaffolds [19]. The addition of triclosan further improved the antibacterial activity of a chitosan–HA PEC five-bilayer coating, attributed to increased surface hydrophobicity [244]. Incorporating polydopamine nanoparticles (a photothermal conversion agent with high photothermal conversion efficiency) into a chitosan-based hydrogel yielded an excellent photothermal antimicrobial ability [163].

Noteworthy is the fact that while some chitosan-based materials may exhibit substantial antimicrobial activity initially, a decline in antibacterial efficiency over time due to bacterial self-adaptation remains a challenge in current research. Existing assumptions often guide research on the antibacterial properties of materials, emphasizing the need for deeper theoretical exploration.

3.3.3.3. Adhesive properties, adhesion-preventive properties, and on-demand removability. Materials showcasing exceptional adhesive properties have garnered significant attention for their promising applications in wound dressing, buccal drug delivery, and eye administration. The mucoadhesive properties of polymer matrices hinge on their ability to hydrate and swell, along with their capacity for physical interactions, such as polymer chain interpenetration and entanglement, and chemical association with mucin glycoprotein [245].

Blending chitosan with other polymers, such as ball-milled modified glutinous rice starch, proves effective in enhancing chitosan's limited mucoadhesive ability, especially at high pH (>pKa) [245]. Electrostatic interactions between chitosan and anionic phosphates on the hydroxyapatite surface, coupled with the hydrophilicity, surface polarity, and intermolecular hydrogen bonding capability of oxidized pectin, resulted in a chitosan-oxidized pectin material with dual soft–hard tissue adhesive properties [246]. Chitosan–dextran sulfate nanoparticles, exhibiting mucoadhesiveness, firmly adhered to the ocular surface [16]. The presence of pyrogallol and aldehyde groups within a gallic acid-grafted chitosan–oxidized *Bletilla striata* polysaccharide–Fe^{3+} hydrogel imparted excellent adhesion strength, comparable even to most commercial fibrin glue (2–40 kPa) [80]. Chen et al. [175] reported that a PEC hydrogel from chitosan, HACC, and alginate could firmly adhere to the skin and other organs (e.g., heart, liver, spleen, lung, and kidney) of rats.

The introduction of mussel-inspired catechol groups into chitosan-based composites, facilitated by mussel-inspired chemistries, introduces adhesive properties to these polysaccharides for biomedical applications. Catechol groups from dopamine [247], gallic acid [80], and hydrocaffeic acid [83,248] have proven effective. Catechol groups form covalent bonds with the amine, imidazole, and thiol groups of mucin on the skin surface through Schiff-base and Michael-type reactions [163,247]. Catechol can be transformed into catechol-quinone groups in the presence of $NaIO_4$, further increasing adhesive strength through initiated intermolecular crosslinking [163]. Catechol-modified succinyl chitosan–catechol-modified HA nanoparticles exhibited excellent mucoadhesive properties on *ex vivo* porcine oral mucosal tissues even after washing with artificial saliva [247]. Rapid inter-chain crosslinking, induced by hematin-grafted chitosan, significantly enhanced tissue adhesion in hematin-grafted chitosan-catalyzed catechol-conjugated hydrogels [248].

Beyond mucoadhesiveness, cell-adhesiveness is crucial. Considering the specific binding of HA and CD44, the incorporation of HA promoted the adhesion of cancer cells to a chitosan–HA–β-glycerophosphate hydrogel [249]. The weakly charged surface of chitosan–carrageenan PEC hydrogel supported attached cell growth [250]. Chitosan-based composites with a larger surface area-to-volume ratio, like nanoparticles, exhibited superior mucoadhesive properties, providing more room for mucin adsorption [232].

To assess the adhesive properties of chitosan-based materials, different force experiments can be conducted to obtain adhesive parameters, such as shear strength (determined by lap-shear tests), interfacial toughness (by peel tests), and tensile strength (by pull-off tests) (Fig. 11). Additional details can be found in previous studies [245,247]. The micro-BCA colorimetric method was also used by analyzing the amount of free mucin [232].

In medical applications of chitosan-based materials, both adhesion prevention properties and adhesive properties are of equal significance. A CMCh–CMCe–collagen membrane, combining the thickening function of CMCe, the procoagulant effect of CMCh, and the antioxidant activity of collagen, demonstrated superior anti-adhesive capability [251]. Li et al. [216] highlighted that the high hydrophilicity of an *N*, *O*-CMCh–aldehyde HA hydrogel and the rapid clearance of HA from the peritoneal cavity as factors making the hydrogel suitable for adhesion prevention. A succinyl chitosan–oxidized dextran hydrogel, containing reactive free aldehydes, created a local toxic environment, preventing unwanted fibroblastic invasion and, subsequently, scarring and adhesions [178].

For chitosan-based materials used in wound dressing, the ability for on-demand removability is crucial. Simply relying on external force for the removal of wound dressings from wound sites may cause additional harm to regenerative tissues. However, current research predominantly concentrates on enhancing the adhesion properties of materials. A promising design direction involves inducing phase separation through the interaction between the amino groups of chitosan and multivalent anions like SO_4^{2-} [71], offering a viable approach for easy peeling off the hydrogel from wound sites.

3.3.3.4. Hemostatic activity. While chitosan itself exhibits commendable hemostatic activity, it falls short of meeting the demands of swift hemostasis in contemporary medical applications. The porous structure and/or high surface area of chitosan-based composite materials, such as chitosan–κ-carrageenan scaffolds [46], *N*,*O*-CMCh–OCS hydrogel [176], chitosan–casein PEC nanofibers [45], chitosan–CS PEC scaffolds [243], quaternized chitosan-SPI sponge [18], enable them to offer more active sites for red blood cells and platelet adhesion, along with blood protein adsorption (Fig. 12). This facilitates the rapid absorption of water content from blood, concentrating and activating coagulation factors [18,45], leading to the formation of a stable wound and achieving prompt hemostasis. The adhered platelets, featuring a deformed pseudopodia structure, can further aggregate, forming platelet clots that reinforce

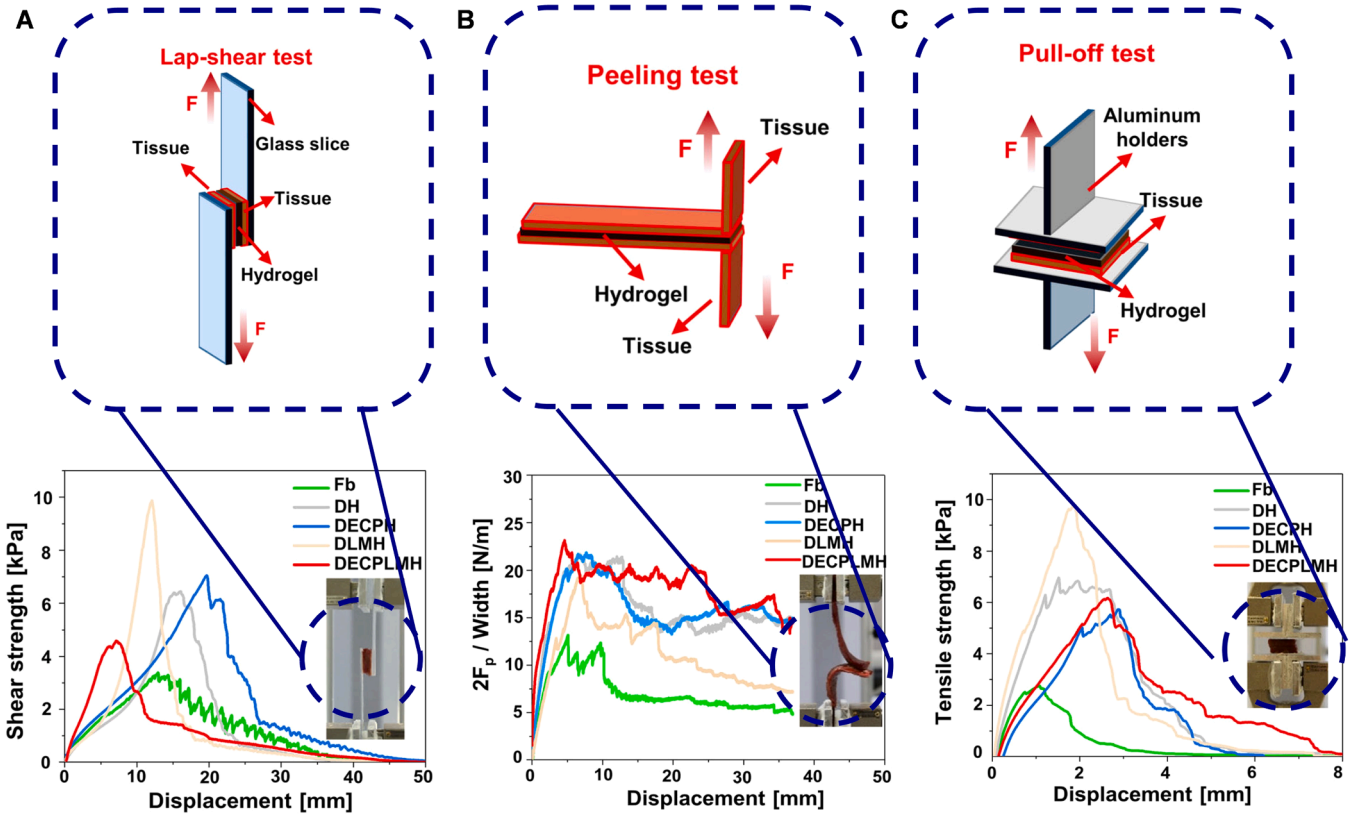

Fig. 11. Schematic representation of force experiments used for evaluating the adhesive properties of chitosan-based materials [83]. Adapted from Springer Nature.

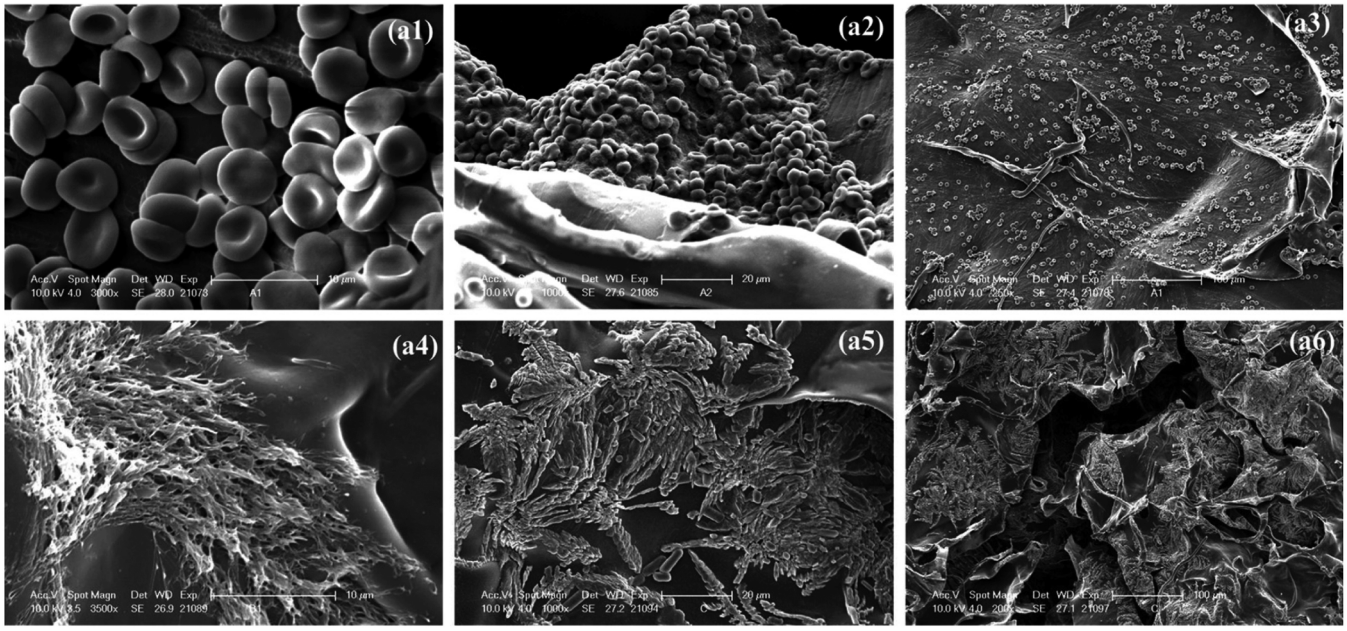

Fig. 12. Red blood cells and platelet adhesion on the chitosan–κ-carrageenan scaffolds [46]. Copyright 2020. Adapted with permission from Elsevier.

fibrin [45,46]. Enhanced hydration and increased water absorption, known to improve the protein adsorption capacity of materials, contribute to thrombosis formation [243].

Besides, the positive surface charge, hydrophobic property, and surface roughness of chitosan-based composites favor the activation of coagulation pathways [18,45,252,253]. Chitosan-based composites with a high positive surface charge can create a "gravitational field", inducing the aggregation of negatively charged blood cells (erythrocytes and platelets) via electrostatic interaction [252]. The positive surface charge also promotes the attachment of exposed phospholipids, such as the negatively charged phosphatidylserine present on the activated platelet surface [45]. Li et al. [176] reported that the strong wet adhesiveness of an *N*,*O*-CMCh–OCS hydrogel resulted from the bonding between aldehyde groups of the hydrogel and amino groups on the tissue surface, facilitating hemostasis. In an *N*,*O*-CMCh–oxidized regenerated cellulose composite gauze, the —COOH groups of oxidized regenerated cellulose bind with Fe^{3+} in the blood fluid, forming a brown gel and contributing to the composite gauze's effective hemostatic capability [254]. In addition, the good water-soluble property of the composite gauze allowed it to concentrate clotting factors for hemostasis by quickly absorbing water from the blood and forming a gel [254].

Incorporating hydrophilic groups from *Bletilla striata* polysaccharide and konjac glucomannan within chitosan-based materials is expected to accelerate the adhesion and concentration of red blood cells, coagulation factors, and platelets, promoting hemostasis [252,253]. Chitosan–CS PEC scaffolds exhibited higher hemostatic ability and better blood cell adhesion than chitosan-alone scaffolds, due to the higher porosity and swelling ability of the PEC scaffolds [243]. In addition, the presence of porous microspheres or microparticles containing polysaccharides (e.g., alginate and starch) facilitated erythrocyte aggregation on chitosan-based composites [252,253], possibly due to increased surface roughness beneficial to blood cells and the adhesion of coagulation factors. Surface potential plays an important role in the adhesion of blood cells. Chitosan-based composites with a high positive surface charge formed a "gravitational field" and induced the aggregation of negatively charged blood cells (erythrocytes and platelets) through electrostatic interaction [252]. A positive surface charge also promoted the attachment of exposed phospholipids, such as the negatively charged phosphatidylserine present on the activated surface of platelets [45]. The synergistic effect of thrombin enabled the rapid transformation of fibrinogen into a three-dimensional fibrin network for capturing and wrapping blood cells to form blood clots [252]. Li et al. [176] further reported that the strong wet adhesiveness of an *N*,*O*-CMCh–OCS hydrogel resulted from bonding between aldehyde groups of the hydrogel and amino groups on the tissue surface, facilitating hemostasis.

To prevent further bleeding or re-bleeding, the ability of chitosan-based composites to maintain clot integrity is essential. Chitosan–casein PEC nanofibers exhibited better clot-holding capability than Celox™ due to higher surface availability, platelet adhesion, and better fibrin network formation [45]. Mechanical compression plays a major role in stopping bleeding. Chitosan-based porous materials quickly absorbed a large amount of plasma, reducing blood loss by compressing the bleeding spot and sealing the broken ends of blood vessels [18].

3.3.3.5. Anticoagulant activity and anti-adhesion to platelets. Chitosan-based composites, such as CMCh–heparin multilayer coating [241] and chitosan–heparin PEC coating [153,255], have demonstrated high resistance to platelet adhesion (as shown in Fig. 13) and activation and protein adsorption, inhibiting thrombus formation. The wettability of a chitosan-based material surface could also influence its anti-adhesive property, as seen in a TMC–heparin PEC multilayer film that significantly reduced bacterial adhesion due to its surface hydrophilicity [74].

3.3.3.6. Antioxidation activity. Chitosan-based composites play a crucial role in safeguarding tissues from oxidative damage and promoting wound healing and tissue regeneration. The inherent antioxidation properties of chitosan, coupled with other biopolymers like HA, lignin, strontium CS and blue crab protein isolate, endow chitosan-based composites in various forms—nanoparticles, sponge, film, scaffold, and hydrogel—with notable reactive oxygen species (ROS)-scavenging ability and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging activity, positively correlated with reaction time [28,61,256–258]. It is noteworthy that a high concentration of lignin could also serve as a pro-oxidant [259]. Additionally, the integration of bioactive compounds such as andrographolide [256] and carotenoids [28] significantly enhanced the antioxidative activity (DPPH radical scavenging and metal chelating were enhanced up to about 15% and 10%, respectively) of chitosan-based composites by exerting synergetic antioxidant effects. Ternary composites like chitosan–collagen–gelatin scaffolds even exhibited a stronger ability (DPPH inhibition percentage: 70%) to

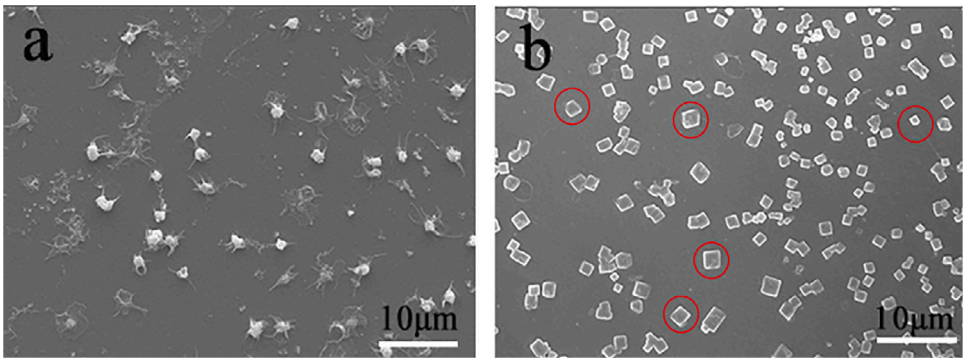

Fig. 13. Platelet adhesion on the polyurethane-coated decellularized scaffold deposited without (a) and with (b) the chitosan–heparin PEC layer (b) [153]. Copyright 2019. Adapted with permission from Elsevier.

scavenge DPPH molecules compared to binary composites like chitosan–collagen and chitosan–gelatin scaffolds [260].

3.3.3.7. Promotion of cell growth, proliferation, and differentiation, as well as biomineralization. Chitosan-based composites have recently evoked intense research interest in biomedical applications due to their capacity to enhance the adhesion, growth, proliferation, and differentiation of target cells, along with their composition and structure resembling natural ECMs. This can be ascribed to the biological activity of biopolymers and the unique structure of chitosan-based composites.

The combination of chitosan, known for enhancing cell differentiation, with other biopolymers like SF, which promotes cell proliferation, collagen, a main ECM component, and heparin, which facilitates endothelialization, can synergistically promote cell growth, proliferation, and differentiation [24,39,153,201,205,261], as well as the formation of mineralization nodule in vitro and osteoblast-specific gene expression [261]. Biopolymers like casein, keratin, and SPI-hydrolyzed products (functional, active peptides) were found to contribute to the adhesion, proliferation, and osteogenic differentiation of target cells on chitosan-based composites by sequestering calcium ions [149], providing cell adhesion sites and stimulating cell–cell interaction [262], and supplying nutrients required for cell proliferation [263], respectively. The composition ratio of biopolymers is crucial; for instance, Lin et al. found that an inadequate keratin concentration (<50%) in a chitosan azide–keratin membrane might result in poor cell attachment, while a 1:1 ratio could enhance the cell migration of human adipose stem cells [264].

The unique 3D structure of chitosan-based composites with a high surface area and high porosity, such as scaffolds, nanofibers, nanofibrous mats, and multilayer coating/films, provides more binding sites for cells, facilitating cell infiltration and growth [24,39,201,205,265,266]. Notably, the hydrophilicity, wettability, surface roughness, and surface charge density of chitosan-based materials also play a key role in facilitating cell attachment and proliferation [17,263,266,267]. For example, the high wettability of chitosan–alginate/pectin coatings was advantageous for the deposition of serum proteins on the coating surface and subsequent cell attachment and proliferation [267]. A chitosan–casein phosphopeptide multilayer coating with a strong negative ζ-potential was reported to be capable of reducing the negative effect of a pure chitosan coating with high positive charge density, favoring the spreading and proliferation of MC3T3-E1 cells [266].

Due to the structural and functional differences between polysaccharides and proteins, chitosan–protein composites can better mimic natural ECMs and often exhibit more pronounced effects on cell growth, proliferation, differentiation, and biomineralization than chitosan–polysaccharide composites. Excitingly, the incorporation of conductive oligomers within a chitosan–polysaccharide composite improved cellular activity and facilitated differentiation [225].

3.3.3.8. Biodegradability. Chitosan-only scaffolds remain stable only in solutions with physiological or higher pH [224]. In addition, chitosan can undergo degradation by lysozyme in the human body [257]. The in vitro degradation of chitosan-based composites may occur due to the biodegradation of biopolymers by corresponding enzymes like lysozyme and hyaluronidase, along with the swelling degradation of hydrophilic biopolymers. The biodegradation of chitosan-based composites, well-modulated and controlled by varying the polymer content in the composite scaffolds [24], allowed for more space for cell growth and greater contact with nutrient media for growing cells [268]. Theoretically, the degradation time of chitosan-based composites should vary according to the specific application. The stable structure formed due to interactions such as ionic interaction, hydrogen bonding, and Schiff base crosslinking between chitosan and other biopolymers results in the controlled degradation of chitosan-based composites.

