Coordination Chemistry Reviews 475 (2023) 214823

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Emerging materials for hemostasis

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ARTICLE INFO

Article history:
Received 11 February 2022
Accepted 3 September 2022

Keywords:
Hemostasis
Hemorrhage
Biomaterial
Hydrogel
Wound healing

ABSTRACT

Severe hemorrhage has posed a serious threat to the health and even life of civilian and military populations and brought serious economic losses. Consequently, it is imperative to develop effective hemostatic materials and strategies. However, numerous hemostatic agents are unable to perfectly meet the requirements of ideal hemostatic agents, and hence strenuous efforts need to be made to develop safe and efficacious hemostatic materials. Recently, the booming achievements have been witnessed in the hemostatic material field. In this review, the general coagulation process, the hemostatic mechanisms, and the design strategies of hemostatic materials are briefly discussed. Subsequently, we introduce the latest investigations on the various external (local) hemostatic materials and internal (intravenous) hemostatic agents including external inorganic hemostatic materials, peptides/proteins with hemostatic activity, polysaccharide hemostats, synthetic hemostatic polymers, and intravenous hemostatic technologies, and summarize the preparation methods, the physical, chemical, and biological properties, and the hemostatic applications of these different materials. This review also briefly discusses some major problems and challenges in the research of various hemostatic materials, hoping to provide valuable insights for the development of new hemostatic materials.

1. Introduction

Blood is opaque red liquid circulating in the heart and blood vessels. Blood belongs to connective tissue and consists of plasma and blood cells. Blood continuously flows and circulates in the cardiovascular system, and is responsible for delivering oxygen and nutrients to tissues. The total amount of human blood is relatively constant, which is necessary for the maintenance of human normal physiological activities. Once the total amount of blood is reduced excessively, it will cause serious results. Normal blood circulation can be hindered after hemorrhage which eventually affects microcirculation and causes hypoxia in brain and other body parts.[1] The condition of patients may deteriorate if their bleeding is not timely controlled, which, in some cases, may induce hemorrhagic shock. Hemorrhagic hypothermia and metabolic acidosis are additional complications. Once these conditions occur, they will damage the normal function of the coagulation system and render hemostasis difficult to be fulfilled. In addition, blood transfusion following massive blood loss amplifies the danger of organ rejection and complicates succeeding operation.[1,2] In the traumatic injuries in battlefield and civilian conditions, considerable hemorrhage from truncal, junctional, as well as internal noncompressible damage can give rise to large prehospital mortalities.[3,4] Moreover, uncontrollable hemorrhage is also the most common reason of death during cardiovascular, hepatic, orthopedic, and spinal operations.[5,6] Blood clotting disorders including hemophilia will make hemostasis more difficult.[7–9]

Owing to the huge casualties and losses caused by severe bleeding, there is a great demand for the development of materials which can quickly and efficiently impede bleeding. Some hemostatic materials have been approved by United States Food and Drug Administration (FDA) (as showed in Table 1). However, for ideal hemostatic agents, it is not sufficient to only achieve rapid and effective hemostasis. It is also supposed to be safe, easy to produce, cheap, convenient to store and use, capable of gaining regulatory approval, and able to treat bacterial infection to a certain extent.[10–13] At present, many of the commercial hemostatic agents do not meet all or most of these requirements, and hence

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https://doi.org/10.1016/j.ccr.2022.214823
0010-8545/

it is necessary to make many efforts to develop more satisfactory hemostatic materials. Fortunately, there have been a wide array of noteworthy investigations for developing promising hemostatic materials recently.

This review will briefly discuss the hemostatic process, and then introduce the general hemostatic mechanism of the existing hemostatic materials and the basic design strategies of hemostatic materials. Subsequently, the researches on various hemostatic materials in recent years (from 2016 to the present) are classified and introduced. According to the application site, the present hemostatic materials could be divided into external (local) hemostatic materials (including inorganic hemostatic materials, hemostatic peptides/proteins, hemostatic polysaccharides, and synthetic polymers) and internal (intravenous) hemostatic agents (including fibrin-, coagulation factor-, and platelet-related hemostats) (Fig.1). We mainly focus on the design/preparation, hemostatic mechanism, and therapeutic performance of these different hemostatic materials. Finally, we summarize the main content of the review and list some current limitations and future directions in this field.

2. Hemostatic mechanisms and strategies

2.1. Coagulation process

According to the relevant researches, hemostasis is a complex physiological process whose key is the formation of hemostatic clots at bleeding sites to stop bleeding through a series of complicated temporal and spatial regulation involving platelets, cells, plasma proteins, and coagulation factors which are inactive under the normal condition.[14,15] Meanwhile, healthy endothelial cells secrete nitric oxide, thrombomodulin, heparin-like molecules, and prostacyclin to avoid blood clotting, and at the same time, to sterically impede the adsorption of clot-relevant proteins on the wall of a blood vessel due to the presence of endothelial glycocalyx.[3] When a blood vessel gets injured, a reflexive local contraction of vascular smooth muscle occurs, which leads to vasoconstriction, thus hindering blood flow and reducing blood loss.[6] The platelets quickly respond to the injured site by undergoing adhesion, activation, and interplatelet aggregation to generate the platelet plug,[16–18] and release some chemicals such as serotonin, thromboxane, and adenosine diphosphate, which augment further vasoconstriction along with platelet aggregation in the bleeding site.[19] This hemostasis process is short-term, and is commonly called "primary hemostasis". Next, the secondary hemostasis occurs, and in this process coagulation cascade is initiated and amplified, and finally fibrinogen is converted into fibrin to form a stable embolism.[20,21]

Coagulation cascade includes intrinsic pathway, extrinsic pathway, and common pathway. The specific process of coagulation cascade is shown schematically in Fig. 2. All the coagulation factors involved in the intrinsic pathway come from blood. The activated partial thromboplastin time (APTT) is usually adopted to reflect the status of intrinsic pathway.[20] Intrinsic pathway is a process from factor XII activation to factor X activation.[22–24] Factor XII is activated to be factor XIIa by contacting with exogenous surface. Independent of calcium ion, factor XIIa activates factor XI to form factor XIa. Then, in the presence of calcium ion, the activated factor XIa helps IX to form IXa. IXa combines with VIIIa to form a 1:1 complex, which is known as tenase complex and responsible for the effective conversion of factor X to factor Xa. In the extrinsic coagulation pathway, the related coagulation factors are not all from the blood.[13,20,25–27] This process is initiated by a tissue factor, which is a kind of protein not present in blood, but is released from the surrounding tissue and vessel walls when the blood vessel is injured. With the participation of calcium ion, the tissue factor forms a 1:1 complex with factor VII. Then VII is activated to form a tissue factor/factor VIIa complex which enables factor X to be rapidly activated to become Xa in the presence of calcium ion. In this process, VIIa works as a protease, while tissue factor acts as a cofactor, which is able to enhance the catalytic activity of VIIa. In clinic, prothrombin time (PT) is used to reveal the status of extrinsic pathway. The common pathway is from the activation of factor X to the formation of fibrin, occurring after the intrinsic and extrinsic pathways.[6,24,28–33] It mainly includes two stages: thrombin formation and fibrin formation. For the formation of thrombin, in the presence of calcium ion and phospholipid membrane, factor Xa and factor Va form prothrombinase complex, namely thromboplastin, which transforms prothrombin into thrombin. For the formation of fibrin, fibrinogen is hydrolyzed into fibrin monomer by thrombin. Moreover, thrombin activates factor XIII to form XIIIa. With the participation of XIIIa and calcium ion, adjacent fibrin undergoes rapid crosslinking to reinforce the platelet plug and promote the formation of a dense hemostatic clot.

2.2. Hemostasis mechanisms of hemostatic materials

As mentioned before, a large number of hemostatic materials have been developed. These hemostatic materials can regulate the above-mentioned hemostasis process through a certain mechanism to accelerate hemostasis. According to the hemostasis mechanism, hemostats can be classified as active and passive hemostatic materials.[34] The active hemostats, such as smectite, fibrinogen, and thrombin, can directly activate and accelerate coagulation cascade, accordingly enhancing hemostatic potency in an active pathway.[6,35,36] However, the potential risks of viral contamination, thrombosis, and general or systemic emboli have hindered the wide applications of these active hemostats in various conditions.[37–39] In contrast to the active hemostatic materials, the passive hemostats including sponges, foams, hydrogels, and cryogels mostly function via extracting fluid from blood to concentrate red blood cells (RBCs) as well as platelets, blocking off or sealing bleeding sites.[34,40–42] Besides, some expandable materials can also produce durable pressure to the vessels to stem bleeding.[43–46] The passive hemostats accelerate the hemostatic process independent of coagulation cascade and they usually have good biocompatibility. On the other hand, they also have an obvious shortcoming, that is, they are inefficient to treat massive hemorrhage.

2.3. Design strategies of hemostats

In recent years, to develop powerful hemostatic materials, some effective strategies have been proposed to design these materials (Fig. 3). Some researchers have made great efforts to change and regulate the particle size, surface morphology, or internal structure of hemostatic materials to improve their physical properties to achieve easier and faster hemostasis. For example, Zhang et al. prepared a type of hemostatic powder originating from SSAD (skin secretion of *Andrias davidianus*).[47] In their work, the hemostatic effect was revealed to be associated with the particle size of the SSAD hemostatic powder, and the SSAD powder with a suitable size displayed the best hemostatic effect. Besides, Xi and coworkers reported a "lotus seedpod surface-like" polysaccharide hemostatic microsphere (PHM) (Fig. 4a).[48] The hemostatic microsphere possessed "macropits on surface" morphology and "micropores in macropits" structure for hemostasis. The unique macropits on the hemostatic microsphere surface could fast guide blood into the micropores to elevate the water absorption rate of the hemostatic microsphere. The pore size declined gradually with blood entering the micropores from micropits and therefore blood coagulation factors could be swiftly concentrated. Moreover, plate-

Table 1
Summary of some FDA-approved external and internal hemostatic agents.

Category	Hemostatic component	Product	Effect/condition	Advantages	Disadvantages
External	Zeolite	Zeolite hemostatic gauze	Adsorbing water molecules and leading to rapid clotting	Inexpensive, easy to produce, stable, and no special storage requirement	Exothermic reaction (sometimes); troublesome to use and requirement of adequate debridement
	Kaolin	Quikclot hemostatic dressing	Activating Factor XII and leading to faster bleeding	Thermally, chemically, and mechanically stable, low-cost, and no exothermic reaction	May be ineffective in patients with coagulopathy
	Collagen	Hemopad; Helistat; Collastat; Avitene; Instat	Inducing platelet aggregation	Superb biocompatibility and absorbability	Foreign body reaction or allergic reaction
	Gelatin	Gelfoam; Surgifoam	Activating platelet aggregation	Superb biocompatibility, absorbability, and low antigenicity	Gelatin swelling may cause compression and necrosis of surrounding tissues
	Fibrin sealants	Tissucol; Artiss; Evicel; Tissucol	Significantly promoting hemostasis	Wide applications	Sometimes insufficient strength and risk of viral transmission
	Glutaraldehyde-crosslinked albumin	Bioglue	Sealing the wound	High hemostatic efficacy	Glutaraldehyde is toxic; risk of blood borne diseases
	Thrombin	D-Stat Dry hemostat; Thrombigel	Promoting the conversion of fibrinogen to fibrin	Effective hemostatic activity	Expensive; a theoretic risk of viral transmission; antigenicity
	Chitosan	ChitoFlex; Axiostat; PosiSep X; Celox; TraumaStat; HemCon	Controlling moderate or severe bleeding	Antibacterial properties, abundant source, trouble-free storage, and good biodegradability	Hemostatic efficiency can be further improved
	Dextran	Bloxx	Stopping bleeding	Good biocompatibility/biodegradability and good water solubility	Hemostatic efficiency needs to be further improved
	Cellulose	BloodSTOP; WoundClot; Surgicel; Topseal; Suntouch	Providing rapid hemorrhage control	Absorbable, preventing infection, good safety, relatively low-cost, easy to obtain/use	Occasional foreign body reactions, relatively slow degradation rate, and limited antibacterial property
	Polyethylene glycol	CoSeal	Sealing the wound	Good biocompatibility, low immunogenicity	Compressing surrounding structures; possible allergic responses
	Cyanoacrylate	Omnex	Sealing the wound	Repairing combat wounds	Toxicity from the cyanoacrylate degradation products
Internal	Coagulation factor VIIa (recombinant)	NovoSeven; NovoSevenRT	Treating congenital bleeding disorder, haemophilia A, and haemophilia B	Reducing bleeding after acute trauma	High cost, potential adverse effects, and difficulty in storage
	Antihemophilic factor VIII (recombinant)	Advate; Eloctate; Kogenate Fs; Kovaltry; Novoeight	Treating congenital bleeding disorder and haemophilia A	Treating the symptoms of congenital and acquired hemophilia A; no additives of human or animal origin	Potential adverse reactions
	Coagulation factor IX (recombinant)	Alprolix; Benefix; Idelvion; Rebinyn	Treating hemophilia B	Maintaining haemostasis; treating hemophilia B	Potential adverse reactions
	Coagulation factor X (Human)	Coagadex	Treating factor X deficiency	Controlling bleeding episodes	May contain infectious agents
	FXIII concentrate (Human)	Corifact	Treating congenital FXIII deficiency	Treating FXIII deficiency	A small risk of virus transmission; requirement of low-temperature storage at 2–8 °C
	Antihemophilic factor/von Willebrand factor complex	Humate-P; Alphanate; Wilate	Treating hemophilia A and spontaneous or trauma-induced bleeding episodes	Treating and preventing bleeding	May contain infectious agents or transmit diseases
	4-Factor prothrombin complex concentrate	Kcentra	Reversing anticoagulation status	Superior hemostatic efficacy; room temperature storage	Increased cost and a risk of thromboembolic complications
	Fibrinogen concentrate	Riastap	Treating acute bleeding episodes in patients with congenital fibrinogen deficiency	Higher safety than fresh frozen plasma	A risk of infectious agent transmission, thrombotic episode, and anaphylactic reaction
	Tranexamic acid	Tranexamic acid	Antifibrinolytic	Greatly improving hemostatic outcomes	Possible side effects

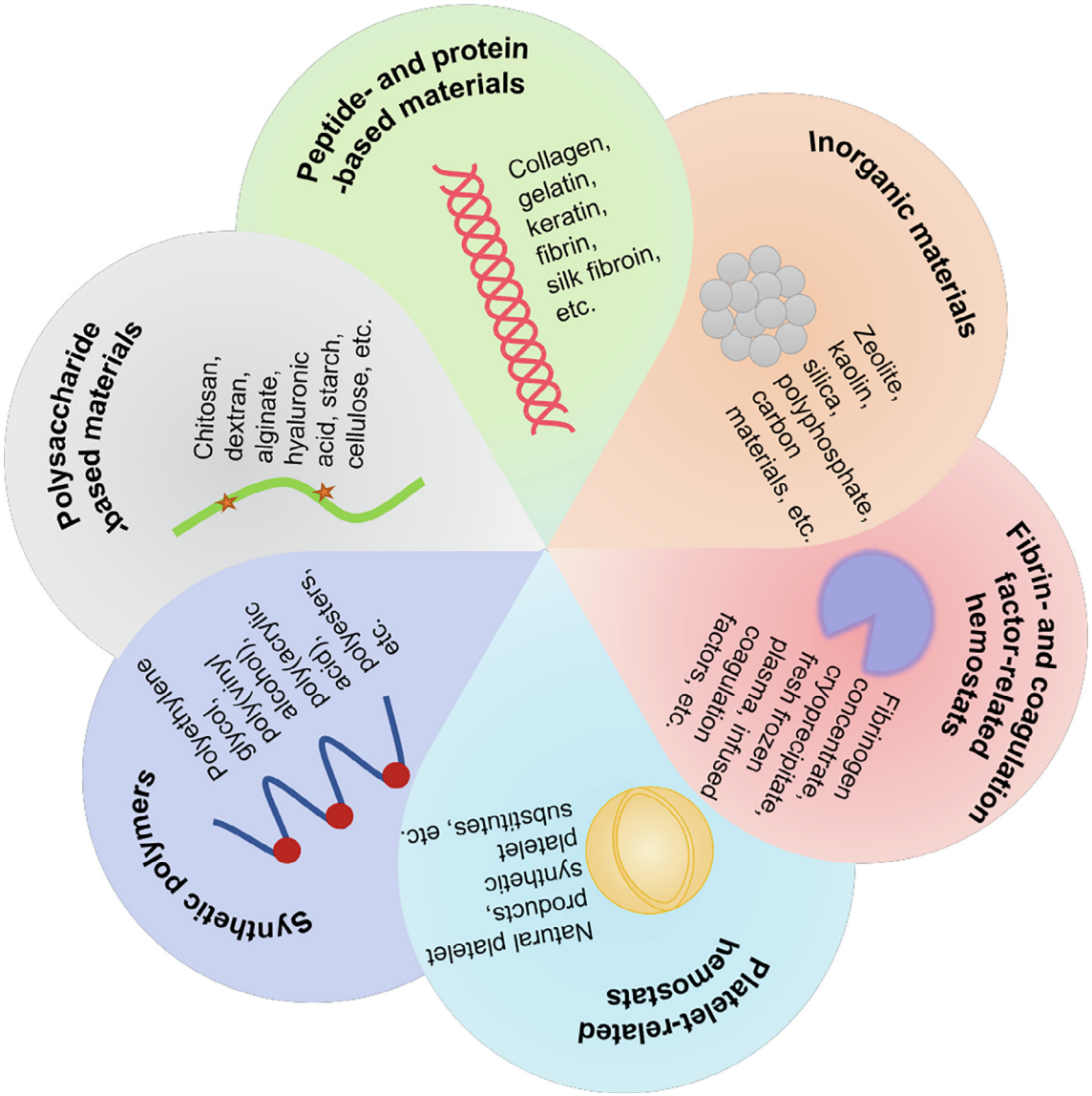

Fig. 1. Schematic illustration of a variety of external hemostatic materials and internal hemostats utilized for hemorrhage control.

lets/erythrocytes were also able to be collected by the macropits (Fig. 4b). After the application of the PHM to the injury site, the physiological coagulation pathway could be initiated and fibrin aggregates were ultimately generated. The produced fibrin could intertwine with PHM, triggering the formation of stable blood clots to enhance hemostasis. PHM_4 displayed the highest water absorption rate (40.7 mL^{-1} s^{-1} cm^{-2}) and quick hemostatic behavior in vivo (the hemostatic time was reduced from 210 s to 45 s). In another study, Wang and co-workers used sodium carboxymethylcellulose, carboxymethyl chitosan (carboxymethyl CS), and γ-(2,3-epoxypropoxy)propytrimethoxysilane (as a crosslinking agent) to construct a composite hemostatic sponge by the one-pot method and the ice segregation-induced self-assembly process.[49] The ice segregation-induced self-assembly process imparted a capillary-mimicking microchannel structure to the composite hemostatic sponge and the unique structure could facilitate the composite hemostatic sponge to achieve ultrafast blood absorption and hemostasis by capillary action. As confirmed in in vitro and in vivo hemostatic tests, the composite hemostat possessed great potential to realize hemostasis in a short period of time. Similarly, Du et al. constructed a microchannelled alkylated CS sponge with rapid shape recovery behavior and high water/blood absorption capacity to cope with lethal noncompressible bleeding and accelerate wound healing.[50] In addition, it also represents an effective and feasible strategy to imitate the structure and characteristics of biological materials to develop biomimetic hemostatic materials with advanced functions. In 2019, Zheng and co-workers synthesized a bioinspired "cotton-like" collagen aggregate/chitin-based biomaterial (V-3D-Ag-col) via a specific gradient-removal solvent method for tissue repair and hemostasis.[51] The advanced collagen aggregate (Ag-col), instead of traditional collagen molecules, was firstly used to fabricate a hemostatic material. The Ag-col, accurately mimicking the natural collagen in the collagenous tissue, exhibited higher hydrophilicity, stronger mechanical properties, and better hemostatic performance than traditional collagen molecules. At the microscale level, the V-3D-Ag-col based on Ag-col presented a three-dimensional (3D) fibrous network structure similar to the blood vessel structure and the unique structure could promote platelet adhesion and aggregation. Moreover, macroscopically, the V-3D-Ag-col displayed a 3D cotton-like appearance, which was favorable for tissue repair. This work emphasizes the feasibility of employing bionic technology to improve the hemo-

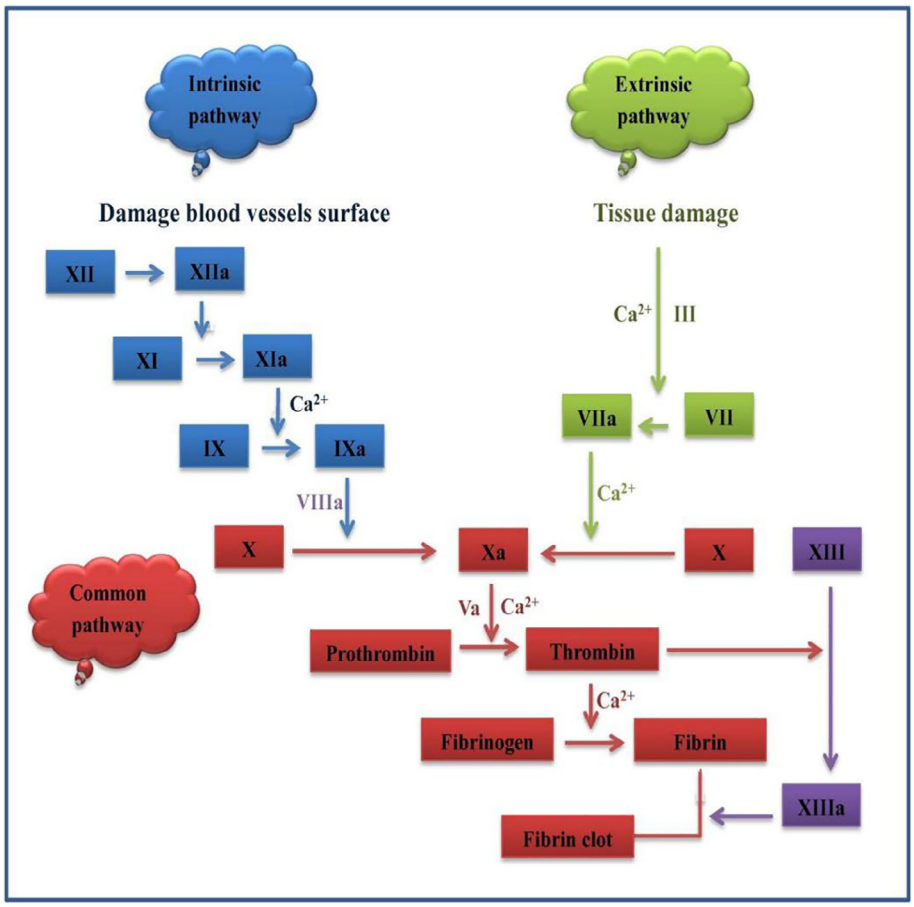

Fig. 2. Scheme illustrating the coagulation process. Reprinted with permission from Ref. [6]. Copyright 2016, Elsevier B.V.

static ability of materials. These studies represent typical examples that confirm the feasibility of improving hemostatic properties by changing the size, morphology, and structure of the materials.

In addition to this strategy, chemical modification is also a robust approach to develop promising hemostatic materials. The chemical modification conducive to activating or aggregating RBCs, platelets, and clotting factors is usually achieved by introducing hydrophilic/hydrophobic moieties or functional groups, which can impart positive/negative charges to the surface of the materials. It is proved that a surface with positive charges can promote platelet adhesion by electrostatic interaction, and a surface with negative charges is capable of stimulating clotting by autoactivation of factor XII.[34,52] For instance, to identify how different chemical modification strategies could improve the hemostatic property of CS, Yan and co-workers investigated the hemostatic effect of surface-modified CS nonwovens.[53] In their research, the quaternary ammonium groups, carboxymethyl groups, and succinyl groups were introduced into the –OH or $–NH_2$ of the glucosamine units on CS nonwoven surface, obtaining TMCS, CMCS, and NSCS nonwovens, respectively. The investigation of blood clotting mechanism indicated that the NSCS and CMCS nonwovens were able to activate the intrinsic coagulation pathway to accelerate blood clotting. NSCS1 nonwoven displayed the least hemostatic time (147 ± 3.7 s) (Fig. 4c) in a rabbit model of ear artery injury. These results suggest that the surface-modified CS nonwoven dressings have the potential to act as a useful material for hemostatic intervention, particularly the NSCS nonwoven dressing. Besides, Hu et al. prepared a self-regenerative hydrogel (COCu) comprised of carboxymethyl CS, oxidated CS with aldehyde groups, and copper-doped carbon dots via a one-pot method. When applied to the incision, the COCu hydrogel could rapidly absorb blood, and then swell to seamlessly seal the wound to avert bleeding.[54] These studies show that the hemostatic property of a material can be significantly improved via chemical modification, highlighting the importance of surface chemistry in modulating the hemostatic performance of the material. Different kinds of materials have different structural and chemical characteristics. Consequently, in consideration of both the features of various materials and specific application requirements, it is necessary to adopt specific chemical modifications to specific materials to realize certain biomedical applications. To explain more clearly, the chemical modification methods suitable for different materials will be further discussed later when each kind of hemostatic material is introduced.

Moreover, the biological strategies also represent an important solution to develop effective hemostatic materials. Currently, there are two main ways to employ the biological strategies for designing hemostatic materials. First, the key biological components in the coagulation process can be directly used, modified, or mimicked for the preparation of hemostatic materials. The understanding of the structure and function of various coagulation-related biological components has been largely deepened over the past years, and meanwhile, these important biological components have been widely used in clinical hemostasis practice. The fresh frozen plasma, cryoprecipitate (containing fibrinogen and various clotting factors), or fibrinogen concentrate can be injected intravenously into the blood to aid in hemostasis. And a variety of recombinant coagulation factors produced by the recombinant

technology have become commercial hemostats to treat bleeding disorders. Furthermore, many reports highlight the feasibility to construct robust hemostatic agents through mimicking the biophysical and biochemical properties of platelet or RBC. For instance, LV et al. prepared bioinspired RBC-like hydrogel microspheres from gelatin, carboxylated CS, and Fe^{3+} (serving as a crosslinker).[55] The microspheres could facilitate the formation of a physical barrier in wound sites and elicit a remarkable hemostatic effect. Second, it is a promising strategy to design hemostatic materials with life-like or bionic properties such as excellent adhesion. Inspired by the excellent adhesive performance of marine mussels, a variety of biomaterials with a satisfactory hemostatic effect have been designed, which will be introduced in Section 4.

Besides the above-mentioned strategies, the preparation of composite materials with dual functions or multiple functions have drawn increasing attention recently. This tactic can integrate the advantages of various materials to overcome the inherent defects of a single material, which is beneficial for designing an ideal hemostatic agent. To give an example, He et al. developed multifunctional composite sponges (ACK sponges) via incorporating traditional Chinese medicine Kangfuxin (an ethanol extract of *Periplaneta americana*) into alginate/carboxymethyl CS through green crosslinking, electrostatic interaction, as well as freeze-drying process (Fig. 4d).[56] The alginate provided high water absorption ability, and carboxymethyl CS provided terrific hemostatic and antibacterial performance. Moreover, Kangfuxin contributed to promoting full-thickness wound healing. Combining

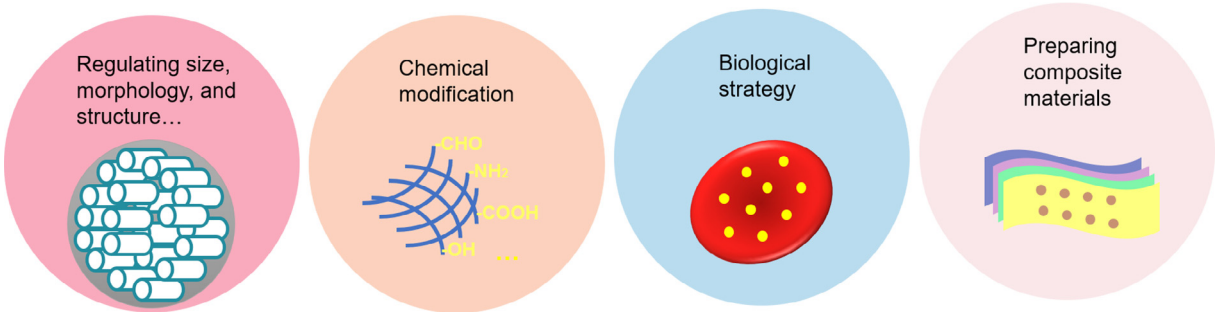

Fig. 3. Scheme illustrating four design strategies of various hemostats.

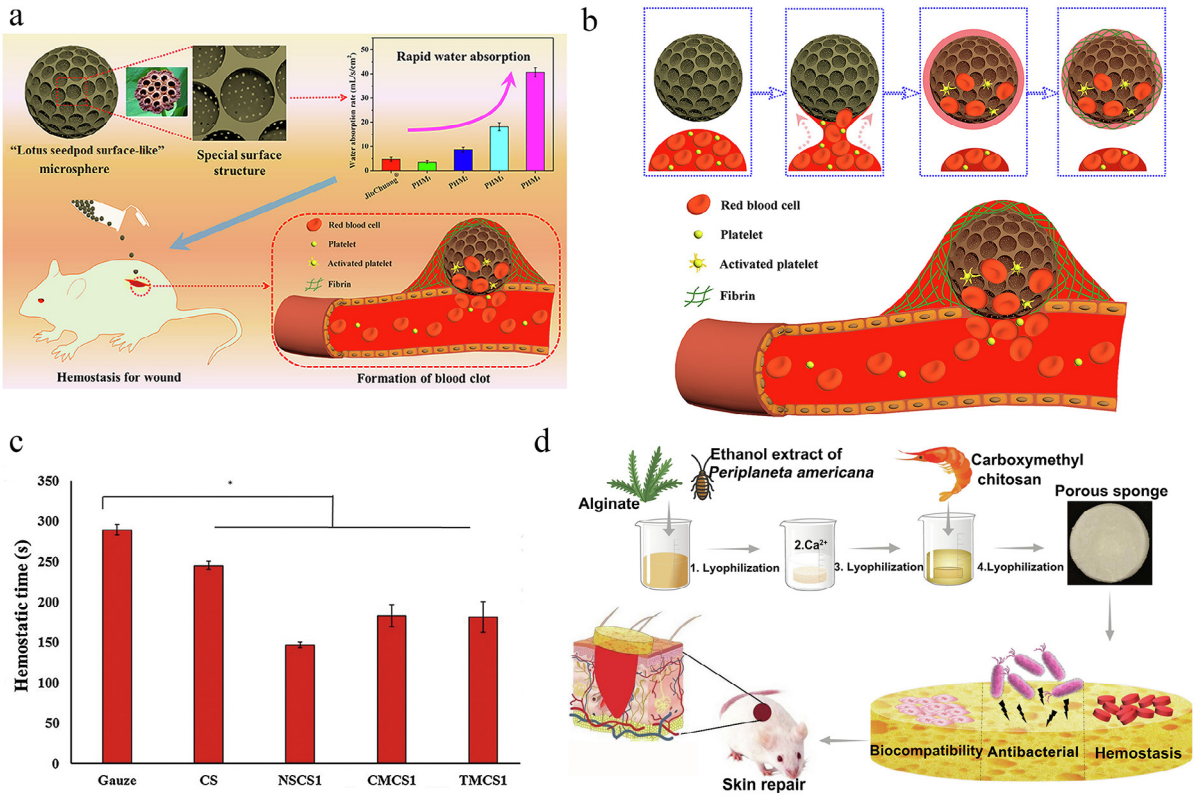

Fig. 4. (a) Scheme of the morphology and structure, water absorption performance, hemostatic mechanism, and hemostatic application of the "lotus seedpod surface-like" polysaccharide microsphere. (b) Scheme showing the specific hemostasis mechanism caused by PHM. (a and b): Reprinted with permission from Ref. [48]. Copyright 2019, American Chemical Society. (c) Hemostatic time of rabbit ear artery injury treated with gauze, CS, NSCS1, CMCS1, or TMCS1. Reprinted with permission from Ref. [53]. Copyright 2018, Elsevier B.V. (d) Scheme of the construction of ACK sponge and its functions in the full-thickness skin repair as an adhesive and a hemostat. Reprinted with permission from Ref. [56]. Copyright 2021, Elsevier B.V.

the advantages of the three components, the composite sponges displayed a high porosity structure, rapid hemostasis, superb antibacterial behavior, good cytocompatibility, and excellent wound healing property.

In another research, Singh et al. prepared a hemostatic hydrogel composed of phosphorylated CS, quaternized CS, tannic acid (TA), and poly-ε-lysine.[57] TA, a natural polyphenol compound containing phenolic hydroxyl groups, displays antiinflammatory, antioxidant, antimicrobial, and hemostatic properties.[58–60] In the study, TA worked as a crosslinker and adjuvant hemostat; the poly-ε-lysine could improve the adhesive and elastic properties of the hydrogel; phosphorylated CS and quaternized CS had the ability to activate coagulation pathways. Owing to the combined effect of all the constituents, the hydrogel exhibited better hemostatic performance than the commercial product Axiostat. Not only organic materials can be combined with organic materials, but also organic and inorganic materials can be hybridized to prepare hemostatic materials with satisfactory properties. The incorporation of inorganic materials into organic polymer-based systems is an effective strategy to improve the mechanical, physical, and chemical properties of the organic polymer-based systems, making them more suitable for clinical hemostatic applications. For instance, Golafshan et al. developed a hemostatic hydrogel by combining laponite nanoplatelet and interpenetrating polymer network hydrogel composed of poly(vinyl alcohol) (PVA)–alginate for treating wounds.[61] The authors proved that the incorporation of laponite into the hydrogel could not only improve its hemostasis performance but also impart desirable physical, mechanical, and biological properties to the hydrogel for wound treatment. Inorganic particles can also be utilized to load organic molecules and then be applied to hemorrhagic wound sites to achieve rapid and efficient hemostasis. An interesting investigation was implemented by Wang et al., who synthesized two types of TA-loaded mesoporous silica via physical adsorption and chemical grafting, respectively, for bleeding control and antibiosis.[62] The TA-adsorbed mesoporous silica (TMS) could remarkably facilitate blood contact due to the good hydrophilicity of TA. The rapid contact between TMS and blood effectively facilitated protein adhesion and promoted the contact activation pathway of clotting cascade to achieve hemostasias. TA could also act as a protein deposition agent to crosslink with plasma protein, forming a physical barrier to prevent blood flowing. In addition, TA has brilliant antibacterial efficacy. When the TA adsorption increased, the hemostatic performance and antibacterial effect of TMS were both improved. Furthermore, the authors revealed that the TA-loaded mesoporous silica prepared through chemical grafting displayed worse hemostatic and antibacterial effects than TMS because the grafted TA replaced the Si–OH on the surface of mesoporous silica, considerably obstructing the contact of mesoporous silica and blood and preventing the release of TA into blood. Furthermore, the synthetic process of TMS was simpler and more time-saving and cost-effective. Thus, compared with the chemical grafting method, the physical adsorption may sometimes be a more practical strategy to prepare hemostatic composite materials. Besides, an ingenious design of composite hemostatic materials is able to endow them with significant functions that cannot be realized by a single material, conducive to the development of robust and smart hemostats. For instance, Li et al. recently constructed negatively-modified microporous starch (MSS)@calcium carbonate ($CaCO_3$) through uniaxial growth of the flower-like $CaCO_3$ on the MSS and then incorporated protonated tranexamic acid into MSS@$CaCO_3$, followed by the addition of thrombin to obtain MSS@$CaCO_3$T for hemostasis.[63] The protonated tranexamic acid imparted the self-propelling property to the MSS@$CaCO_3$ particle through bubble detachment mechanism, and thrombin could enhance the blood coagulation potency of the particle. As demonstrated by the authors, MSS@$CaCO_3$T had the ability to travel against blood flow via bubble detachment, enabling them to approach deep/inaccessible bleeding sites for realizing successful hemostasis. Specifically, MSS@$CaCO_3$T halted bleeding within ~ 50 s and ~ 3 min when treating deep hemorrhage sites of animal liver and femoral artery, respectively. This work demonstrates that rational combination of different materials can endow the composite hemostatic particles with self-propelling property and enable them to serve as robust and smart hemostatic materials to successfully control hemorrhage in irregular/perforating wounds.

3. Inorganic materials for external hemostatic applications

Up till now, various inorganic materials have been studied for external hemostasis. The inorganic hemostats generally act through three key mechanisms: (1) absorbing water from blood and concentrating blood components at the hemorrhage site, (2) activating the blood clotting cascade, and (3) functioning as a physical barrier to hinder blood flow.[6,64,65] Based on these mechanisms, inorganic hemostatic agents can effectively promote hemostasis and accelerate the stop of bleeding. Compared with organic materials, inorganic hemostatic materials are often cost-effective, physically/chemically stable, easy to produce as well as transport, require no special storage condition, and contain no human- or animal-derived proteins. However, some problems also limit the development of inorganic hemostats. First, inorganic hemostats are usually hard to be degraded at wound sites, and hence debridement is usually required to remove the unnecessary inorganic hemostats after hemostasis. Second, the exothermic reaction of some inorganic hemostats after water absorption will lead to serious burns. Third, when granular inorganic hemostatic agents are dispersed in blood vessels, embolism may be caused to induce a serious risk to human body.

3.1. Silicate minerals

3.1.1. Zeolite

Zeolites, whose typical pore size is typically less than 2 nm, belong to a family of crystalline aluminosilicates.[66–68] Zeolites have cage-like cavities suitable for accommodating water molecules and positively charged ions including Ca^{2+} and Na^{+} which can further help to entrap more water molecules by electrostatic interactions. Moreover, zeolites show long-term physical and chemical stability, and are cheap and biocompatible. Nevertheless, some zeolite-based hemostats such as QuikClot (Z-Medica) are troublesome to use and require adequate debridement.[69] In addition, this kind of zeolitic hemostat has serious side effects, especially thermal injuries induced by the exothermic reaction resulting from the water absorption by zeolite.[70] Up till now, despite the notable benefits of zeolites, the development of zeolitic hemostatic materials with ideal characteristics for hemostasis remains challenging. Recently, Yu et al. developed a flexible zeolite–cotton hybrid hemostat combining meso-/micro-porosity, stability, and blood coagulation capacity.[65] The mesoporous chabazite-type zeolites were tightly bound onto the surface of cotton fibers via an on-site template-free growth route to fabricate a hybrid hemostatic material (termed mCHA-C). The mCHA-C hemostatic material had superior hemostatic property over many other clay/zeolite-based hemostats, such as the frequently used kaolin clay-coated gauze (Combat Gauze, CG). There were more blood loss and active component leakage when the animals were treated with CG (Fig. 5a). By contrast, a flat and open wound surface was observed after controlling bleeding with mCHA-C, which enabled a clear visualization of the surgical area and made meticulous

debridement dispensable. Moreover, owing to the facile fabrication of cotton by weaving and knotting, mCHA-C could be used as the basic material for the construction of various textile-based wearable systems. Therefore, this study provides a feasible approach to prepare wearable systems with hemostatic function to help people deal with sudden bleeding in their daily life.

The heat generated by zeolite is conducive to hemostasis via enhancing platelet function,[71] but losing control will bring about serious burns. It is a challenge to balance the advantages and disadvantages. To this end, in a recent study, Liang and co-workers designed a zeolite/crosslinked graphene sponge (Z-CGS), which managed thermal release of zeolite through the heat conduction of graphene (graphene oxide, GO).[72] The Z-CGS realized the excellent control of the wound temperature below 42 °C, while naked zeolite caused the wound temperature to reach 70 °C. In a rat artery injury model, Z-CGS stopped hemorrhage in 69 s, quicker than that achieved using Quikclot Combat Gauze. Therefore, Z-CGS represents an excellent composite that can combine the advantages of both graphene and zeolite, while getting rid of the weaknesses of the basic units. The work also highlights that the thermal conductibility of graphene can avoid the serious burns caused by the zeolites in hemostasis process.

3.1.2. Kaolin

Kaolin is a clay composed of mineral kaolinite ($Al_2Si_2O_5(OH)_4$) and a two-layer 1:1 silicate.[73] Kaolin has the capability to accelerate the natural clotting process in human body, because when it contacts with plasma, it can induce the activation of coagulation factor XII (FXII) related to the intrinsic blood coagulation cascade due to the negatively charged surface of the material.[74] Kaolin is thermally, chemically, and mechanically stable, contains no human- or animal-derived protein, bears low-risk as an allergen, and is low-cost, which makes it suitable for serving as a contact hemostatic agent.[39,75–77]

The two-dimensional nanoclay kaolinite has been employed in early intervention to stop blood loss. For instance, Long et al. rationally investigated the interactions between kaolinite and hemocytes.[78] The results revealed that when kaolinite powder was used to halt bleeding at the wound site, kaolinite could rapidly adsorb water molecules from the blood, and instantaneously accelerate the activation of FXII to FXIIa to stimulate the intrinsic clotting pathway and generate thrombin, thus causing fibrin formation and platelet activation and aggregation (Fig. 5b). Furthermore, the authors believed that the kaolinite nanoclay with looser aggregation and smaller nanosheets presented better hemostatic capability. Therefore, it is expected that controlling the aggregate state and particle size/thickness of the kaolinite/two-dimensional nanoclay nanosheets may represent a promising strategy for boosting the hemostatic capacity of these materials. In addition, the construction of composite materials also represents a good approach to improve the hemostatic property of kaolin-based hemostats.[76,77] For example, in 2017, Sun et al. presented a simple strategy to construct porous composite microspheres (CSMS-K) via blending CS with kaolin.[76] According to their study, the CSMS-K had a large quantity of surface and interior pores, which were beneficial to enhance the water-absorbing capacity of CSMS-K. The CSMS-K also displayed superior hemostatic efficacy than chitosan porous microspheres (CSMS) due to the synergetic hemostatic effect of kaolin and CS. In the rat liver laceration and tail amputation models, the blood loss and hemostatic time of the CSMS-K3 group were both decreased compared with those of the CSMS group. Besides, Cui and co-workers incorporated sheet-like kaolinite into polyvinylpyrrolidone electrospun fibers to construct hemostatic membranes for use as rapid hemostatic bandages.[77] The hemostatic membrane owned hydrophilic surface, robust framework, and plentiful hemostatic functional sites, and showed excellent hemostatic effect in a tail amputation model and a liver and spleen injury model of rat. These studies highlight that the combination of inorganic kaolin and organic materials is a good strategy to develop materials for hemostasis. The organic materials in the formed composite materials usually have good biocompatibility and high kaolin loading capacity, and can be easily developed into wound dressings. In addition, the loading of kaolin can impart excellent hemostatic performance to the composite material.

3.1.3. Smectite

Smectite clay is 2:1 phyllosilicate made up of an octahedral alumina layer sandwiched between two tetrahedral silica layers.[73] Smectite possesses a large surface area, a great cation exchange capability, and high viscosity due to their small particle sizes.[79,80] Compared with kaolin, smectite displays higher absorption, swelling, plasticity, and viscosity, allowing it to be an excellent candidate for the applications in industrial and medical fields.[6,73,81] In terms of hemostasis, they can absorb plenty of water resulting from their structure.[79] And when smectite contacts with the blood, the negative charge on its surface results in the activation of the intrinsic clotting pathway.[82] Smectite has been used to prepare the commercial hemostatic agent, WoundStat,[83] indicating its robust capacity to stop bleeding.

As a member of the smectite family, laponite, $Na_{0.7}[(Mg_{5.5}Li_{0.3})Si_8O_{20}(OH)_4]_{0.7}$, is a synthetic nanoclay composed of a layered construction with 30 nm in diameter and 1 nm in thickness.[84–86] Laponite is able to absorb water in blood and promote the concentration of clotting factors and hemocytes, contributing to hemostasis.[87,88] Gaharwar et al. reported a gelatin–laponite hydrogel and validated that this hydrogel decreased the blood coagulation time by 77 %.[87] The incorporation of laponite nanoplates into the hydrogel also improved its shear-thinning property, making it more suitable for hemorrhage management. Rajabi et al. prepared a hydrogel using gelatin methacrylate (GelMA) and thiolated gelatin as the matrix, and introduced polydopamine-functionalized laponite to the matrix to enhance the adhesion strength, mechanical properties, and blood clotting ability.[88] The authors proved that the presence of polydopamine-functionalized laponite drastically controlled the biodegradability, mechanical properties, and swelling ratio of the nanocomposite hydrogels. Furthermore, the nanocomposite hydrogels exhibited strong tissue adhesiveness, superb recovery ability, and considerably less blood coagulation time than GelMA/thiolated gelatin hydrogel. This study reveals that laponite is able to be introduced into some polymer systems, which is conducive to fabricating composites with improved hemostatic ability. Furthermore, the poor physical and mechanical properties of polymers can also be improved by the introduced laponite, making the composite material more beneficial for hemostasis application. However, it is noteworthy that the authors found that the introduction of laponite caused increased hemolysis rate, probably resulting from its negative surface charges. Fortunately, the authors mentioned that the functionalization of the surface of laponite with polydopamine was beneficial for reducing the hemolytic activity of laponite, conducive to the further application of laponite in biological systems.

3.1.4. Rectorite

Rectorite (REC) is a mixed layer 2:1 silicate mineral which has a regular interstratification of low-charge swellable smectite-type galleries and high-charge non-swellable mica-type galleries.[89] Several reports have revealed that rectorite is capable of promoting hemostasis and shows large potential for developing hemostats.[90–94] As an example, Li and co-workers combined REC and CS to obtain a maltose-like injectable hemostatic nanocomposite.[93] The viscous nanocomposite shortened the clotting time by

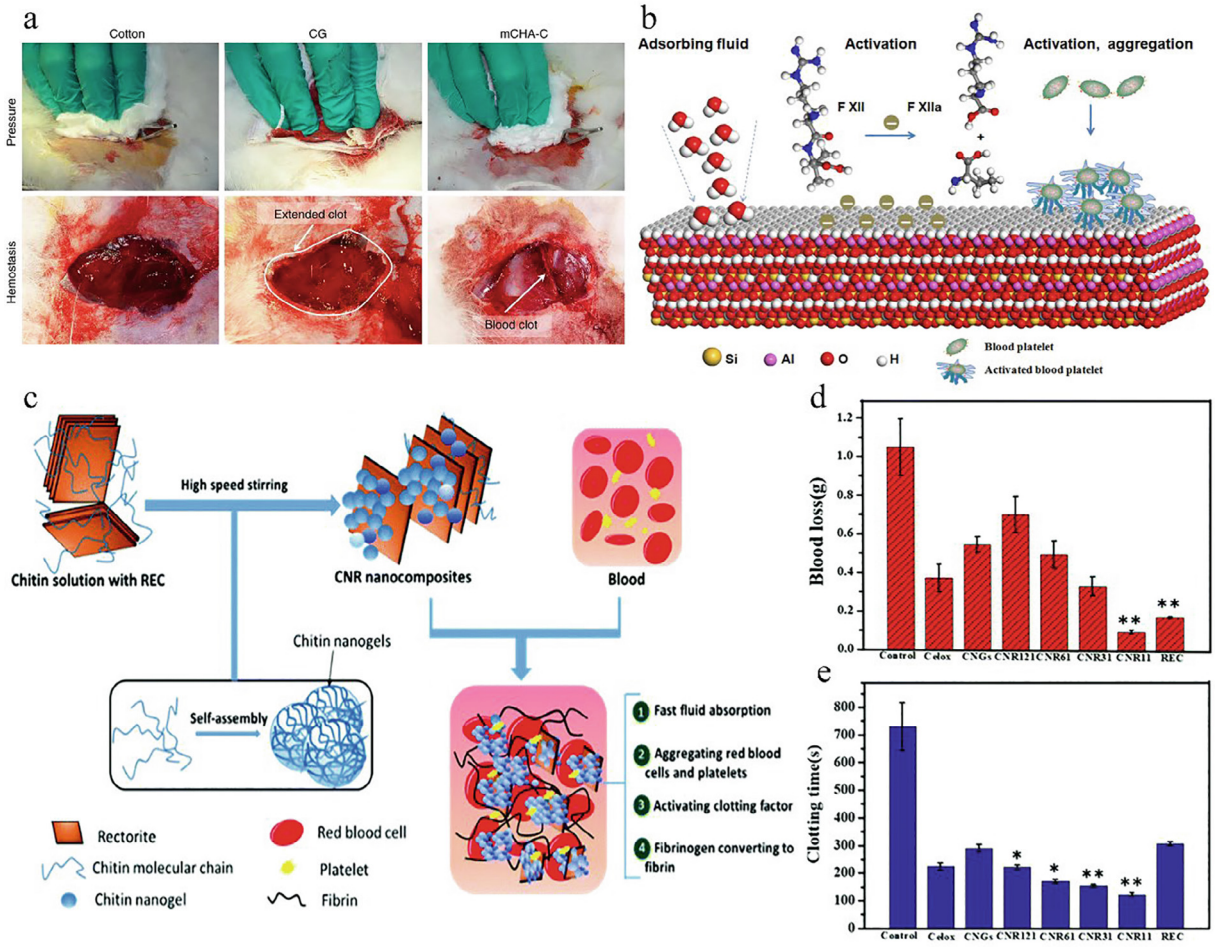

Fig. 5. (a) Photographs showing the hemostasis results via exerting manual pressure on the lethal femoral artery injury of rabbit with cotton, CG, or mCHA-C. Reprinted with permission from Ref. [65]. Copyright 2019, Nature Publishing Group. (b) Demonstration of the hemostatic mechanism of kaolinite nanoclay. Reprinted with permission from Ref. [78]. Copyright 2019, Elsevier B.V. (c) Scheme illustrating the preparation process and hemostatic mechanism of CNR nanocomposite. (d,e) Blood loss (d) and clotting time (e) of control, Celox, CNGs, CNR121, CNR61, CNR31, CNR11, and REC in a rat tail amputation model. (c–e): Reprinted with permission from Ref. [94]. Copyright 2019, Royal Society of Chemistry.