The electrostatic interaction of chitosan and polysaccharides (e.g., carrageenan, CS, strontium CS, κ-carrageenan, and alginate) reduced the degradation rate of chitosan by preventing the protonation of amino groups on chitosan and were capable of maintaining the morphological and mechanical performance of the resulting materials, especially PEC composites, during the earlier stages of tissue regeneration [46,224,250] and in enzyme-containing environments [100,257]. However, the high rates of ionization of chitosan and CS at acidic (pH = 4) and alkaline pH (pH = 9), respectively, resulted in the rapid breakdown (almost 90% degradation in 48 h at pH 4 and 80% at pH 9) of chitosan–CS PEC scaffolds [243]. The hydroxyl groups within chitosan and agarose supported the formation of intra- and interchain hydrogen bonds, preventing faster degradation of the resulting hydrogel scaffolds [206]. In addition, the structure of biopolymers can influence the degradation behavior of chitosan-based composites. The tri-saccharide side chains of xanthan gum acted as a barrier to enzymatic attack, blocking the access of lysozyme to the cleavage sites of chitosan [15]. Due to the stable structure formed by Schiff base crosslinking, chitosan–OHA hydrogels were expected to be completely degraded in vivo in 3 months [269], while a CMCh–OHA hydrogel even showed a degradation rate equivalent to the rate of abdominal tissue infiltration [270].

Also, some studies [252] evaluated the in vivo degradation behavior of chitosan-based composites by implanting the composite materials into an animal model followed by histological analysis. A microporous corn starch particles-loaded chitosan–konjac glucomannan–dialdehyde starch porous material exhibited excellent degradation capacity in vivo, completely degrading within 42 days [252].

There is a relationship between the degradation rate and swelling ability of chitosan-based materials. The incorporation of hydrophilic keratin within chitosan led to more interaction with water molecules, resulting in higher swelling and a higher degradation rate [17].

3.3.4. Electroconductivity and photothermal performance

The 3D crosslinking network of the chitosan-based PEC composites

may provide ion migration channels for electrolyte ions within the hydration layer along the polyzwitterion chains, thereby enhancing their ionic conductivity [271]. For example, a chitosan–alginate PEC hydrogel exhibited a high ionic conductivity of 0.051 S·cm^{-1} [173]. A HACC–alginate PEC hydrogel, enriched with Cl^- ions, exhibited good conductivity (1.14×10^{-3} S/cm) and could illuminate an LED bulb in a circuit (Fig. 14A) [175]. The electroconductivity of a chitosan–pectin PEC film endowed the PEC film-coated glassy carbon electrode (GCE) with a faster electron transfer ability than a bare GCE (Fig. 14B) [272]. A chitosan–gelatin nanofiber-modified enzyme electrode showed a higher current response compared to a chitosan–gelatin film-modified enzyme electrode (Fig. 14 C) [204]. Wang et al. [273] asserted that the abundance of hydroxyl groups with high electronegativity in starch caused a chitosan–starch film to exhibit outputs with opposite polarity in triboelectric power generation (Fig. 14D).

Introducing conductive oligomers like aniline pentamer into a chitosan–alginate–agarose cryogel enhanced electroactivity by increasing the electrical and ionic conductivity [225]. Polyphenolic compounds, such as dopamine, tannic acid, and gallic acid, were reported to exert photothermal effects when coordinated with Fe^{3+} by absorbing near-infrared light [80]. Chen et al. [80] engineered a gallic acid-grafted chitosan–oxidized *Bletilla striata* polysaccharide–Fe^{3+} DN hydrogel, utilizing Schiff base crosslinking between gallic acid-grafted chitosan and oxidized *Bletilla striata* polysaccharide, along with the crosslinking between pyrogallol and Fe^{3+}. The photothermal effect of the hydrogel enabled accelerated gelation, on-demand degradation, and rapid sterilization [80].

4. Biomedical applications of biofunctional chitosan–biopolymer composite materials

To tailor the properties of biopolymer composites for distinct biomedical applications, researchers have innovatively crafted a variety of functional chitosan composites. These have found applications in controlled release and target delivery, wound healing, tissue engineering, blood purification, tissue engineering, gene delivery, and coatings on biomedical implants (Table 7). Below, we spotlight instances of chitosan-based composites tailored for specific biomedical applications, achieved through formulation design involving molecular design and materials design, as well as polymer blending.

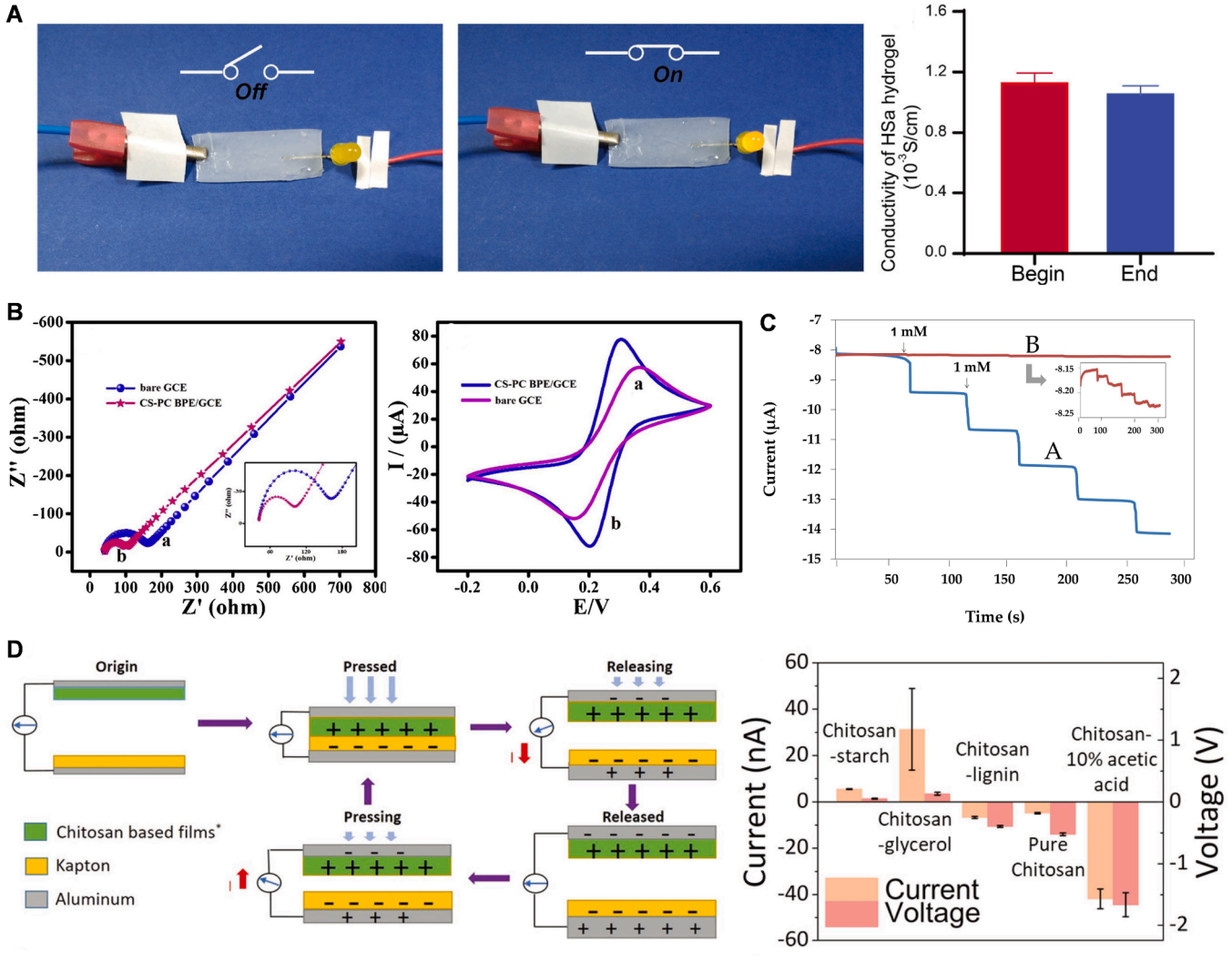

Fig. 14. (A) Conductivity of the hydroxypropyltrimethyl ammonium chloride chitosan–alginate polyelectrolyte complex hydrogel [175]. Copyright 2022. (B) Electroconductivity of the chitosan–pectin polyelectrolyte complex film-coated glassy carbon electrode [272]. Copyright 2019. (C) Amperometric responses of the chitosan–gelatin nanofiber/film-modified enzyme electrode [204]. (D) Working mechanism and open-circuit voltages of the chitosan-starch film-based triboelectric nanogenerator [273]. Copyright 2018.
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Table 7
Applications of chitosan-based bio-functional composite materials.

Application	Properties	Formulations and forms
Wound Dressing	1. Maintain high humidity 2. Self-healing 3. Adsorb excess wound exudate 4. Permit the exchange of gases 5. Good water absorption capacity 6. Antibacterial 7. Provide thermal insulation 8. Biocompatible; does not provoke allergic reaction; non-toxic and non-immunogenic 9. Physically strong even in wet conditions; highly elastic to adapt to the wound site 10. Promote wound hemostasis 11. Increase myofibroblasts; promote collagen remodeling and blood vessel neoformation 12. Easy to dispose of at the end of use without trauma	– Chitosan/alginate, PEC sponge [187] – Chitosan/type I collagen, nanofibrous mats [205] – Gallic acid grafted chitosan/oxidized *Bletilla striata* polysaccharide/Fe^{3+}, hydrogel [80] – CMCh/aldehyde HA, hydrogel [379] – Chitosan/collagen, hydrogel [288] – Chitosan/pectin, membrane [290] – Chitosan/casein, nanofibers [45] – Quaternized chitosan/SPI, sponge [18] – Hydroxypropyl chitosan/SPI, film [263] – Chitosan/fibrin, scaffolds [19] – Chitosan/blue crab protein isolate, hydrogel [28] – Chitosan/konjac glucomannan/microporous starch, porous materials [252] – Chitosan/alginate/*Bletilla striata* polysaccharide, sponges [253] – Chitosan/κ-carrageenan, porous materials [46] – Chitosan/agarose, film [123] – Chitosan/casein, PEC nanofibers [45] – Chitosan/collagen/alginate, cushion [382] – Chitosan/alkali lignin, hydrogel [375] – Chitosan quaternary ammonium salt/alginate, PEC hydrogel [175] – Carboxylated chitosan/collagen/HA, hydrogel [158]
Hemostatic agents	1. High swelling and porosity property 2. Good mechanical strength 3. Excellent bactericidal activity 4. Dramatic hemostatic capability 5. Good cytocompatibility and blood compatibility	– *N*,*O*-CMCh/oxidized regenerated cellulose, composite gauze [254] – Chitosan/CS, PEC scaffolds [243] – Chitosan/casein, PEC nanofibers [45] – Quaternized chitosan/SPI, sponge [18] – Chitosan/konjac glucomannan/microporous starch, porous materials [252] – Chitosan/κ-carrageenan, scaffolds [46] – *N*,*O*-CMCh/oxidized CS, hydrogel [176] – Chitosan/alginate/*Bletilla striata* polysaccharide, sponges [253]
Postsurgical adhesion prevention	1. Suitable mechanical strength and in vivo degradation properties 2. Anti-adhesive capacity 3. Preventing scarring and adhesions	– Succinyl chitosan/oxidized dextran, hydrogel [178, 292] – *N*,*O*-CMCh/aldehyde HA, hydrogel [216] – CMCh/CMCe/collagen, membrane [251]
Hemoperfusion sorbents for sepsis treatment during blood purification	1. Antimicrobial activity; anticoagulating 2. High adsorption capacity; sufficient mechanical strength; porous microstructure 3. Biocompatible; non-hemolytic; non-cytotoxic	– Chitosan/κ-carrageenan, hydrogel beads [164]
Bone tissue engineering	1. Biodegradable (biodegradation rate similar to the new tissue formation rate) 2. High tissue compatibility; non-toxic 3. Conducive to cell adhesion, proliferation, and osteogenic differentiation 4. Suitable mechanical strength (compressive strength) 5. High porosity; highly interconnected porous structure (facilitating cell migration and the diffusion of oxygen and nutrients into scaffolds) 6. Good water absorption and structural stability	– Chitosan/alginate, porous scaffolds [224] – Chitosan/SF, nanofibrous membrane scaffolds [39] – Chitosan/SF, 3D porous scaffold [383] – Chitosan/strontium CS, scaffolds [257] – Phosphorylated chitosan/xanthan gum scaffolds [15]
Cartilage tissue engineering	1. Highly interconnected 3D porous structure (facilitating cell migration and the diffusion of oxygen and nutrients into scaffolds) 2. Maintain cell viability; promote cell adhesion, proliferation, and differentiation 3. Suitable viscoelastic properties (to fill the gaps in cartilage-damaged areas) 4. High water content; excellent mechanical properties; good blood compatibility 5. Mimicking the native cartilage environment of cells	– CMCh/OCS, hydrogel scaffolds [293] – Chitosan/carrageenan, hydrogel [250] – Chitosan/agarose, hydrogel scaffolds [206] – Hexanoyl glycol chitosan/acetylated HA, injectable hydrogel [154] – Chitosan-chloride/chitosan-glutamate/HA, scaffolds [297] – Chitosan/HA dialdehyde [269] – Glycol chitosan/gellan gum, hydrogel [384]
Nerve tissue regeneration	1. 3D porous spatial structure 2. Excellent biodegradability without cytotoxicity or inflammatory reaction 3. Support cellular infiltration, attachment, proliferation, and differentiation 4. Promote vascular regeneration; accelerate tissue regeneration	– Chitosan/collagen, scaffolds [24] – Chitosan/keratin, membrane [17] – Chitosan/alginate/agarose, hydrogel [225] – Chitosan/heparin, scaffolds [298]
Vascular tissue engineering	1. Appropriate mechanical strength 2. Bio-durability and biodegradability 3. High cell adhesion and proliferation 4. Prevent bacterial infection 5. Inhibit thrombosis	– Chitosan/gelatin, bilayered scaffold [268] – Chitosan/heparin, coating [299] – Chitosan/heparin, PEC coating [153,255]
Hepatic tissue engineering	1. Stable 3-D spatial microenvironment 2. Highly open porous structure 3. Good biocompatibility and biodegradability	– Chitosan/galactosylated HA/heparin, scaffold [300]

(*continued on next page*)

Table 7 (*continued*)

Application	Properties	Formulations and forms
Gene carrier	1. Excellent stability in the tumoral extracellular environment 2. Targeted properties 3. High encapsulation efficiency and cellular uptake rate	– Chitosan/bovine type I collagen, scaffolds [286] – Trimethyl chitosan chloride/HA, nanoparticles [234] – Chitosan/HA, nanoparticles [233] – Chitosan/HA dialdehyde, nanoparticles [179] – Chitosan/heparin, fibers [309]
In vitro platform for cell culture	1. Highly interconnected pore structure 2. Suitable swelling stability 3. Recapitulate the in vivo molecular microenvironment	– Chitosan/CS, scaffolds [294] – Chitosan/HA, PEC scaffolds [12] – Chitosan/SF, nanofibers [201]
Tissue adhesion	1. Good cytocompatible 2. Excellent tissue adhesion capacity	– Chitosan/oxidized pectin, PEC nanofiber membrane [246] – Hematin-grafted chitosan/catechol-conjugated chitosan, hydrogel [248] – (4-Hydroxyphenyl) propionic acid-modified glycol chitosan, hydrogel [92]
Coatings for commercial Ti/Mg/Co-Cr-Mo alloys	1. Enhanced antibacterial properties (to prevent the accumulation of bacteria, provide a contact-killing surface, and inhibit bacterial adhesion and proliferation) 2. Cell adhesion and proliferation promotion 3. Excellent hemocompatibility	– Chitosan/HA, multilayer film [244] – Chitosan/casein phosphopeptides, bilayer film [266] – Chitosan/SF, hydrogel coating [301] – Chitosan/alginate, coatings [267] – Chitosan/pectin, coatings [267] – Chitosan/heparin, PEC multilayer coating [239] – Chitosan/κ-carrageenan, coatings [302] – Chitosan/heparin, coating [241]
Functional medical sutures	1. Reliable mechanical strength 2. Good antibacterial properties	– Chitosan/HA, bilayer PEC film [44] – Chitosan/heparin, fibers [309]
Controlled release and delivery of drugs	1. pH-sensitive; mucoadhesive; targeted delivery property 2. Good biocompatibility 3. Be able to carry therapeutic agents 4. Good mechanical properties 5. pH- or temperature-responsive swelling behaviors 6. Controllable drug release rate	– Chitosan/gelatin/alginate/TPP, beads [199] – Chitosan/CS, hydrogel [128] – Chitosan/CS, nanoparticles [222,237] – Catechol-modified chitosan/HA, nanoparticles [247] – CMHC/HA, injectable hydrogel [219] – Chitosan/HA, injectable hydrogel [220] – Chitosan/modified glutinous rice starch, film [245] – Chitosan/lotus root amylopectin, hydrogel particles [274] – Chitosan/enzyme hydrolyzed starch, nanoparticles [277] – Chitosan/κ-carrageenan, PEC multilayers on nanocapsules [278] – Chitosan/xanthan gum, PECs [105] – *N*-Trimethyl chitosan/sodium carboxymethyl xanthan gum, PEC hydrogel [76] – Chitosan/locust bean gum, nanoparticles [279] – Chitosan/gellan gum, nanoparticles [281] – Chitosan/katira gum, nanoparticles [280] – CMCh/oxidized gellan gum, DN gel [177] – Chitosan/dextran sulfate, nanoparticles [16,193,282,331] – CMCh/OCS, chitosan microspheres loaded hydrogel [275] – Chitosan/low methoxyl pectin, nanoparticles [232] – Chitosan/caseinate, PEC nanoparticles [98] – Chitosan/dialdehyde xanthan gum/hypromellose, hydrogel scaffolds [68] – Chitosan/pectin/gum Arabic, membrane [9] – Chitosan/gelatin, multilayers [385] – Chitosan/poly (glutamic acid)/alginate, PEC hydrogel [174] – Chitosan/CMCe, polyampholyte microgels [207] – Chitosan/collagen, hydrogel [276] – Chitosan/alginate/agarose, conductive hydrogels [225] – Chitosan/HA/TPP, PEC nanoparticles [104] – Chitosan/casein, core-shell structure microparticles [159] – *N*-acetyl-L-cysteine (NAC)/L-cysteine (CYS) functionalized chitosan/casein, nanohydrogels [25] – Chitosan or stearic acid conjugated chitosan/egg yolk high-density lipoprotein, PEC nanoparticles [84] – *O*-CMCh/gum Arabic, coacervates [231]
Encapsulation of bioactive components and probiotics	1. High encapsulation efficiency 2. Good storage stability 3. High thermal stability	– Chitosan/CS, PECs [99] – Chitosan/HA/TPP, PEC nanoparticles [104]

(*continued on next page*)

Table 7 (*continued*)

Application	Properties	Formulations and forms
	4. Resistant to the harsh gastrointestinal environment	– Chitosan/gum Arabic, nanoparticles as a Pickering emulsion stabilizer [330] – Chitosan/gum Arabic, film [386] – Chitosan/dextran, multilayer films on nanocapsules [195] – Chitosan/dextran sulfate, PEC multilayer coating [285] – Chitosan/CS, nanoparticles [334] – *N*-acetyl-L-cysteine (NAC)/L-cysteine (CYS) functionalized chitosan/casein, nanohydrogels [25]
Electrochemical sensors or biosensors	1. High sensitivity; rapid response time; low detection limit 2. Good reproducibility 3. Long-term stability 4. Low electrooxidation potential of NADH 5. High recovery index 6. Prominent selectivity, stability, and reproducibility	– Chitosan/gelatin, nanofibers [204] – Chitosan/pectin, PECs [272]
3D printing	1. Achieve a continuous flow 2. Maintain a stabilized printed structure 3. Injectability, appropriate yield strength 4. Suitable viscosity and mechanical strength 5. Good printability and post-printing shape fidelity	– Chitosan/gelatin, PEC hydrogel [307] – Chitosan/guar gum, ink [306] – CMCh/alginate/agarose, gel [303] – Catechol-conjugated chitosan, scaffold [305] – Glycol chitosan/oxidized HA, hydrogel [218] – MA glycol chitosan/MA keratin, hydrogel [93]
Smart hydrogel actuators (soft grippers, smart encapsulators, and bioinspired lenses)	1. Exhibit smart swelling behavior 2. Programmatic deformation to a variety of shapes	– Chitosan-cellulose/CMCe, bilayer hydrogel [221]

Abbreviations: carboxymethyl cellulose (CMCe), carboxymethyl chitosan (CMCh), carboxymethyl hexanoyl chitosan (CMHC), chondroitin sulfate (CS), double network (DN), hyaluronic acid (HA), oxidized chondroitin sulfate (OCS), polyelectrolyte complex (PEC), silk fibroin (SF), soy protein isolate (SPI), tripolyphosphate (TPP).

4.1. Controlled release and target delivery

Crafting controlled release and target delivery systems is crucial for enhancing the bioavailability of drugs, bioactive compounds, and genes. Chitosan-based composite systems, with their distinctive features, serve act as efficient platforms for these applications.