43 % in vitro due to the hemostatic ability of REC. It was confirmed that the viscous nanocomposite could firmly adhere on skin and hinder bleeding successfully in an in vitro porcine skin model. Similarly, Zhang et al. synthesized a chitin nanogel/REC nanocomposite for hemostasis (Fig. 5c).[94] Chitin chains were intercalated into REC and the subsequent mechanical high-speed stirring produced chitin nanogels, which were assembled on the REC nanoplate surface via electrostatic interaction to form a structure similar to sandwich. It was revealed that the nanocomposite showed encouraging biocompatibility and negligible hemolysis (<3.5 %) in in vitro experiments. The nanocomposites with the chitin/REC ratios of 1/0, 1/1, 3/1, 6/1, and 12/1 were named as CNGs, CNR11, CNR31, CNR61, and CNR121. In the rat tail incision, CNR11 exhibited the best hemostatic effect with hemostasis time (121.7 ± 6.2 s) and blood loss (0.097 ± 0.01 g) shorter and less than other samples and positive control group (Celox, a kind of CS-based hemostat) (Fig. 5d and e). The hemostatic activity of the nanocomposite was attributed to the rapid adsorption and aggregation of RBCs and platelets by chitin and the stimulation of a coagulation cascade by REC. Owing to its enhanced biocompatibility and hemostatic activity, chitin nanogel/REC nanocomposite may be applied as a safe and economical hemostatic material.

3.1.5. Halloysite

Halloysite ($Al_2Si_2O_5(OH)_4{\cdot}2H_2O$) is a kind of naturally occurring aluminosilicate nanoclay showing an interesting hollow tubular scroll structure.[95,96] It has been confirmed to be biocompatible and be able to foster blood coagulation.[97–99] Udangawa et al. fabricated cellulose–halloysite hemostatic nanocomposite fibers (CHNFs) via a one-step wet–wet electrospinning process.[99] These biocompatible CHNFs displayed 2.4 times faster plasma coagulation time and 1.3 times faster whole blood coagulation time in comparison with QuikClot Combat Gauze. The significant reduction of coagulation time made this nanocomposite a potential life-saving material for victims of quick blood loss, such as soldiers and patients undergoing major surgery, or for the patients with hereditary coagulation disorders who encounter bleeding problems.

3.1.6. Bioglass

Bioglass (SiO_2-CaO-(Na_2O)-P_2O_5), also called bioactive glass, which contains silica, calcium ions, and phosphate ions, plays a key role in initiating the clotting cascade.[100] It has been widely reported that silica can activate FXII and then activate coagulation cascade reaction.[101,102] Calcium is a cofactor which is required in several different phases of coagulation cascade reaction.[20,31,103] According to relevant researches, phosphate is also

able to activate coagulation cascade and make the formed fibrin clots more stable.[104,105] Hu et al. described that, due to its nanoscale dimension, the nano-sized bioglass has distinct properties that would further facilitate the aggregation of coagulation factors and blood proteins at the hemorrhage site and aid in stable blood clot formation.[106] Nevertheless, owing to the sharp morphology and brittleness of bioactive glass particles, which may lead to cell damage or inflammatory response, the bioglass particles are typically combined with biopolymers to form composite materials for wound healing treatment.[107–109] For example, Tansaz et al. prepared soy protein isolate/nanoscale bioactive glass composite film functioning as wound dressing and reported its additional favorable properties such as hemostatic capacity and considerable cytocompatibility.[108] Lately, Sundaram and co-workers reported that incorporating nanobioglass (nBG) into CS hydrogel could realize rapid blood clotting.[109] The prepared CS-nBG hydrogel demonstrated good cytocompatibility. In in vitro blood clotting test and in vivo organ injury models, the CS-nBG hydrogel displayed better hemostatic property than the CS hydrogel containing no nBG due to the synergistic effect of CS and nBG. The mesoporous bioactive glasses (MBGs), a generation of nanostructured bioceramics, with the form of 80 % SiO_2–15 % CaO–5 % P_2O_5 was originally developed by Yan et al.[110] It combines the advantages of bioactive glass and mesoporous silica.[111,112] It has displayed huge potential for clinical hemostatic application because of its unique characteristics, such as high porosity, ordered mesoporous channel structure, high surface area, and large pore volume.[113,114] To date, there have been several studies that employ MBGs for developing potent hemostatic materials.[115,116] For instance, Yao et al. mixed MBG and quaternized CS to develop a shape memory cryogel with the functions of antiinfection, hemostasis, and wound healing promotion.[115] Moreover, Pourshahrestani et al. constructed serial 1 % Ga_2O_3-containing mesoporous bioactive glass–chitosan (Ga-MBG/CHT) composite scaffolds through a lyophilization process.[116] The hemostatic property, antibacterial activity, and biocompatibility of the Ga-MBG/CHT composite scaffolds were significantly improved due to the incorporation of Ga-MBG. Nevertheless, the authors found that the incorporation of Ga-MBG would result in declined porosity and water uptake of the composite scaffolds, hindering the further development of MBG-based hemostatic materials. Therefore, it is desirable for future researchers to propose effective strategies to overcome this challenge.

3.2. Silica

3.2.1. Mesoporous silica nanoparticles (MSNs)

MSNs with good biocompatibility are especially suitable for being developed to be hemostatic agents, such as NuStat and TraumaStat, due to their large surface area, highly ordered pore structure, and alcoholic hydroxyl groups.[117,118] MSNs can be easily immersed in the blood through the formation of intermolecular hydrogen bonds with water molecules, thus facilitating the contact between MSNs and blood. MSNs possess mesoporous structure which can cause siphon effect when MSNs contact with blood. MSNs absorb water in blood which concentrates RBCs, platelets, and coagulation factors and then accelerates the formation of thrombus.[119] Further, the negative charges on the surface of MSNs are conducive to activating clotting factor XII and other coagulation-related proteins to hasten clotting cascade.[120] Based on the above hemostatic mechanisms, MSNs have been employed to prepare hemostatic agents and they were reported to have better in vivo hemostatic activity in comparison with CG.[118,121] Nevertheless, there are still some difficulties in developing MSN-based hemostatic materials.[112,119,122] For example, the poor tissue adhesion of MSNs makes them be easily flushed away by high-speed blood flow. Additionally, the MSNs dispersed in the blood may bring about systemic embolization. Moreover, it is troublesome to remove the powdery MSNs from the wound site. Some studies have been conducted to improve the properties of mesoporous silica for hemostasis.[123,124] For example, in 2018, Chen et al. synthesized the urushiol-functionalized MSNs (MSN@U) serving as a hemostat.[123] The urushiol possessed the long hydrophobic alkyl group and the hydrophilic catechol group which caused the self-assembly of MSN@U at the blood/air interface. The alkyl group formed a hydrophobic layer to prevent blood from oozing, while the catechol group allowed MSN@U to tightly adhere onto the blood vessel through forming covalent bonds. Furthermore, MSN@U could accelerate clotting cascade reactions because the negatively charged phenolic hydroxyl groups of urushiol could activate coagulation factor XII and the MSN could also foster coagulation cascade as mentioned before. Owing to these effects, MSN@U could act as an efficient hemostat with a hemostasis time of only 22 ± 2 s on a rat liver laceration. Both in vitro and in vivo assays confirmed that the blood compatibility of the composite material MSN@U was better than that of MSN. The composite material has both the strong tissue adhesion provided by urushiol and the superior clotting ability offered by MSN, making it a promising hemostatic agent for clinical application. In another example, Chen and co-workers fabricated a safe and quick hemostatic sponge by coordinating MSNs with a glycerol-modified *N*-alkylated CS sponge (GACS).[124] MSN and *N*-alkylated CS sponge both had hemostatic effect and glycerol was used to increase the hydrophilicity, which was conducive to enhancing the blood absorption capacity of the composite material. MSN–GACS showed enhanced whole blood absorption and platelet adhesion potential relative to CG. Moreover, in liver and femoral artery injury models of rabbit, MSN–GACS displayed better hemostatic efficacy and lower cardiovascular toxicity than CG. In summary, MSN–GACS is a promising hemostat for prehospital hemostasis. However, a hemostatic material that only has hemostatic function sometimes cannot meet the needs of patients, and hence in some cases researchers used MSNs to prepare biomedical materials with dual functions of hemostasis and antibiosis by loading antimicrobial agents, such as silver nanoparticle (AgNP), antibiotics, or antibacterial peptides.[62,125] For instance, Nie and co-workers prepared AgNP-incorporated mesoporous silica granules (AgNP-MSG) via one-pot sol–gel processing.[125] The AgNPs displayed broad spectrum and nontolerant antibacterial activity, which could reinforce the antibacterial activity of the composite. In a liver injury model of rat, bleeding was efficiently stemmed within only 7 s by 5 % AgNP-MSG, > 5 times faster than commercialized hemostatic gauze. These results implied that AgNP-MSG may find promising applications as a dual-function hemostatic agent in trauma treatment.

3.2.2. Biosilica

Diatoms belong to unicellular eukaryotic algae which are covered with silica cell walls. Biosilica can be obtained from diatoms.[126] Feng et al. reported that the diatom-biosilica with negatively charged surface could notably activate the cofactors HWK-kininogen and prekallikrein and blood coagulation factors XI and XII to foster the intrinsic blood coagulation, giving rise to favorable hemostatic ability of diatom-biosilica.[127] Additionally, different from the synthesized mesocellular silicon-based materials with pore sizes of 2–50 nm, the biosilica possesses interesting hierarchical porous structure from nano to micro scale (primary pore: 1 μm, secondary pore: 200 nm, tertiary pore: 50 nm). The unique hierarchical porous structure endows the biosilica with more robust hemostatic function.[128] Wang and co-workers found that increasing liquid absorption capacity/specific surface area and declining size are feasible strategies to reinforce the coag-

ulation performance of diatom frustules.[129,130] Moreover, the diatom frustules displayed satisfactory blood compatibility and low cytotoxicity. In another study, Li et al. fabricated calcium-doped biosilica (Ca-biosilica) from diatoms via feeding diatoms with calcium chloride and purification of the diatoms through acid-oxidative treatment (Fig. 6a).[128] Ca-biosilica possessed efficient water absorbability, satisfactory biocompatibility, and superb hemostatic effect. As shown in Fig. 6b, Ca-biosilica displayed the minimum clotting time (88.34 ± 28.54 s) comparable to that of Quickclot zeolite in a rat-tail amputation model. Besides, there was one-third blood loss in the Ca-biosilica group (0.21 ± 0.16 g) compared with that in the Quickclot zeolite group (0.63 ± 0.09 g) (Fig. 6b). It was considered that the notable hemostatic performance of Ca-biosilica was attributed to the following reasons: (1) The quick water absorption of Ca-biosilica was beneficial for concentrating clotting factors and platelets, therefore accelerating thrombin generation. (2) The diatom surface with rich silanol groups could provide negative charges to promote the activation of coagulation factors. (3) The Ca^{2+} (the clotting factor IV) doped on the surface of diatoms could activate the intrinsic clotting cascade. In another example, Wang et al. rationally designed CS/dopamine/diatom-biosilica composite beads (CDDs) for quick hemostasis with great biocompatibility.[131] They combined CS with diatom-biosilica to prepare CDDs using dopamine as a bioglue. The CDDs possessed a porous internal structure contributing to fast and massive water absorption, which helped to quickly staunch hemorrhage (83 s, 22 % of the control group). Recently, Zhang et al. prepared a composite sponge for bleeding control based on hydroxybutyl CS and diatom-biosilica.[132] The composite sponge displayed hierarchical porous structure, favorable fluid absorbability, and robust hemostasis ability (coagulation time shortened by 70 % compared with control). These investigations highlight that the combination of diatoms with other ingredients with hemostatic activity (such as inorganic calcium ion or organic CS) may be a better strategy for the preparation of efficient and safe hemostatic materials than using diatoms alone for hemostasis intervention.

3.3. Phosphate-based hemostatic materials

3.3.1. Phosphate minerals

Some phosphate minerals, especially those that make up human bone, have also been applied to prepare hemostatic materials.[133–135] For instance, Song et al. first synthesized hydroxyapatite nanoparticles-*graft*-poly(D,L-lactide) nanocomposites and then fabricated them into porous microspheres via a modified double emulsion solvent evaporation process.[133] Subsequently, part of the hydroxyapatite nanoparticles were exposed on the surface of the porous microspheres by alkali treatment. Owing to the particle structure and surface charge of the hydroxyapatite nanoparticles, the fabricated porous microspheres possessed robust protein adsorption capacity, which was beneficial for facilitating the adhesion of platelets and the formation of clots. The hydroxyapatite nanoparticles also provided a high Ca^{2+} concentration for hemostasis. Moreover, the poly(D,L-lactide) copolymer could work as a skeleton to offer a large surface area promoting the contact between the fabricated porous microspheres and blood. Due to these hemostatic mechanisms, the fabricated porous microspheres offered significant advantages for acting as an effective hemostat both in vitro and in vivo. In another example, Zheng and co-workers adopted the freeze-drying method to fabricate a porous and highly hydrophilic hemostatic aerogel by combining inorganic ultralong hydroxyapatite nanowires with organic PVA (as the binder).[134] The hemostatic aerogel rapidly absorbed liquid from blood to concentrate platelets/blood cells and effectively prevented bleeding in rat liver and rabbit femoral artery models.

Recently, Pillai et al. developed a strategy to enhance the hemostatic behavior of CS hydrogel through incorporating nano whitlockite ($Ca_{18}Mg_2(HPO_4)_2(PO_4)_{12}$) which could release Ca^{2+}, Mg^{2+}, and PO_4^{3-} ions to simultaneously initiate coagulation cascade.[135] Compared with the CS hydrogel, the nano whitlockite-incorporated CS hydrogel caused faster blood clot formation in an in vitro blood coagulation test and achieved more effective hemostasis in the Sprague–Dawley rat models of liver and femoral artery injuries.

3.3.2. Polyphosphate

As a procoagulant agent, inorganic polyphosphate is stored in dense granules in platelets.[136] Polyphosphate is beneficial for hemostasis due to the following mechanisms: (1) initiating the contact pathway of the blood clotting cascade, (2) enhancing the activation of coagulation factor V, (3) stabilizing fibrin clot, and (4) promoting the feedback activation of factor XI by thrombin.[104,105,137,138] Ong et al. refined the hemostatic performance of CS hydrogel by incorporating polyphosphate and revealed that polyphosphate could be used as a valuable hemostatic adjuvant.[139] Momeni et al. evaluated in vitro degradation and hemostatic performance of polyphosphate coacervates.[140] The results revealed that the polyphosphate coacervates degraded rapidly in Tris-buffered saline or fetal bovine serum solution and they remarkably reduced the clotting time particularly when very long chain polyphosphates were used in an assay of whole blood clotting. It was concluded that polyphosphate coacervates hold huge potential for use as a degradable hemostatic agent. In another study, Sakoda and co-workers developed a hydrogel hemostat consisting of hyaluronan conjugated with polyphosphate.[141] The gelation time of the hydrogel was <5 min and the hydrogel showed great biocompatibility and degradability. The hydrogel accelerated the clotting rate of human plasma ex vivo, and displayed strong hemostatic ability comparable to fibrin glue in an in vivo mouse liver hemorrhage model.

3.4. Inorganic carbon materials

3.4.1. Carbon aerogels (carbon sponges)

Carbon aerogels (or carbon sponges) are lightweight materials which display a 3D network, extremely low density, porous structure, and high specific surface area.[142,143] They can be produced from GO, a nanomaterial whose unique properties make it attractive for the biomedical applications like tissue engineering, drug delivery, and cancer diagnosis/therapy.[144–146] GO presents a two-dimensional planar structure, is hydrophilic, and has the capacity to incorporate functional groups or molecules onto their surfaces.[147] Crosslinked graphene sponge (CGS) is a promising hemostatic agent with huge potential for trauma treatment.[148] As shown in Fig. 7a, the CGS could quickly absorb plasma to induce the formation of a blood cell layer, thus hastening coagulation. Nonetheless, CGS cannot stimulate hemocytes to foster traumatic hemorrhaging control.[149] To enhance its hemostatic effect, some promising strategies have been proposed.[150–152] For example, Quan and co-workers used 2,3-diaminopropionic acid (a medicinal amino acid) to synthesize a 2,3-diaminopropionic acid-crosslinked graphene sponge (DCGS) for bleeding control.[150] This carboxyl-functionalized DCGS could not only rapidly absorb plasma, but also stimulate platelets and erythrocytes to change their usual structure/form to facilitate blood coagulation. The authors validated that it was an efficient strategy to enhance the hemostatic effect via the introduction of functional groups (like carboxyl group) contributing to enhancing the interface interaction between cell and graphene. Additionally, the embedment of the components with hemostatic activity is also capable of enhancing the hemostatic performance of CGS. For example, Liang and co-workers developed

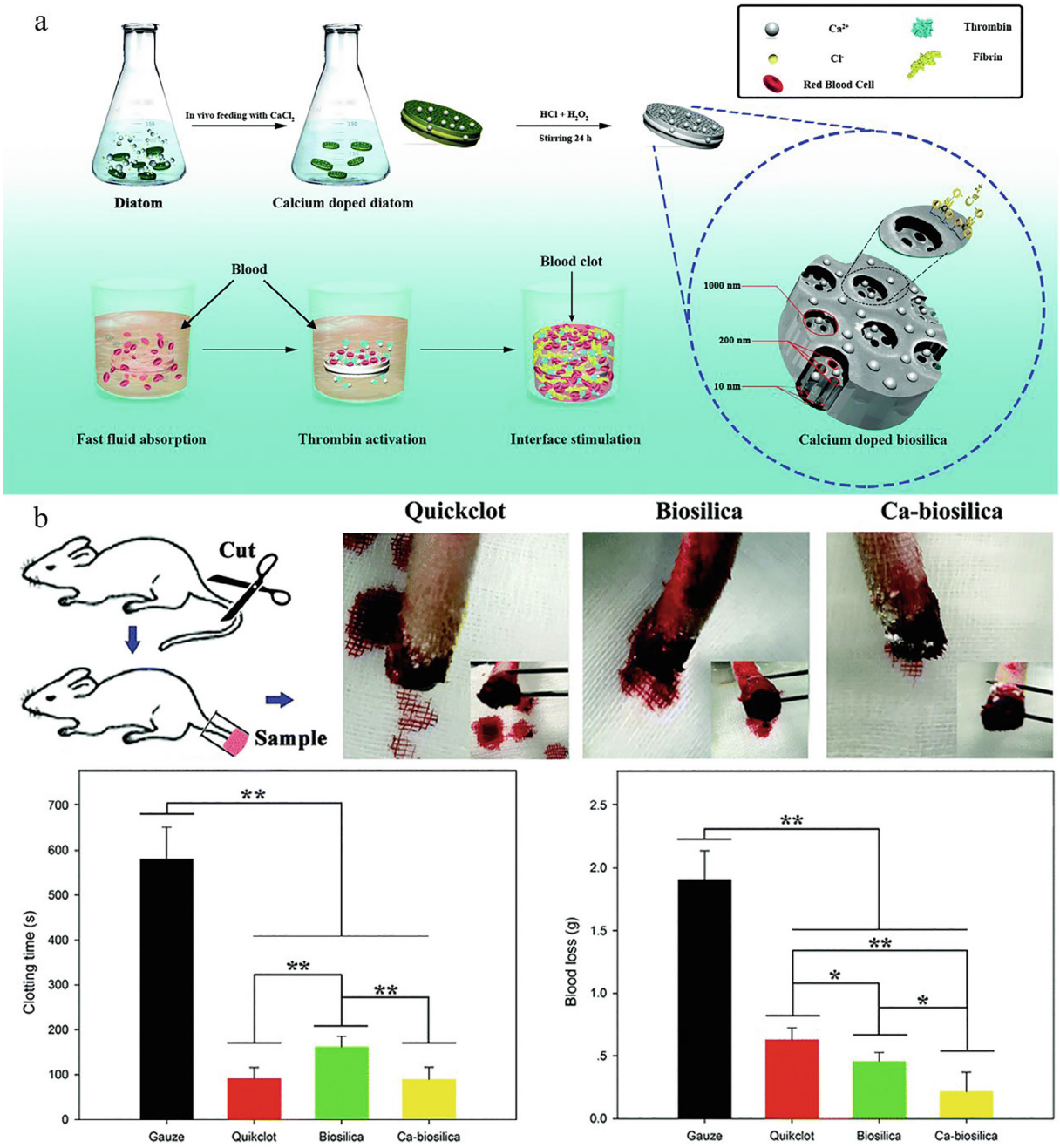

Fig. 6. (a) Scheme showing the synthesis and hemostatic process of Ca-biosilica. (b) (Top) Scheme of the establishment of the rat tail amputation model and photographs showing the evaluation of hemostatic performance by contacting gauze, the commercial Quickclot zeolite, biosilica, and Ca-biosilica separately with the bleeding wounds. (Bottom left) Clotting time results. (Bottom right) Blood loss results. (a and b): Reprinted with permission from Ref. [128]. Copyright 2018, Royal Society of Chemistry.

a graphene–kaolin composite sponge through a facile hydrothermal reaction.[151] The graphene–kaolin composite sponge staunched bleeding in around 73 s in the rabbit artery injury test. Consequently, these researches prove that incorporating some additional antibleeding constituents into CGS provides a feasible strategy for designing CGS-based hemostatic materials. In addition, the additional components may endow the composites with more functions, such as antibiosis and wound healing. For instance, in 2018, Mellado and co-workers prepared composite aerogels (GO-PVA-SK and GO-PVA-SD) by a sol–gel process based on PVA and GO, incorporating the extracts of grape skin or seed containing plentiful proanthocyanidins (PAs or condensed tannins), for wound treatment.[152] The prepared composite aerogels had low density and porous structure to absorb water and blood. PAs have good antibacterial and antiinflammatory activities and can promote wound healing. This work highlights the usability of a GO-based aerogel for not only trauma bleeding treatment but also wound healing.

The pure GO has various limitations in the hemostasis application due to its potential thrombosis, high hemolysis rate, and cytotoxicity. On the premise of maintaining the hemostatic activity of GO, these problems are able to be settled by combining GO with some polymers to form stable structures, which can prevent GO from escaping from the composite materials to avert the potential

damage of GO to human body.[153,154] For instance, Chen et al. provided a facile solution-mixing freeze-drying approach to combine GO and natural polysaccharides through hydrogen bonding to construct *Bletilla striata* polysaccharide/GO composite sponge (BGCS) with favorable biocompatibility.[153] The BGCS could boost blood clotting within only 30 s without anticoagulant in the whole blood coagulation evaluation and it could halt bleeding within 50 s in the tail amputation model of rat. The hemolysis rate and cytotoxicity of BGCS were lower than those of GO. Likewise, to address the safety issue of GO sponges, Zhang et al. prepared a series of *N*-alkylated CS/GO composite sponges based on the hydrogen bonding and electrostatic interaction between *N*-alkylated CS and GO via the dilute solution freeze phase separation and drying process.[154] The sponges displayed superb mechanical stability, absorption capability, and biocompatibility. Besides, the hemostasis time of the *N*-alkylated CS/GO composite sponge with a GO ratio of 20 % was shorter than that of Celox in a rabbit model of femoral injury.

3.4.2. Other inorganic carbon materials

In addition to graphene sponge, carbon nanotube (CNT) and carbon nanofiber have also been applied to construct hemostatic materials.[155–157] For instance, Zhao et al. used glycidyl methacrylate-functionalized quaternized chitosan (QCSG) and CNT to prepare injectable antibacterial conductive cryogels for trauma bleeding treatment and wound healing promotion.[155] These cryogels exhibited strong mechanical strength (Fig. 7b), and presented terrific blood uptake capability and fast blood-triggered shape recovery resulting from their interconnected and macroporous structure (Fig. 7c). Moreover, the shape memory cryogels in a shape-fixed state were able to be injected into the deep, narrow, or irregularly shaped wounds (Fig. 7d). Importantly, cryogel with 4 mg mL^{-1} CNT (QCSG/CNT4) showed exceptional hemostatic function in a lethal noncompressible bleeding model of rabbit liver volume defect and better hemostatic capability than CG in the standardized circular liver hemorrhage model. These results suggest that the injectable cryogels can be suitable hemostatic candidates for treating irregularly shaped and noncompressible bleeding in critical situations. In a later research, Li et al. raised an effective strategy for achieving bleeding control through constructing a superhydrophobic surface with immobilized carbon nanofibers.[156] The authors believed that carbon nanofibers could not only promote rapid fibrin growth, inducing quick hemostasis, but also had superhydrophobicity, contributing to averting blood wetting to decrease blood loss and bacterial attachment. Additionally, the contact between the superhydrophobic surface of carbon nanofiber and the clot is minimal, allowing an unforced removal of the hemostat without triggering secondary bleeding. In the rat back-bleeding model, the average blood loss was 0.3 ± 0.7 mg for the carbon nanofiber gauze, which was only ~ 1.5 % of that for normal gauze (19.8 ± 9.0 mg). This work highlights the advantages of utilizing superhydrophobic materials (such as carbon nanofiber) to develop effective hemostatic patch materials, including preventing excessive blood loss and disadvantageous bacterial attachment, as well as allowing easy removal of the hemostat.

3.5. Metal-containing materials

Some metal-containing materials have been proved to have procoagulant activity. For example, Ag NPs have been reported to be able to accelerate thrombin generation and activate platelets.[158,159] Fe_2O_3 NPs can stabilize thrombin and facilitate bleeding cessation.[160] The hollow CeO_2 NPs with rough surface also help hemostasis.[161] The Al_2O_3 films possess charges and can bind to fibrinogen, thus activating the intrinsic clotting pathway and accelerating platelet activation and fibrin formation.[162] Furthermore, as mentioned above, calcium ion is a cofactor which is associated with several critical phases of coagulation cascade.[29,31] Zinc ion is considered to have the capability to increase the rate of fibrin clot formation caused by thrombin and the deficiency of zinc ion can notably hamper coagulation cascade and fibrin formation, which is detrimental to the cessation of bleeding.[163] Based on the procoagulant activity of these metal NPs or metal ions, some researchers have incorporated them into various organic or inorganic substrates to develop effective hemostatic materials.[128,164] For instance, Lan and co-workers fabricated a CS/gelatin/sodium hyaluronate dressing with Ag NPs (CGSH/Ag50) via freeze-drying for bleeding control.[164] CGSH/Ag50 had strong blood absorption capacity and could promote platelet activation and aggregation through the positively charged surface and the stimulation of Ag NPs. It was demonstrated that CGSH/Ag50 could rapidly control bleeding in rabbit liver and ear injury models. In addition, CGSH/Ag50 also displayed good biocompatibility, antibacterial activity, and the ability to drastically promote full-thickness wound healing. To be noted, the authors found that CGSH/Ag60 (with a higher content of Ag NPs in comparison with CGSH/Ag50) presented lower platelet aggregation relative to CGSH/Ag50, which may result from the detrimental effect of Ag NPs to the platelets, hindering the activation and aggregation of platelets. Consequently, the potential toxicity of Ag NPs should be taken into account when preparing the hemostatic materials containing Ag NPs. In another work, Liu and co-workers used a freeze-drying technique to prepare a composite sponge comprised of Ce-containing MBG and CS for hemostasis.[165] The authors found that Ce might have the ability to further promote platelet aggregation and the composite sponge possessed superior hemostatic effect compared to gelatin sponge.

4. Organic materials for external hemostatic applications

There are a wide variety of organic hemostatic materials, comprising (1) peptide- and protein-based hemostatic materials, (2) polysaccharide-based hemostatic materials, and (3) synthetic polymer-based hemostatic materials. For (1), they often have good biocompatibility and satisfactory hemostatic ability, and there are several hemostatic mechanisms for this type of hemostatic materials, including stimulating the platelets and inducing platelet aggregation (e.g., collagen and gelatin), sealing the wounds (e.g., fibrin sealant and glutaraldehyde-crosslinked albumin), forming hemostatic barriers to entrap and concentrate blood components (e.g., self-assembling peptides), and transforming fibrinogen into fibrin (e.g., thrombin). However, the high cost, potential risk of virus transmission, and possible immunogenicity may limit the practical hemostatic applications of peptide- and protein-based hemostats. For (2), they have also attracted particular attention due to their significant advantages, including rich sources, low price, good stability, low immunogenicity, and excellent biocompatibility/biode gradability. However, the hemostatic activity of polysaccharide materials remains to be further improved. For (3), they can be industrially produced and prepared with some other adjuncts to improve their biocompatibility and clinical performance, and they usually exhibit relatively high stability.[166] However, the production cost of synthetic polymers is usually higher than that of natural polymers, and the poor biodegradability and potential cytotoxicity will also impede their use for practical hemostatic applications.[166]

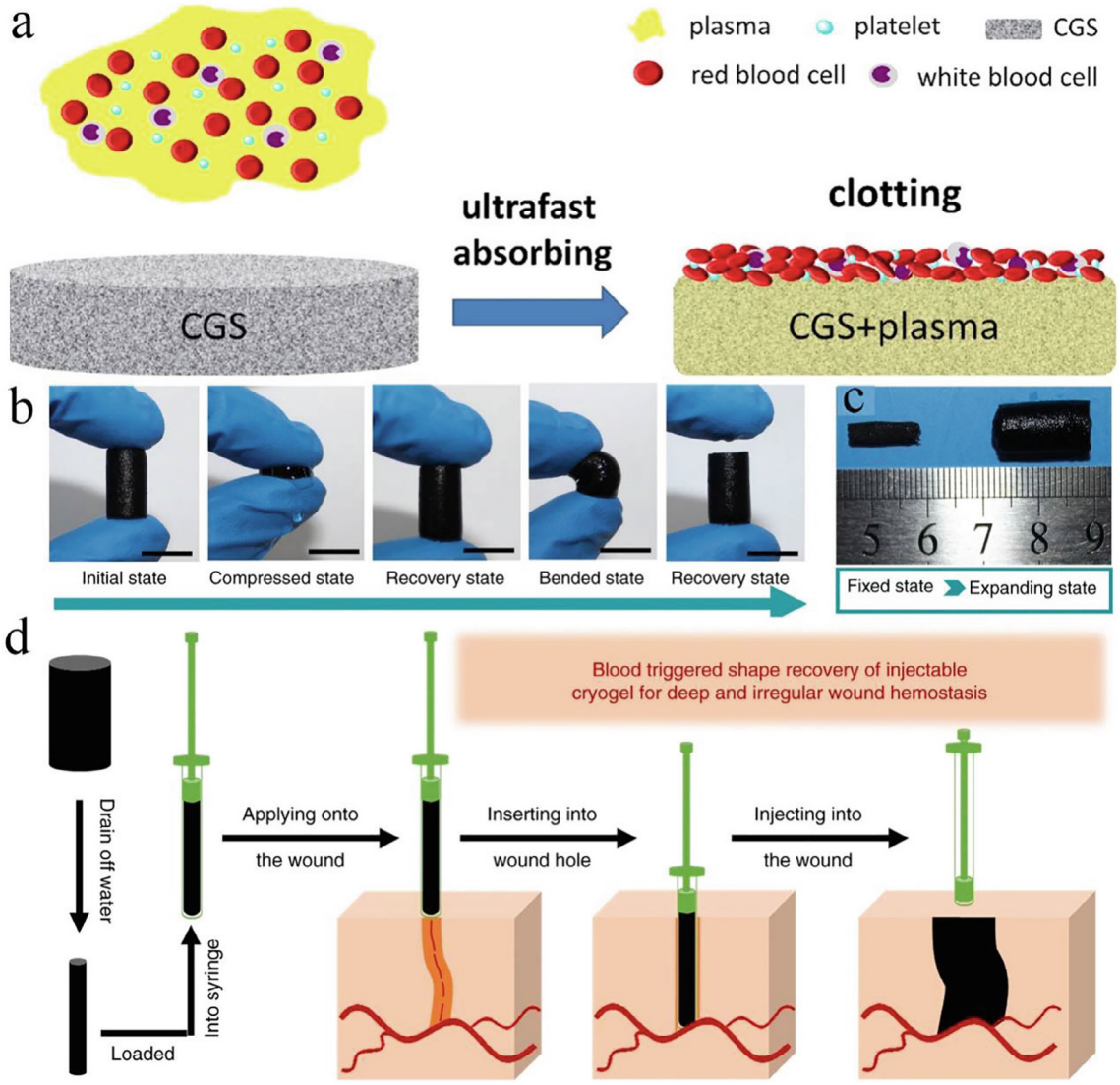

Fig. 7. (a) Schematic diagram of the hemostatic mechanism of CGS. Reprinted with permission from Ref. [148]. Copyright 2015, Elsevier B.V. (b) Photographs displaying the compression and bending resistance ability of QCSG/CNT4 cryogels. (c) Photograph showing the shape-fixed state after squeezing out free water (left) and the expanded state after absorbing some water (right). Scale bar: 1 cm. (d) Scheme illustrating the hemostatic application of the injectable shape memory cryogel in a deep and irregular wound. (b–d): Reprinted with permission from Ref. [155]. Copyright 2018, Nature Publishing Group.

4.1. Peptide- and protein-based hemostatic materials

4.1.1. Collagen

Collagen as a kind of natural protein has been reported to be an effective hemostatic agent.[167,168] Collagen is the most abundant protein in the human body (nearly 30 % of the total protein weight), and it mainly exists in the extracellular matrix.[169] It has good biodegradability (i.e., it can be degraded into physiologically acceptable compounds in vivo), superb biocompatibility, low antigenicity, and excellent cell-binding performance.[170] The role of collagen in controlling bleeding is that it can stimulate the platelets, induce platelet aggregation, and foster the release of clotting factors.[168,171] Many researchers have prepared a series of biomedical hemostatic materials based on collagen.[172,173] For example, Sun et al. proved that chemical crosslinking could help enhance the ability to resist collagenase degradation and improve the mechanical performance of collagen sponges.[172] Besides, He et al. developed recombinant collagen by genetic engineering and fermentation technology and prepared hemostatic sponge using the obtained recombinant collagen.[173] The recombinant collagen had good stability, high hydrophilicity, exceptional biocompatibility, and was free of animal virus risk. Compared with natural collagen sponge, the recombinant hemostatic sponge promoted blood coagulation more effectively in vitro and in vivo. This work highlights the great advantages of using recombinant collagen instead of natural collagen to prepare more ideal hemostatic agents.

Some natural polysaccharides have also been utilized to prepare composite materials with collagen for trauma bleeding treatment. [174,175] For instance, Yan et al. reported a collagen sponge reinforced with CS/calcium pyrophosphate nanoflowers (CPNFs-Col sponge) for bleeding control (Fig. 8a).[174] They synthesized the CPNFs through a one-pot preparation technique and subsequently mixed them with collagen to obtain CPNFs-Col sponge through a lyophilization process. With the specific properties like the positively charged surface rich in amine groups, rapid water uptake ability, and large specific surface area (952.5 m^2/g), the CNPFs-Col sponge caused the adhesion of platelets and haemocytes, activated the intrinsic pathway of clotting cascade, promoted the blood coagulation, and stanched bleeding both in vitro and

in vivo. As displayed in Fig. 8b, within 1 min after the contact between CPNFs-Col sponge and blood cells, the CPNFs-Col sponge-30 could change the state of the blood cells. A large number of blood cells stretched out their pseudopodia on the CPNFs-Col sponge-30 surface, improving the aggregating activity of haemocytes. Nevertheless, no pseudopodium was found in the collagen sponge group. Then from 2 to 3 min, haemocytes continued to aggregate to generate a haemocytes layer. The haemocytes on the surface of CPNFs-Col sponge-30 formed a tight junction with each other through pseudopodia. By contrast, in the collagen sponge group, no intercellular connection was observed. Finally, from 4 to 5 min, the plasmatic fibrinogen was activated and converted to fibrin monomer in the CPNFs-Col sponge-30 group. Later, the fibrin monomers began to crosslink and formed fibrin clots. Correspondingly, no fibrin clots formed in the collagen sponge group. Furthermore, the CNPFs-Col sponge was able to be completely biodegraded within 3 weeks and it was appropriate for peritoneal adhesion prevention and postoperative treatment. To improve the hemostatic capability of collagen, Li et al. developed some collagen/oxidized microcrystalline cellulose (collagen/OMCC) sponges with varied mass fractions of OMCC (Fig. 8c), designated as M1–M4.[175] The biodegradable M2, presenting the best platelet activation, could reduce the APTT and exhibited rapid hemostatic efficacy in two injury models. The hemostatic mechanism of M2 was summarized from two aspects: physical and physiological hemostasis (Fig. 8d). Physical hemostasis was related to blood vessel blockage. The M2 sponges favored rapid blood absorption and had a number of hydrophilic carboxyl groups which were able to be combined with Fe^{3+} in hemoglobin to generate a gel to block the distal end of the capillary, conducive to expediting hemostasis. Physiological hemostasis was related to the activation of clotting factors and the adhesion and aggregation of platelets. When M2 was in contact with the bleeding wound, it activated intrinsic coagulation pathway through the increase of FXIIa. Furthermore, the porous structure of M2 could offer a scaffold for platelet adhesion and aggregation. The collagen/OMCC composite material effectively enhanced the hemostatic ability of single-collagen sponges and showed broad application prospects as an effective absorbable hemostat for hemorrhage control in various surgeries.

4.1.2. Gelatin

Gelatin is a class of denatured protein derived by thermal or enzymatic degradation or by partial acid or alkaline hydrolysis of collagen.[176] Gelatin is cheap and easily available and it has attracted much attention as a type of biomedical material due to its admirable characteristics such as good biocompatibility, biodegradability, and low antigenicity.[177] Gelatin is able to activate platelet aggregation and can be applied as an absorbable hemostat, as demonstrated by Xie et al. in a recent study.[178] Specifically, the authors developed an ultralight hemostatic gelatin sponge composed of continuous nanofibers via a conjugate electrospinning method.[178] The as-prepared gelatin sponge owned high surface area, porous structure, and nanofiber network, and exhibited good compressibility/water absorption capability and the ability to activate and gather platelets to hasten the platelet embolism formation. Nevertheless, sometimes only employing a single gelatin material for hemostasis will inevitably encounter the problem that the single gelatin material is not effective enough to control severe hemorrhage. Consequently, researchers began to focus on combining gelatin with different types of polymers to improve its thermal stability, mechanical properties, and hemostatic performance.[179,180] For instance, Luo et al. compared two kinds of in situ injectable hydrogels for preventing bleeding: the self-crosslinked gelatin hydrogel and the hyaluronic acid (HA)/gelatin hydrogel.[179] Compared with the gelatin hydrogel, the thermal stability of the self-crosslinked gelatin hydrogel and the HA/gelatin hydrogel was both enhanced. In addition, the hemostatic capability of the HA/gelatin hydrogel was validated to be greater than that of the self-crosslinked gelatin hydrogel in a liver-bleeding rat model. The combination of gelatin with other polymers not only represents an excellent strategy to construct gelatin-based materials with superior hemostatic property, but also can endow gelatin-based materials with more functions. In another example, Huang and co-workers synthesized several dry cryogel hemostats with interpenetrating polymer network via cryopolymerization of gelatin and dopamine.[180] The gelatin could accelerate bleeding cessation and the polydopamine played a crucial role in imparting antioxidant ability and photothermal antibacterial activity to the as-prepared cryogels. Moreover, the interpenetrating polymer network endowed the cryogels with strong mechanical property, favorable injectability, and shape memory property. In several animal incision models, the cryogels always exhibited the shortest hemostatic time and the least blood loss compared with normal gauze and gelatin hemostatic sponge. Especially, it could control deep narrow noncompressible bleeding and deep massive noncompressible bleeding in the liver defect deep narrow noncompressible bleeding model of rabbit and in the subclavian artery and vein complete transection model of swine, respectively. Moreover, the cryogels also presented satisfactory antibacterial effect and could promote wound healing. Later, Huang et al. rationally designed a shape-memory and biodegradable cryogel originating from gelatin and Ag NPs for hemostasis, antiinfection, and burn wound healing acceleration.[181] The as-prepared biodegradable cryogel caused significantly lower blood loss than commercial gelatin sponge in the noncompressible liver hemorrhage model of rat. It is expected that the fabricated cryogels with low cost, facile synthesis, and convenient carry and use may find various applications in the future. In addition to gels, microparticles with hemostatic activity can also be developed by crosslinking gelatin with other polymers. For instance, Sezer et al. proposed a feasible strategy to crosslink gelatin with sodium oxidized regenerated cellulose to yield hemostatic microparticles.[182] The obtained hemostatic microparticles displayed excellent biocompatibility and the ability to expedite bleeding cessation.

The biochemical properties of gelatin can be improved via chemical modification to further improve its applicability.[183–185] For example, Zhou et al. fabricated an adhesive by catalysis of TA-modified gelatin with transglutaminase.[183] The transglutaminase was able to induce a covalent binding between gelatin and the related amino acids in the tissue and catalyze the acyl transfer reaction between the lysine ε-amino group and the glutamine γ-carboxyamide group in gelatin. Moreover, the amino groups in the tissue could react with the carbonyl groups of TA and the hydrogen bonding could be produced between the amino groups in the tissue and the catechol hydroxyl groups in TA. All the three interactions enabled the as-prepared hydrogel to adhere to the tissue rapidly, accelerating bleeding cessation and wound healing. Furthermore, GelMA has been synthesized via adding methacrylate groups to the gelatin and the resulting GelMA can serve as a photocrosslinkable hydrogel.[186] Several researchers have developed photocrosslinkable hemostatic hydrogels based on GelMA.[187,188] For instance, Hong and co-workers prepared a photoreactive hydrogel by using GelMA, *N*-(2-aminoethyl)-4-(4-(hydroxymethyl)-2-methoxy-5-nitrosophenoxy)butanamide (NB) linked to HA (HA-NB), and lithium phenyl-2,4,6-trimethylbenzoyl phosphinate (LAP) (serving as a polymerization initiator).[187] After ultraviolet (UV) irradiation, the photoreactive hydrogel could undergo quick gelling and fixation to adhere to and seal the injuried cardiac walls and arteries. Moreover, the hydrogel was capable

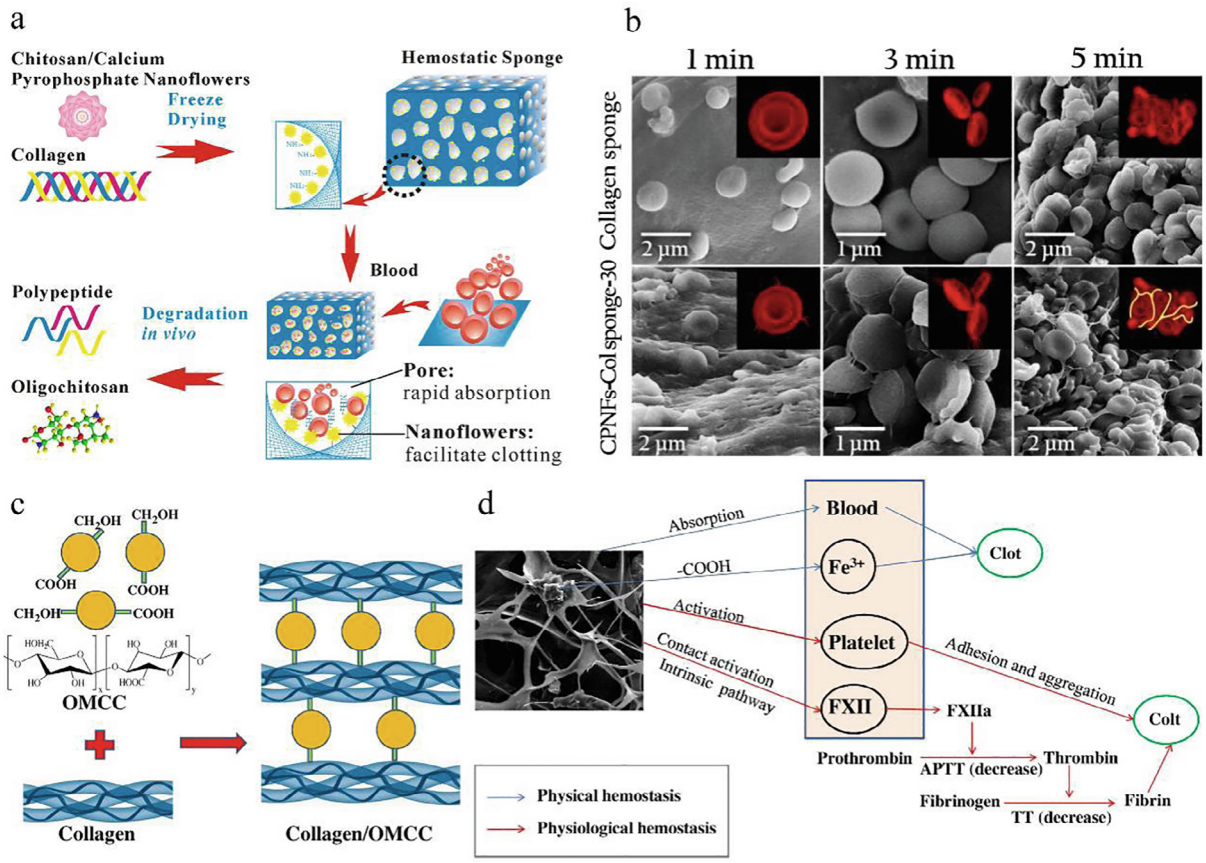

Fig. 8. (a) Schematic representation of the preparation process and degradation mechanism of CPNFs-Col sponge. (b) Scanning electron microscopy (SEM) images showing the interfacial interactions between RBCs and collagen sponge and between RBCs and CPNFs-Col sponge-30. (a and b): Reprinted with permission from Ref. [174]. Copyright 2017, Elsevier B.V. (c) Possible intermolecular interactions between OMCC and collagen in the collagen/OMCC. (d) Tentative hemostatic mechanism of M2. (c and d): Reprinted with permission from Ref. [175]. Copyright 2017, Elsevier B.V.

of preventing high-pressure haemorrhaging from cardiac penetration holes of pig hearts and from incision wounds of pig carotid arteries. Similarly, Cao and co-workers synthesized a biodegradable hydrogel using TA, GelMA, gallic acid-functionalized Ag NPs, and polyphosphate through the simple photopolymerization caused by UV light.[188] The hydrogel could be degraded at the wound site and release the polyphosphate to activate the clotting pathway. Besides, the hydrogel also displayed satisfactory antibacterial effect and huge potential in facilitating infected wound healing. However, the UV irradiation may induce oxidative DNA damage to cells, which will hinder the application of UV-crosslinkable hemostatic agents. To solve this tissue, Guo et al. developed a visible light-crosslinkable hemostatic bioadhesive gel containing reptilase and GelMA.[189] The GelMA could be in situ crosslinked via free radical polymerization in the presence of visible light with the help of Eosin Y (a visible light photosensitizer) to instantaneously seal the injured tissues and the reptilase (a procoagulant enzyme) could effectively transform fibrinogen into fibrin to accelerate hemostasis. The bioadhesive gel rapidly caused hemostasis on rat tail cut (about 34 s) and liver incision (about 45 s), showing its great hemostatic potential. Notably, Chen et al. combined GelMA, adenine acrylate, and $CuCl_2$ to prepare a self-healing, adhesive, and antibacterial hydrogel through the hydrogen bonding, covalent bonding, and coordination effect between Cu^{2+} and the carboxyl groups (from gelatin) for the promotion of diabetic wound healing.[190] The hydrogel exhibited excellent antibacterial and hemostatic effects in a liver injury model of mouse and accelerated skin wound healing in diabetic mice.

4.1.3. Keratin

Keratin is a kind of natural protein which is classified as intermediate filament, the cytoskeletal component of desmosome cellular junction.[191] The keratins are derived from cytoplasmic epithelia and epidermal appendages, such as hair, wool, feather, hooves, horns, and nails.[192,193] Owing to the excellent cellular attachment, biocompatibility, and biodegradability, keratins have been employed in wound healing, nerve regeneration, bone regeneration, hemostasis, and cell culture.[194–196] Theoretically, the earliest record on the use of human hair keratin for bleeding treatment is from a Chinese medical book in the 5th century, which mentioned that burnt human hair might reduce blood leakage and impede bleeding.[197] Till date, a variety of keratin products in the form of hydrogel, NP, sponge, and fiber have been used as hemostats.[193,194,197,198] The keratins can bind and activate platelets to prevent bleeding.[193] In addition, keratin-derived biomaterials are capable of considerably reducing plasma clotting lag time and promoting fibril lateral assembly to accelerate hemostasis.[198,199] Based on the hemostatic characteristic of keratin, Wang and co-workers synthesized an expandable keratin sponge based on the expandable property of polyacrylamide and the superb hemostatic capability of keratin for the hemostasis of a penetrating trauma.[200] This sponge achieved efficacious hemostasis in a penetrating liver hemorrhage of rat and a femoral artery transection hemorrhage of swine. Another related research

on keratin hydrogel conducted by He et al. is also worthy of attention.[201] The authors demonstrated that in situ injection of the keratin hydrogel after intracerebral hemorrhage surgery could improve the therapeutic effect by preventing postoperative rebleeding. Keratin can also be combined with other bioactive agents to construct materials with a variety of biomedical functions. For example, Li and co-workers prepared human hair keratin-conjugated insulin hydrogel to accelerate full-thickness skin regeneration and the hydrogel exhibited stronger hemostatic capability and better wound healing effect than the keratin hydrogel.[202]

Although keratin hydrogels show good hemostatic efficacy in these previous studies, the hydrogels are difficult to store and carry, and sometimes require preparation or mixing before use.[203] To address this issue, Luo et al. firstly extracted kerateine from human hair and then used it to prepare NPs via a modified emulsion diffusion technique.[197] The kerateine NPs considerably reduced the coagulation time and blood loss in the tail amputation and liver puncture models of rat.