4.1.1. Encapsulation of drugs

Biodegradable chitosan-based composite materials in different forms such as hydrogels [68,76,220,225,274–276], DN gels [177], films [9245], and nanoparticles [16,277–282], are highly acknowledged as drug delivery carriers for oral local delivery [245,247], oral administration [105], controlled release formulations [76], antifungal drug carriers [281], ophthalmic applications [16,282], targeted drug delivery [174,193,232,237], and neural disorder therapies [225]. These materials boast cytocompatibility [76,219,220], good mechanical stability [177,275], high encapsulation efficiency (EE) [76,274], pH-responsiveness [174,207,219], thermo-responsiveness [207], controlled release properties [275,279], sustained-release characteristics [247,274,282], targeted delivery properties [174,193], excellent adhesion to oral mucosa [245,247], enzyme-degradability [219], injectability [220,275], and potency-enhancing effects [280,281] (summarized in Table 7).

Buccal drug delivery has garnered significant attention for its advantages over oral delivery, offering low first-pass metabolism and improved bioavailability [245,247,283]. Notably, solution-cast composite films of hydrophilic lidocaine hydrochloride-loaded chitosan and ball-milling modified glutinous rice starch demonstrated excellent mucoadhesive properties, facilitating high permeation flux across porcine mucosa [245]. The incorporation of catechol groups into a genipin-crosslinked chitosan hydrogel loaded with lidocaine hydrochloride exhibited outstanding in vitro mucoadhesion to porcine buccal tissue. This formulation allowed sustained drug release in vivo for at least 3 h without causing inflammation or adverse reactions (Fig. 15A-C) [283]. In addition, mucoadhesive doxorubicin-loaded catechol-functionalized succinyl chitosan–catechol-bearing HA nanoparticles, obtained through a solution mixing method followed by freeze-drying, offered an extensive surface area. This unique feature enabled interaction with the cancer cell membrane, facilitating enhanced cellular uptake and intracellular accumulation of doxorubicin [247].

Chitosan–dextran sulfate nanoparticles have garnered significant interest in ophthalmic applications for their ability to prolong the residence time of drugs on the ocular surface (up to 4 h) and enhance corneal penetration. For example, ciprofloxacin-loaded chitosan-dextran sulfate PEC nanoparticles (EE of 83%) obtained through the solution mixing method exhibited robust antimicrobial activity and, importantly, proved non-irritant to the ocular surface (Fig. 15D, E) [282].

Chitosan-based composites can shield drugs from the challenging gastrointestinal environment by incorporating diverse interactions (e.g., polyelectrolyte complexation, complex coacervation, Schiff base, van der Waals force, and hydrogen bonding) and crosslinkers. This strategy effectively mitigates burst release, ensuring a controlled and gradual release at the target site, thereby minimizing gastrointestinal side effects of drugs [9,76,98,174,207,219,279]. For example, curcumin encapsulated within a chitosan–lotus root amylopectin hydrogel significantly reduced release content (less than 16%) in simulated gastric fluid (SGF) and allowed sustained release in simulated intestinal fluid, which was possibly due to the hydrogen bonding between chitosan and curcumin [274]. Utilizing a solution mixing method combined with centrifugation, Hanna et al. [76] fabricated a ciprofloxacin-encapsulated (with an EE of up to 93.8%) TMC–sodium carboxymethyl xanthan gum PEC hydrogel with bacteriostatic activity. The hydrogel, exhibiting high drug-loading efficiency, demonstrated faster and higher ciprofloxacin release compared to the low drug-loading efficiency counterpart [76].

While certain chitosan-based hydrogel carriers may exhibit weak mechanical properties and a high initial drug release rate, strategies such as incorporating BSA-loaded GA crosslinked chitosan microspheres into a CMCh–CS hydrogel (Fig. 15F) [275] and constructing nattokinase (a thrombolytic enzyme)-loaded genipin/TG crosslinked chitosan–casein microparticles with a bilayer shell–core structure (Fig. 16A) [159] can significantly reduce the initial release of bioactive compounds (Fig. 15G). These modifications enable chitosan-based composites to

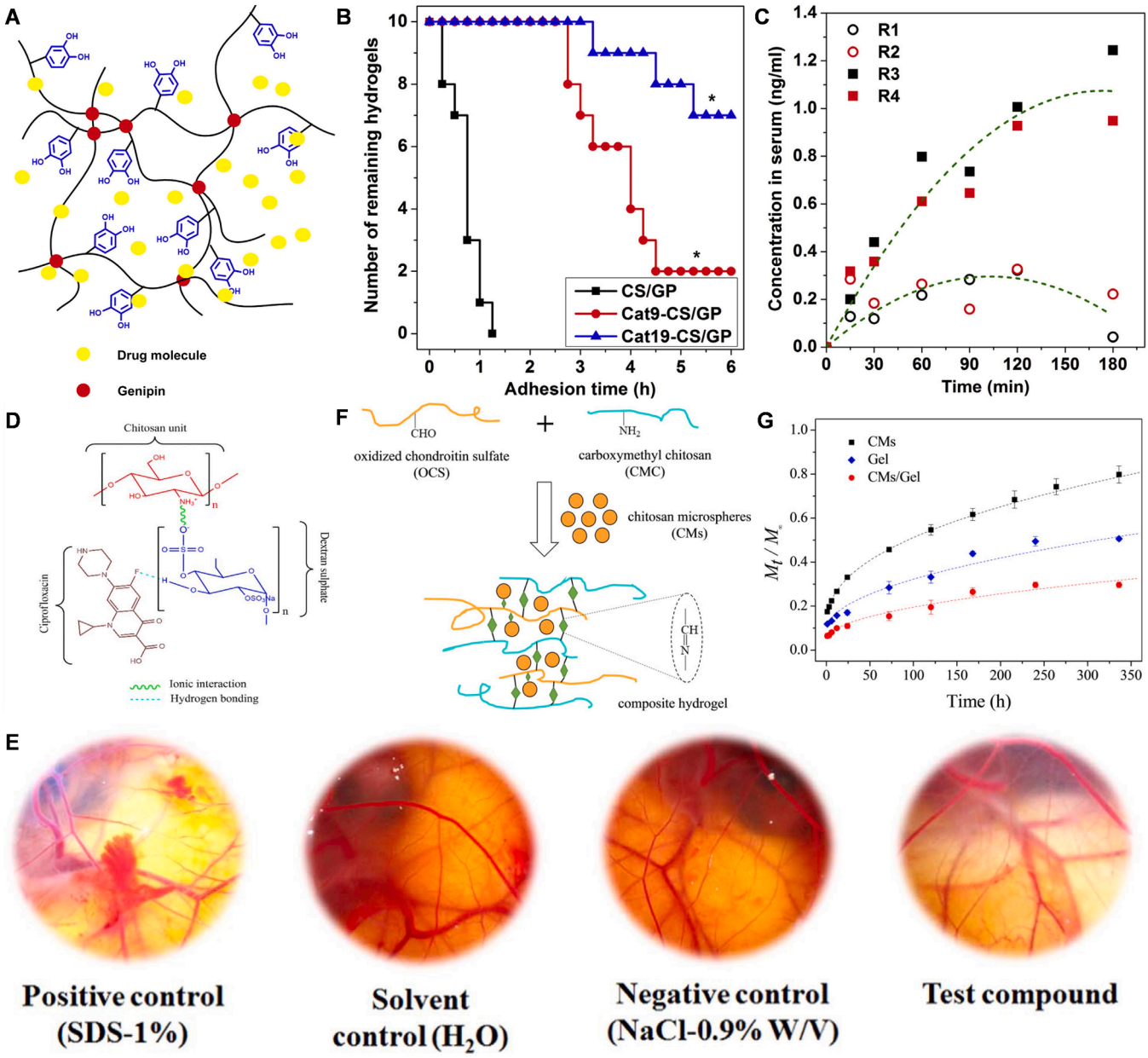

Fig. 15. Structural diagram (A), in vitro mucoadhesion (B), and controlled release properties (C) of the genipin-crosslinked catechol-functionalized chitosan hydrogel [283]. Copyright 2015. (D) Schematic representation of the interaction within ciprofloxacin-loaded chitosan–dextran sulfate polyelectrolyte complex nanoparticles and (E) hen's egg test chorioallantoic membrane (HET-CAM) assay [282]. Schematic representation of the development (F) and drug release pattern (G) of the carboxymethyl chitosan–chondroitin sulfate hydrogel loaded with chitosan microspheres [275]. Copyright 2017.
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resist the harsh gastrointestinal environment before reaching the absorption site (Fig. 16B) [159,275]. In efforts to enhance the oral bioavailability of heparin, Maretti et al. [284] encapsulated chitosan-heparin PECs within solid lipid nanoparticles to achieve pH-controlled release, and the resulting PECs-loaded nanoparticles exhibited high potential for oral absorption.

Chitosan-based composites with targeting capabilities have garnered significant interest in achieving precise drug delivery in oncology and cancer treatment. For example, bortezomib-loaded (loading capacity: 98.5%) folate receptor-targeted chitosan–CS nanoparticles, designed through a simple solution mixing method [237], and curcumin-loaded (EE: 68.43%) cetuximab-conjugated chitosan–LM citrus pectin nanoparticles, obtained via an ionic gelation method (as illustrated in Fig. 16E) [232], facilitated high compound accumulation in the tumor area and enhanced compound uptake (Fig. 16C, D). Consequently, these formulations effectively suppressed tumor proliferation [232].

Apart from introducing targeting ligands onto the surface of chitosan-based composites, there is substantial interest in introducing stimulus-response properties to achieve targeted delivery. For example, the redox-responsive feature of enzymatically disulfide-crosslinked chitosan–HA LbL self-assembled microparticles, obtained through a sacrificial template method (Fig. 16F) [229], and the pH-sensitivity of drugs (ciprofloxacin and ceftriaxone)-loaded chitosan–dextran sulfate PEC nanoparticles synthesized via an LbL deposition method [193], conferred targeting ability to chitosan-based composites towards the tumor site. These properties significantly extended the retention time of loaded compounds in the blood and organs, underscoring the substantial potential of these composites for tumor-targeted delivery and controlled

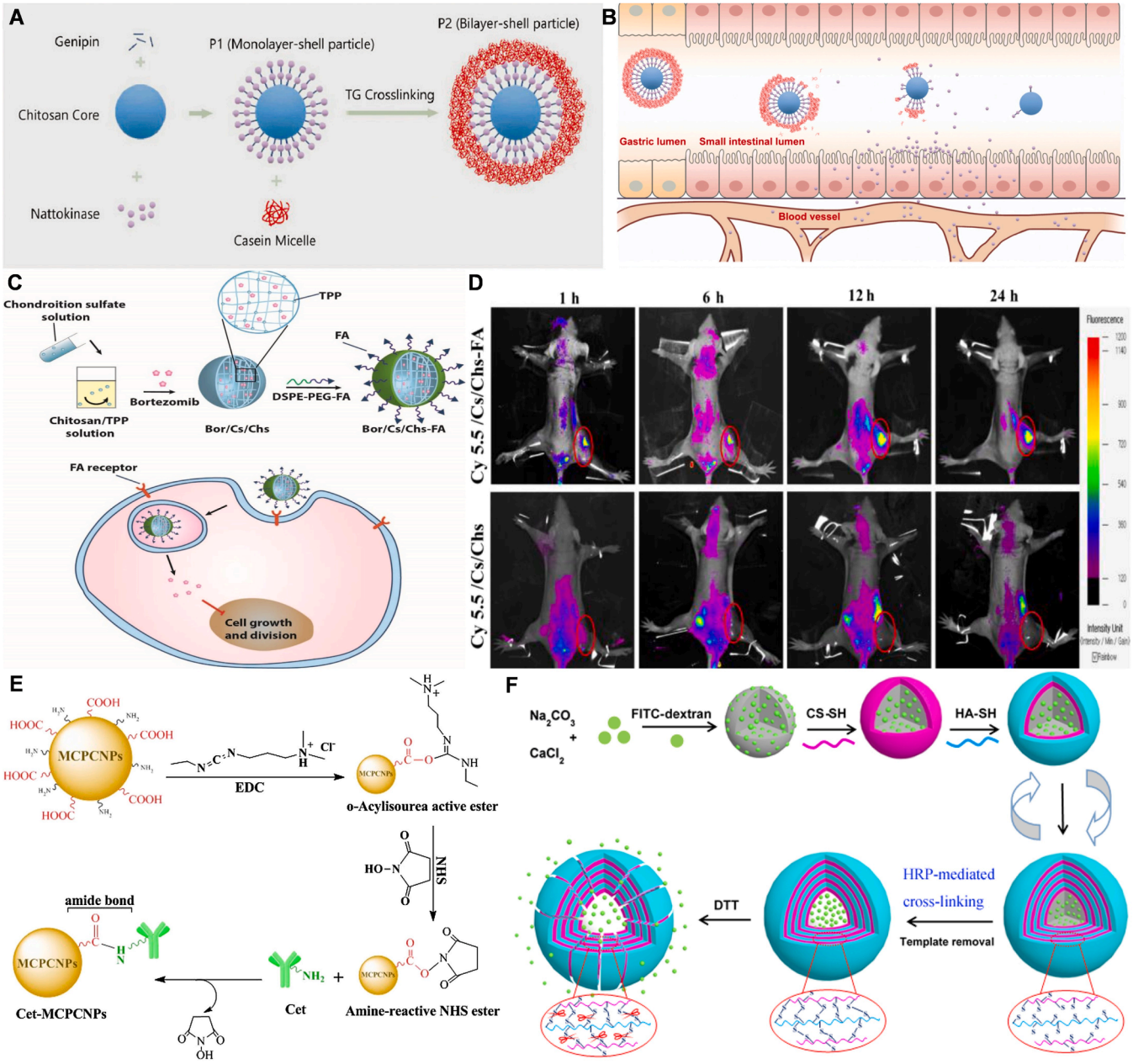

Fig. 16. Schematic representation of the preparation of the chitosan–casein microparticles (A) and the digestion and adsorption of nattokinase in the intestine (B) [159]. Copyright 2020. Schematic representation of the preparation of the design of the folate receptor-targeted chitosan–chondroitin sulfate nanoparticles (C) and its targeting properties (D) [237]. (E) Schematic illustration of the preparation of the cetuximab-conjugated chitosan–LM citrus pectin nanoparticles [232]. Copyright 2019. (F) Schematic representation of the design of the enzymatically disulfide-crosslinked chitosan–hyaluronic acid layer-by-layer (LbL) self-assembled microparticles [229]. Copyright 2018.
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drug release.

While certain chitosan-based composite materials showcased outstanding features, instances of uncontrollable and incomplete drug release have been observed [245]. Although, in the majority of cases, chitosan-based composites offer superior protection compared to individual components, there are rare instances where potential polymer conformational changes might lead to slightly weaker performance compared to the single component [197].

4.1.2. Encapsulation of bioactive compounds and probiotics

Utilizing chitosan-based encapsulation systems for the encapsulation of bioactive compounds and probiotics serves as a solution not only to ensure the protection of encapsulated compounds against external agents but also to enhance the bioavailability and solubility of these compounds.

Chitosan-based composite materials find application in encapsulating various bioactive components, including egg white-derived peptides [25], probiotics [285], trypsin inhibitors [196,197], and polyphenol [195], owing to their high EE and the resilience against the harsh gastrointestinal environment and elevated temperatures (Table 7). For instance, trypsin inhibitor-loaded chitosan–whey protein isolate (WPI) nanoparticles, developed using a nanoprecipitation method [196,197], and amphiphilic *N*-acetyl-L-cysteine (NAC) or L-cysteine (CYS)-functionalized chitosan–casein nanohydrogels loaded

with hydrophobic curcumin (EE: up to 63%) and hydrophilic egg white-derived peptides (EE: up to 67%), prepared via the solution mixing method [25], effectively safeguarded the loaded compounds from high temperature (up to 80 °C) and acid conditions (e.g., gastric media and SGF), demonstrating remarkable storage stability at room temperature for 21 days. These formulations not only enhanced the bioavailability of bioactive compounds [25] but also contributed to the physiological effects of such compounds, such as the hypoglycemic effect and pancreas tissue repair [196].

In numerous inflammatory diseases, tissue damage arises from an excess of neutrophil-derived ROS [258]. Butyrate-loaded chitosan–HA nanoparticles exhibited inherent ROS-scavenging activity, mucoadhesiveness, and resistance to cell internalization, facilitating the controlled release of butyrate. This is attributed to the natural radical-scavenging properties of chitosan and HA, coupled with hydrogen bonding and hydrophobic interactions occurring between chitosan and mucin [258].

For efficient protective encapsulation of probiotics, Thomas et al. [285] studied the encapsulation effect of a chitosan–dextran sulfate PEC coating with two bilayers, prepared via LbL deposition, on the probiotic *Saccharomyces boulardii*. The PEC coating significantly enhanced probiotic viability (by 2.69 CFU/100 mg) and conferred selective permeability to the coated cells, showcasing promising potential in maintaining the integrity and viability of probiotics [285]. In the co-delivery of polyphenol (caffeic acid, tyrosol, vanillic acid, and *p*-coumaric acid), the multilayer coating of chitosan–dextran sulfate four-bilayers (shell)-coated capsules with a hollow core, designed through a sacrificial template method, enabled the controlled release of polyphenol [195].

Notably, in the context of chitosan-based multilayer coatings, the number of bilayers plays a crucial role in the encapsulation effect. Excessive bilayers prove detrimental for substances using reversible penetration, as they must traverse a certain number of layers to reach the hollow core of the capsule. Consequently, increasing the bilayer count neither facilitates higher compound loading nor delays their release [195].

4.1.3. Gene delivery

Chitosan-based composite materials are widely utilized for the delivery of nucleic acids, with chitosan–HA composites standing out for their combination of low toxicity and superior gene encapsulation capability from chitosan and its derivatives, along with the receptor-mediated internalization of the HA. This makes them well-situated for targeted delivery in cells overexpressing HA receptors, such as CD44 (commonly upregulated in a number of tumors) [179,233,234,236]. Gene delivery studies have explored chitosan–bovine type I collagen scaffolds [286], trimethyl chitosan–alginate nanoparticles [287], and trimethyl chitosan–dextran sulfate nanoparticles [287].

Studies by Lallana et al. [233] and Liang et al. [179] demonstrated that RNA (mRNA and/or siRNA)-loaded chitosan–HA nanoparticles, obtained through the solution mixing method with optional TPP cross-linking, could achieve CD44-targeted RNA delivery. These nanoparticles exhibited exceptional stability (at pH 5–7 under 37 °C) and high EE for two RNAs (EE > 95%), enabling controlled RNA release (Fig. 17A, B). Notably, nanoparticles with high-DD chitosan efficiently entered tumor/cancer cells through CD44 receptor-ligand-mediated endocytosis. In addition, the nanoparticles accelerated targeted gene silencing, as demonstrated by the delivery of cy3-siRNA, specific accumulation at the tumor site, and significant tumor suppression (Fig. 17C-E) [179]. In

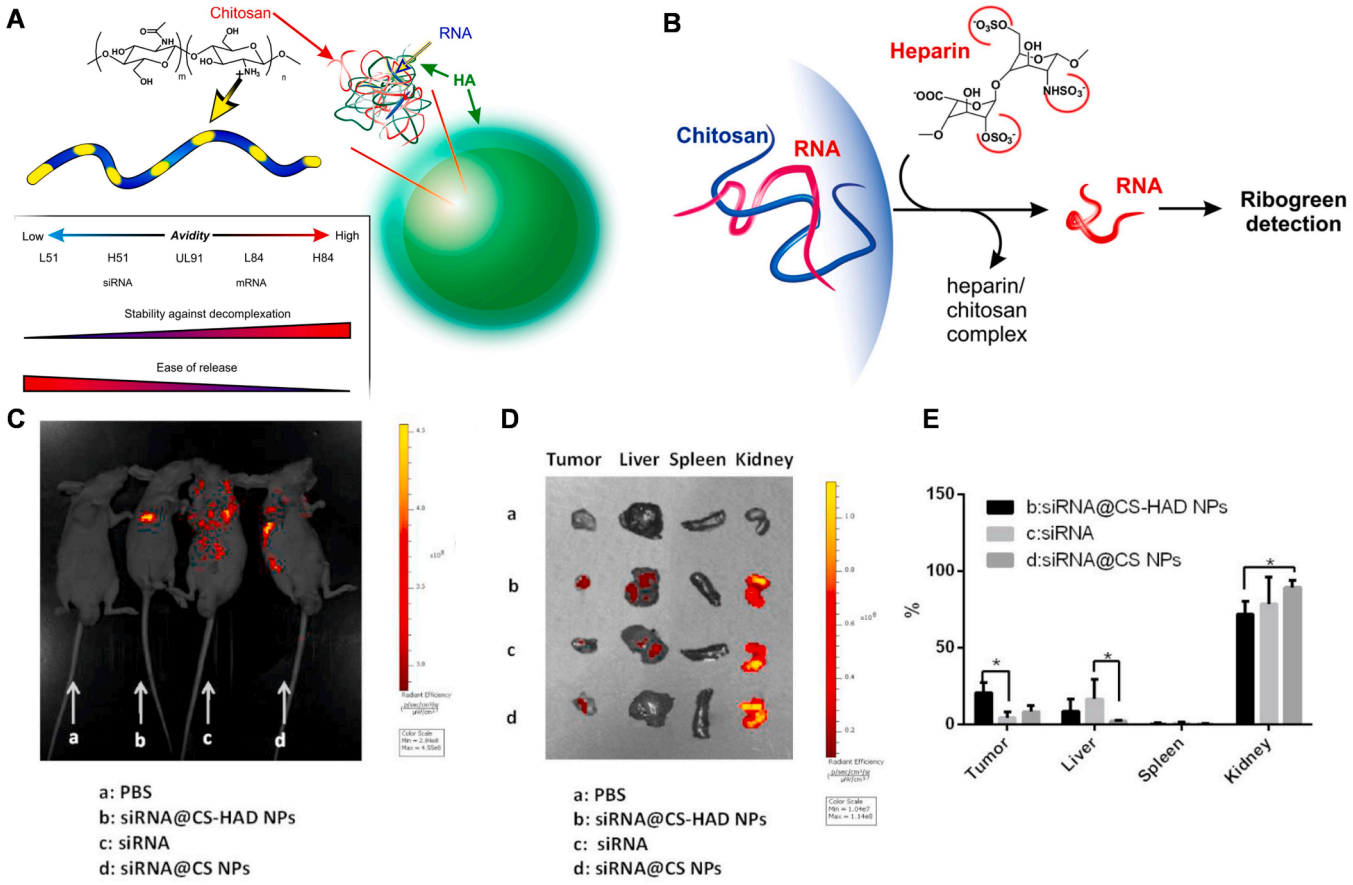

Fig. 17. Schematic representation of the mechanism of the formation of the RNA-loaded chitosan–hyaluronic acid nanoparticles (A) and the release of RNA from the nanoparticles (B) [233]. Copyright 2017. (C-E) The targeted delivery of siRNA by the chitosan–HA dialdehyde nanoparticles [179].
(a) Adapted with permission from the American Chemical Society. (b) Adapted from Elsevier.

another investigation, tumor-targeted trimethyl chitosan–HA PEC nanoparticles, created through an ionic gelation method, exhibited even higher gene loading efficiency (~100%), substantial cellular uptake (>90%), and appropriate stability in serum (up to 8 h) [287].