4.1.4. Fibrin

Fibrinogen, fibrin, thrombin, and activated platelets are the key components of the hemostatic clot formation. Fibrin is the natural provisional protein matrix formed by its precursor, fibrinogen, and it plays an important role in the enzymatic cascade related to blood coagulation.[204] Fibrin sealant, consisting of fibrinogen and thrombin, is a topical hemostat, tissue adhesive, and sealant. It has been employed in the United States as a laboratory- or blood bank-derived product since the 1980 s.[205] In addition, fibrin glue is the earliest successful surgical sealant commercially available as Tissucol, Beriplast, Bolheal, and Biocol. However, its practical application is restricted due to its low strength, sometimes insufficient tissue-sealing ability, and risk of contamination with some viruses.[206–208]

Some researchers have constructed composite materials containing fibrin to achieve multiple antibacterial and hemostatic applications. To give an example, Sundaram et al. constructed a tissue adhesive chitin–fibrin gel with tigecycline-loaded gelatin NPs for preventing hemorrhage and controlling bacterial infection.[209] The prepared gel could form in situ in 1 min and showed outstanding tissue adhesive property and good cytocompatibility. The gel could also realize rapid hemostasis within 84 and 154 s under liver (oozing) and femoral artery (pressured) bleeding conditions. The tigecycline could be released continuously from the composite gel, which was beneficial for preventing bacterial infection. These results proved that the fibrin-based composite adhesive materials, in addition to their hemostasis property, also have the ability to load drugs and can successfully achieve drug delivery.

4.1.5. Silk fibroin

The FDA-approved silk fibroin (SF) is a natural biopolymer and has been extensively applied in the biomedical field, such as the use as biomaterials for implants and sutures.[210,211] SF is low-cost and can be obtained from various sources. It also provides tunable mechanical property and satisfactory biocompatibility/biode gradability for biomedical applications. As reported, the SF sponge has a notable effect on fostering platelet aggregation and can decrease blood loss.[212] Bai et al. rationally designed a silk-based sealant with immediate hemostasis ability and superior wet adhesion through introducing TA to SF.[213] In their study, the as-prepared silk-based sealant showed high intrinsic toughness, strong adhesion to wet tissues, and instant hemostatic ability (within 30 s). Therefore, the silk-based sealant could be used in suturelessly sealing tissues in dynamic and humid biological environments. Similarly, Zhu et al. fabricated a TA-SF-diclofenac potassium (diclofenac potassium, an antiinflammatory drug) hydrogel for use as a wound sealant.[214] The hydrogel showed strong wet adhesion ability, satisfactory hemostatic property in a tail truncation model of rat, and outstanding antiinflammatory effect in an animal tooth extraction model. In another appealing research, Wang and co-workers fabricated a double-network cellulose/SF hydrogel (CSH) with drastically enhanced mechanical strength via a green gas (CO_2)-mediated chemical crosslinking strategy in the absence of toxic crosslinking agents.[215] Cellulose and SF were firstly covalently crosslinked in NaOH/urea solution, which produced a primary network. Next, CO_2 gas was introduced to reduce the pH value and then the pH decrease caused ordered aggregation of cellulose chains and connected hydrogen bonding between these cellulose chains, resulting in the formation of hydrogels with improved mechanical properties (Fig. 9a). The CSHs had low hemolysis and could hasten blood coagulation and reduce blood loss. As displayed in the hemostatic test, for the CSH with 1 wt% SF (CSH-1), the hemostatic time was 105.25 ± 21.55 s and the blood loss was about 0.81 ± 0.10 g, which were better than gauze (216.25 ± 31.02 s, 1.83 ± 0.26 g) and comparable to the collagen-based products (90.25 ± 16.88 s, 0.89 ± 0.13 g) (Fig. 9b and c). Consequently, this work exemplifies the use of a green gas-mediated crosslinking strategy to fabricate mechanically robust and biocompatible hydrogels for hemostasis purposes. Although great efforts have been made to develop SF-based composite hemostatic materials, it is challenging to clarify the exact effects of SF itself in the composites. In addition, until now, the detailed hemostatic mechanism of SF is still not very clear. It has been reported that the gellable SF could form a physical barrier to block the bleeding site and SF might activate platelets and trigger the intrinsic blood clotting pathway to accelerate blood clotting.[212,216] Consequently, future studies concerning how the SF promotes blood coagulation are desirable.

4.1.6. Self-assembling peptides

Self-assembling peptide hydrogel hemostatic materials have received extensive attention due to their self-assembling characteristic and inherent biocompatibility.[217,218] An earlier study showed that self-assembled peptides could accomplish rapid and complete hemostasis through forming nanofiber barriers and concentrating blood components at the bleeding site.[217] RADA16-I is a representative self-assembling peptide, with the peptide sequence of CH_3CO-RADARADARADARADA-$CONH_2$.[219] Owing to its high tendency to form stable β-sheet structure, RADA16-I has the ability to spontaneously self-assemble into highly ordered nanofibers, which are beneficial for entrapping blood components like platelets and erythrocytes.[220,221] Additionally, the peptide molecules can transform into gels for being applied on bleeding sites to inhibit hemorrhage.[217] In addition to their fast and effective hemostatic property, self-assembling peptides also have an advantage that they can be degraded into carbamide molecules and then be eliminated from the human body.[218] To improve the direct application of self-assembling peptides to wounds, Hsu et al. developed a hemostatic bandage based on the RADA16-I nanofibers.[221] The bandage with great thermal robustness was observed to accelerate hemostasis in porcine skin wounds in comparison with normal gauze. However, the low pH value (around 3–4) of the RADA16-I solution is an inevitable disadvantage, which may hinder the biomedical application of RADA16-I. The acidic RADA16-I solution may result in cytotoxicity and even inflammation after direct injection.[218,222] Zhao et al. developed a type of peptide with pH-responsiveness, named RATEA16 (CH_3CO-RATARAEARATARAEA-$CONH_2$), via modifying the acidic amino acids (aspartic acid) in RADA16-I to threonine acid (a neutral amino acid) or glutamic acid (a weakly acidic amino acid).[223] Wei et al. found that compared with the RADA16-I solution, the RATEA16 solution had a substantially increased pH of 6–7.[218]

Furthermore, RATEA16 possessed rapid gelation ability and great biocompatibility. In the rabbit liver wound model, RATEA16 displayed a rapid blood clotting ability and achieved complete bleeding cessation within around 40 s. Besides the above two self-assembling peptides, Chen et al. developed an amphiphilic short peptide I_3QGK with low cytotoxicity and immunogenicity, which was able to self-assemble into long nanoribbons in the aqueous solution (Fig. 9d).[224] After being added with transglutaminase (TGase), the peptide solution underwent a sol–gel transition to form a hydrogel. The peptide solution presented a more efficient and rapid hemostatic effect through promoting platelet adhesion and gelling blood. In the liver wound experiment of rat, the hemorrhage was impeded rapidly when the I_3QGK aqueous solution was used to treat the bleeding wound (Fig. 9f). By contrast, bleeding was considerable in the control group (Fig. 9e). Moreover, Hao et al. validated the strong synergetic effect between I_3QGK and the natural polysaccharide *O*-carboxymethyl CS in accelerating blood coagulation.[225] These features of I_3QGK endowed it with great promise for clinical hemostasis applications in future.

4.1.7. Glutaraldehyde-crosslinked albumin

The glutaraldehyde-crosslinked albumin is a widely-used protein-based sealant without intrinsic hemostatic activity.[226,227] This sealant contains bovine serum albumin, which can be crosslinked by glutaraldehyde through the covalent interaction between the aldehyde groups of glutaraldehyde and the amine groups of albumin. It usually achieves hemostasis depending on its strong sealing and adhesive properties, and can thus serve as an effective sealant during operations on large blood vessels. BioGlue consisting of bovine serum albumin and 10 % glutaraldehyde has been approved by FDA.[228] Nonetheless, glutaraldehyde has a certain degree of toxicity and may kill cells in the surrounding tissues and need to be used with caution.

4.1.8. Thrombin

The fibrinogen can be cleaved by thrombin into fibrin and then the fibrin provides a hemostatic lattice to promote the aggregation of platelets and the formation of blood clots at the bleeding wounds. Therefore, thrombin can be utilized as an excellent hemostatic aid for wound treatment. At present, several thrombin-based hemostatic products have been approved by FDA, namely bovine thrombin, human thrombin, and recombinant thrombin. The antigenicity of bovine thrombin and the theoretic risk of viral transmission associated with the use of human thrombin pose formidable challenges to the clinical application of thrombin products. The recombinant thrombin was developed to avoid these risks. For hemostasis intention, the thrombin can be used alone, in combination with fibrin, or in conjunction with another hemostat.[229]

4.1.9. Other hemostatic peptides

After effortless chemical and enzymatic hydrolysis, collagen will be transformed into peptides.[230] The collagen has excellent hemostatic effect and peptides are the chief components of collagen, and therefore, the peptides that are derived from collagen may be an exceptional material for hemostatic application. Based on this fact, Ouyang et al. synthesized CS/tilapia peptides (obtained from collagen) microspheres (CS/TPM) by using CS to encapsulate tilapia peptides via an ionic crosslinking technique and then constructed a composite sponge (S-CS/TPM) for bleeding control using CS as the matrix and CS/TPM as fillers.[230] Compared with CS and CS/TPM, S-CS/TPM presented better hemostatic efficacy in the ear artery and femoral artery hemorrhage models of New Zealand rabbit. Recently, cationic peptides have become appealing for biomedical applications on account of their unique merits. Cationic peptides exert antibacterial effect by adhering to the negatively charged bacterial surfaces, leading to the disruption of bacterial membranes, the leakage of cytoplasmic contents, and the eventual bacterial death.[231,232] Additionally, the positively charged cationic peptides can interact with platelets and blood cells by electrostatic interaction to provoke platelet activation and blood cell aggregation. Zhu et al. developed a cationic short peptide (RRRFRGDK)-conjugated hybrid hydrogel dressing for hemorrhage control and antibacterial purpose.[233] They showed that conjugating the cationic peptide RRRFRGDK to the surface of the hydrogel (which was based on poly(ester amide)) could enhance the hemostatic and antibacterial capabilities of the hydrogel and avoid possible side effects of the peptide such as hemolysis and cytotoxicity. The as-fabricated composite hydrogel displayed robust mechanical strength, good water-absorbing capacity, and good cytocompatibility/hemocompatibility. The composite hydrogel had good adhesion capacity of platelets and blood cells and reduced hemostatic time in a mouse liver injury model. Moreover, the composite hydrogel could accelerate wound healing in an in vivo infected wound model. Moreover, inspired by mussels, Lu et al. synthesized thermo-responsive polypeptides through the ring-opening polymerization of α-amino acid derivatives of *N*-carboxyanhydride.[234] These polypeptides displayed excellent hemostatic performance and wound healing promotion ability in the osteotomy gap and skin incision models, and the osteotomy gap remodeling and skin incision healing were accomplished in all rats within 2–9 weeks. This study highlights the potential of using synthetic peptides to develop multifunctional biomedical materials for not only bleeding treatment but also for other purposes like wound care. The structure and function of synthetic peptides can be easily regulated due to its programmability, which is conducive to the design and development of the multifunctional materials based on synthetic peptides.

4.2. Polysaccharide-Based hemostatic materials

4.2.1. Chitosan

Chitosan (CS) was fabricated by *N*-deacetylation of chitin, the second most plentiful polysaccharide in nature.[235,236] CS has been validated to be a valuable material in the biomedical engineering and biotechnology fields due to its good biocompatibility, biodegradability, and wound healing effect. CS can foster blood coagulation through promoting platelet activation and erythrocyte aggregation, possibly because of its polycationic feature and its nonspecific binding to cell membrane.[237–239] Many researches have been implemented to clarify the details of the hemostatic mechanism of CS.[45,139,240] CS-based materials may be the most promising hemostats because of CS's effective blood coagulation potential, low cost, the abundance of its source material chitin, trouble-free storage and long shelf-life, antibacterial property, stimulatory effect on tissue regeneration, and biodegradability.[42,241] Commercially available CS-based hemostats such as HemCon bandage, Celox gauze, TraumaStat, and Chitoflex dressing have been widely applied in battlefield and civil emergence.[242–244] Although the hemostatic efficiency of CS has been well verified in in vitro and in vivo studies, it remains a large challenge in considerably enhancing its hemostatic capacity without compromising its advantages including biocompatibility and biodegradability. To address this issue, Pan et al. constructed porous CS@zinc alginate (ZnAlg) microspheres by introducing ZnAlg to CS to improve the hemostatic efficiency of CS.[245] In the rat tail amputation and liver laceration models, the hemostatic time for CS@ZnAlg was 134 ± 5 s and 73 ± 5 s, respectively, and the blood loss was 0.201 ± 0.011 g and 0.194 ± 0.012 g, respectively. Both of them were less than those of the CSMS group. In another work, Sun at al. fabricated porous chitosan-silica composite microspheres (CSMS-S) through loading MSNs to CS microspheres (CSMS) via the

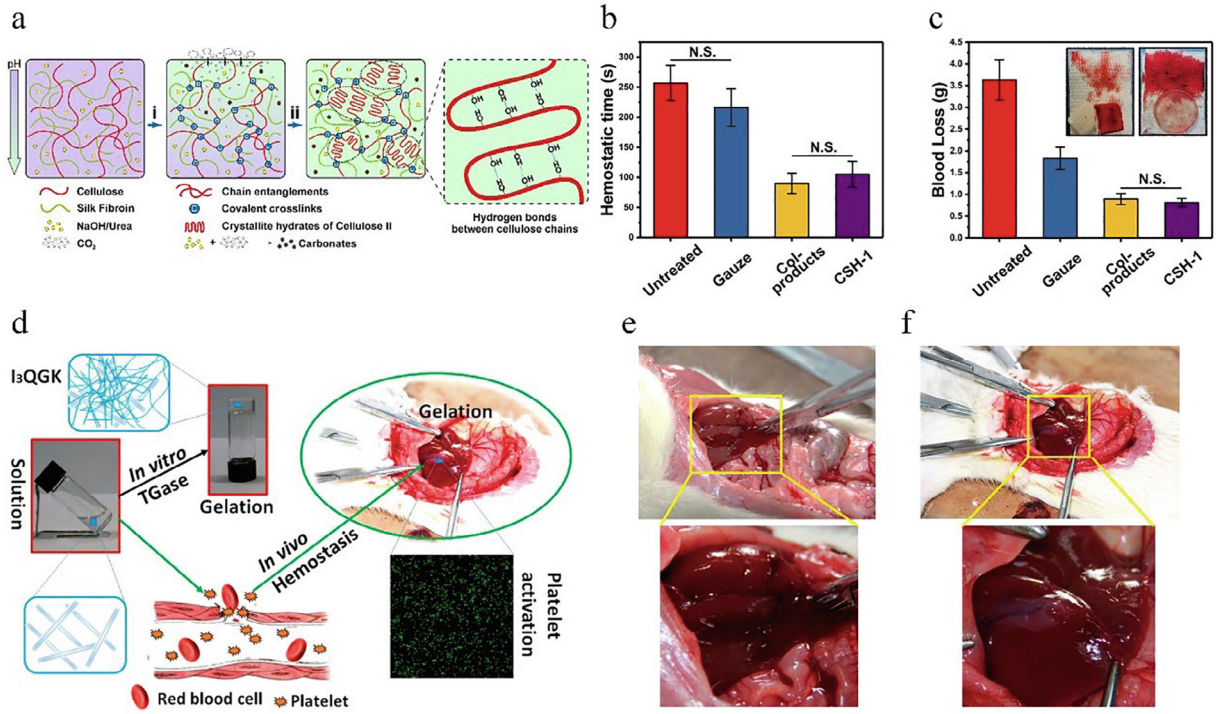

Fig. 9. (a) Schematic diagram of the preparation of double-network CSH. (b and c) Hemostatic time and blood loss evaluation results of CSH-1 and other control samples (gauze and Col-products) in a rabbit liver model. (a–c) Reprinted with permission from Ref. [215]. Copyright 2020, American Chemical Society. (d) Schematic diagram depicting the gelation procedure and hemostatic application of the short peptide I_3QGK. (e) Photographs showing the bleeding in the sagittal cut on the left lobe of rat liver without any treatment (the control group). (f) Photographs showing the stop of bleeding in the sagittal cut on the left lobe of rat liver treated with the I_3QGK aqueous solution (the I_3QGK group). (d–f) Reprinted with permission from Ref. [224]. Copyright 2016, American Chemical Society.

microemulsion, thermally induced phase separation, and surfactant templating technique.[246] The hemostatic capability of CSMS-S was drastically enhanced relative to the single component CSMS due to the synergetic hemostatic effects from MSNs and CS. These studies emphasized that the addition of inorganic antihemorrhagic constituents to the CSMS is an easy and practical alternative for improving the hemostatic efficiency of CSMS.

Some studies have also focused on the preparation and improvement of CS-based dressings for hemostatic application.[247–249] For instance, Saporito and co-workers prepared sponge-like dressings based on CS, glycosaminoglycan (HA or chondroitin sulfate), and tranexamic acid by lyophilization for trauma bleeding treatment.[248] The release of tranexamic acid was rapid, and it could act synergistically with CS to accelerate blood clotting. Furthermore, the glycosaminoglycan was conducive to improving the bioadhesive property of the dressings, thus promoting the contact between wound and wound dressing to heighten hemostatic effect. In another work, Huang et al. used calcium chloride ($CaCl_2$) as an initiator for clotting and two biomaterials (CS and squid ink polysaccharide) as carriers to construct a wound healing spongy dressing.[249] The squid ink polysaccharide could activate FXII to promote blood coagulation, contributing to the improvement of the hemostatic capability of the obtained spongy dressing. Compared with absorbable gelatin sponge and CS dressing, the spongy dressing showed a smaller hemorrhage volume and a shorter hemostatic time in rabbit ear artery, femoral artery, and hepatic artery bleeding experiments. Moreover, various kinds of active ingredients have also been employed to construct CS-derived dressings for bleeding control.[250–252] For instance, Seon et al. developed a CS dressing coated with recombinant batroxobin (a thrombin-like enzyme with coagulation capacity derived from snake venom).[250] The results demonstrated that the recombinant batroxobin could act in a synergetic manner with CS to promote blood clotting. Besides, Patil et al. incorporated calcium and silica NPs into a CS–gelatin xerogel to further enhance the hemostatic activity.[251] Sundaram et al. entrapped potassium aluminium sulfate (a vasoconstrictor) and $CaCl_2$ into CS hydrogel to augment the hemostatic activity of CS.[252] Besides, Choudhary and co-workers fabricated antibacterial and hemostatic scaffolds via incorporating a graphene–silver–polycationic peptide nanocomposite into CS for wound healing application.[253] The graphene provided unique mechanical property for the scaffolds, and the polycationic peptide and AgNPs endowed the scaffolds with high antimicrobial activity. Additionally, the hydrophilicity of the polycationic peptide and the large surface area of graphene provided good fluid absorption capacity for the scaffolds, which was beneficial to expediting hemostasis. These investigations on CS-based hemostatic dressings highlight that CS shows great promise in being used as an important material to combine with a variety of other components (including polysaccharides, synthetic polymers, enzymes, inorganic NPs, etc.) for improving the hemostatic performance of the single CS dressing.

Different from the way of improving hemostatic properties through the synergistic hemostatic effects of different components, Leonhardt et al. developed a composite hydrogel that could increase the surface area of CS to promote hemostasis.[254] They used β-cyclodextrin polyester hydrogel as a sacrificial macroporous carrier, which can be degraded under the physiological condition, to construct a CS-loaded cyclodextrin hydrogel, achieving an increase in the surface area of CS to elevate its hemostatic efficiency. The authors demonstrated from in vivo experiments that the CS-loaded cyclodextrin hydrogel exhibited a shorter hemostasis time and a considerably lower amount of blood loss as compared with two commercial hemostatic dressings, and was favorably biocompatible.

Unfortunately, although CS has been widely applied in the fabrication of hemostatic materials, it has a fatal deficiency that it can only be dissolved in acidic solutions. This deficiency severely hampers the biomedical applications of CS.[255] To settle this problem, researchers began to focus on the chemical modification of CS. The chemical modification of CS achieved through introducing functional groups to CS could improve its solubility and other properties without affecting its main functions.[255,256] For example, the carboxymethyl or alkyl groups can be introduced to CS to increase its solubility in neutral or alkaline solutions without compromising its cationic feature. As a result, the development of CS derivative-based hemostatic materials has emerged as a prevailing strategy to prepare effective hemostats.[257,258] To give an example, Li and co-workers developed a self-healing in-situ-injectable hydrogel based on the oxidized chondroitin sulfate and *N*,*O*-carboxymethyl CS for antibleeding and antiinfection applications.[259] In a recent study, Pang and co-workers rationally designed a mechanically strengthened tissue adhesive through the incorporation of chitin nano-whiskers into a hydrogel composed of carboxymethyl CS and dextran dialdehyde.[260] The mechanically strengthened tissue adhesive provided great promise for biomedical application due to its excellent hemostatic, antibacterial, biocompatible, and biodegradable properties, and it could also avoid undesired tissue adhesion, relieve inflammation, and accelerate wound repair. Zhang and co-workers developed a dodecyl-modified CS-coated pagoda-like multilayer microneedle patch for the applications of hemostasis and tissue fixation (Fig. 10a).[261] Inspired by the unique hierarchical microstructure of the stings/feet of the insects, the authors fabricated the multilayer microneedle patch via a step-by-step mold replication process, which provided the advantages of easy operation, high adjustability, and flexibility. The microneedle patch was able to fix onto various tissues through physical interlocking due to the existence of multilayer structure without worrying about the influence of big blood flow. Furthermore, the dodecyl-modified CS coating was able to anchor onto the cell membrane, inducing blood cell coagulation and promoting bleeding cessation. Further, satisfactory hemostatic effects were presented while treating the liver hemorrhage, spleen hemorrhage, and kidney hemorrhage in rabbits with the multilayer microneedle patch (Fig. 10b–e).

Additionally, Wang and co-workers synthesized and characterized a series of *N*-alkylated chitosan (NACS) with different degrees of alkyl group substitution and different carbon chain lengths of the alkyl groups, and subsequently fabricated corresponding NACS nanofiber membranes (NACS-NM) by an electrospinning technique (Fig. 11a).[262] The NACS-NM was not cytotoxic and could facilitate the activation of platelets and coagulation factors, probably due to the high surface area, porosity, hydrophobicity, and blood uptake of NACS-NM and the crosslinking structure of the nanofibers. This work develops a strategy to significantly improve the hemostatic property of CS via grafting hydrophobic groups. Moreover, Wang et al. combined quaternized CS with soy protein isolate to prepare a porous hemostatic sponge via chemical crosslinking and the composite sponge not only achieved a comparable hemostatic effect relative to the commercial gelatin sponge but also exhibited satisfactory antibacterial activity.[263] Very recently, Yin et al. fabricated a nanofibrous membrane using PVA and quaternary ammonium *N*-halamine chitosan (CSENDMH, obtained via grafting quaternary ammonium and *N*-halamine to the CS chain) for hemostasis and antibiosis (Fig. 11b).[264] The morphological and water-absorbing capability studies displayed that the membrane possessed a uniform bead-free network and porous structure similar to natural extracellular matrix along with high hydrophilicity. The hemostatic performance of PVA, PVA/CSENDMH, and PVA/CSENDMH-Cl (chlorinated PVA/CSENDMH) membranes were evaluated by in vitro whole blood clotting assay. The blood clotting index (BCI) is a relative parameter used to quantitatively estimate hemostatic property, and a lower BCI value shows the stronger hemostatic ability of a material. The BCI values for the above three types of membranes were decreased considerably in comparison with that of control group (Fig. 11c), indicating the good hemostatic capability of the three types of membranes. PVA provided superabsorbent nature, which was able to promote platelet aggregation and the following clot formation as displayed in Fig. 11d. For the membranes with CS derivative, i.e., PVA/CSENDMH and PVA/CSENDMH-Cl membranes, the formed clots appeared darker and the BCI value was lower compared with PVA membrane. The above result suggested that the quaternary ammonium groups and protonated amine groups of CSENDMH could attract the negatively charged residues on erythrocyte membranes, triggering strong hemagglutination, and these groups could facilitate platelet aggregation and adsorb plasma proteins and fibrinogen. Furthermore, the antimicrobial assay revealed the enhanced antibacterial ability of the PVA/CSENDMH and PVA/CSENDMH-Cl membranes against both Gram-positive and Gram-negative bacteria caused by the synergistic effect of quaternary ammonium and *N*-halamine group. This work emphasizes that grafting quaternary ammonium and *N*-halamine groups to the CS can provide great convenience for researchers to develop materials with enhanced hemostatic and antibacterial functions. In another research, as shown in Fig. 11e, Wu et al. prepared thiol-modified chitosan (TMC) via the reaction between mercaptosuccinic acid and CS and then immobilized AgNPs onto TMC via the in situ reduction of silver ions with tea polyphenols to afford a composite sponge (TMC/AgNPs) for staunching bleeding and preventing infection.[265] AgNPs acted as antibacterial agents in the process of hemostasis. The sulfhydryl groups of TMC could bind AgNPs to promote the immobilization of AgNPs and control the release rate of AgNPs, avoiding the cumulative toxicity of AgNPs. Additionally, the sulfhydryl groups could promote the crosslinking between CS molecules to form a complex network structure, which was able to trap platelets and RBCs for inducing blood coagulation.