Beyond cancer gene delivery, Yang et al. [286] discovered that the freeze-dried chitosan–bovine type I collagen scaffold, loaded with the plasmid vector encoding the human bone morphogenetic protein-7 (BMP-7) gene, demonstrated enhanced proliferation and odontoblastic differentiation behaviors compared to a pure chitosan–collagen scaffold. This formulation further facilitated the in vitro and in vivo differentiation of human dental pulp stem cells [286].

4.2. Wound healing

Biopolymer materials with the ability to enhance wound healing and prevent scarring are in high demand for wound healing. Chitosan-based composites emerge as promising materials for wound healing, thanks to their outstanding functional properties, such as self-healing, antimicrobial activity, adhesive properties, on-demand removability, and hemostatic activity.

4.2.1. Wound dressing

Chitosan-based composite materials, as summarized in Table 7, have found widespread application as wound dressing materials, owing to their self-adaptation, self-healing, and removability [71], biocompatibility [288], excellent bacterial infiltration resistance ability [289], capability to accelerate wound healing [290], controlled degradability [46], and excellent tissue compatibility [224].

A freeze-dried non-toxic chitosan–κ-carrageenan porous material with controlled degradability proves effective in reducing clotting time, facilitating stable-clot formation and faster thrombin generation, and serves as a promising dressing material for wound healing during hemorrhage [46]. The mechanical strength of chitosan-based composites is crucial for wound dressing applications. Chitosan–alginate scaffolds, fabricated through freeze-drying and $CaCl_2$ crosslinking, exhibited significantly increased mechanical strength (about three times) compared to a pure chitosan scaffold [224]. Importantly, these scaffolds demonstrated excellent tissue compatibility and fostered collagen formation and vascularization after implantation into the muscles of rats for 4 weeks [224]. To address the limitations of traditional hydrogels for surgical implantation, such as a lack of in-situ injection ability, Zhang et al. [249] developed a chitosan–HA hydrogel incorporated with sodium glycerophosphate through a simple solution-mixing method. The resulting hydrogel exhibited body-temperature-sensitivity, pH-sensitivity, and injectability and could transform from a solution state to a gel state under physiological conditions. This hydrogel is applicable to sites inaccessible by surgery [249].

Deep burn wounds, involving damage to epidermal and dermal layers and underlying tissues, pose significant wound-management challenges. Lei et al. [158] constructed a hydrogel from carboxylated chitosan–collagen–HA using the solution mixing and freeze-drying method with TG as a crosslinker. The resulting hydrogel demonstrated good mechanical strength and antimicrobial activity, effectively preventing bacterial infection and promoting burn wound healing better than DUO DERM (a commercial film) in a deep second-degree burn model [158].

In addition to the careful material composition selection, designing material forms suitable for wound dressings is equally crucial. A chitosan–corn starch composite sponge with asymmetric wettability and good biodegradability (Fig. 18A-C) [289] and chitosan–type I collagen bilayers-coated nanofibrous mats with good mechanical properties and good hydrophilicity (Fig. 18D-F) [205] have been developed via freeze-drying and stearic acid modification, and electrostatic LbL self-assembly, respectively. Both composites exhibited excellent antibacterial activity and promoted cell attachment, growth, and proliferation. However, the former reduced the risk of wound adhesion, while the latter decreased wound-closure time, promoted collagen production, and mitigated excessive scar formation in a rat model, showcasing the promising potential for wound dressing [205,289].

The water-rich structure of the hydrogel proves advantageous for the transport of molecules and nutrients between the hydrogel and the external environment, allowing for the mimicry of in vivo cell functions. Chen's group [80] employed gallic acid-grafted chitosan and oxidized *Bletilla striata* polysaccharide to create an injectable, self-healing, and antibacterial DN hydrogel with good adhesive property in the presence of Fe^{3+} for infected and susceptible wound healing (Fig. 19). The hydrogel effectively closed the full-thickness skin wound and promoted wound healing. In addition, the hydrogel's combination of photothermal effect and antibacterial activity rendered it effective in facilitating the healing of bacterial infection wounds [80].

Bioactive components, including antioxidants (e.g., carotenoids), antibacterial agents (e.g., silver sulfadiazine and flavonoid), immune regulators (e.g., dehydroepiandrosterone and arginine derivatives), and cell-penetrating peptides, have been incorporated into chitosan-based composite systems to expedite wound healing [19,28,187,288,290,291]. Sari et al. [290] demonstrated that a solution-cast chitosan–pectin membrane immobilizing a *Musa paradisiaca Linn* extract effectively accelerated the wound healing process; it promoted epithelial tissue proliferation, resulting in an 86.97% wound reduction after 10 days, compared to a sterile gauze dressing with povidone-iodine (75.29% wound reduction) [290].

In all, chitosan-based composite materials have demonstrated inherent advantages in promoting wound healing and skin regeneration. However, it is noteworthy that existing research often overlooked a crucial property—on-demand removability—that merits consideration for further clinical applications.

4.2.2. Blood clotting

Post-traumatic bleeding and acute bleeding caused by diseases continue to present challenges to worldwide healthcare systems, demanding urgent development of effective hemostatic agents. Chitosan-based composite materials (as shown in Table 7) have proven effective as hemostatic agents due to their excellent hemostatic effects. Apart from constructing chitosan-based hemostatic materials, doping materials with coagulation factors like thrombin may enhance hemostatic efficiency [252].

Both chitosan–casein PEC nanofibers, constructed via self-assembly [45], and antibacterial quaternized chitosan–SPI sponge, developed through a solution mixing and freeze-drying method using EGDE as a crosslinking agent (Fig. 20A) [18], achieved rapid blood clotting within a short time, demonstrating hemostatic efficiency comparable to, or significantly better than, commercially available hemostatic products (e.g., Celox™ and gelatin sponge) (Fig. 20B). Another study [176] showcased that the antibacterial, injectable, and self-healable CMCh–OCS hydrogel, obtained via a solution mixing method (Fig. 20C), could adapt to irregular wound surfaces, achieving complete hemostasis at 120 s in a mouse liver bleeding model (Fig. 20D) [176]. In light of this, this hydrogel emerges as a qualified candidate for blood clotting applications.

Apart from chitosan-based binary composites, chitosan-based multicomponent composite materials in sponge or other forms have also been employed for hemostasis. According to the studies by Wang et al. [253] and Shi et al. [252], the chitosan–alginate–*Bletilla striata* polysaccharide hemostatic sponges, constructed via a solution mixing and freeze-drying method, and a thrombin-occupied microporous corn starch particles (TOMSP)-loaded chitosan–konjac glucomannan–dialdehyde starch porous material, synthesized via a one-pot process followed by freeze-drying (Fig. 20E, F), demonstrated superiority in hemostasis and achieved rapid hemostasis with a low blood loss.

4.2.3. Postsurgical adhesion prevention

Researchers have endeavored to identify effective approaches for

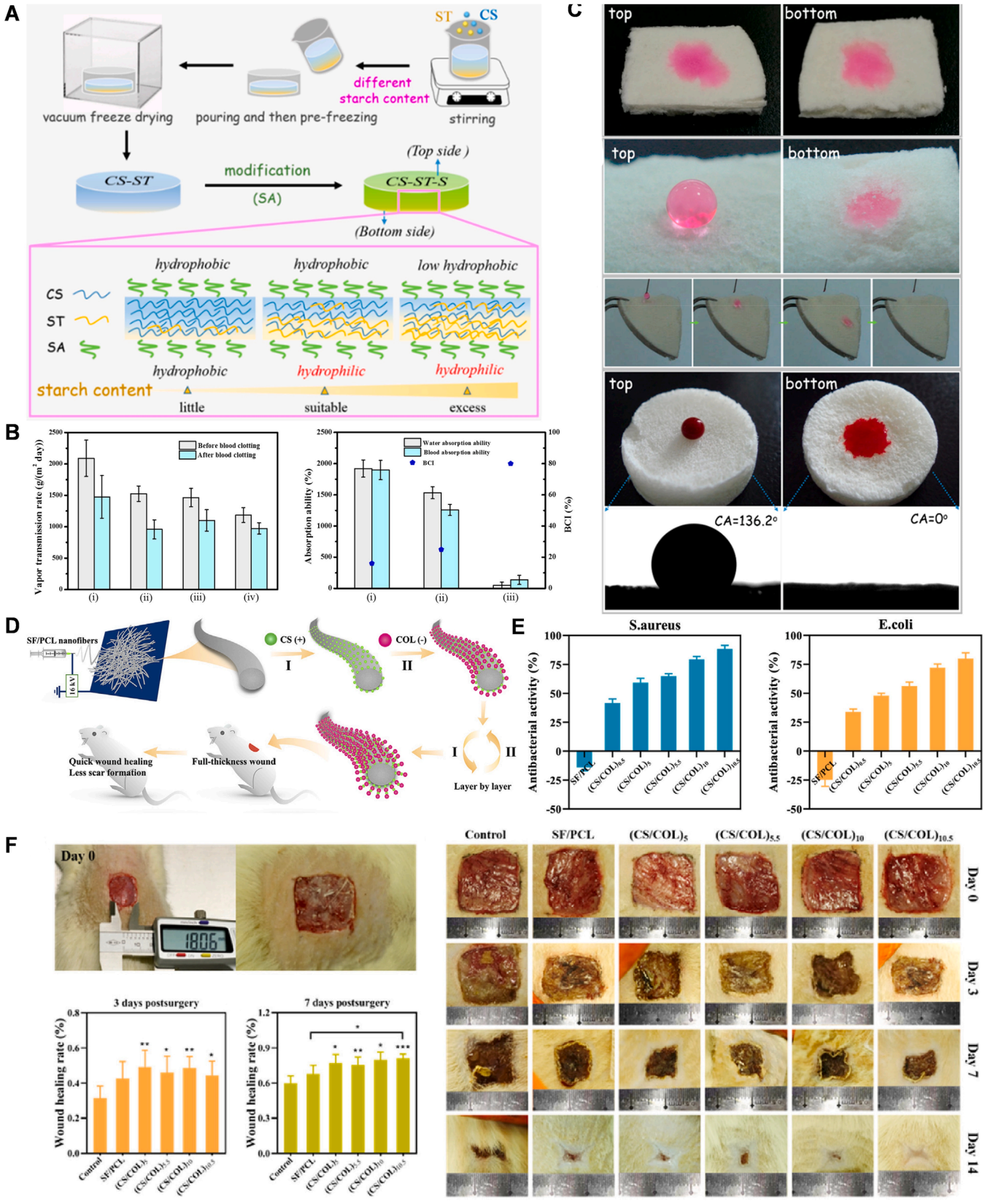

Fig. 18. (A) Schematic representation of the chitosan–corn starch composite sponge with its excellent water and blood absorption ability (B) and asymmetric wettability (C) [289]. Copyright 2019. (D) Schematic illustration of the preparation of the chitosan–type I collagen-coated SF–polycaprolactone nanofibrous mats. Antibacterial activity (E) and wound healing effects (F) of the nanofibrous mats [205].
(a) Adapted with permission from the American Chemical Society. (b) Adapted from Elsevier.

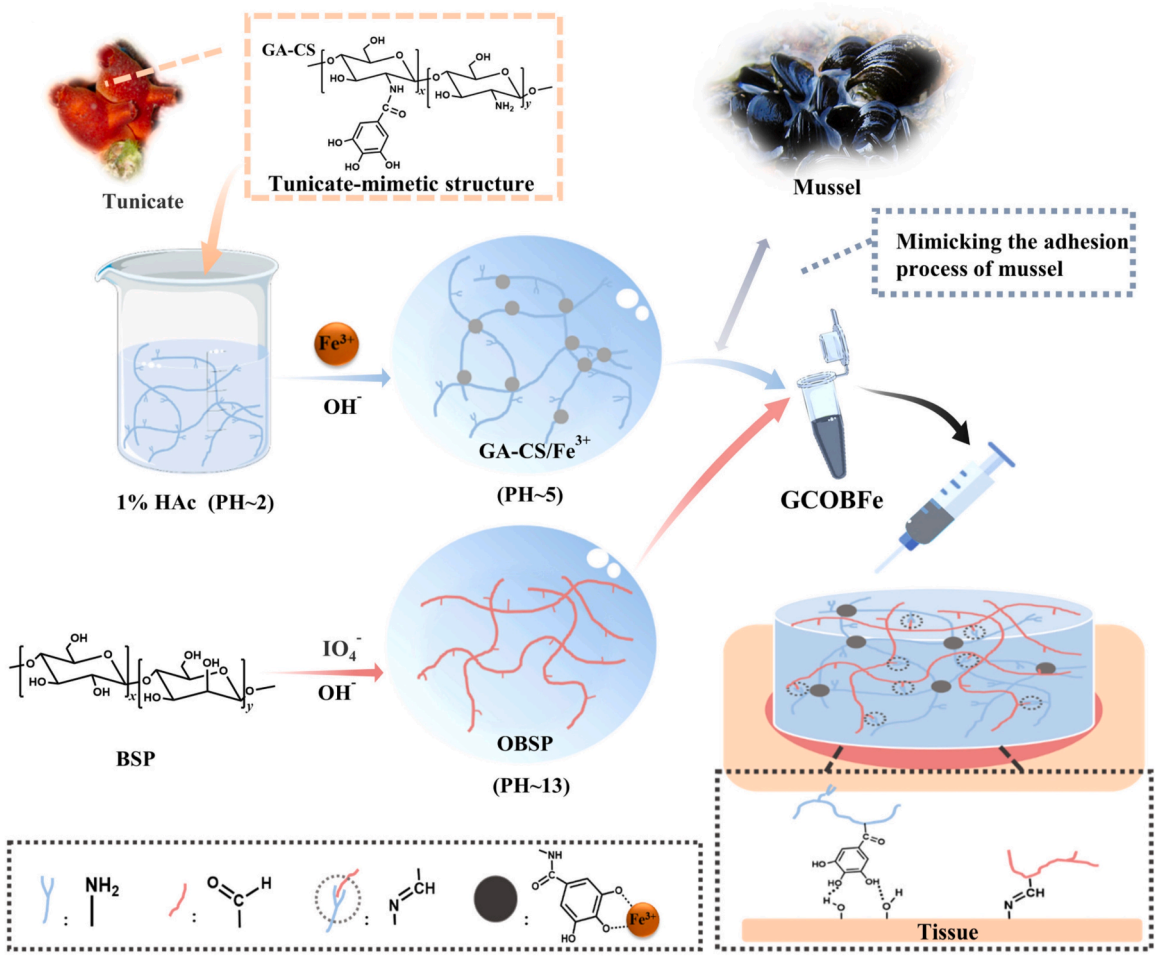

Fig. 19. Schematic diagram of the design and preparation of the gallic acid-grafted chitosan–oxidized *Bletilla striata* polysaccharide–Fe^{3+} hydrogel [80]. Copyright 2021. Adapted with permission from Elsevier.

preventing postoperative adhesions, with considerable attention directed towards chitosan-based composite materials, particularly biodegradable and injectable in situ crosslinking hydrogel systems. For example, the potential applications of a succinyl chitosan-oxidized dextran composite hydrogel [178,292], an *N,O*-CMCh–OHA hydrogel [216], and a CMCh–CMCe–collagen composite membrane [251] in adhesion prevention have been explored due to their proven effect.

In-ear, nose, and throat surgeries to prevent postsurgical adhesion, Aziz et al. [178] engineered succinyl chitosan–oxidized dextran composite hydrogel through Schiff-base reaction between amine and aldehyde groups, inhibiting fibroblast proliferation and reducing scarring and adhesions when used as a nasal packing following endoscopic sinus surgery [178]. Li et al. [216] developed a non-toxic *N,O*-CMCh–OHA hydrogel with excellent biodegradability and hemocompatibility. The hydrogel, formed through Schiff-base reaction (Fig. 21A, B), exhibited pH-responsive swelling behavior, good cytocompatibility, and the ability to prevent fibroblast invasion. It significantly reduced peritoneal adhesion formation in a rat model of sidewall defect-cecum abrasion, with complete recovery within 14 days, outperforming a commercial HA hydrogel and normal saline (Fig. 21C-H). Histological analysis demonstrated remesothelialization of the damaged cecum and defected abdominal wall, indicating its promising potential for postoperative adhesion prevention (Fig. 21I-N) [216]. Cai et al. [251] developed a CMCh–CMCe–collagen composite membrane with superior anti-adhesive capability through solution casting and TG crosslinking. The membrane effectively prevented postoperative adhesion by reducing collagen synthesis, addressing collagen deposition as the main cause of peritoneum adhesion (Fig. 21O-Q) [251].

4.3. Tissue engineering

In recent times, tissue engineering strategies incorporating three elements—biological scaffolds, growth factors, and seed cells—have emerged as a promising therapeutic approach for regenerating bone or cartilage defects [293]. The prevalent approach for repairing bone or osteochondral defects involves implanting cell-seeded biopolymer-based scaffolds, with a particular emphasis on chitosan-based materials.

4.3.1. In vitro cell culture

Chitosan-based 3D scaffolds (summarized in Table 7), such as chitosan–HA PEC scaffolds obtained through a straightforward thermally induced phase separation followed by lyophilization [12] and chitosan–CS scaffolds obtained via a solution mixing and freeze-drying method [294], serve as in vitro cell culture platforms. These scaffolds, characterized by high porosity, effectively replicate in vivo cell environments, providing a diffusion-limited setting absent in 2D cultures. Consequently, they prove effective in fostering cell proliferation and the formation of cell aggregates or spheroids [12]. Moreover, these chitosan-based composites demonstrated the ability to enhance the gene expression of biomarkers, showcasing their potential for in vivo cell culture. This capability offers more predictive insights into the in vivo performance of cells, especially tumor and cancer cells.

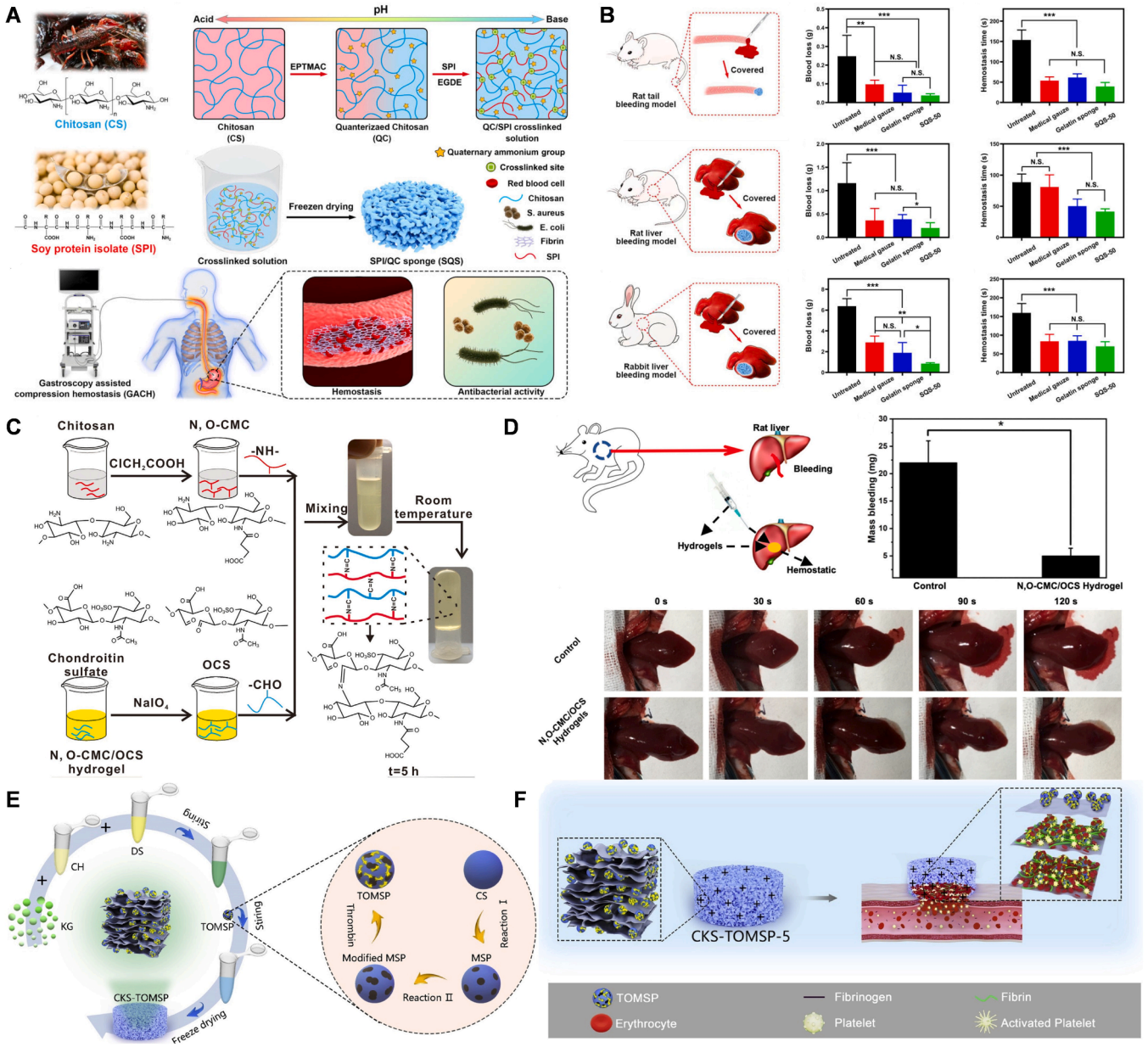

Fig. 20. (A) Schematic illustration of the preparation of the quaternized chitosan–soy protein isolate sponge for acute upper gastrointestinal bleeding. (B) Blood clotting effect of the sponge on an animal model [18]. (C) Schematic illustration of the preparation of the carboxymethyl chitosan–oxidized chondroitin sulfate hydrogel. (D) Hemostatic capability of the hydrogel on bleeding mouse liver samples [176]. Copyright 2021. (E) Schematic illustration of the preparation of the thrombin-occupied microporous corn starch particles-loaded chitosan–konjac glucomannan–dialdehyde starch porous material and its hemostatic mechanism (F) [252]. Copyright 2020.
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4.3.2. *Tissue adhesion*

Boda et al. [246] fabricated chitosan nanofiber membranes through electrospinning, employing GA as a crosslinker. The nanofiber membrane was subsequently coated with oxidized pectin using spin coating to augment surface mucoadhesiveness (Fig. 22A). The resulting PEC membrane demonstrated strong adhesion to an oral mucosal tissue mimic (porcine esophagus). Simultaneously, it exhibited excellent *ex vivo* adhesion to a hard-tissue, enamel mimic (hydroxyapatite). Additionally, the chitosan nanofiber membrane displayed a pH-responsive controlled release of antimicrobial peptides (D-GL13K and 1018), showcasing the potential of the PEC membrane as a dual soft–hard tissue bioadhesive for gingival grafts while providing protection against oral infections [246]. In another study [248], a hematin-grafted chitosan-catalyzed catechol-conjugated chitosan hydrogel was successfully developed at physiological pH without the need for horseradish peroxidase (Fig. 22B, C). The gelation time could be regulated by the concentration of H_2O_2, and the resulting hydrogel exhibited superior adhesion force (33.6 KPa) compared to that of the conventional pH-initiated hydrogel (20.6 KPa) [248]. This indicates the potential of such adhesive hydrogels for biomedical applications.