Besides the preparation of hemostatic and antibacterial agents, the construction of CS-based adhesives can also be achieved via the chemical modification of CS. The introduction of catechol groups to CS is a well-established approach for synthesizing mussel-inspired hydrogel adhesives. Owing to their strong adhesive and cohesive strengths under a wet condition, mussel-inspired materials have attracted intensive attention from many researchers.[266–269] Dopamine is an important bioactive small molecule which can easily self-polymerize with oxygen as an oxidant under an alkaline condition.[267,270] The catechol in dopamine has a versatile reaction capacity favorable for the strong attachment to diverse inorganic/organic surfaces. Furthermore, the catechol group can be converted to quinone which can react with amines, thiols, and imidazole residues to form strong covalent bonds. Based on the above-mentioned properties of dopamine or catechol, numerous researchers began to introduce dopamine or catechol into the conventional hemostatic materials to endow them with good tissue-adhesive property and enhanced mechanical strength.[269,271–274] CS is one of the excellent candidate materials to combine with dopamine or catechol for developing ideal hemostatic agents.[275–277] For example, Yang and co-workers employed polyethylene glycol monomethyl ether modified glycidyl methacrylate functionalized CS (with better solubility than CS), methacrylamide dopamine, and zinc ion to prepare a multifunctional adhesive with both antibacterial and hemostatic functions.[276] In another work, to meet the challenges of coagulopathic hemorrhage/noncompressible hemorrhage, Zhao et al. developed expandable dry cryogels, which were based on polydopamine crosslinked CS, with the advantages of fast blood-sucking expansion and good biodegradability.[277] The shape of the dry cryogel could be easily fixed by

compressing, and the resulting shape-fixed cryogel could be injected into narrow, deep, and irregular bleeding site with the help of syringe and it could recover after absorbing the blood (Fig. 12a). In the liver trauma model of mouse, the standardized circular liver section model of rat (Fig. 12b), and the liver defect noncompressible hemorrhage model of rabbit (Fig. 12c), the cryogel displayed superior hemostatic effect than gelatin sponge and Combat Gauze.

Besides, the catechol moiety can be introduced into CS by the chemical modification approach due to the presence of amino groups in CS. A number of reports have underlined the superiority of developing potent hemostatic agents based on catechol-functionalized CS.[278–281] For instance, Huang et al. developed a catechol-conjugated CS hydrogel for treating intractable bone defects/bleeding.[278] The catechol-conjugated CS hydrogel could quickly form an integrated hydrogel to completely fill the defective areas and strongly adhere to the bleeding areas after being injected into the bone defective sites and irregularly shaped/internal hemorrhaging areas. In an ilium bone defect model of rabbit, the hydrogel caused quick hemostasis and significantly reduced blood loss. In another example, Shin et al. prepared hemostatic hypodermic needles whose surfaces were coated by partially crosslinked catechol-functionalized CS which could seal punctured tissues via undergoing an in situ solid-to-gel phase transition.[279] As dis-

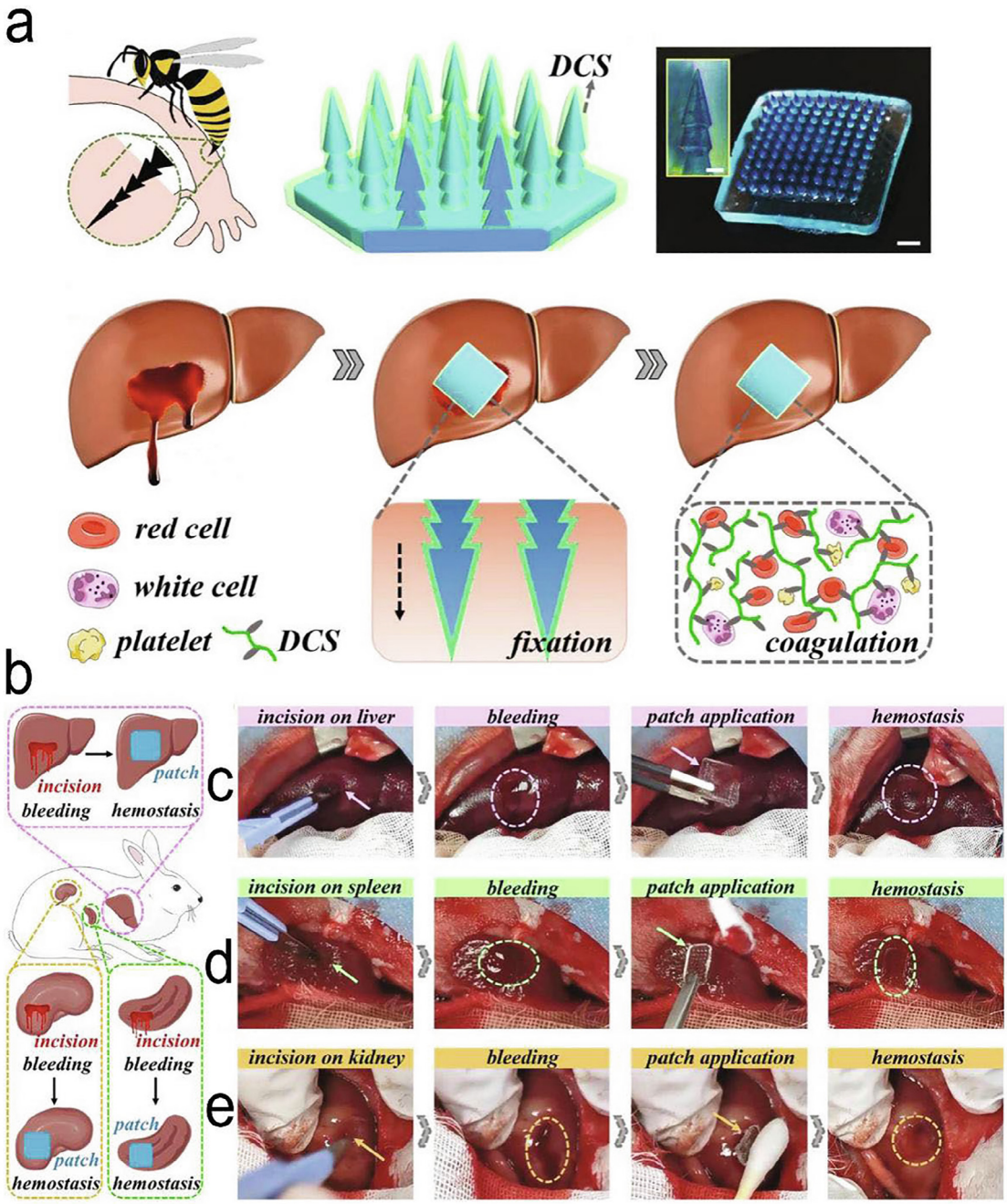

Fig. 10. (a) Scheme illustrating the design and hemostatic activity of the pagoda-like multilayer microneedle patch. (b) Scheme showing the bleeding control of the liver, spleen, and kidney of rabbits using the microneedle patches. (c) Photographs showing the establishment and treatment of the liver bleeding model of rabbit. (d) Photographs showing the establishment and treatment of the spleen bleeding model of rabbit. (e) Photographs showing the establishment and treatment of the kidney bleeding model of rabbit. (a–e): Reprinted with permission from Ref. [261]. Copyright 2021, Elsevier B.V.

played in animal models, the survival rate of the mice with hemophilia after syringe puncture of jugular vein was 100 %. Whereas, venipuncture with the bare needles caused the complete death of all the haemophilic mice due to excessive bleeding. Therefore, the self-sealing hemostatic needles are able to avoid bleeding following puncture, especially for patients with haemophilia or coagulopathy, which has important practical values in clinic. Likewise, to achieve reversible and controllable wet adhesion, Xu and coworkers reported a thermo-responsive wet adhesive called CS–catechol–poly(*N*-isopropyl acrylamide).[280] The poly(*N*-isopropyl acrylamide) (the thermal responsive polymer chain) and catechol were chemically tethered to the CS backbone to obtain the CS–catechol–poly(*N*-isopropyl acrylamide). The as-synthesized conjugate displayed a reversible gel–sol transition when the temperature was cycled above and below 35 °C (the lower critical solution temperature), and therefore could achieve a dynamic switch between wet adhesion and lubrication on skin surface. The as-synthesized conjugate-coated syringe needles presented instantaneous hemostasis after taking the needles away from the punctured sites in the mouse veins. In a recent report, Wu at al. developed smart indwelling needles possessing on-demand switchable hemostatic and anticoagulation abilities by modifying the inner and outer surfaces of the indwelling needles with an anticoagulant magnetic Fe_2O_3 NPs–dopamine-conjugated heparin and hemostatic catechol-functionalized CS coating, respectively.[281] The strategy reported in this study may inspire researchers to develop biomaterials and biomedical devices with switchable hemostasis and anticoagulation function in the future.

Besides the hemostatic needle, a hemostatic swab was also prepared by Shin et al. using a mussel-inspired chitosan–catechol conjugate (CHI-C) to coat common cotton-ball swabs.[282] In contrast to conventional cotton-based swabs that realize hemostasis through compression and blood absorption, the as-prepared swabs achieved hemostasis by generating the self-sealing membranes resulting from the rapid intermolecular interactions between CHI-C and whole blood proteins. It was reported that the blood protein/CHI-C composite sealing membrane could significantly reduce the bleeding of normal and coagulation disease (e.g., diabetes) models. Usually, 10 % blood loss of total blood volume (TBV) is lethal for a mouse, and thereby, the blood loss (%) was evaluated using a ratio of the measured blood loss in the experiment to 10 % TBV. In a mouse liver hemorrhaging model (Fig. 12d), the blood loss was 29.7 ± 3.7 % in the group of commercial cotton swabs, and it was markedly reduced to 8.8 ± 0.3 % if CHI-C-coated swabs were used (Fig. 12e). In the rat model, the results were similar and the blood loss was 12.7 ± 4.1 % in the

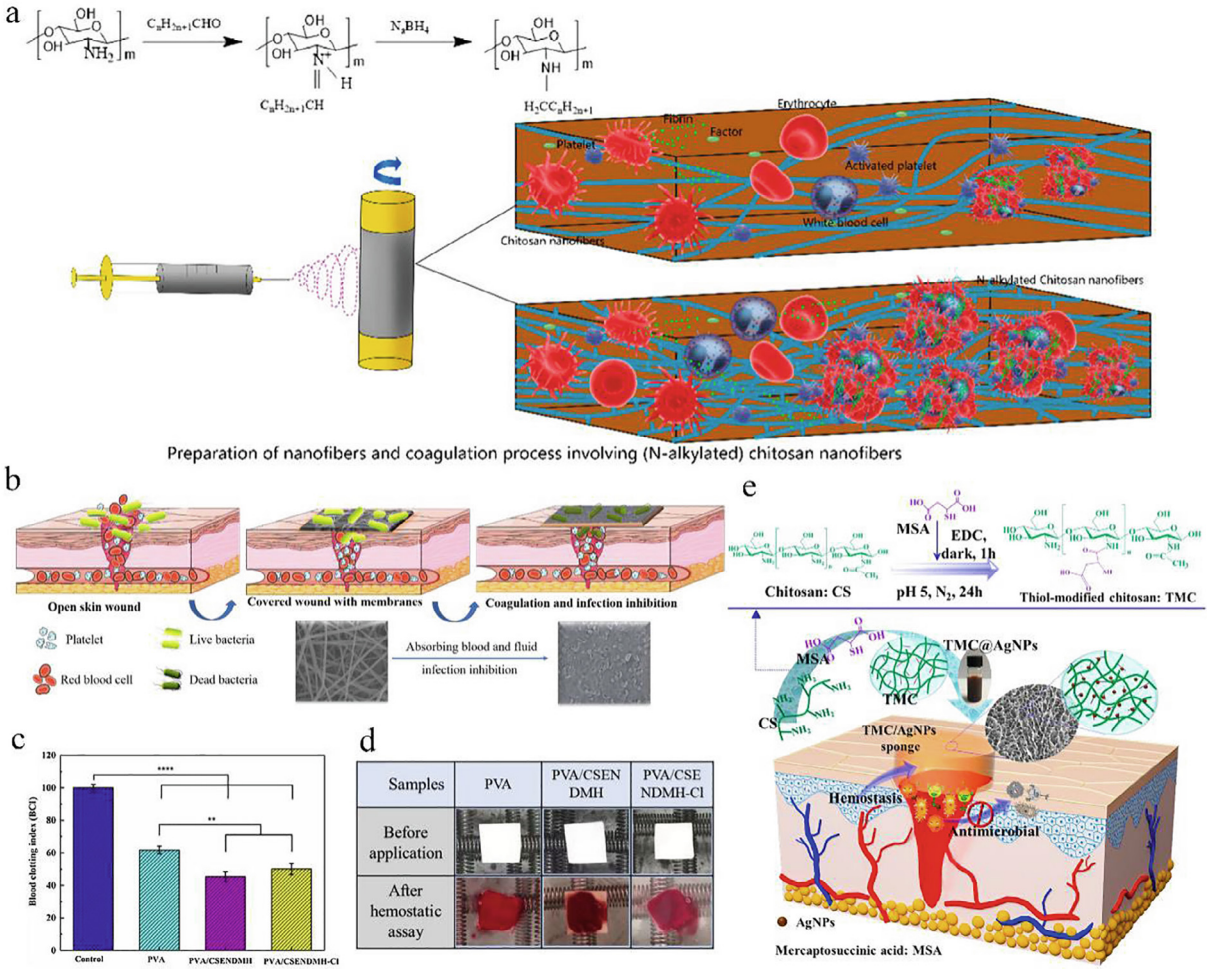

Fig. 11. (a) Scheme depicting the preparation of nanofibers and the coagulation process involving (*N*-alkylated) CS nanofibers. Reprinted with permission from Ref. [262]. Copyright 2018, American Chemical Society. (b) Schematic illustration of the hemostatic and antibacterial mechanisms of the nanofibrous membranes. (c) BCI values of the three membrane-treated groups and the control group (without nanofibrous membrane treatment) in a whole blood clotting assay. (d) Photographs displaying quicker clot formation on the PVA/CSENDMH and PVA/CSENDMH-Cl membranes than PVA membrane. (b–d): Reprinted with permission from Ref. [264]. Copyright 2020, Elsevier B.V. (e) Scheme presenting the construction of TMC/AgNPs sponge for hemostasis and antimicrobial applications. Reprinted with permission from Ref. [265]. Copyright 2020, American Chemical Society.

group of the uncoated swabs, but decreased to only 3.0 ± 1.0 % in the group of CHI-C-coated swabs (Fig. 12f). The inset photographs in Fig. 12f showed that there were more bloodstains on bare swabs than on CHI-C-coated swabs after contacting with liver hemorrhage sites. The hemostasis mechanism of the CHI-C/cotton swabs could be demonstrated by SEM morphological studies. Numerous microscale aggregates appeared and adhered to the surface of CHI-C/cotton composite microfibrils after blood contact (Fig. 12g). By contrast, no aggregate was found for the uncoated swabs (Fig. 12h). This study highlights the potential of using the catechol-conjugated CS with self-sealing property in developing simple but potent hemostatic swabs.

Besides the catechol groups, the pyrogallol groups can also be introduced to CS through chemical modification to fabricate tunicate-inspired hydrogel adhesives. To give an example, Sanandiya and co-workers prepared a pyrogallol-functionalized CS-based hydrogel as a sealant for internal tissues via conjugating gallic acid to CS.[283] The tunicate-inspired hydrogel showed 2-fold better adhesion capability in wet condition compared with fibrin glue in the in vitro adhesion test. Additionally, the hydrogel displayed a drastically stronger ability to promote blood clotting and platelet adhesion than the parent polymer CS. TA, which contains several catechol/pyrogallol groups, has been employed for constructing CS-based hydrogels that have robust adhesive and hemostatic capacities.[284,285] For example, Qiao et al. developed a hemostatic CS/TA/SF hydrogel via crosslinking CS and SF with TA, and the hydrogel could be instantly obtained following mixing CS, TA, and SF solutions (Fig. 13a).[284] The amide groups in SF and the hydroxyl groups and amino groups in CS could form hydrogen bonds with the abundant phenolic hydroxyl groups in TA, which led to the formation of a crosslinked CS/SF network. The network was expected to play an important role in impeding the escape of platelets and RBCs and absorbing wound exudates. The fabricated hydrogel displayed strong wet tissue adhesion, which was vital to promote wound closure and prevent blood leakage. The hydrogel stopped bleeding in liver hole, liver cut, heart hole, and tail cut of rats (Fig. 13b) and displayed satisfactory hemostatic effect in the ear artery bleeding, femoral artery bleeding, liver cut bleeding, and cardiac puncture bleeding models of rabbits.

However, the preparation of the tunicate-inspired hydrogels generally requires some extraneous enzymes (like tyrosinase and horseradish peroxidase) or oxidizing agents (like $NaIO_4$ and Fe^{3+}) to facilitate the hydrogel crosslinking.[286] To avoid the use of extraneous enzymes or oxidizing agents, Ma et al. developed a liquid bandage, i.e., a photoresponsive CS hydrogel (termed NB-CMC) obtained via modifying *o*-nitrobenzyl alcohol to the carboxymethyl CS backbone, for emergency wound care.[287] The NB-CMC could be easily formed without the introduction of any toxic crosslinking agent and extraneous photoinitiator. Under UV irradiation, the *o*-nitrobenzene in NB-CMC was converted to *o*-nitrosobenzaldehyde, which could crosslink with the amino groups on tissue surface, enabling the liquid bandage to have excellent tissue adhesive performance. In this way, the limitation of some current tissue adhesives (without the ability to effectively control hemorrhage and avert wound infection) could be overcome. Both in vitro and in vivo studies displayed the exceptional hemostatic effect of the liquid bandage resulting from its robust blood cell adhesion and blood coagulation capabilities. Besides, the liquid bandage was endowed with potent antibacterial activity originating from the carboxymethyl CS, which could cause the dysfunction or destruction of the bacterial plasma membrane. Furthermore, the liquid bandage also exhibited enhanced wound healing ability in a full-thickness cutaneous wound model of rat. The design of the liquid bandage represents an important advancement in developing hemostatic materials with multiple functions including strong adhesive property, as well as significant hemostatic and antibacterial performance for trauma emergency management. Nonetheless, it is worth noting that the liquid bandage needs to take effect under UV irradiation, which may become an obstacle against its practical use since UV irradiation is usually inaccessible for sudden bleeding.

4.2.2. Dextran

Dextran is a glucose polymer composed mainly of linear chains of α-1,6-linked glucopyranose residues, and it contains abundant hydroxyl groups for conjugation. In comparison with CS, almost all the commercialized dextran molecules are water-soluble, making them convenient for synthesis in aqueous media.[288] Dextran has some merits, such as wide sources, low cost, and good biocompatibility/biodegradability, and can be used to reduce the in vivo immunogenicity of enzymes or proteins.[289,290] These advantages make dextran attractive as a type of hemostatic material. For example, dextran can be utilized to prepare dressings with high water absorption capacity, thus allowing the dressings to absorb a large amount of water in the blood to concentrate clotting factors, RBCs, and platelets to accelerate clot formation at the bleeding site.[291] Bloxx is a typical dextran-based dressing composed of the dextran polymer fixed to the standard gauze laparotomy pad and it has been approved by FDA for local treatment of hemorrhaging sites and temporary management of severely hemorrhaging traumatic injuries/surgical wounds. Recently, instead of just using natural dextran, people began to pay attention to preparing hemostatic materials with various superior properties through the chemical modification of dextran.[292–294] For instance, Liu et al. prepared porous sponges (SHDP or SHDQ) of crosslinked HA/cationized dextran via the self-foaming process of HA and poly((2-dimethyl amino)-ethyl methacrylate)-grafted dextran (Dex-PDM) or partially-quaternized Dex-PDM with the sodium trimetaphosphate as a crosslinker.[292] The bleeding could be effectively stemmed by SHDP and SHDQ sponges in a mouse hemorrhaging liver model. Meanwhile, the SHDQ sponge displayed better hemostatic activity than the SHDP sponge, which might result from the more cationic charges of the SHDQ sponge. The result suggests that imparting more cationic charges to nonionic dextran through the introduction of polycations or cationic moieties represents an effective strategy to develop dextran-based hemostatic materials. In another research, Liu and co-workers fabricated an aldehyde dextran sponge with a pore size of ∼30–50 μm by lyophilization for hemorrhage control.[293] The aldehyde or acetal groups were introduced into the dextran sponge by dextran oxidation, which endowed the aldehyde dextran sponge with excellent tissue adhesion and high blood absorption capacity. The aldehyde dextran sponge achieved efficient hemostasis and notable blood loss decrease in the femoral artery, ear vein, and liver injuries of rabbit. The oxidized dextran (OD) with aldehyde groups also provides huge potential to react with gelatin and CS (or the derivatives of gelatin and CS with amine side groups) to form a range of hydrogels with multiple functions including bleeding control, bacterial infection treatment, and tissue adhesion.[295–298] Du and co-workers developed a hemostatic hydrogel dressing consisting of OD and hydrophobically modified CS.[297] It was verified that the precursor solution of the hydrogel exhibited the ability to coagulate heparinized whole blood in vitro. The in vivo hemostatic capability of the hydrogel was also proven in a rat liver hemorrhage model. Similarly, Gao and co-workers prepared a self-healing injectable hydrogel (termed OD/EPL hydrogel) through crosslinking OD with ε-poly-L-lysine (EPL, an antimicrobial peptide) for antimicrobial and hemostatic applications, and the crosslinking was based on the Schiff-base reaction between the aldehyde groups of OD and the amino groups of EPL (Fig. 14a and b).[298] The hydrogel encapsulated the base fibroblast growth factor (bFGF), which could be released sustainably to promote

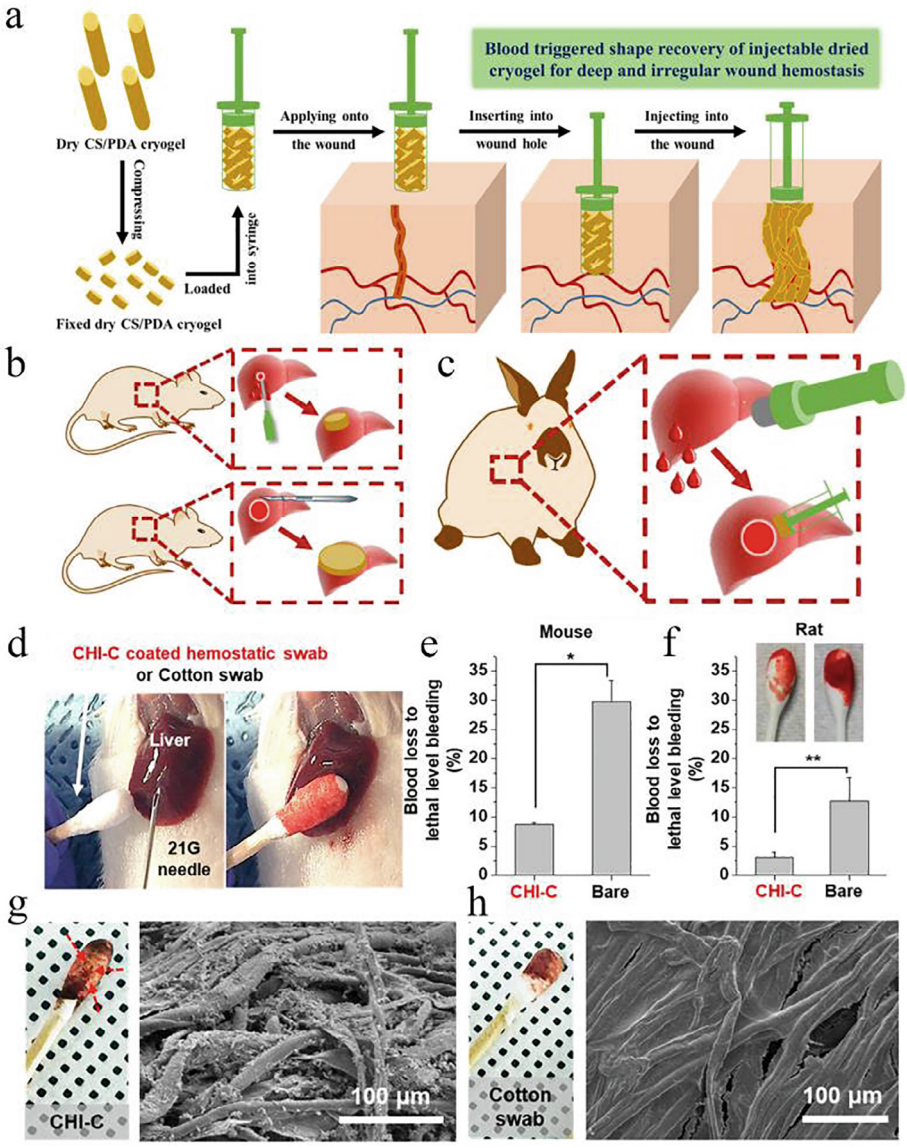

Fig. 12. (a) Scheme illustrating the use of expandable/injectable cryogel for treating deep and irregular wound bleeding. (b) Scheme illustrating the establishment and treatment of the liver trauma model of mouse and the standardized circular liver section model of rat. (c) Scheme illustrating the establishment and treatment of liver defect noncompressible hemorrhage model of rabbit. (a–c): Reprinted with permission from Ref. [277]. Copyright 2021, Elsevier B.V. (d) Photographs showing the evaluation of the hemostatic performance of the CHI-C-coated swab or the commercially available cotton swab following mouse liver puncture caused by 21 G needles. Blood loss to lethal level bleeding results from the punctured liver of (e) mouse and (f) rat following compressing gently with the CHI-C-coated swab or the commercially available cotton swab. The insets in (f) display the blood-absorbed CHI-C-coated swab (left) and commercially available cotton swab (right). SEM images displaying the surface morphology of the lyophilized (g) CHI-C-coated swab and (h) commercially available cotton swab following in vivo blood contact. (d–h): Reprinted with permission from Ref. [282]. Copyright 2018, American Chemical Society.