4.3.3. *Bone tissue engineering*

Addressing broken or damaged bones has long posed a challenge for doctors and patients. However, in tissue engineering, biodegradable scaffold materials offer a promising therapeutic strategy for bone injuries. Chitosan-based materials have been extensively investigated for the development of tissue engineering scaffolds that can mimic the components of the natural ECM of bone, as detailed in Table 7.

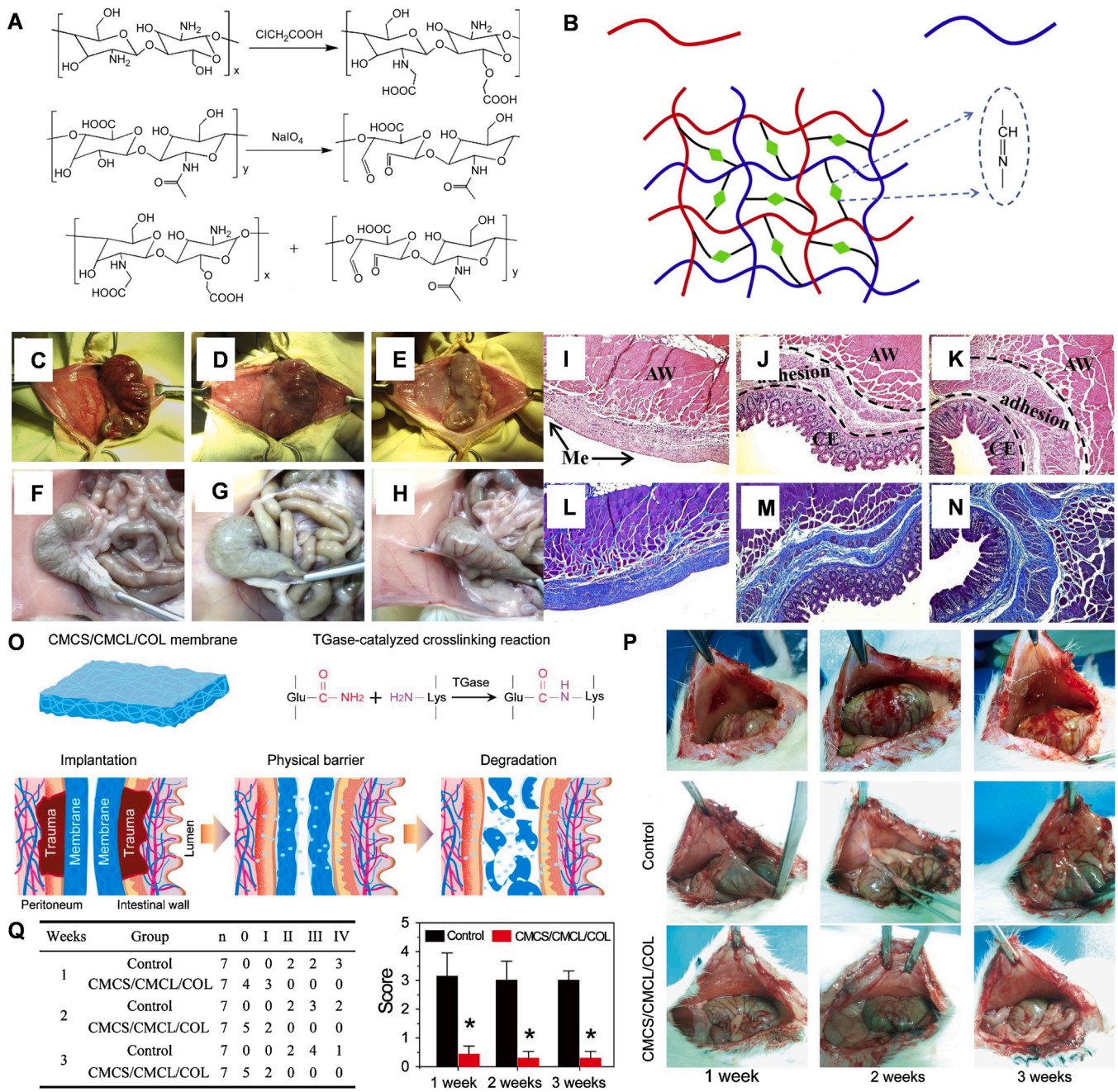

Fig. 21. Schematic illustration of the synthesis (A) and structure (B) of the *N*,*O*-carboxymethyl chitosan (CMCh)–aldehyde hyaluronic acid (HA) hydrogel. Prevention effect on the postoperative abdominal adhesion of a rat defect-cecum abrasion model treated with normal saline (C, F), the HA hydrogel (D, G), and the *N*,*O*-CMCh–aldehyde HA hydrogel (E, H). Histological images of tissues from rats treated with the *N*,*O*-CMCh–aldehyde HA hydrogel (I, L), the HA hydrogel (J, M), and normal saline (K, N) [216]. Copyright 2014. (O) Schematic representation of the mechanism of the TG-crosslinked carboxymethyl chitosan–carboxymethyl cellulose–collagen composite membrane for postsurgical adhesion prevention. (P, Q) Postsurgical adhesion prevention effect of the membrane [251]. Copyright 2018. (a) Adapted with permission from Elsevier. (b) Adapted with permission from Elsevier.

For example, a chitosan–strontium CS scaffold with a porous structure, developed via a solution mixing and freeze-drying method using β-glycerol phosphate and sodium hydrogen carbonate as gelling agents (Fig. 23A), demonstrated the capability to significantly reduce the inflammatory response and osteoclastogenesis. It also enhanced osteogenesis, promoting cell attachment, growth, and differentiation toward the osteogenic lineage and supporting the mineralization of bone structure (Fig. 23B-D) [257]. Additionally, a chitosan–SF nanofibrous membrane scaffold (pore size: 0.71 μm) prepared through an electrospinning method was shown to facilitate the infiltration of osteoblasts, bone formation, and the expression of osteogenic marker genes [39].

In reality, biopolymer scaffolds struggle to closely mimic the natural periosteum. Bombaldi de Souza et al. [15] demonstrated that the addition of the non-ionic surfactant Poloxamer 188 (Kolliphor® P188) and polydimethylsiloxane into a phosphorylated chitosan–xanthan gum scaffold, prepared via drying at 37 °C, yielded porous (pore size: 850–1097 μm) and mechanically reinforced matrices. Improved osteogenesis was demonstrated with a larger pore size (>300 μm) of implants [295]. These resulting biodegradable scaffolds could concentrate native bone morphogenetic proteins and induce osteogenesis and showed low thrombogenicity compared to Teflon® (a standard implantable material) [15].

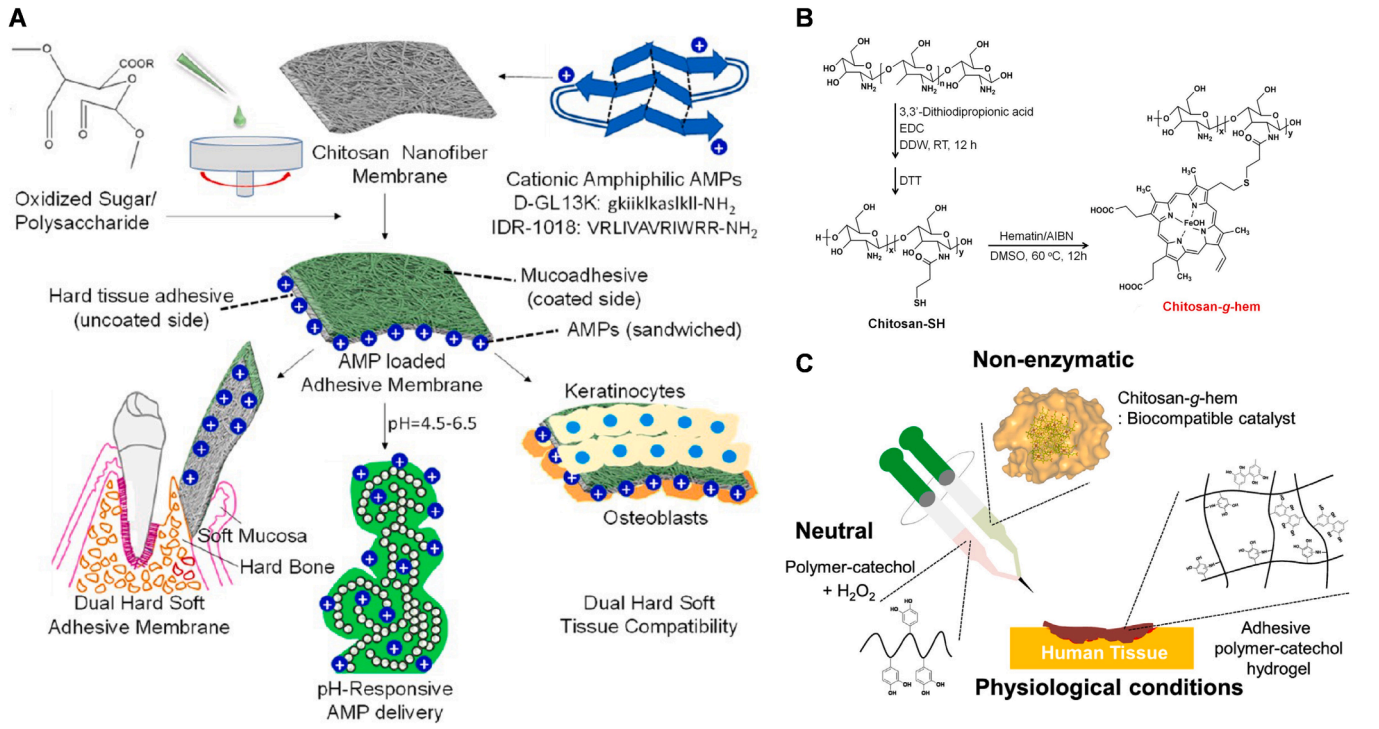

Fig. 22. (A) Schematic diagram of the preparation of the chitosan–oxidized pectin nanofiber membrane for tissue adhesion [246]. Copyright 2020. Schematic diagram of the preparation of the hematin-grafted chitosan catalyzed catechol-conjugated chitosan hydrogel (B) and in situ adhesive property of the hydrogel (C) [248]. Copyright 2014.
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4.3.4. *Cartilage tissue engineering*

Recently, biopolymer-based materials, especially chitosan-based materials [154,206,250,293], have assumed a crucial role in cartilage tissue engineering research. This prominence is attributed to their notable biocompatibility, excellent mechanical properties, controlled biodegradability rate, high attachment rate and proliferation of cells, compatibility with the ECM of articular cartilage, and the ability to provide a biocompatible microenvironment for cell growth, chondrogenic differentiation, and ECM production (for more details, refer to Table 7).

Taking advantage of the electroneutrality of chitosan in an alkali/urea aqueous system, Liang et al. [250] developed a novel chitosan–κ-carrageenan PEC hydrogel with pH- and salt-sensitive behaviors, using epichlorohydrin (ECH) as a crosslinking agent. The resulting hydrogel exhibited excellent mechanical properties (Fig. 24A), good blood compatibility, favorable for cell adhesion and proliferation, and demonstrated the ability to induce chondrogenic differentiation of ATDC5 cells in vitro (Fig. 24B, C).

In fact, achieving optimal in vivo cartilage repair is challenging with chitosan-based scaffolds alone. Researchers tended to enhance the repair effect by combining chitosan-based scaffolds with cells, drugs, growth factors, and even ECMs (Fig. 25) [154,206,269,293,296,297]. For example, the integration of ECM (Fig. 25A) and transforming growth factor-β3 (TGF-β3) (Fig. 25C) within chitosan-based composites has been shown to improve cellular adhesion and chondrogenesis [206]. This approach provided a biocompatible microenvironment for cartilage cell growth [206,293], making it suitable for cartilage repair and regeneration.

Nevertheless, the impact of exogenous additives is not consistently positive. Neethu et al. [269] found that loading chondrocytes within a chitosan–HA dialdehyde hydrogel did not significantly improve the quality of regenerated cartilage; it only facilitated the integration of the regenerated cartilage with the native cartilage, compared to a chitosan–HA dialdehyde hydrogel alone. Additionally, the inclusion of ECM in a chitosan–agarose hydrogel scaffold notably reduced compression strength and modulus by diminishing interactions between agarose and chitosan chains [206].

4.3.5. *Nerve tissue engineering*

Lately, chitosan-based composite materials [17,24,225] have gained prominence in promoting peripheral nerve tissue regeneration and treating disorders due to their cytocompatibility without cytotoxicity, modulated degradation behavior, and the ability to enhance the attachment, migration, and proliferation of nerve cells (Table 7).

A biomimetic chitosan–keratin membrane, prepared via solution casting, induced a higher formation of blood vessels in the chick embryo chorioallantoic membrane. This property made it suitable as a protective nerve wrap around damaged nerves to prevent post-operative nerve adhesion, as a nerve guidance conduit to bridge two nerve stumps, or as a luminal filler to enhance the nerve guidance conduit (Fig. 26) [17].

However, the effect of chitosan-based composite materials on accelerating nerve regeneration was limited, especially for nerve damage with a long gap (over 3 cm). Various growth factors and neurotrophic factors have been utilized in combination with chitosan-based composite materials for nerve regeneration [225,298]. An aniline pentamer (electroconductive oligomers)-incorporated chitosan–alginate–agarose conductive hydrogel, developed via a cryo-gelation process [225], and nerve growth factor-loaded chitosan–heparin scaffolds obtained by immersing freeze-dried chitosan scaffolds in a heparin solution followed by oven drying [298], could enhance the viability, attachment, and proliferation of nerve cells (e.g., Schwann cells). Importantly, nerve cells cultured in a 3D aniline pentamer-incorporated chitosan–alginate–agarose conductive hydrogel were induced to differentiate into dopaminergic neurons using different cocktail neurotrophic factors for 9 or 12 days [225]. Consequently, these growth factor/neurotrophic factor-loaded chitosan-based materials with robust nerve regeneration capabilities offer distinct advantages for nerve tissue engineering.

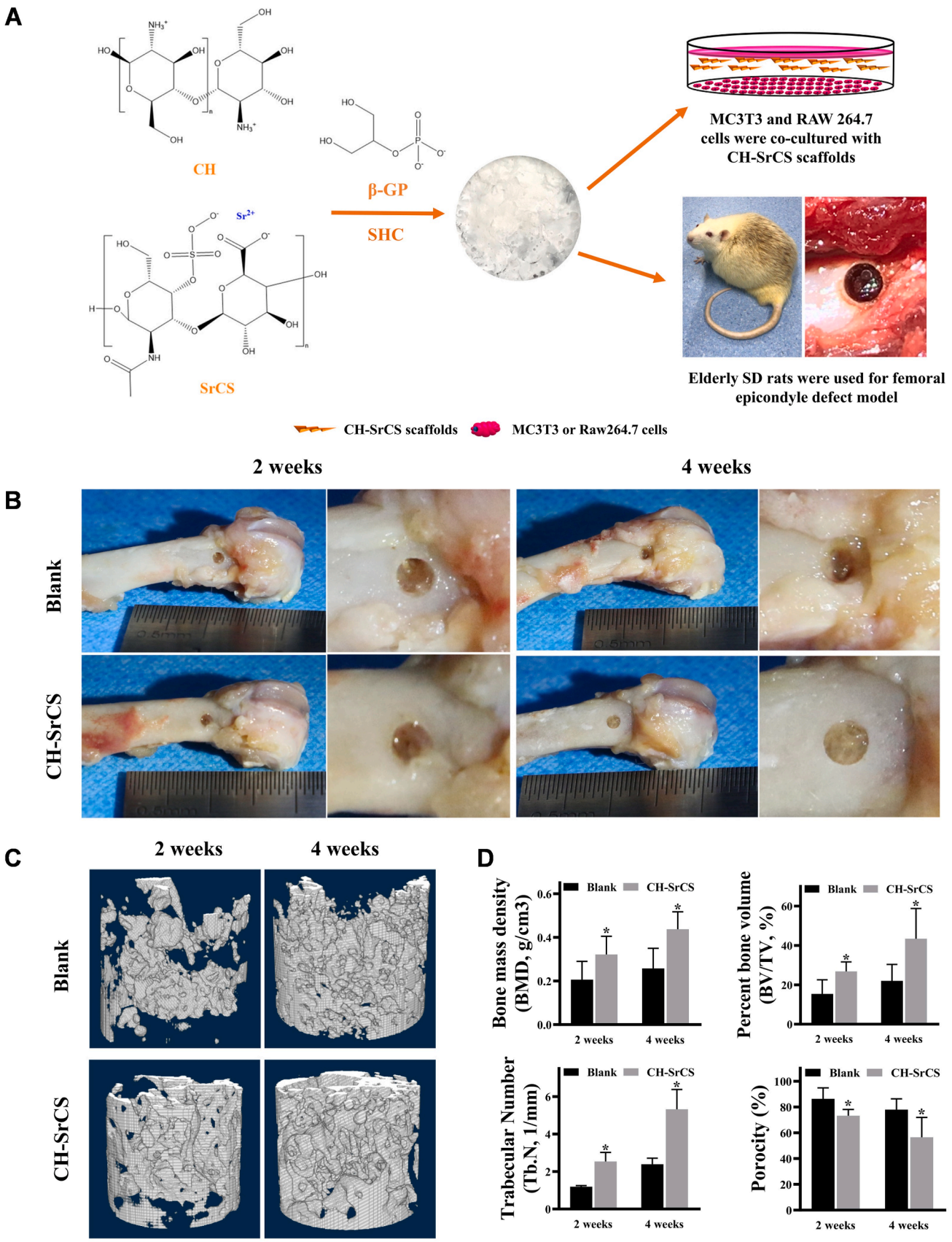

Fig. 23. (A) Schematic diagram of the chitosan–strontium chondroitin sulfate (CS) scaffold for bone tissue engineering. (B) Photos and (C) 3D models of new bone formation (obtained via microcomputed tomography) showing the facilitation effect of no scaffold and the chitosan–strontium CS scaffold on the mineralization of the bone structure and new bone formation in a rodent bone defects model. (D) Images of quantitative parameters of the newly formed bone in the rat's bone defects area [257]. Copyright 2014. Adapted with permission from Elsevier.