endothelial cell migration and angiogenesis, thus quickening wound healing. The OD/EPL hydrogel impeded hemorrhaging within only 6 min in a rat liver injury model. This work illustrates that the reaction between OD with aldehyde groups and other bioactive polymers with amino groups can be adopted for the construction of dextran-derived hydrogels for hemostasis application and beyond. In addition, dextran can also be utilized for the preparation of microgels for hemostasis.[299] The microgels are colloidal particles with the macromolecular network structures and with the sizes varying from tens of nanometers to several micrometers, and they have the ability to swell in water and capture a large amount of water.[300] This water absorption ability is important for rapid hemostasis. For example, Yan and co-workers adopted an emulsion polymerization method to prepare polymerized glycidyl methacrylate derivative dextran/acrylic acid (poly(DEX-GMA/AAc)) microgel particles as a kind of hemostatic agent.[299] It was revealed that the microgel particles showed significant swelling ratio of 68.95 g g^{-1} (Fig. 14d), which was 8.4 times larger than that of Arista (a clinically used microporous polysaccharide hemosphere). Besides, the gelation time of the microgel particles was very short (only 10–13 s). When the microgel particles were used on wounds, it absorbed water in blood and then rapidly formed a gelled film to stop bleeding (Fig. 14c). Compared with the commercial hemostat Flashclot, the microgel particles exhibited better in vitro clotting capability. Moreover, poly(DEX-GMA/AAc) did not lead to exothermic burn while absorbing water, which was superior to the performance of Flashclot. Both hemostasis time and blood loss were dramatically decreased by the microgel particles in the rabbit hemorrhage models of ear artery, ear vein, liver

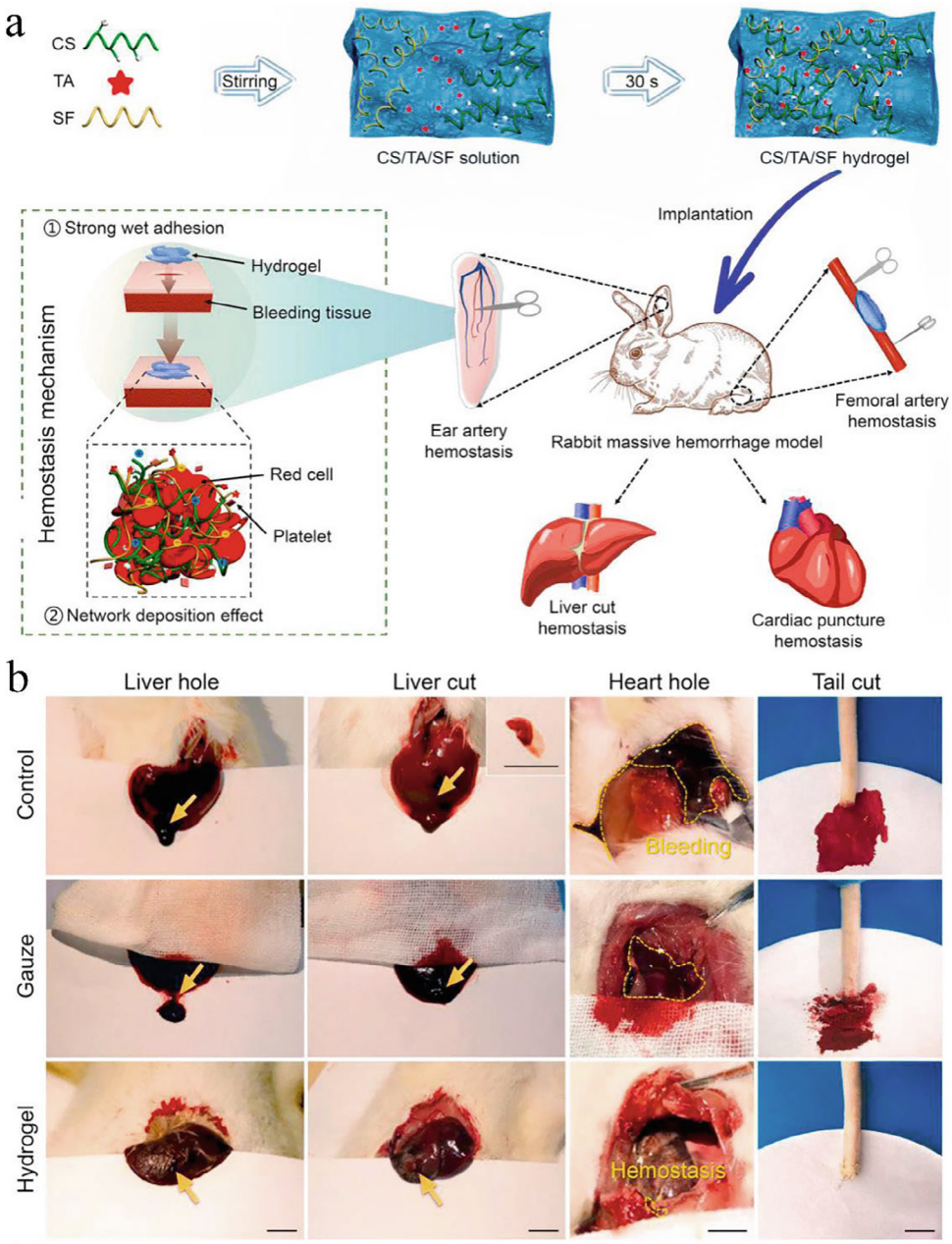

Fig. 13. (a) Scheme illustrating the fabrication, hemostasis mechanism, and hemostatic application of the CS/TA/SF hydrogel. (b) Photographs showing the treatment of different wounds of rats with gauze or the CS/TA/SF hydrogel. The untreated wound-bearing rats were set as control groups. Scale bar = 1 cm. (a and b): Reprinted with permission from Ref. [284]. Copyright 2021, Elsevier B.V.

artery, and femoral artery. This research identifies that microgel particles can be developed to be effective hemostatic materials.

4.2.3. Alginate

Alginate is a type of natural anionic polymer originating from seaweed, and has been frequently employed in drug delivery, wound healing, and tissue engineering due to its relatively low cost, mild gelation condition, and exceptional biocompatibility. [301–303] Some metal cations like Ca^{2+} can function as ionic crosslinking agents to crosslink alginate molecules to form gels based on the coordination between metal cations and alginate chains.[304] The formed gels facilitate the concentration of platelets and RBCs, thereby accelerating hemostasis. Besides, owing to its abundant carboxyl groups, alginate (and some of its derivatives) is negatively charged, which is able to activate clotting factors. [305,306] Based on the above properties, alginate is considered as a promising hemostatic material. However, the weak mechanical strength, poor chemical stability, and insufficient long-term efficacy severely limit the further hemostatic applications of alginate-based hemostatic agents, especially against massive hemorrhage.[307] To date, a broad array of alginate-based composites with satisfactory biocompatibility, enhanced hemostatic function, and even antibacterial effect have been developed for hemostasis.[308–313] For example, Jin et al. prepared a composite microsphere via sodium alginate, carboxymethyl CS, and collagen for bleeding treatment.[309] The results displayed that the composite microsphere could both halt bleeding and accelerate wound closure. In addition, the composite material had no obvious intracutaneous stimulation reaction and could be finally degraded in vivo. In a recent study, Jin et al. fabricated a berberine (an ammonium salt

with good antibacterial activity)-coated alginate-based composite microsphere.[312] The authors proved that berberine could enhance the hemostatic performance of the composite microsphere via promoting blood cell adhesion/aggregation. In another research, Huang et al. prepared a series of hemostatic microspheres by emulsion crosslinking of SF and sodium alginate.[313] The microspheres possessed rough surface morphology, which could promote the adhesion of platelets/RBCs, thus elevating hemostatic efficiency. Besides, Tong and co-workers prepared a poly(γ-glutamic acid)/alginate/AgNP composite microsphere via in situ UV reduction and emulsion internal gelation for hemostatic and antibacterial applications.[314] Compared with the conventional chemical reduction process, the in situ UV reduction method with alginate as a reductant and a stabilizer endowed the fabricated AgNPs with better antibacterial effect and biocompatibility. The composite microsphere had a hollow and porous network structure, which was important for its water absorption and blood coagulation behaviors. Meanwhile, as described by the authors, the presence of poly(γ-glutamic acid) also enhanced the hemostatic effect of the composite microsphere.

Apart from microspheres, other forms of materials like foams, sponges, hydrogels, and scaffolds have also been prepared by alginate for hemostatic applications.[307,315–317] Wang and co-workers prepared a series of PVA/alginate composite foams via crosslinking reaction and lyophilization process.[307] The PVA/alginate composite foams could quickly absorb plasma (due to their strong water uptake capacity) and stimulate hematocytes (due to the highly rough surface) to foster blood coagulation. In addition, the authors found that the composite foams with a higher alginate content displayed an amplified capability to potentiate thrombus generation and hematocyte adhesion/aggregation, which might be caused by the negative charges of alginate. Moreover, the composite foams displayed superb flexibility, shape-adaptive ability, and over 2000 % volume expansion property, which provided great convenience for them to entirely fill and adapt to different shapes of wound cavities. As a result, the composite foams may find applications in controlling massive hemorrhage and treating irregularly shaped/deep wounds. In another study, Che et al. fabricated a hemostatic/antibacterial sodium alginate/gelatin sponge via sequential spray-assisted layer-by-layer (LBL) assembly of HA and poly(hexamethylene biguanide) hydrochloride (PHMB) (Fig. 15a).[315] To synthesize sodium alginate/gelatin sponge, gelatin solution and sodium alginate solution were firstly mixed and lyophilized, and then the freeze-dried sodium alginate/gelatin was saturated in $CaCl_2$ ethanol solution and glycerol aqueous solution sequentially to prepare a sodium alginate/gelatin sponge. Later, a polyelectrolyte multilayer film was fabricated through spray-assisted LBL assembly. Based on the in vitro clotting test and in vivo liver injury model assessment, the sponge exhibited exceptional hemostatic activity through aggregating and activating hematocytes. Moreover, the HA layer endowed the coated sponge with better biocompatibility and the PHMB layer could kill the bacteria. When encountering bacteria, the HA layer could be degraded by the hyaluronidase which was secreted by bacteria, and then the PHMB layer could be exposed to kill bacteria. Based on the high versatility of LBL method, the HA layer and the PHMB layer can be easily replaced with some other types of oppositely charged layers to generate diverse forms of hemostatic systems with multiple functions for meeting specific application requirements. In another study, Yan et al. synthesized a mussel-inspired injectable hydrogel through an in situ crosslinking of catechol- and aldehyde-modified alginate and adipic dihydrazide-modified poly(L-glutamic acid), and the in situ crosslinking was caused by the Schiff base reaction between the aldehyde groups of the former and the hydrazide groups of the latter.[316] The introduced catechol groups could endow the injectable hydrogel with sufficient adhesive strength, which was favorable for the hydrogel adhering to the bleeding site to form a hemostatic barrier. The hemorrhage was quickly and effectively controlled in a rat liver bleeding model. In addition to organic polymers, incorporation of inorganic materials into alginate-based hydrogels is also an effective strategy to improve the physical and chemical properties of the hydrogels, making them more suitable for practical hemostatic applications. For example, Ai et al. designed a silver nanocluster-decorated alginate/SiO_2 nanofiber composite scaffold with excellent swellable, antimicrobial, and hemostatic properties.[317] The silver nanoclusters were selected in this work as antibacterial agents. The hemostatic scaffold possessed good hydrophilicity and a honeycomb porous structure, which endowed the scaffold with rapid swelling property (which could bring pressure to the blood vessel to hamper blood outflow) and high blood absorption capacity that were favorable for rapid hemostasis. As indicated in a rabbit femoral vascular injury model, the bleeding was immediately stopped in 10 s and the blood loss was only $\sim$ 0.1 g after the use of the composite scaffold. Since alginate can be developed into various forms of hemostatic materials, such as hemostatic microspheres, foams, sponges, hydrogels, and scaffolds, and it can also be combined with a variety of active components (including organic and inorganic materials) to prepare composite hemostatic agents with multiple biological functions, we believe that the alginate-based hemostatic materials may find more practical applications in the near future.

4.2.4. Hyaluronic acid

Hyaluronic acid (HA) is a type of linear anionic polysaccharide composed of a repeated disaccharide unit of (1–3)- and (1–4)-linked β-D-glucuronic acid and *N*-acetyl β-D-glucosamine monomer.[318] HA is one component of the extracellular matrix and displays excellent biocompatibility. Furthermore, HA is able to promote dermal regeneration and plays a crucial role in angiogenesis and tissue regeneration.[319–324] In recent years, the HA-derived hemostatic hydrogels have aroused the interest of many researchers due to their exceptional merits.[325–327] Zhu and co-workers constructed a rapidly hemostatic and sustainably antibacterial hybrid hydrogel by using aminoethyl methacrylate hyaluronic acid (HA-AEMA), methacrylated methoxy polyethylene glycol (mPEG-MA), and chlorhexidine diacetate (CHX)-loaded nanogels (CLNs) (Fig. 15b).[325] The hybrid hydrogel exhibited a 3D microporous structure and displayed admirable mechanical property, swelling ability, and low cytotoxicity. The hybrid hydrogel could function as a physical barrier to impede bleeding when used to treat injuries and then it could absorb a large amount of water in the plasma to concentrate blood cells and clotting factors, thus accelerating blood agglutination. In addition, the hydrogel showed a sustainable antibacterial activity for over 10 days due to the slow release of CHX. In an in vivo mouse model, the hydrogel displayed quick hemostasis capability and could significantly accelerate wound healing.

Besides, Wang et al. prepared a series of porous antioxidant cryogels from adipic dihydrazide-modified HA and dopamine with antibleeding and antibacterial functions.[326] The HA possessed a high water absorption capacity, contributing to the better hemostatic effect of the prepared cryogel than gelatin sponge and gauze when treating the liver trauma of mouse and the deep noncompressible liver hemorrhage of rat. The dopamine endowed the cryogel with great photothermal antibacterial ability, conducive to wound infection prevention. In another investigation, An et al. prepared a hydrogel system based on serotonin-conjugated HA for use as a hemostatic adhesive.[327] Serotonin is a blood coagulation mediator which can activate platelets,[328] and therefore lead to the release of platelet granules encompassing various hemostatic factors, like von Willebrand factor, platelet factor IV,

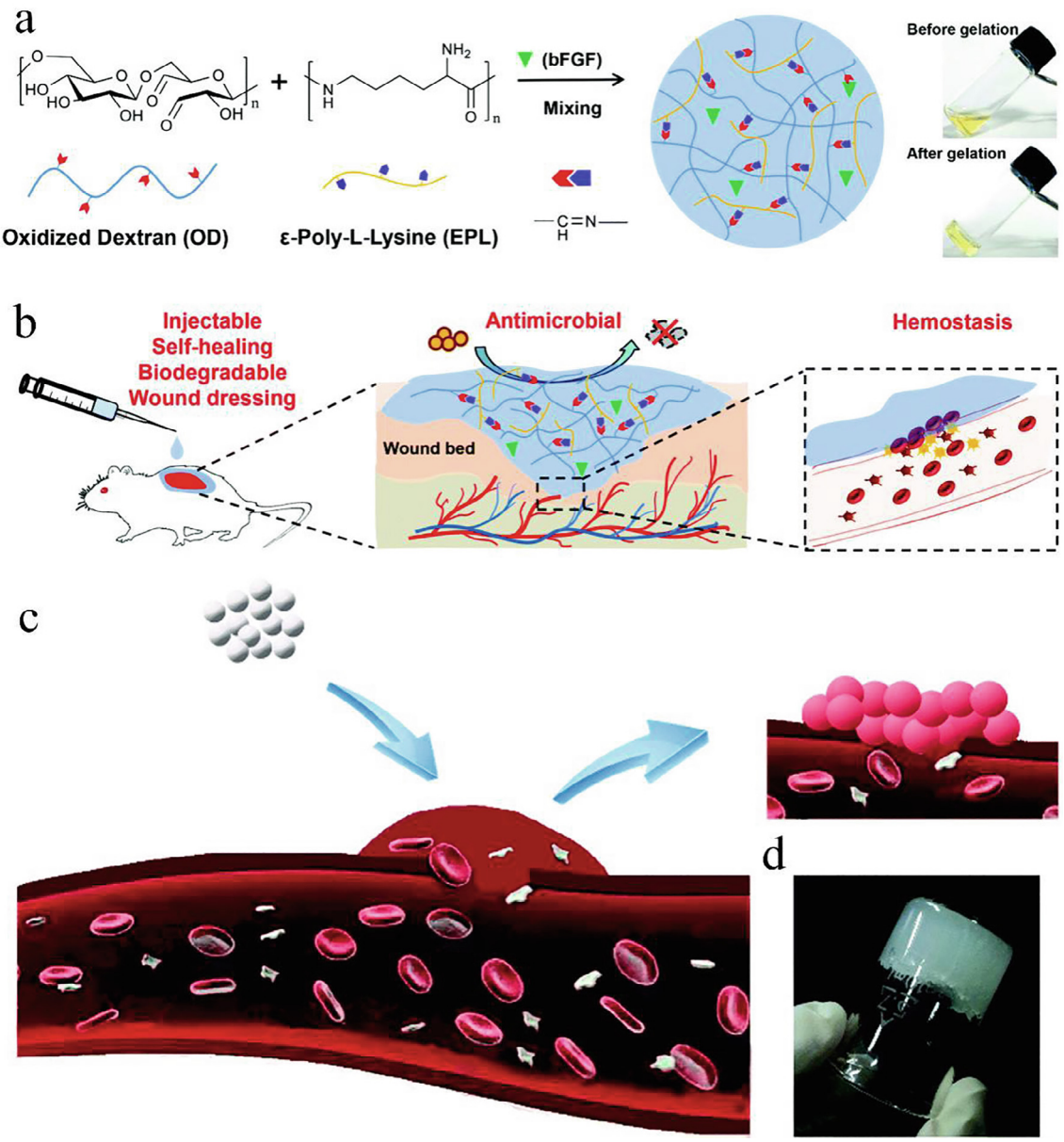

Fig. 14. (a) Schematic representation of the designed OD/EPL hydrogel. (b) Schematic diagram depicting the multiple functions (i.e., the hemostatic, antimicrobial, and wound healing promotion capacities) of the OD/EPL hydrogel. (a and b): Reprinted with permission from Ref. [298]. Copyright 2020, Royal Society of Chemistry. (c) Scheme illustrating the use of poly(DEX-GMA/AAc) microgel particles for hemostatic application. (d) Photograph of poly(DEX-GMA/AAc) microgel particles in a swollen state. (c and d): Reprinted with permission from Ref. [299]. Copyright 2017, Royal Society of Chemistry.

factor V, and fibrinogen. Compared with fibrin glue (a commercialized fibrin-based hemostat), the serotonin-conjugated HA hydrogel displayed drastically improved in vivo hemostatic activity when treating normal or hemophilic injuries due to the synergistic effect of the hydrogel (which acted as a physical barrier) and serotonin (which could activate platelets). Besides, as described by the authors, the hydrogel system averted abnormal tissue adhesion after hemostasis and offered significant clinical advantages as a multifunctional hemostatic adhesive.

Because sometimes a single HA hydrogel is not effective enough for dealing with complex bleeding situations, it is necessary to combine HA hydrogels with other functional materials or employ HA hydrogels to load bioactive small molecules to prepare composite hemostatic materials to meet the complicated clinical demands including hemostasis, antibiosis, tissue adhesion, etc.

4.2.5. Starch

Starch is composed of two fractions: one is amylose in which α-D-glucopyranose units are linked via α-1,4-glycosidic bonds, and the other is amylopectin made up of many short chains linked via α-1,6-glycosidic bonds.[329] Starch hemostatic materials are a kind of absorbable and biodegradable hemostatic agents. Microporous starch is a typical starch hemostatic agent with large surface area, high porosity, and exceptional water uptake ability. It could rapidly absorb the water in the plasma, thus concentrating blood cells and coagulation factors to promote the stop of hemorrhage.[330] In recent years, starch hemostatic agents have been widely used in surgical hemostasis for its low cost, broad sources, high hydrophilicity, and good biocompatibility/degradability.[331] Compared with other polysaccharide-based hemostatic materials such as CS, starch comes from plants and does not contain animal

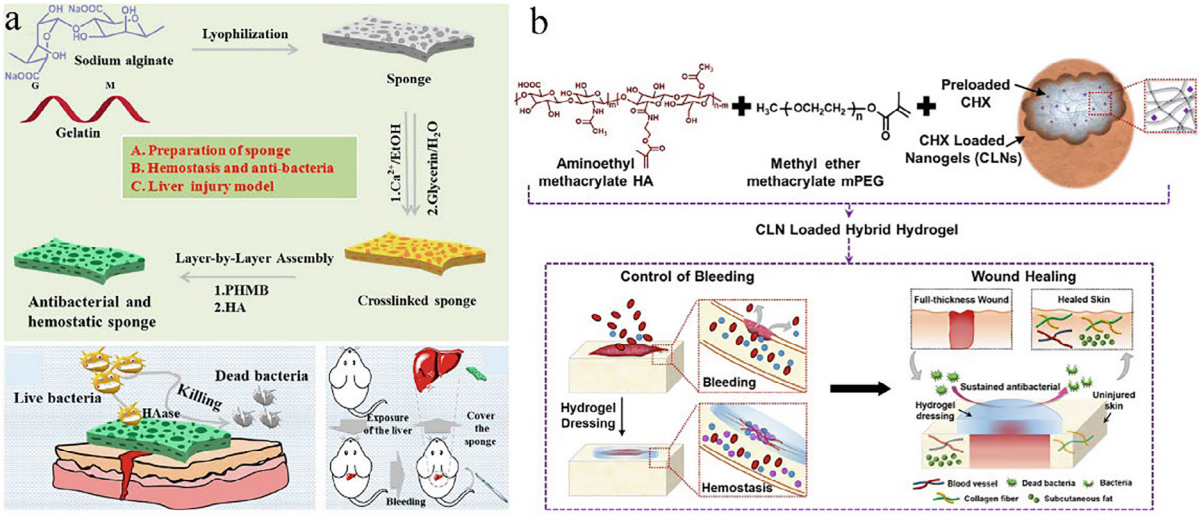

Fig. 15. (a) Schematic representation of the fabrication route and the hemostatic/antibacterial applications of the sodium alginate/gelatin sponge. Reprinted with permission from Ref. [315]. Copyright 2020, American Chemical Society. (b) Schematic diagram depicting the fabrication and bleeding control and wound healing promotion applications of the CLN-loaded hybrid hydrogel. Reprinted with permission from Ref. [325]. Copyright 2018, American Chemical Society.