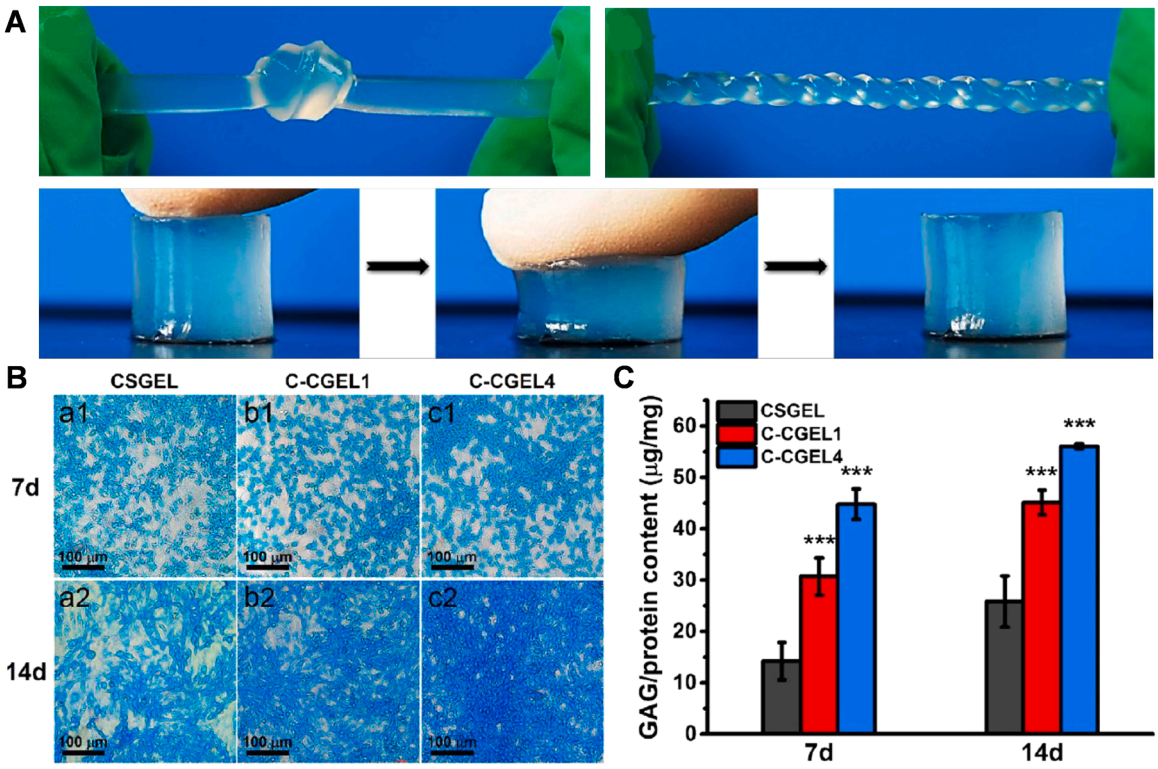

Fig. 24. (A) Photos of the chitosan–κ-carrageenan polyelectrolyte complex hydrogel with excellent mechanical properties. (B, C) Effect of the hydrogel in promoting chondrogenic differentiation [250]. Copyright 2018. Adapted with permission from the American Chemical Society.

4.3.6. *Skin tissue engineering*

Chitosan-based composite materials have garnered significant attention for the fabrication of artificial skin. In pursuit of an artificial skin substitute for regenerative medicine applications, Vivcharenko et al. [123] prepared a solution-cast chitosan–agarose film exhibiting a slightly acidic pH of 5.98. This pH value is advantageous for maintaining the viability of fibroblasts. The resulting film, in a wet state, demonstrated elasticity (elongation at break equal to 23%) and Young's modulus (0.02 MPa) comparable to natural skin tissue. It also displayed high exudate absorption capacity (3.3 mL of plasma, 4.4 mL of serum, 1 g of biomaterial), biodegradability, and non-toxicity. These properties are beneficial for the growth and proliferation of human skin fibroblasts, making it suitable for use as a skin substitute [123].

4.3.7. *Vascular tissue engineering*

The development of artificial blood vessels, especially small-caliber artificial blood vessels, has recently garnered significant attention due to challenges associated with immune rejection and the limited source of autologous blood vessels. However, commonly used synthetic polymer materials possess inherent limitations, such as the potential toxicity of the large concentration of biodegradation products accumulated in the biological media [268].

Chitosan-based composites, such as chitosan–gelatin bilayered 3D scaffold constructed via a solvent casting/particulate leaching method (Fig. 27**A**, B) [268], chitosan–heparin decorated bacterial nano-cellulose tubes (Fig. 27C) [299], and LbL assembled chitosan–heparin-coated polyurethane decellularized scaffold (Fig. 27D, F) [153,255], have been investigated for blood vessel tissue engineering. Beyond displaying desirable mechanical and elastic strengths, controllable swelling and biodegradation behaviors, and high cell adhesion and proliferation [268], these chitosan-based composites also exhibited higher water permeability—signifying potential nutrient exchange between the vascular exterior and interior—compared to a clinically applied expanded polytetrafluoroethylene (ePTFE) artificial blood vessel [299]. It is worth noting that while these composites slightly inhibited cell proliferation, the LbL assembled chitosan–heparin-coated polyurethane decellularized scaffold maintained vessel patency even after 5 months of implantation (Fig. 27E) [153].

4.3.8. *Hepatic tissue engineering*

Fan et al. [300] incorporated epidermal growth factors into a chitosan–galactosylated HA–heparin scaffold by freeze-drying, leveraging the high affinity of heparin with growth factors. Hepatocytes aggregated to form multicellular spheroids within the scaffolds, displaying outstanding metabolic activities, including albumin secretion, urea synthesis, and ammonia elimination [300]. Consequently, the scaffold holds promise as a candidate for liver tissue engineering.

4.4. *Coatings on biomedical implants*

Surface modifications, including surface coating, have been explored to enhance the clinical performance (e.g., cell adhesion, proliferation, and differentiation, as well as corrosive resistance) of biomedical implants, such as Ti and its alloys [244,267,301] and Co–Cr–Mo alloy [266], and to improve biological acceptance as reflected by integration performance and post-implantation healing. Recently, chitosan-based composite materials have gained increasing interest as coatings for biomedical implants due to their outstanding antibacterial properties [244], cellular affinity [301], and abilities to promote cell proliferation and differentiation [266,267,301], as well as accelerate collagen deposition and calcium deposition [267].

An LbL assembled pH-sensitive heparin-tobramycin micelles-loaded chitosan–heparin PEC multilayer coating on a Ti substrate, assisted by polydopamine to enhance the binding strength between the multilayer and substrates (Fig. 28A, B), enabled prolonged drug release at acidic body regions, providing orthopedic implants with enduring antibacterial functionality [239]. The chitosan–heparin composite coating further improved the antibacterial performance and hemocompatibility of

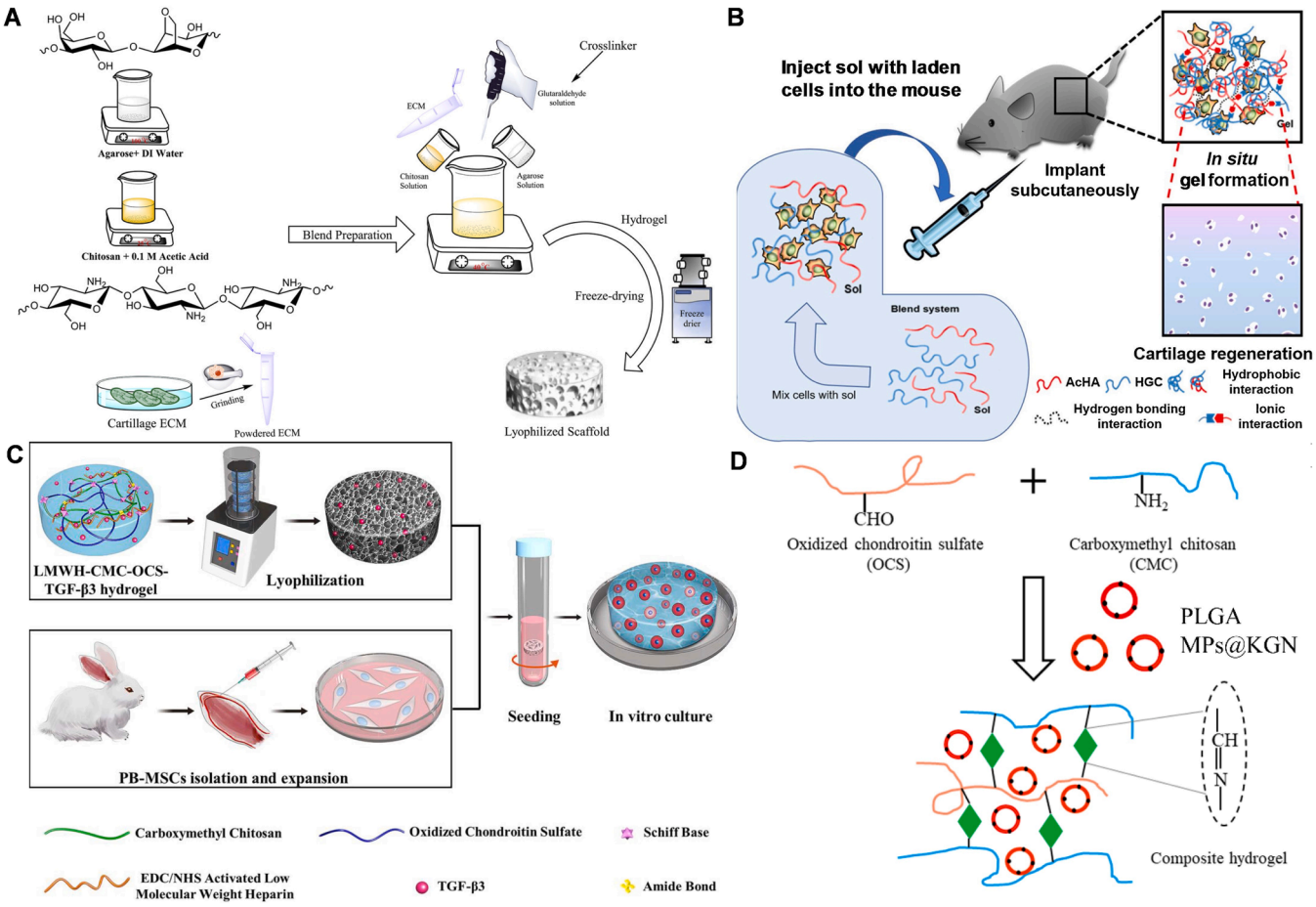

Fig. 25. (A) Schematic diagram of the fabrication of the chitosan–agarose hydrogel scaffold for cartilage tissue engineering [206]. Copyright 2020. (B) Schematic illustration of the design of the cell-loaded glycol chitosan–hyaluronic acid hydrogel [154]. Copyright 2020. (C) Schematic diagram of the formation of the growth factor-β3-loaded carboxymethyl chitosan–oxidized chondroitin sulfate hydrogel [293]. (D) Schematic representation of the preparation of the kartogenin-loaded chitosan–chondroitin sulfate hydrogel [296].
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alkali-treated Ti substrates (Fig. 28C) [241]. A 30-bilayered heparin-loaded LbL self-assembled chitosan–κ-carrageenan coating on Mg alloys pretreated using micro-arc oxidation was developed [302]. The resulting coating facilitated the sustained release of heparin, ensuring excellent hemocompatibility over time (Fig. 28D) [302]. In light of this, these chitosan-based composite coatings exhibit promising potential for applications as coatings on biomedical implants.

The ability to promote cell adhesion and proliferation is crucial for chitosan-based materials, ensuring effective integration of the implant with the surrounding tissue. A chitosan–alginate/pectin coating [267] and an LbL-deposited chitosan–casein phosphopeptide multilayer film [266] demonstrated high wettability, promoting cell attachment and proliferation, ALP activity, collagen retention, and calcium deposition [267]. Additionally, they increased osteoblast-gene-expression levels, facilitating osteoblast maturation [266]. The enhanced wettability of a chitosan–alginate coating could reduce acute inflammation caused by neutrophils and the degree of fibrosis, thereby allowing for improved osseointegration at the implant–host tissue interface [267]. These chitosan-based coatings hold promise as effective surface modifications for biomedical implants.

4.5. 3D bioprinting

3D bioprinting has ushered in a paradigm shift in tissue engineering (in vitro), enabling the production of functional tissue constructs for modeling studies, disease treatment, and transplantation therapy [303, 304]. The development of biopolymer-based bioink is pivotal for organ and tissue replacement and/or regeneration through 3D printing [218]. When designing bioinks for practical applications, the flow properties of bioinks and the mechanical properties of printable objects are two critical considerations [218]. Printability, immediate curability of the polymeric network, and stability of biopolymer-based materials are crucial factors for producing mechanically stable objects in 3D bio-printing [218,305]. Chitosan-based composite materials, especially chitosan-based self-healing hydrogels, have been extensively developed for 3D bioprinting applications [218,303,305–307].

A chitosan–guar gum ink, prepared through a solution mixing method, exhibited shear-thinning behavior and maintained post-printing shape fidelity [306]. Direct-ink-writing (DIW) printing of cells within biomaterials offers opportunities for in vitro modeling and regenerative medicine in tissue engineering [303]. An ATDC5 cell-loaded glycol chitosan–OHA self-healing hydrogel, designed based on the formation of dynamic and reversible covalent bonds, including imine bonds between glycol chitosan and OHA and acylhydrazone bonds formed between OHA and ADH (Fig. 29A), allowed cells to differentiate normally without being affected by the printing process (Fig. 29B), suggesting its potential as tissue engineering scaffolds [218]. In a study by Gu et al. [303], a novel 3D neural mini-tissue construct was obtained through the in situ differentiation of frontal cortical human neural stem cells (hNSCs) into functional neurons and supporting

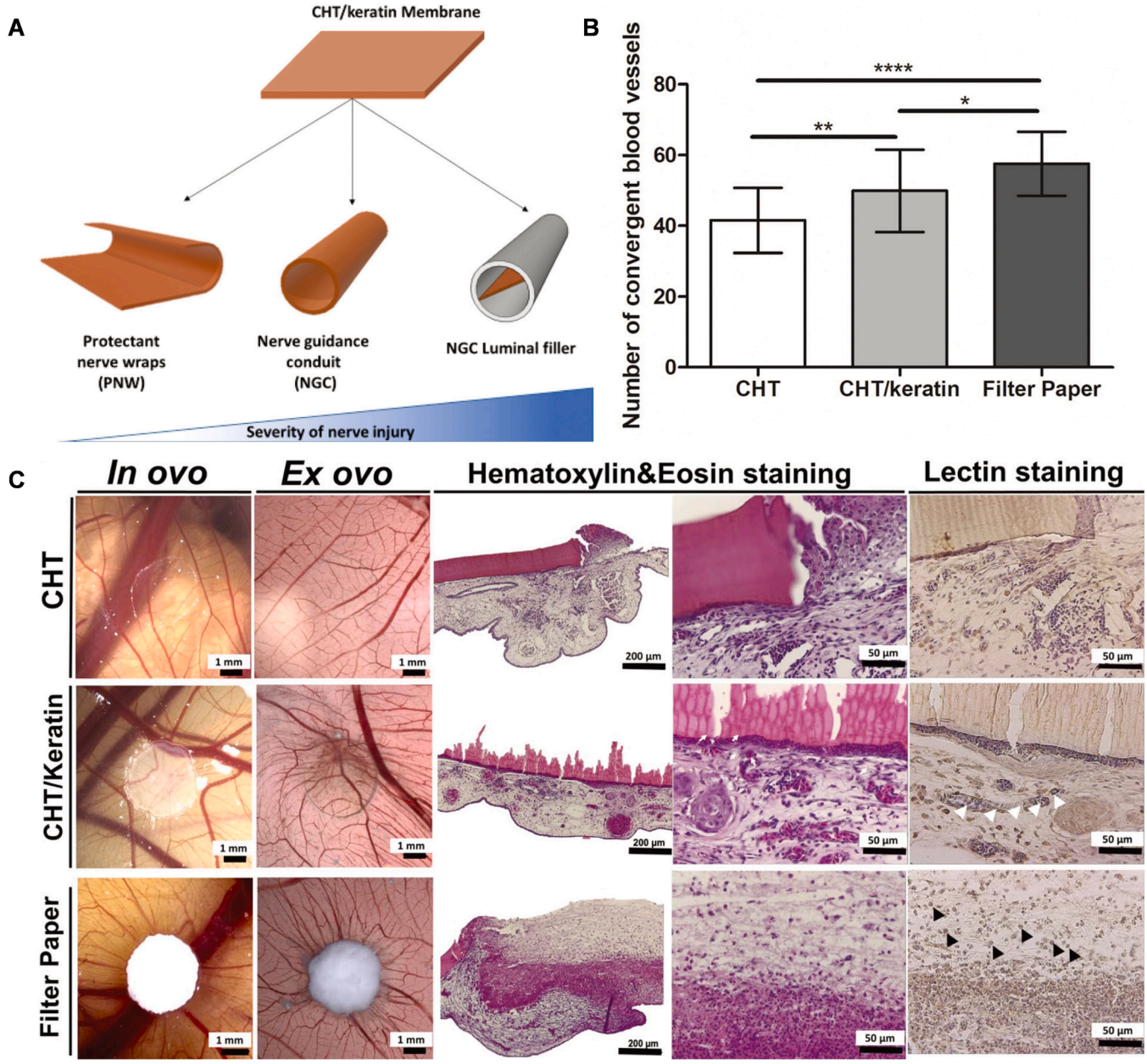

Fig. 26. (A) Schematic mechanism of the chitosan–keratin membrane on nerve injury. (B) *Ex ovo* quantification of angiogenic response of the bare chitosan membrane and the chitosan–keratin membrane. (C) Angiogenic response (*in ovo* and *ex ovo*) of the bare chitosan membrane, filter paper, and the chitosan–keratin membrane after 4 days of implantation on a chick embryo chorioallantoic membrane [17]. Copyright 2019. Adapted with permission from the Royal Society of Chemistry.

neuroglia in a CMCh–alginate–agarose composite gel, chemically crosslinking with $CaCl_2$ following 3D printing (Fig. 29C). The composite gel maintained stable stiffness from day 10 and significantly accelerated the upregulation of neuronal marker and other neuronal subtype-relevant transcripts [303]. Printed scaffolds loaded with stem cells show promise for accelerating neuronal, neuroglial, and synapse formation. A stem cell-laden MA glycol chitosan–MA keratin bioink (Fig. 29D, E) was developed, demonstrating excellent mechanical strength and biocompatibility [93].

4.6. Biosensor and electrochemical sensors

Advancements in science and technology, coupled with new performance requirements for materials in biomedical applications, have led to the design and development of biopolymer-based biosensors and electrochemical sensors. Notably, chitosan-based sensors have emerged for the detection and measurement of drugs, disinfectants, and even human physiological signals [175,204,272,308].

A biosensor utilizing electrospun chitosan–gelatin nanofibers [204] and an electrochemical sensor with a chitosan–pectin PEC coating (Fig. 30A, B) [272] have been employed for the detection of hydrogen peroxide in disinfectants and the simultaneous determination of metribuzin and metronidazole, respectively. Both sensors demonstrated excellent reproducibility, high stability, high sensitivity, and low detection limit for the targeted substances. The latter sensor exhibited exceptional anti-interference ability. The PEC chitosan–pectin film-coated glassy carbon electrode (GCE) stands out as an excellent electrochemical sensor for detecting specific analytes in human blood [272].

Beyond drug detection, chitosan-based composites find utility in

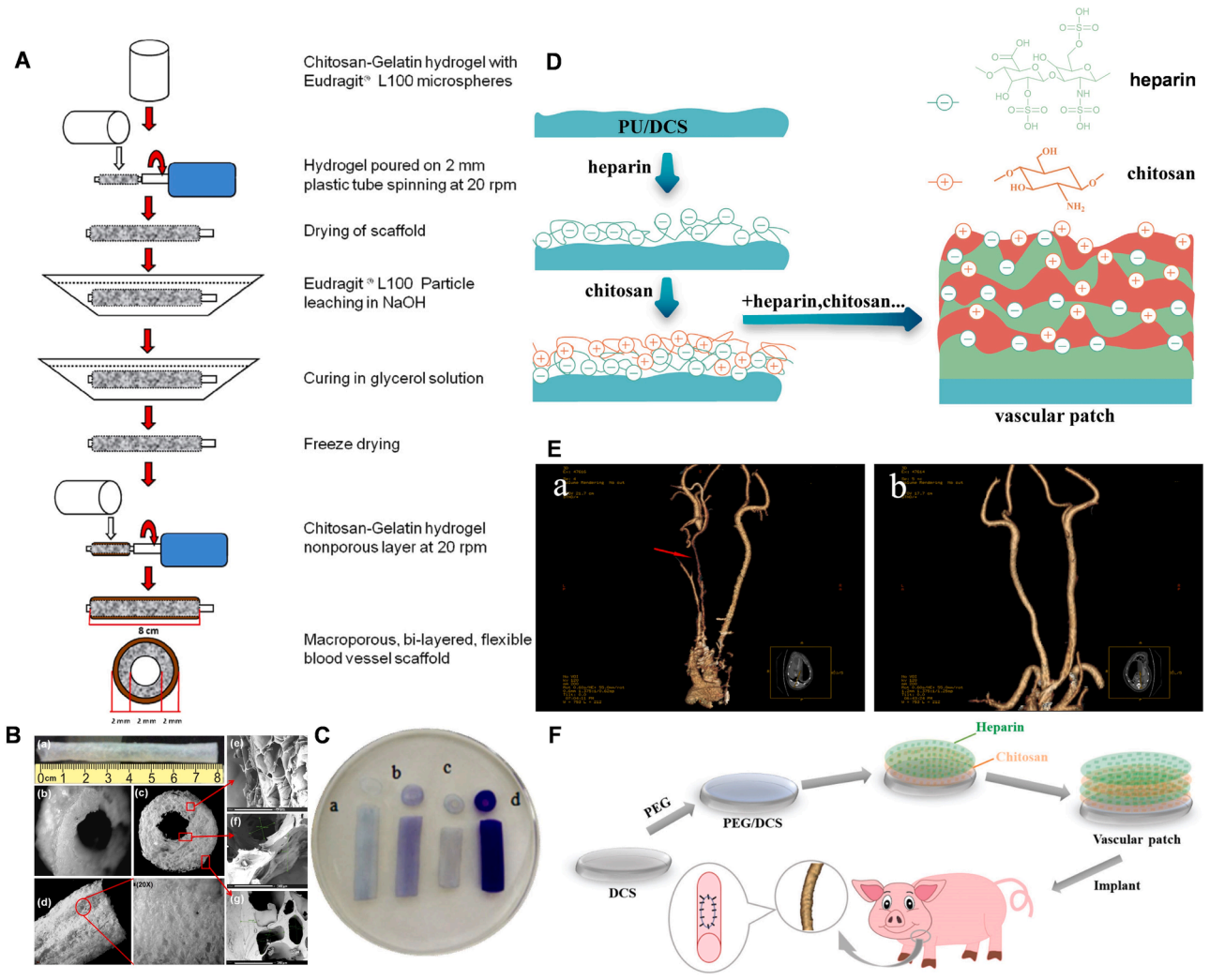

Fig. 27. (A) Schematic diagram of the preparation of the chitosan–gelatin bilayered 3D scaffold. (B) Stereoscope images of the scaffold [268]. Copyright 2017. (C) Photograph of the chitosan–heparin coated bacterial nano-cellulose tubes [299]. Copyright 2017. (D) Schematic representation of the preparation of the chitosan–heparin polyelectrolyte complex (PEC)-coated polyurethane decellularized scaffold substrate. (E) Computed tomography angiography images of the scaffold [153]. Copyright 2019. (F) Schematic representation of the preparation of the chitosan–heparin PEC-coated poly(ethylene glycol) decellularized scaffold [255]. Copyright 2022.
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monitoring human physiological signals. A dressing-integrated sensor, relying on an electroconductive HACC–alginate PEC hydrogel with a "Magic Cube"-like structure, constructed via solution casting followed by acid treatment (Fig. 30C) [175], and a damper with a frequency-selective damping property based on a chitosan–porcine skin gelatin interpenetrating hydrogel (Fig. 30F) obtained by a simple solution mixing method followed by gelation at 4 °C [308], were capable of detecting human body movements, such as those of the throat and joints (Fig. 30D), and continuous physiological signals (including mechanical biophysiological signals and electrophysiological signals) without signal processing, unaffected by the subject's physical activity (e.g., breath and walk), and resistant to noisy conditions (Fig. 30G), respectively. In addition, the ability of a HACC–alginate PEC composite hydrogel to monitor subtle shrinkage by calculating the electrical resistance change during deformation indicates its potential for monitoring wound closure and providing information on changes in wound area during wound healing [175]. The chitosan–porcine skin gelatin interpenetrating hydrogel damper, with excellent mechanical noise-damping capability and stability (Fig. 30E), could expedite the application of soft bioelectronics without requiring a signal-processing step [308].

4.7. Other biomedical applications

4.7.1. Functional medical sutures

Enhancing traditional sutures with functional biopolymers offers a range of biological benefits. Chitosan-based materials stand out as excellent choices for suture development due to their reliability.

Mohammadi et al. [44] innovatively created a medical suture with controlled drug release and antimicrobial properties. They achieved this by coating a chitosan–HA bilayer PEC film on nylon monofilaments using an LbL method. The ionic interaction between the biopolymers not only prevented the exfoliation of the coated bilayers but also reduced the friction coefficient, highlighting its potential for use as a suture [44].

In a separate study, Do et al. [309] developed chitosan–heparin fibers using an interfacial polyelectrolyte complexation technique (Fig. 31A). These fibers exhibited remarkable flexibility and tensile strength, meeting the average tensile strength requirement (guideline value of 220 MPa for size 6–0) of a natural suture. Utilizing 64-stranded chitosan–heparin fibers as sutures demonstrated their ability to navigate needle-punctured tissue with minimal friction, remaining mechanically intact throughout the entire wound closure procedure. The fibers also

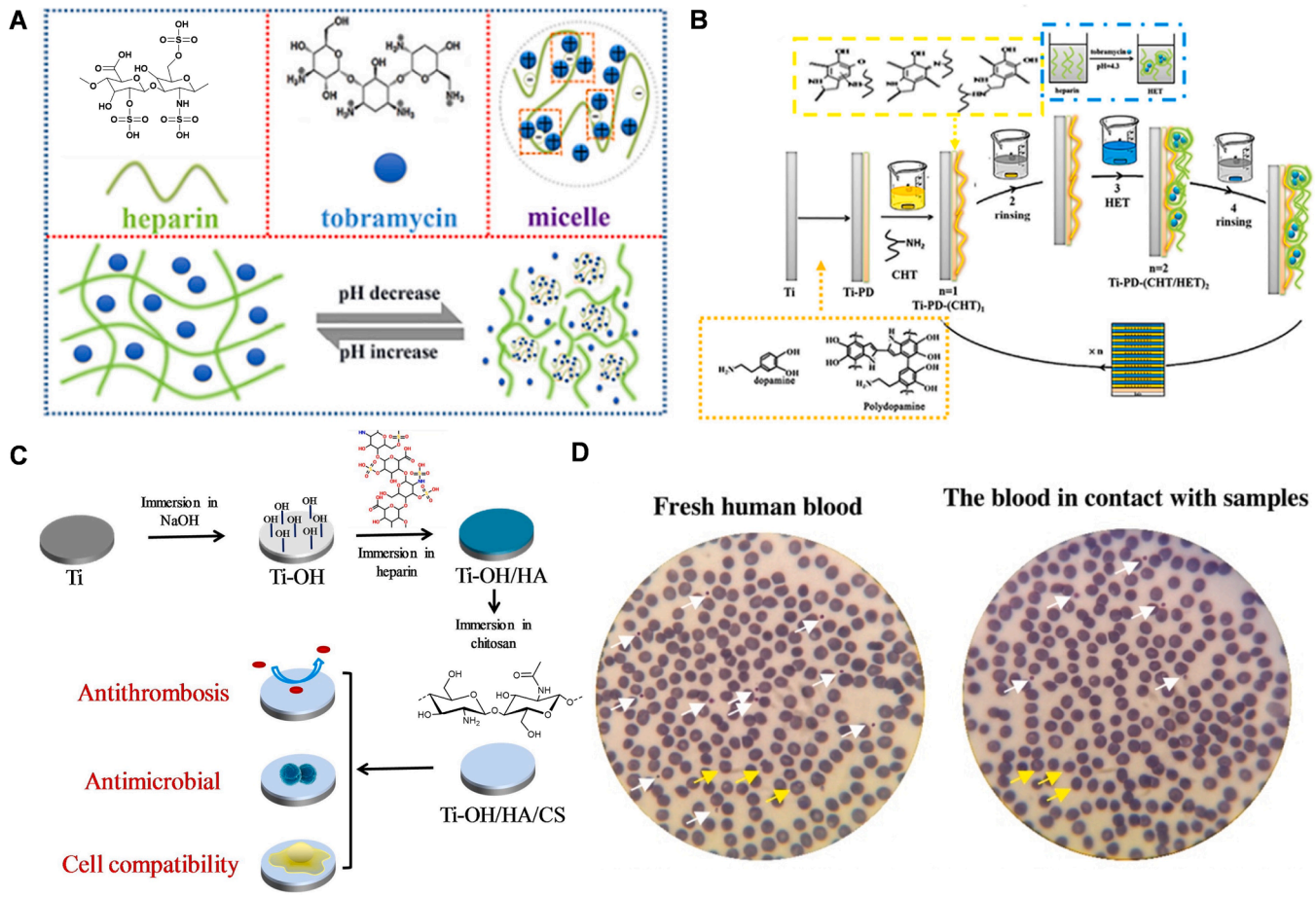

Fig. 28. Schematic representation of the mechanism (A) and preparation (B) of the pH-sensitive heparin–tobramycin micelles-loaded chitosan–heparin polyelectrolyte complex multilayer coating [239]. Copyright 2018. (C) Schematic representation of the design of the heparin-loaded layer-by-layer (LbL) self-assembled chitosan–κ-carrageenan coatings on Mg alloys [241]. Copyright 2018. (D) Optical microscopic images of the blood treated with the heparin-loaded LbL self-assembled chitosan–κ-carrageenan coating [302]. Copyright 2022.
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proved effective in tissue ligation (Fig. 31B) [309].

4.7.2. Blood purification

In an effort to mitigate bacteria burden and reduce endotoxin levels in septic blood during blood purification, Li et al. [164] engineered chitosan–κ-carrageenan hydrogel beads. These nonhemolytic and non-cytotoxic beads, featuring a core-shell structure formed through a phase inversion and genipin crosslinking method, were immersed in a KCl solution to create a carrageenan gel shell structure (Fig. 32A). The resulting hydrogel beads, characterized by a porous structure, demonstrated anticoagulant and antimicrobial activity. Moreover, they exhibited high removal efficiency against bacterial and endotoxins in septic blood models, underscoring their significant potential as a hemoperfusion sorbent for sepsis treatment during blood purification (Fig. 32B, C). [164].

4.7.3. Thrombolytic therapy

Polypyrrole nanoparticles adorned with glycol chitosan–heparin, showcasing a broad absorption band (700–900 nm) in the UV range within the NIR region, demonstrated the ability to efficiently dissolve a $FeCl_3$-instigated thrombosis model under 2.45 W/cm^2 exposure, without damaging surrounding healthy tissues (Fig. 33) [238]. Consequently, these nanoparticles, combining glycol chitosan and heparin, hold significant promise for thrombolytic treatment.

4.7.4. Free radical scavengers

Vecchies et al. developed lactose-modified chitosan–HA coacervates through drop-by-drop injection of HA into a lactose-modified chitosan solution. The resulting coacervates exhibited a scavenging effect that could mitigate the generation of H_2O_2 by neutrophils, serving as an effective scavenger for ROS [112].

4.7.5. Smart hydrogel actuators

Taking inspiration from the bilayer structure found in plant organs, Duan et al. [221] engineered a pH-responsive chitosan–cellulose/CMCe bilayer hydrogel using LbL solution casting and ECH as a crosslinker. This hydrogel actuator, created through these methods, served as a versatile soft gripper capable of performing mechanical tasks in harshly acidic environments. Additionally, it functioned as a smart encapsulator for trapping microspheres and found application in stomach-specific drug delivery (Fig. 34). Furthermore, the hydrogel actuator doubled as a smart lens, with adjustable focus facilitated by the pH-sensitive swelling behavior of the bilayer hydrogel [221].

5. Summary

Considerable efforts have been invested in conceptualizing and crafting biofunctional chitosan biopolymer composites tailored for biomedical applications. The notable advancements and the surge in related studies underscore the compelling allure of these biofunctional chitosan biopolymer composites. This review delves into diverse

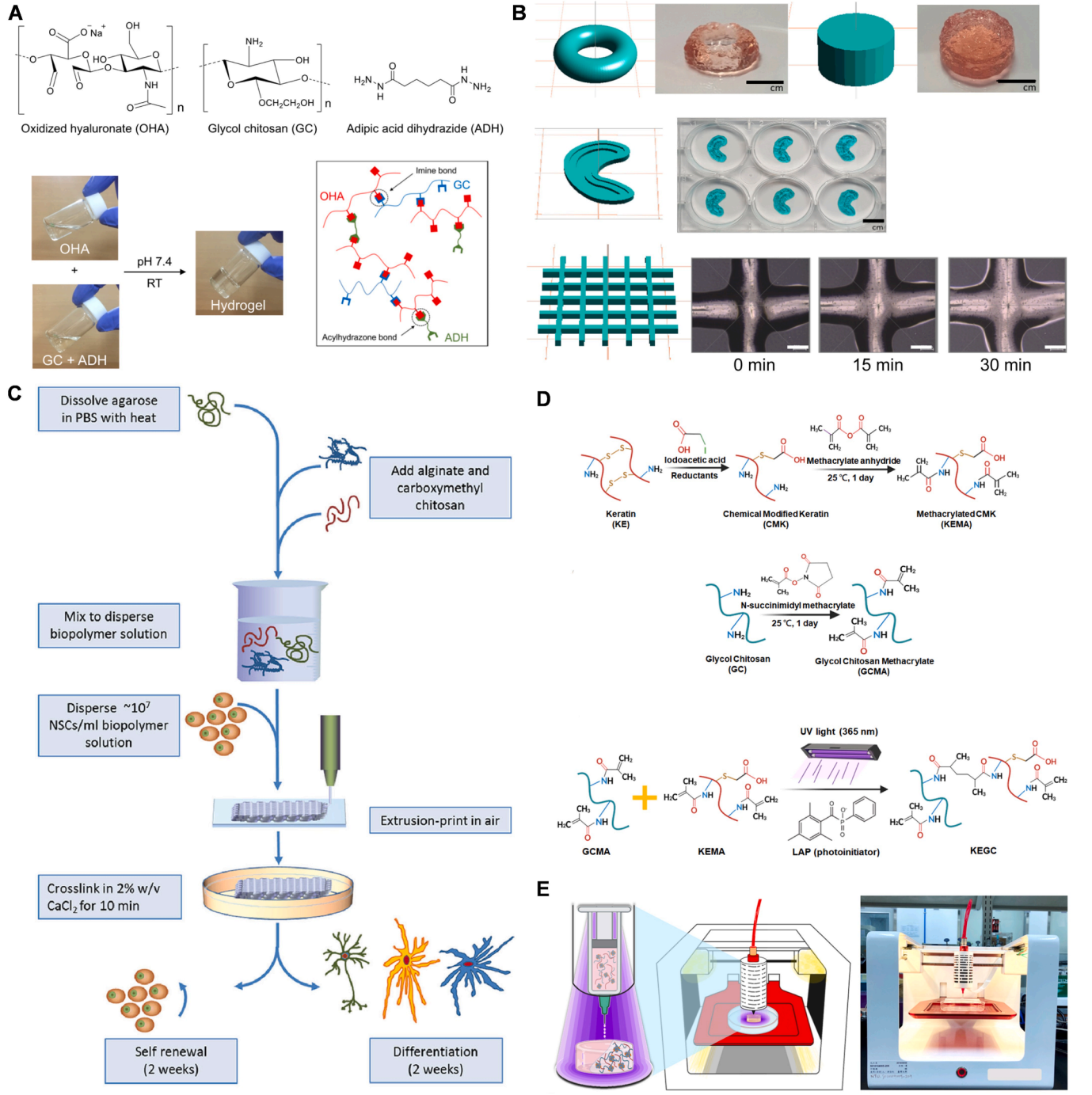

Fig. 29. (A) Schematic diagram of the preparation and structure of the glycol chitosan–oxidized hyaluronic acid self-healing hydrogel. (B) 3D-printed glycol chitosan–oxidized hyaluronic acid hydrogel with different shapes [218]. Copyright 2019. (C) Schematic representation of the preparation of the 3D neural mini-tissue construct using the carboxymethyl chitosan–alginate–agarose bioink for 3D culture and differentiation [303]. Copyright 2016. Schematic diagram of the preparation (D) and bioprinting (E) of the glycol chitosan methacrylate–keratin methacrylate bioinks [93]. Copyright 2022.
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functional chitosan-based composite systems, offering insights into the future research of biopolymer-based functional materials crucial for biomedical technology development. It highlights the following developments and findings in this area:

1) **Targeted applications:** Various established and emerging biomedical applications, including controlled release and target delivery, wound healing, tissue engineering, gene delivery, biomedical implant coatings, functional medical sutures, 3D bioprinting, biosensors, and blood purification, among others, are discussed. This article summarizes, evaluates, and compares clinically required functional features offered by various chitosan composites, such as biocompatibility, non-toxicity, suitable mechanical properties, and biodegradability.
2) **Biopolymer hybridization:** Extensive literature confirms that designing formulations that amalgamate innate functional properties

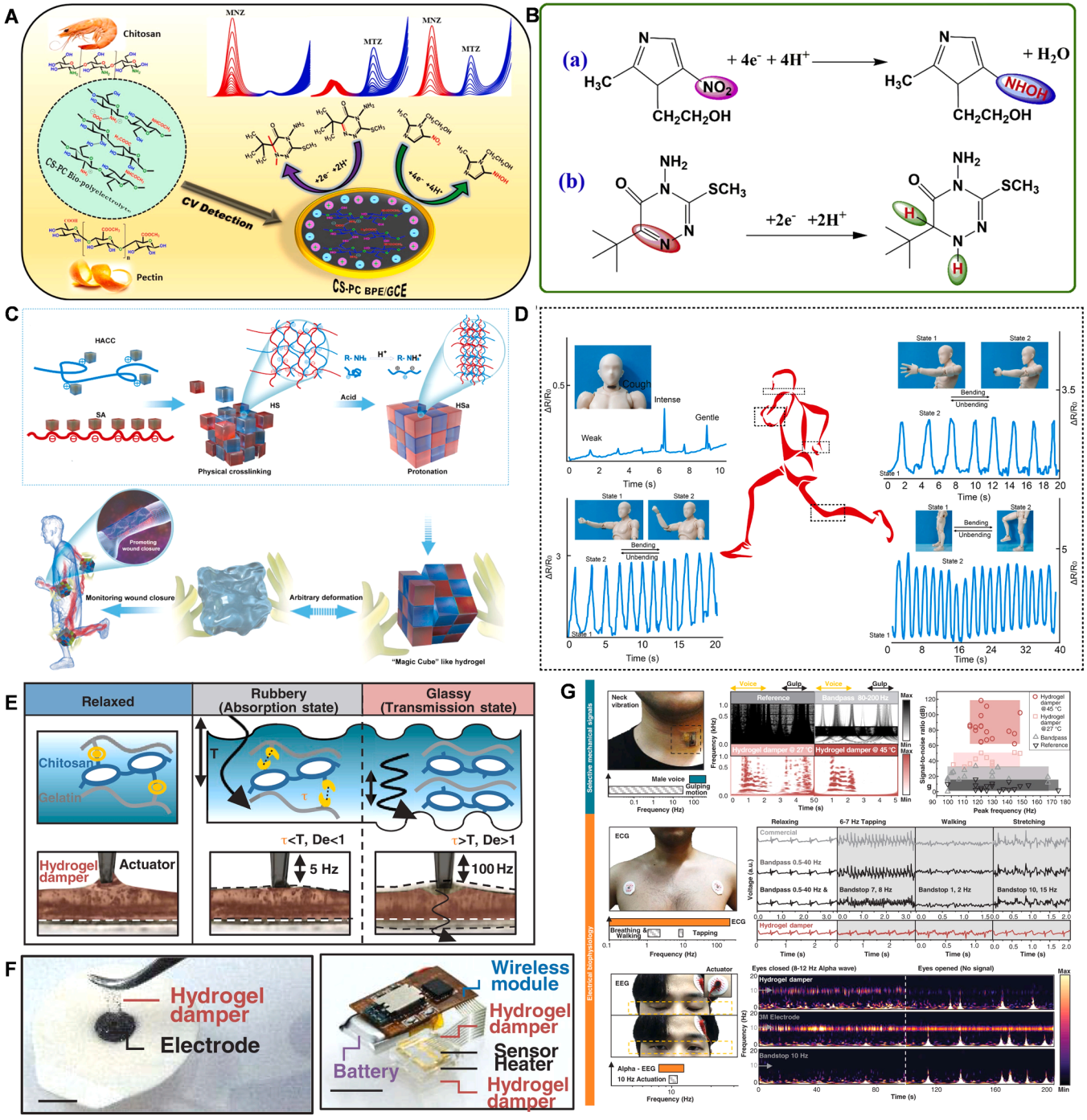

Fig. 30. (A) Schematic representation of the preparation of the chitosan–pectin polyelectrolyte complex for simultaneous electrochemical determination. (B) Feasible electro-reduction mechanisms for metronidazole (a) and metribuzin (b) [272]. Copyright 2019. (C) Schematic representation of the preparation of the hydroxypropyltrimethyl ammonium chloride chitosan–alginate polyelectrolyte complex hydrogel for wound closure monitoring. (D) Movement sensing of the hydrogel [175]. Copyright 2022. (E) Schematic representation of the selective low-frequency damping of the chitosan–gelatin hydrogel damper. (F) Construction of the hydrogel damper. (G) Dynamic noise-damping of the chitosan–gelatin hydrogel damper used for the high signal-to-noise ratio detection of biophysiological signals [308]. Copyright 2022.
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(e.g., antimicrobial activity, adhesive properties, hemostatic activity, and promotion of cell growth, proliferation, and differentiation) of biopolymers opens up extensive possibilities for creating materials exhibiting collective characteristics or synergistically heightened properties and functionality.

3) **Molecular design:** Numerous studies emphasize the necessity of modifying biopolymers through molecular design to introduce functional groups and motifs to biopolymer chains. These strategies enable distinct molecular bonding/interactions (e.g., ionic interaction, Schiff base linkage, amidation reaction with EDC/NHS activation, and Diels-Alder addition reaction) and chemical bonding (e.g.,

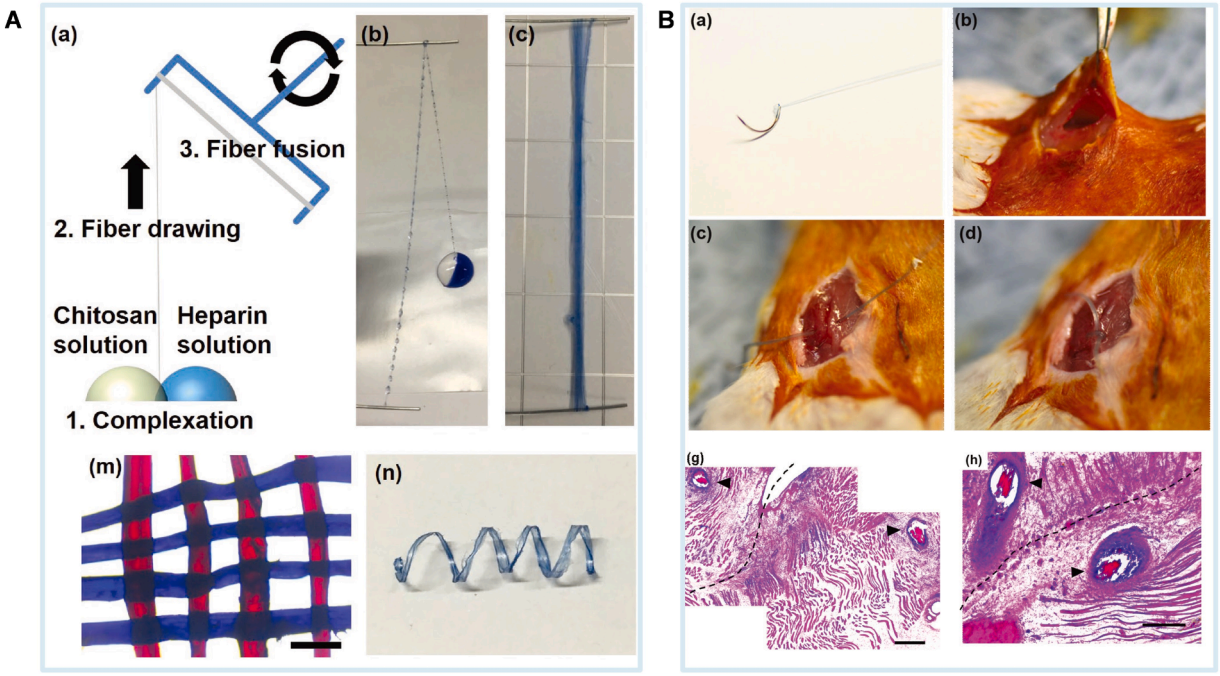

Fig. 31. (A) Schematic diagram of the fabrication of the chitosan–heparin fibers with high flexibility and different forms. (B) *In vivo* application of the 64-stranded chitosan–heparin suture [309]. Copyright 2017. Adapted with permission from John Wiley & Sons Inc.

hydrogen bonding, ionic interaction, and coordinate bonding), imparting chitosan-based composites with pH-/thermal responsiveness, targeted properties, UV-crosslinkability, and self-healing ability—attributes highly sought after for biomedical applications.

4) **Material forms:** Past research in this field has demonstrated that chitosan-based functional composite materials can be easily produced into various forms, including membranes/films, hydrogels, aerogels, ionogels, particles, sponges, and fibers, which is essential to meet the specific needs of biomedical applications.

6. Future perspectives

While biopolymer composites have played a crucial role in biomedical applications, future development in this domain should prioritize tackling challenges and capitalizing on opportunities in the following four aspects (also refer to Fig. 35 below):

1) **Property/functionality enhancement:** The development of chitosan-based composite materials for biomedical applications is still in its nascent stage, presenting significant opportunities to craft more chitosan-based composites with innovative functional properties. Addressing the heightened demands of biomedical applications, particularly vascular tissue engineering that necessitates antibacterial activity, anticoagulation ability, elasticity, and the promotion of cell growth, cell differentiation, and vascularization, is imperative. While perfusable vascular systems are essential for constructing thick organs or tissues mimicking original body parts, vascularization remains a significant obstacle in tissue engineering applications [310]. Further research endeavors should concentrate on elucidating how biopolymer-based materials can manifest these multiple attributes. Besides, investigations should delve into the impact of external factors during materials preparation, such as pH, ionic strength, and additional processing factors (e.g., ultrasound, microwave, and homogenization), alongside the dynamic conditions in the human body during materials usage, on material properties and performance stability. This exploration is pivotal for crafting biopolymer-based materials with customized properties, stimulus-responsiveness, and in vivo stability, thereby enhancing their utility in biomedical applications.

2) **Biosafety, biocompatibility, and ease of use:** The development of chitosan-based composites with desired properties and functionality encounters persistent challenges concerning diminished biosafety or biocompatibility, or other potential side effects on the human body. Diverse strategies, particularly chemical approaches, have been employed to modify biopolymers, ameliorating the thermodynamic incompatibility between chitosan and specific other biopolymers (e.g., casein, quinoa protein, and WPI), and crosslinking biopolymer chains. Also, additional substances are frequently incorporated into biopolymers for functionality enhancement. The potential toxicity and limited biosafety of integrated ingredients and modification/crosslinking strategies have not been comprehensively considered or evaluated. For instance, crosslinkers, notably those with recognized toxicity (e.g., GA and ECH), are prevalent in most chitosan-based composite formulations, augmenting mechanical properties but eliciting concerns about potential toxicity. While long-term toxicity assessment is indispensable, future material design should concentrate on bio-safer chitosan-based composites through "green" crosslinking strategies (e.g., using bioderived crosslinkers such as gelatin and employing physical or enzymatic crosslinking strategies). Besides, the potential adverse effect during application merits consideration. This concern is exemplified by certain rapid transdermal curing hydrogels based on the photopolymerization of methacryloyl C=C bonds under UV irradiation [90], with their application potentially causing irreversible skin damage at the irradiated site. Hence, body-friendly in-situ crosslinking strategies are deemed more favorable. More considerations encompass potential allergens in chitosan-based materials, strategies for their removal, and ensuring material safety. Last but not least, the evaluation of biocompatibility and biodegradability for most materials has predominantly been in vitro thus far, necessitating a shift to experiments that mirror the human body's conditions and the use of mammal models closer to humans in animal experiments.

3) **Cost-effectiveness and scalability:** Designing and actualizing materials should encompass considerations of cost-effectiveness and

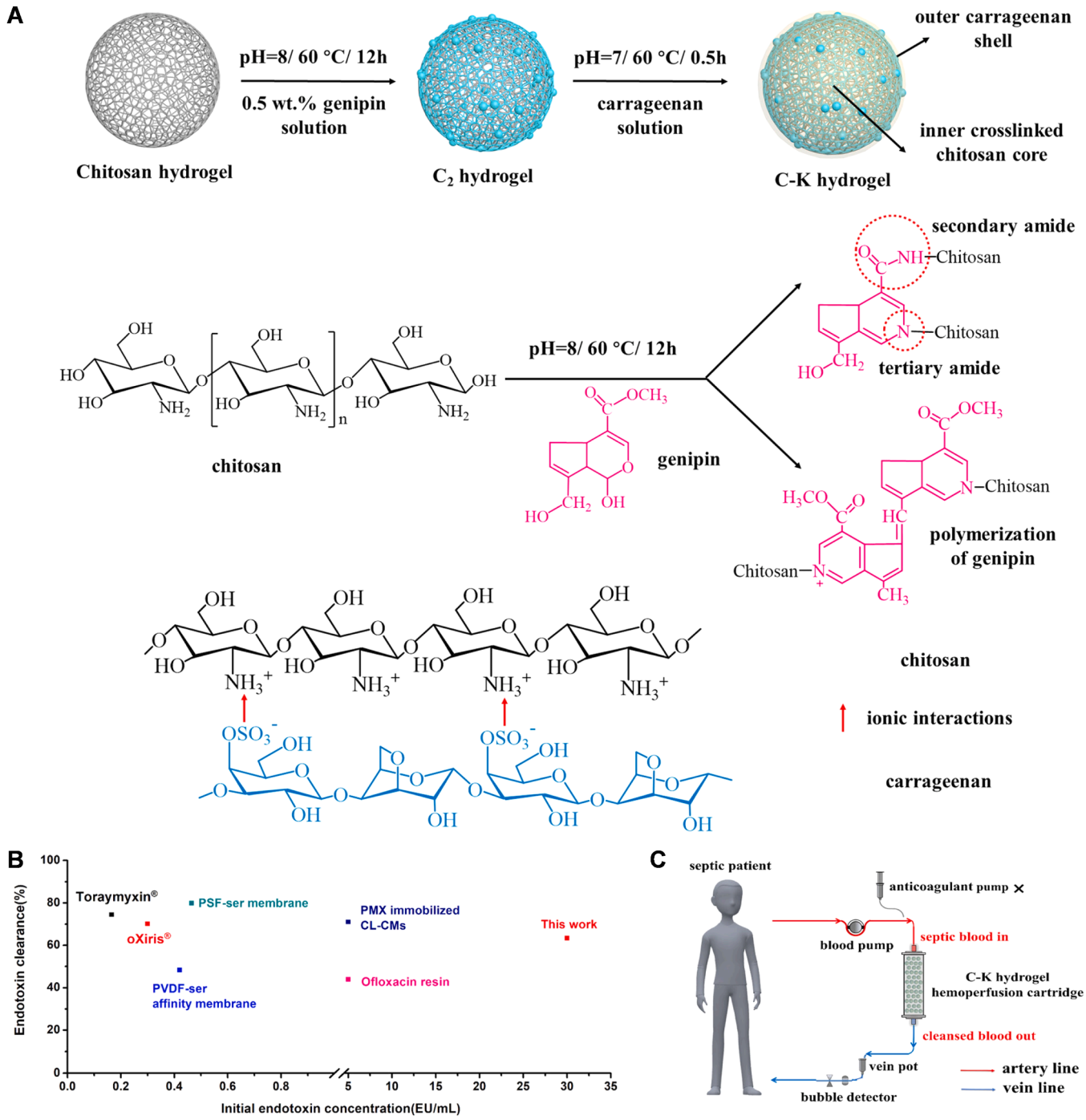

Fig. 32. (A) Schematic illustration of the preparation of the chitosan–κ-carrageenan hydrogel beads. (B) Comparison of the endotoxin clearance of the chitosan–κ-carrageenan hydrogel beads and typical clinical products. (C) Schematic diagram of a hemoperfusion procedure [164]. Copyright 2020. Adapted with permission from Elsevier.

scalability, factors intricately linked to the intricacy of materials functionalization and processing. For instance, the synthesis of chitosan–azide conjugate necessitates multiple purification cycles (five times) [262], potentially amplifying process complexity. Certain chemical modification methods like MA modification [90,91,160], graft copolymerization based on EDC/NHS [25,80,82,86], and quaternization [76,77,79] typically require supplementary steps like distilled water dialysis to eliminate unreacted reagents, presenting challenges to water resources. The intricate production steps of certain chitosan-based composite materials, like chitosan–heparin fibers produced via interfacial polyelectrolyte complexation techniques [309], confine them to laboratory-scale production. Hence, future research on the development of biopolymer-based composite materials should concentrate on modification and production processes that are cost-effective and scalable, ensuring their feasibility for real-world applications.

4) **Applications widening:** While biopolymer composite materials show promise in various biomedical applications, certain areas like postsurgical adhesion prevention, tissue adhesion, tissue engineering, and 3D bioprinting are still in their early stages, and challenges persist in designing for these future applications. For instance, in bone tissue engineering, it is crucial to develop materials tailored to a

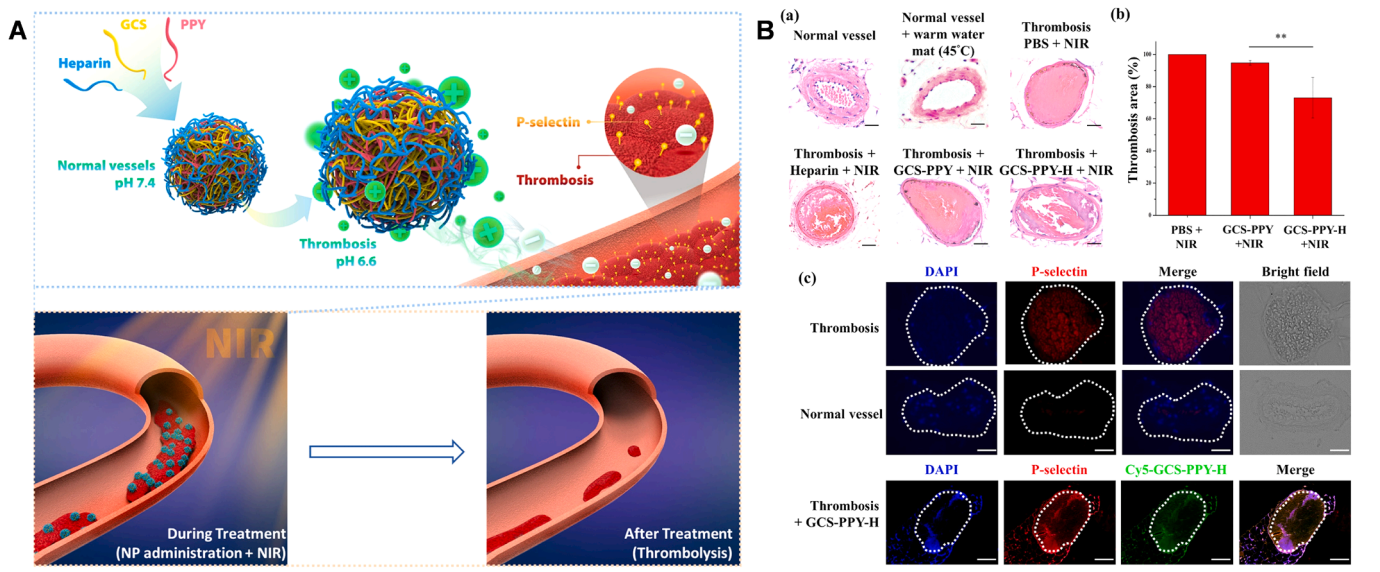

Fig. 33. (A) Schematic illustration of the thrombolysis therapy using the glycol chitosan–heparin decorated polypyrrole nanoparticles. (B) Thrombolytic effect of the glycol chitosan–heparin decorated polypyrrole nanoparticles on $FeCl_3$-induced murine mesenteric thrombosis animals [238]. Copyright 2021. Adapted with permission from the American Chemical Society.

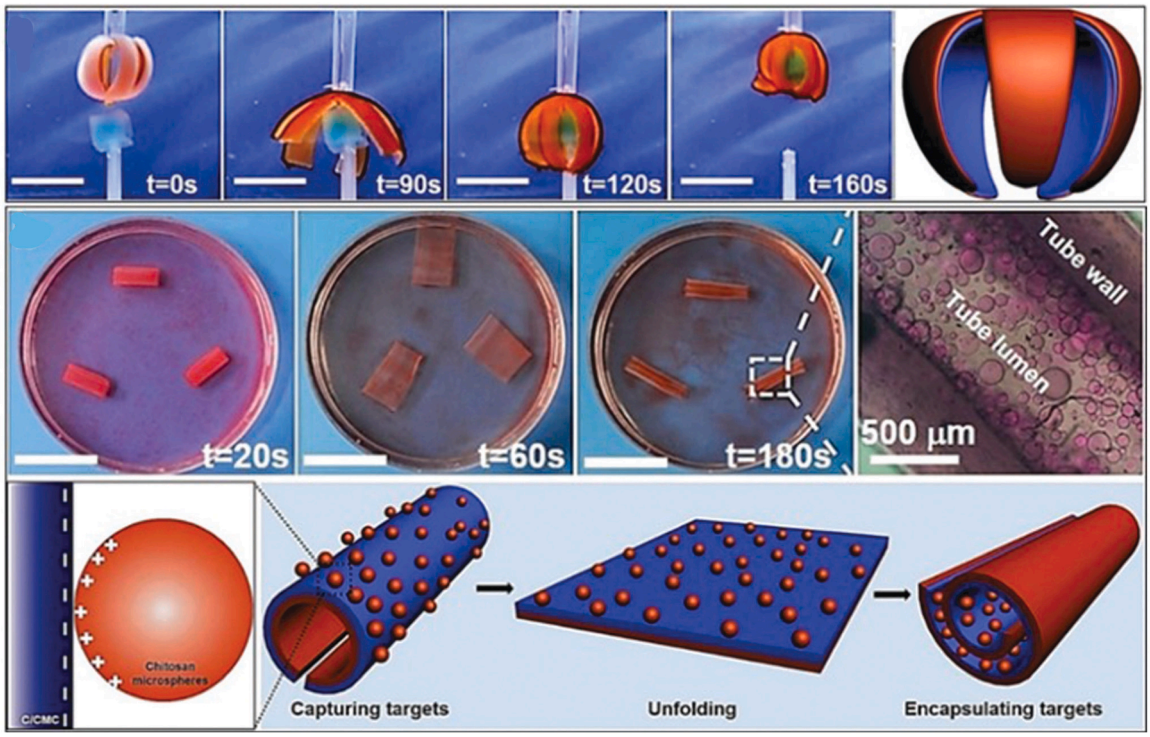

Fig. 34. Photographs of the chitosan–(cellulose–carboxymethyl cellulose) hydrogel as a soft actuator showing pH-triggered deformation behavior [221]. Copyright 2017. Adapted with permission from the Royal Society of Chemistry.

patient's health conditions and specific defects. Current models often rely on healthy young animals, limiting their relevance. Similarly, some applications of chitosan–biopolymer composites, such as periodontal tissue engineering, lack comprehensive studies, focusing mainly on cell growth on chitosan-based scaffolds. Secondly, there is untapped potential in the biomedical domain for chitosan-based composites. Many areas remain unexplored, including clinical contrast agents and cardiac tissue engineering. Addressing a significant issue in cardiac tissue engineering, chitosan-based composites with high electroconductivity and suitable tensile strength could enhance electrical integration with host tissue. Precision imaging in tumor imaging faces technical challenges, and here, the stimulus-responsive properties and targeting properties of chitosan-based composite materials may enable precise tumor site imaging as contrast agents. To unlock the full spectrum of potential, focusing on application-oriented material design strategies and advancing innovations tailored for specific uses is the key. Emphasizing the aforementioned three focal points—enhancing property/functionality, mitigating adverse effects on the human body, and improving cost-effectiveness—we anticipate a broader application spectrum for

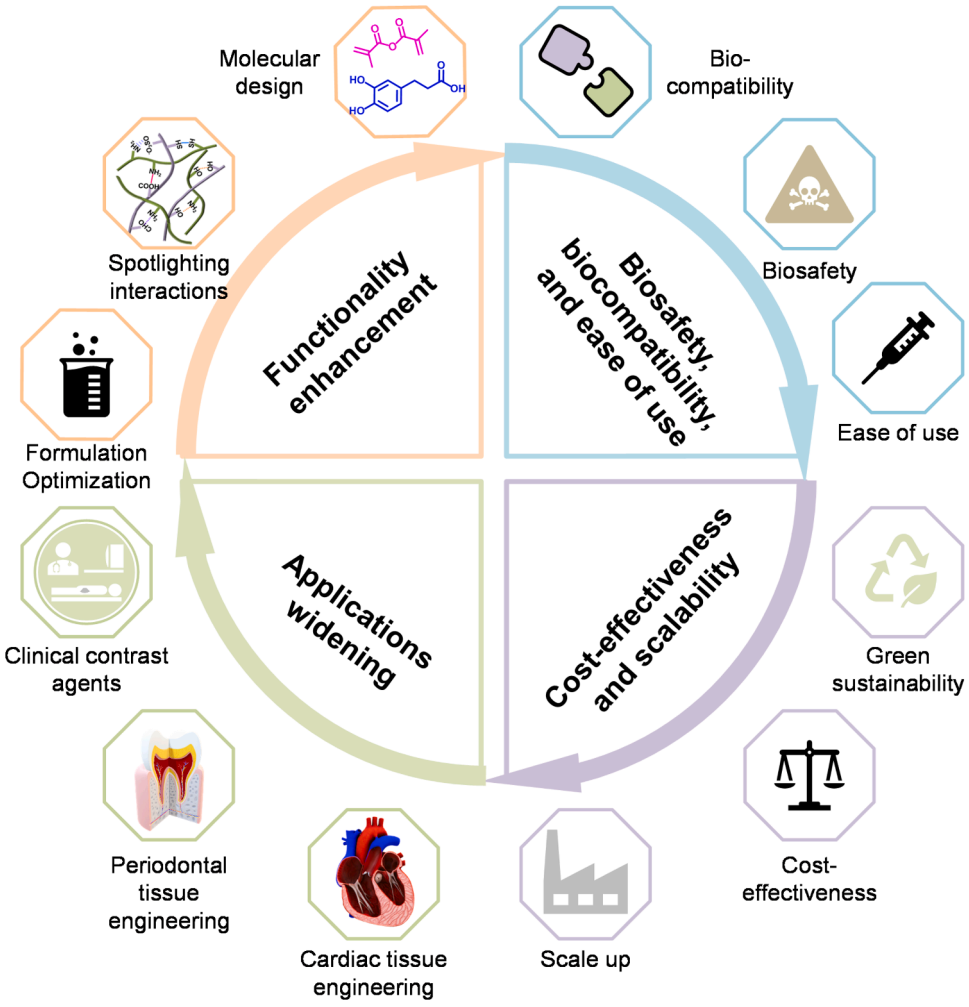

Fig. 35. Overview of the future perspectives of chitosan-based composites for biomedical applications.

versatile chitosan-biopolymer composites in a diverse array of biomedical applications.

CRediT authorship contribution statement

Qiao Dongling: Resources. **Guo Yabin:** Writing – original draft, Visualization. **Liu Peng:** Resources. **Zhao Siming:** Resources. **Zhang Binjia:** Visualization, Supervision, Resources, Funding acquisition. **Xie Fengwei:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Binjia Zhang reports financial support was provided by National Natural Science Foundation of China. Binjia Zhang reports financial support was provided by Fundamental Research Funds for the Central Universities. Fengwei Xie reports financial support was provided by Engineering and Physical Sciences Research Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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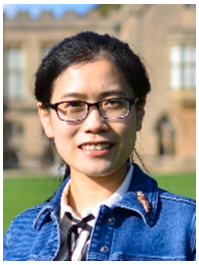

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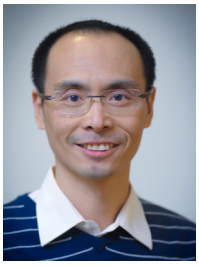

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