or human blood components and proteins, avoiding the potential dangers of allergy and virus transmission. Moreover, it can be completely degraded in vivo, thus preventing the secondary damage caused by material removal.[332] However, the hemostatic performance of starch hemostatic agents is not enough to control severe bleeding because of its lack of effectual components to activate coagulation factors. Great efforts have been made in recent years to improve the hemostatic efficiency of starch hemostatic materials.[333–336] For instance, a type of cationic modified starch microspheres was developed by Chen et al. for hemostatic application.[335] Corn starch was first hydrolyzed by enzymes and then modified with quaternary ammonium groups through etherification reaction to obtain the cationic modified starch microspheres. The starch microspheres showed porous structure, superior swelling capacity (1008 %, ~4-fold higher than that of pure starch) and high water absorption ratio (304.2 %, ~4-fold higher than that of pure starch), all of which facilitated their physical hemostatic behavior. Besides, as indicated in in vitro studies, the cationic modified starch microspheres engendered the adhesion of platelets and RBCs, and then activated the blood chemical clotting system on account of their positive charges. The hemostatic capacity of the modified starch microspheres was significantly improved via the synergistic effect of the physical absorption hemostatic mechanism and chemical activation hemostatic mechanism. This study suggests that introducing positive charges into starch microspheres by chemical modification provides a chemical hemostasis pathway to improve the hemostatic property of starch hemostatic agents. Furthermore, endowing starch hemostatic agents with negative charges can also accelerate bleeding cessation based on the fact that negative charges could activate coagulation cascade via the intrinsic pathway to accelerate thrombin and fibrin clot formation.[34,337] For example, carboxymethyl starch is a derivative of starch, some of whose hydroxyl groups are modified into the carboxymethyl groups. On account of carboxymethylation, carboxymethyl starch became an anionic polysaccharide with good water solubility and biodegradability. At the same time, the negative charges of carboxymethyl starch could promote hemostasis. Chen and co-workers verified that carboxymethyl starch could accelerate not only the extrinsic clotting pathway but also intrinsic clotting pathway.[336]

In addition to the introduction of positive or negative charges to starch materials via chemical modification, researchers have also focused on the incorporation of various active hemostatic ingredients (such as calcium ion, thrombin, tranexamic acid, and hemostasis-related peptide) into starch hemostatic agents for activating the coagulation cascade process or inhibiting fibrinolysis, thus achieving rapid and effective hemostasis.[46,338–344] To give an example, Zhu and co-workers prepared calcium ion (Ca^{2+})-exchange crosslinked porous starch microparticles (Ca^{2+}-CPSMs) via inverse crosslinking emulsion, alcohol–alkaline treatment, and Ca^{2+}-exchange method for hemostatic application.[338] Through the coordination of physical hemostatic mechanism (rapid liquid uptake capacity and porous surface structure of Ca^{2+}-CPSMs) and the chemical activation of coagulation process via Ca^{2+}, the Ca^{2+}CPSMs achieved a satisfactory hemorrhage control in a tail amputation model of mouse. Similarly, Hou et al. synthesized a mesoporous zinc-calcium silicate- and microporous starch-based composite for hemostasis.[339] According to their study, incorporating mesoporous zinc-calcium silicate into microporous starch remarkably improved the degradability, water-absorbing capacity, and hemostatic ability of the composite. In addition, the composite could inhibit the growth of *Escherichia coli* due to the antibacterial effect of zinc ions. In another investigation, Liu et al. constructed a multilayer-structured absorbable microparticle (MQ_xT_y) composed of plant polyphenol and starch, for the efficient and safe control of bone defects with intractable and sustained hemorrhage.[340] Specifically, MQ_xT_y was prepared via coating multiple layers of TA and quaternized starch onto the starch microparticles via LBL assembly. MQ_xT_y exhibited good biocompatibility and superb degradability. In addition, the MQ_2T_2 with the outmost polyphenol layer was endowed with the capacity to induce RBC aggregation and platelet adhesion/activation, and thus it showed the best hemostatic performance. In a cancellous-bone-defect model of mouse, MQ_2T_2 exhibited advantageous hemostatic effect and markedly accelerated bone repair. In this study, a simple LBL technology was applied to modify the surface of starch microparticles to improve their hemostatic performance, which provides a practical approach for developing advanced hemostatic materials to treat intractable bleeding such as bone-defect-caused bleeding. In another example, Li and co-workers developed a 3D carrier to effectively control bleeding, based on the modified starch loaded with thrombin.[341] The incorporation of thrombin effectively enhanced the hemostatic activity of the composite and shortened the bleeding time in a rabbit ear injury model. In addition, consid-

ering that the current hemostatic materials commonly focus on the acceleration of the formation of blood clots, but ignore the inhibition of fibrinolysis, another crucial way to promote coagulation and elevate survival rate, Su et al. rationally designed an antifibrinolytic tranexamic acid-loaded crosslinked microporous starch (TACMS).[342] As proved by the authors, the addition of tranexamic acid to TACMS effectively inhibited fibrinolysis and increased the blood clot strength, therefore promoting blood coagulation.

Moreover, to ensure the successful use of a starch-derived hemostatic material for massive hemorrhage control, Yang et al. prepared a hemostatic sponge (TRAP-Sp) for noncompressible and massive hemorrhage control by immobilizing thrombin-recep tor-agonist-peptide (TRAP) onto the starch/polyethylene glycol (PEG) sponge, which was prepared by foaming process and crosslinking reaction.[46] The TRAP functioned as a strong platelet activator and induced platelet aggregation, and then promoted the formation of hemostatic plugs to stop bleeding. As demonstrated in rat liver defect noncompressible hemorrhage and artery uncontrollable hemorrhage models, the combination of TRAP and starch/PEG sponge endowed the TRAP-Sp with powerful hemostatic ability to hinder noncompressible and massive hemorrhage. Similarly, antimicrobial peptides can also be introduced into starch-based hemostatic agents to endow the hemostatic agents with antibacterial function, thus reducing the risk of wound infection. As an example, to elevate the antibacterial performance of starch sponges, Yang and co-workers developed a starch-based macroporous sponge which was immobilized covalently with an antimicrobial peptide KR12 via thiol–ene photo-click reaction.[343] The introduction of the antimicrobial peptide endowed the composite sponge with high antibacterial activity for preventing bacterial infection.

Moreover, starch materials have also been adopted to develop hemostatic adhesives. Cui et al. developed an injectable tissue-adhesive hydrogel, which was composed of dopamine, starch, and succinic anhydride.[345] The incorporation of dopamine endowed the injectable hydrogel with a high tissue adhesive strength and therefore the hydrogel could form a barrier at the bleeding site to avoid blood leakage.

4.2.6. Cellulose

Cellulose, one of the most abundant natural polysaccharide polymers in nature, is formed through repeated connection of D-glucose units and possess properties like good biodegradability and chemical modification potential. Cotton is a cellulosic polymer and cotton fabrics are acknowledged as a type of common hemostatic material for their softness, low-skin-irritating property, and good breathability.[346,347] Using cotton fabrics to press and bandage the wound is a simple and common way to deal with bleeding. The cotton fabrics have good water uptake capability, which allows them to absorb water quickly from the blood, consequently causing the concentration of RBCs, platelets, and clotting factors. Nonetheless, it is not perfect to impede bleeding using cotton fabrics due to their defects including limited hemostatic capacity and nonnegligible risk of adhesion with wounds. Carboxymethylation is an efficient approach to overcome the aforementioned defects of cotton fabrics.[348,349] The carboxymethylation of cotton fabrics can be realized by the interaction between specific acids and the hydroxyl groups of the cotton fabrics under alkaline conditions. Different from common cotton fabrics, carboxymethylated cotton fabrics are slippery and swollen after absorbing water, so it is easier for them to be removed from wounds.[350] Besides, the water uptake capability of the cotton fabrics may be further improved by carboxymethylation, possibly because of the increase of hydrophilic groups (e.g., carboxyl group).[351] More importantly, the acidic carboxyl groups of the carboxymethylated cotton fabrics will bond with Fe^{2+} in hemoglobin, producing a rubber block to close the blood vessel, and will stimulate the aggregation and adhesion of platelets to expedite blood coagulation.[349] In addition, carboxymethylation of cotton fabrics can also increase their antimicrobial activity.[352] As an example, Wang and co-workers obtained a modified cotton fabric with excellent water-absorbing ability by a carboxymethylation process.[353] The modified cotton fabric could rapidly absorb liquid, leading to the adhesion/aggregation of the blood cells to achieve blood coagulation. In addition, the modified cotton fabric-treated group had a shorter hemostatic time in comparison with the cotton fabric-treated group as demonstrated in a rat liver injury model.

Another vital downside of the commonly used cotton gauze is that it absorbs too much blood, which may cause unnecessary blood loss or even severe damage to human body. To this end, Wang et al. prepared a Janus-type cotton fabric via a facile spray-coating approach for bleeding control.[354] The Janus fabric was superhydrophilic on one side via being sprayed with carboxymethyl CS solution and was superhydrophobic on the other side constructed with paraffin. The hydrophilic surface was able to absorb blood and promote hemostasis, while the hydrophobic surface could reduce blood loss through averting the excessive absorption of blood. In vitro and in vivo tests demonstrated that the Janus fabric presented a better hemostatic capability than the cotton fabric. In conclusion, this work provides an easy and feasible strategy to achieve effective hemostasis without excessive blood loss only through changing the wettability of hemostatic cotton materials, which may promote the further development of hemostats.

Oxidized cellulose produced by oxidation of cellulose, can be endowed with various physical and chemical properties through the modulation of oxidizing conditions, including oxidant, pH, temperature, and reaction time.[355,356] Oxidized cellulose has been employed to treat hemorrhage in a range of clinical surgeries due to its superb hemostatic performance. It can stanch bleeding by physical and chemical processes. When oxidized cellulose is placed in the bleeding place, it can absorb liquid to concentrate blood cells and coagulation factors, and then it can also act as a physical barrier to block blood flow.[357,358] In addition, it can induce platelet aggregation due to its hydroxyl groups.[359] Unfortunately, the exact hemostatic mechanism of oxidized cellulose remains unidentified.[360] Oxidized cellulose can be nonregenerated (ONRC) or regenerated (ORC, with organized fibers formed prior to oxidation).[361] ONRC-based topical hemostatic materials showed seemingly better hemostatic performance relative to ORC-based topical hemostatic materials, but ORC is more suitable for clinical use based on the cytotoxicity results.[360,362] ORC is one of the most widely applied absorbable topical hemostats for controlling "internal" bleeding such as the intra-abdominal and intraoral hemorrhage.[363,364] It can be located in hemorrhaging spaces and then stays in situ to dissolve. Surgicel gauze, a typical ORC product for clinical use, can rapidly promote blood coagulation and effectively control bleeding during cerebral surgery.[363,365] Additionally, the low pH caused by its carboxylic acid groups is able to inhibit the bacterial growth.[366,367] To further improve the hemostatic performance of ORC, three kinds of carbon nanotubes (unmodified multiwalled carbon nanotubes, functionalized carbon nanotubes with carboxyl groups, and functionalized carbon nanotubes with amino groups) were separately grafted to ORC gauzes by Cheng et al.[367] In comparison with the original ORC gauze, the functionalized CNT-modified ORC gauze could dramatically reduce the bleeding time in ear artery and liver injury models of rabbit. The hemostatic property of ORC can also be improved only by changing the morphology of ORC physically without using the chemical grafting method or introducing any other material. To give an example, Wang et al. developed a powdered form of ORC, which was composed of the aggregates of ORC

fine fibers, for effective hemostasis.[368] Owing to their more favorable surface area and surface energetics, the ORC aggregates showed a stronger ability to promote coagulation compared with their constituent ORC fine fibers. In addition, when the particle size distributions of the ORC aggregates were similar, the ORC aggregates with higher sphericity values displayed better hemostatic efficacy. The results indicated that the efficacy of the powdered hemostat was related to its physical morphology, which may inspire researchers to further improve the hemostatic effect of powdered hemostats through the two means, i.e., regulating the surface area and modulating the surface energetics of the hemostatic materials.

Despite its numerous advantages and unique properties for controlling internal bleeding, ORC also displays several inherent disadvantages and is sometimes incompetent for certain injuries, constraining its clinical applications.[364] For instance, ORC with limited antibacterial property is unable to effectively kill acid-resistant bacteria and fungi.[369] Additionally, in vivo implanted ORC displays relatively slow degradation rate (4–8 weeks for complete degradation).[370,371] These disadvantages largely hinder the development and clinical application of ORC hemostatic materials.

During the past decades, the rapid development of nanoscience and nanotechnology has substantially changed the research of cellulose materials.[372] Nanoscale cellulose (nanocellulose) can be extracted from this naturally derived cellulose via the top-down chemically/mechanically induced deconstructing method.[373] Nanocellulose has abundant functional hydroxyl groups, which can bond together and then release water molecules in the aqueous solution to facilitate the formation of a fibrous network.[374,375] Nanocellulose can be divided into cellulose nanocrystals (CNCs), cellulose nanofibrils (cellulose nanofibers), and bacterial cellulose.[376] As a nanoscale material, nanocellulose possesses unique characteristics, such as special morphology/geometrical dimensions, high specific surface area, surface chemical reactivity, mechanical reinforcement, biocompatibility, and biodegradability. Zheng et al. prepared an injectable porous sponge (SSAD-CS) based on cellulose nanofibers (CNFs), CNCs, and SSAD.[377] As shown in Fig. 16a, the authors added SSAD powder to the CNC suspension, and then the mixture was ultrasonicated to obtain a uniform SSAD@CNC dispersion. The CNF suspension was subsequently added to the dispersion and the resulting SSAD@CNC/CNF mixture was then freeze-dried to generate the SSAD-CS. CNFs functioned as a backbone. SSAD not only acted as a bioactive component, providing exceptional antibacterial effect and biological activity, but also contributed to improving the stability of the sponge in water. CNCs helped SSAD disperse well in water. After injected into the injured sites on rat livers, the SSAD-CS, possessing good blood absorption ability and shape memory property, expanded rapidly and exerted pressure to the injured sites to hinder bleeding (Fig. 16b). In addition, the SSAD-CS was also able to rapidly concentrate platelets/RBCs to accelerate blood coagulation. In a noncompressible hemorrhage model, the SSAD-CS presented more effective hemostatic performance than the gelatin sponge.

In another example, Mendes and co-workers constructed a hemostatic cryogel through blending aldehyde-functionalized CNCs with platelet lysate.[378] The platelet lysate could effectively promote blood agglutination. The covalent crosslinking could be formed between the amine groups of the platelet lysate proteins and aldehyde-functionalized CNCs via Schiff base bonds, which enhanced the structure stability of the cryogel and averted cryogel disintegration during the cryogel hydration process. Compared with commercial gelatin sponge, the as-prepared cryogel absorbed more blood in a shorter time in vitro and displayed similar hemostatic performance in the in vivo liver defect model. Moreover, Cheng and co-workers fabricated hemostatic sponges with Janus feature based on CNFs and organosilanes through heterogeneous mixing and freeze-drying process.[379] The Janus sponge had both hydrophilic and hydrophobic layers. The hydrophilic layer could absorb water from blood to accelerate blood clotting, and the hydrophobic layer could inhibit blood penetration. The Janus sponge decreased blood loss by nearly 50 % in the femoral artery injury model and significantly prolonged the survival period in the carotid artery injury model, in comparison with the commercial gauze.

Oxidized nanocellulose can be made through selectively changing primary hydroxyl groups to carboxyl groups on the CNF surface.[380] Oxidized nanocellulose is bioabsorbable, biocompatible, and commercially available. Up till now, oxidized nanocellulose has shown potential in the development and fabrication of safe and valuable hemostatic materials.[381–383] As an example, Shefa et al. prepared a thrombin-loaded 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-oxidized cellulose nanofiber (TOCN)–silk fibroin scaffold (TOCN-SF-Th) via the reaction between the amino groups of SF or thrombin and the carboxyl groups of TOCN for bleeding control.[382] SF held the potential to facilitate the cell attachment and increase the blood coagulation activity of the scafford, and thrombin was involved in the coagulation pathway and helpful for rapid hemostasis (Fig. 17a). As displayed in Fig. 17b–d, TOCN-SF5-Th (5 indicated that the SF concentration used for the fabrication of the composite scaffold was 5 %) exhibited the highest blood absorption (5500 %) and significantly decreased hemostatic time (114 s) in a rabbit ear artery bleeding model. The reduction of blood loss and bleeding time of TOCN-SF5-Th was similar to the commercial hemostat (Floseal) in rat liver avulsion and tail amputation models, which indicated that the TOCN-SF5-Th could be a promising hemostatic candidate for topical hemostasis. In another study, Sultana and co-workers developed multifunctional freeze-dried scaffolds composed of TOCN and CS and loaded with an antibacterial compound lawsone.[383] The scaffolds could be prepared via the reaction between the amine groups of CS and the carboxyl groups of TOCN. The scaffolds achieved effective hemostatis and wound healing in the tail amputation model of rat and the full-thickness cutaneous-wound model of rat, respectively. Besides through covalent bonds, the active components with the amino groups can also be introduced into the carboxylated nanocellulose materials to develop multifunctional composites through the noncovalent interactions between amino groups and carboxyl groups. As an example, in 2018, Liu et al. developed a green nanocomposite hydrogel (CNF/G/Ag) based on an interpenetrating polymeric network via introducing gelatin and aminated AgNPs to carboxylated CNFs.[384] The interactions among the multiple components caused the formation of an interpenetrating polymeric network, which eventually led to the formation of noncovalently (via the formation of dynamic ionic bridges between the amino groups of aminated AgNPs/gelatin and the carboxyl groups of carboxylated CNFs/gelatin) crosslinked hydrogel CNF/G/Ag. The CNF/G/Ag revealed good self-recovery, mechanical, and antibacterial properties, as well as satisfactory hemostatic performance, which were beneficial for wound healing.

In a recent study by Yuan and co-workers, a hemostatic nanocomposite (OBC/COL/CS) was developed through coupling cationic CS to anionic oxidized bacterial cellulose (OBC) via electrostatic attraction in the presence of collagen (COL) (Fig. 17e).[364] Owing to the synergy of OBC, COL, and CS, the OBC/COL/CS nanocomposite showed greater blood clotting activity, increased adhesion of platelets and erythrocytes with lower blood loss, as well as ultrafast cessation of bleeding, relative to the Surgicel gauze. In addition to excellent hemostatic capacity, OBC/COL/CS also possessed good cytocompatibility. The fibroblast morphology was presented by calcein acetoxymethyl ester (calcein-AM) stain-

ing after culturing the fibroblasts on composites for 1, 2, and 3 days (Fig. 17f). The corresponding results revealed that the fibroblasts were scarcely attached to Surgicel and OBC since the majority of the cells were round in shape. By contrast, the cells on OBC/CS or OBC/COL/CS held normal morphology and could adhere to the material surface, displaying a strong proliferative ability. The considerable cytotoxicity of Surgicel and OBC gauzes might be related to the low pH created by the free carboxyl groups of Surgicel and OBC gauzes. However, in OBC/CS and OBC/COL/CS, the acidity of OBC could be neutralized through the amino protonation of CS. Based on this research, we speculate that it is an easy strategy to combine OBC with CS by electrostatic attraction for preparing composite biomaterials with better hemostatic effect and biocompatibility, which provides a solution to avoid the adverse effect of free carboxyl groups of OBC.

Other cellulose derivatives have also been used to prepare hemostatic materials. For instance, hydroxyethyl cellulose (HEC), a kind of nonionic cellulose ether, possesses good biocompatibility and ultrahigh water retention capability.[385] The plentiful hydroxyl groups also endow HEC with facile modification and conjugation properties.[386] Wang and co-workers prepared a quaternized HEC/mesocellular silica foam (MCF) hydrogel sponge (termed QHM) by one-pot radical graft copolymerization for hemostatic and antibacterial applications.[387] The quaternization could endow HEC with potent broad-spectrum antimicrobial ability and good blood cell/fibrinogen adhesion property. The addition of MCF into QHM further activated FXII to accelerate blood coagulation (Fig. 18a). A series of QHMs were obtained via the introduction of different amounts of MCF into the hydrogels. The QHMs presented instantaneous water-triggered expansion and superabsorbent capability, and hence facilitated the concentration of blood components. As confirmed by hematoxylin and eosin (H&E) staining, a number of blood cells could be trapped into the pores of the QHMs, elevating blood cell aggregation (Fig. 18b). In addition, the QHM1 showed decreased blood loss than commercially available hemostats in a noncompressible bleeding model of lethal rabbit liver defect. Moreover, the QHMs also possessed excellent antibacterial activity and satisfactory cytocompatibility.

4.2.7. Other polysaccharide-based materials

Besides the above introduced polysaccharides, a number of researches have focused on the use of other polysaccharides for the construction of hemostatic materials.[388–391] As an example, Zhang and co-workers prepared an injectable and self-healing agarose-based hydrogel with pH-responsive property by dynamic Schiff-base linkages formed after mixing the agarose–ethylenediamine conjugate solution and the dialdehyde-functionalized PEG solution.[388] It was revealed that the agarose-based hydrogel had short gelation time, interconnected porous morphology, high mechanical strength, and superb deformability. The hydrogel was capable of efficiently stanching the severe trauma bleeding in in vivo hemostatic experiments on rabbit livers.

Carrageenan is also an appealing hemostatic material. It is a linear sulfated polysaccharide polymer containing alternating β-(1,3)- and α-(1,4)-linked galactose residues. Carrageenan has a similar structure to that of natural glycosaminoglycans, and it is obtained via extraction of certain classes of red seaweeds. Kappa carrageenan has one sulfate group per disaccharide unit and can be

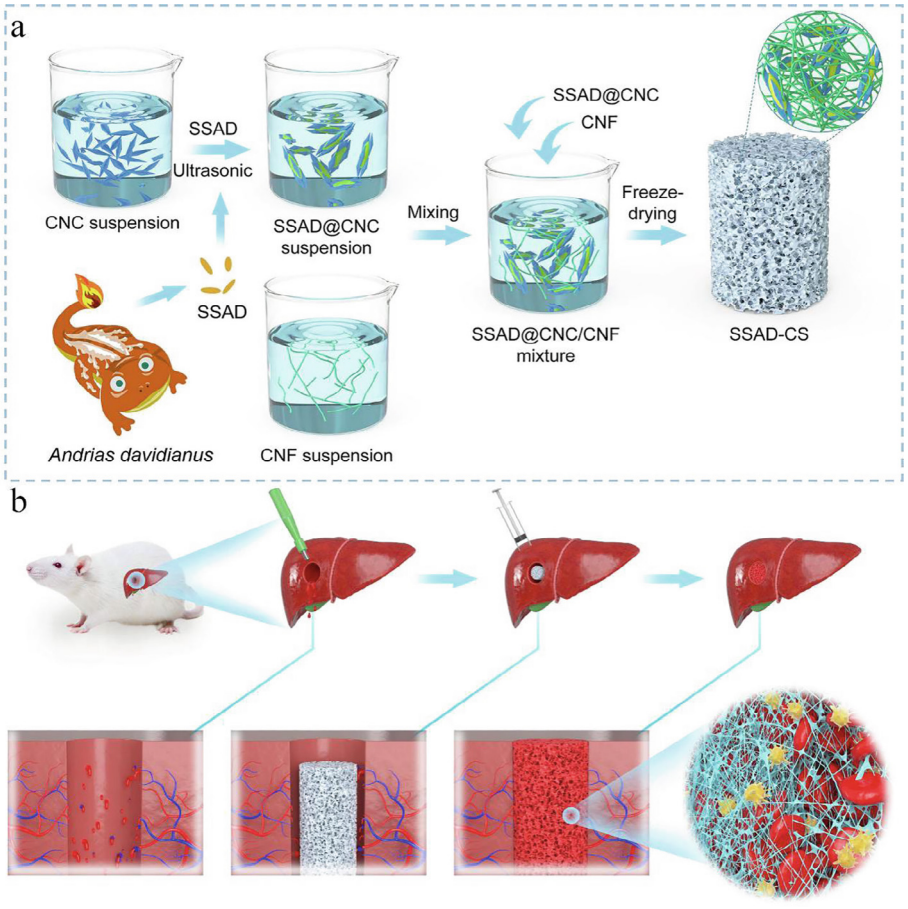

Fig. 16. (a) Schematic diagram showing the preparation route of SSAD-CS. (b) Schematic illustration presenting the hemostatic effect of SSAD-CS on a noncompressible torso hemorrhage model. (a and b): Reprinted with permission from Ref. [377]. Copyright 2021, Elsevier B.V.

utilized to fabricate thermotropic and ionotropic gels.[389,390] Lokhande and co-workers reported an injectable nanoengineered hydrogel composed of kappa carrageenan and two-dimensional nanosilicate for wound healing and tissue regeneration.[391] In another example, Zhong et al. examined the pro- or anti-inflammatory effects and hemostatic activity of a bioflocculant, MBF-15, an exopolysaccharide extracted from a type of alkaliphilic bacteria.[392] The MBF-15 held the antiinflammatory property and exhibited a higher hemostatic activity than CS as demonstrated in a rat model. Besides, Roy and co-workers reported a poly(*N*-vinyl imidazole)-crosslinked β-cyclodextrin hydrogel, which could realize rapid hemostasis in the major renal arterial hemorrhage model of rat.[393]

4.3. Synthetic polymers for hemostasis

4.3.1. Polyethylene glycol (PEG) and hyperbranched polyglycerol

As a hydrophilic synthetic polymer, PEG has good biocompatibility, nonimmunogenicity, and superb structural flexibility, and has thus been widely used in various biomedical fields.[394,395] One of the common biomedical applications of PEG is to prepare sealants, which can not only seal tissues, but also promote hemostasis due to their ability to seal blood vessel in the form of hydrogel.[10,396] The commercial synthetic sealants are mostly PEG-based, including Progel, DuraSeal, and CoSeal.[397] Nevertheless, there are some safety concerns in the use of PEG-based sealants, including possible allergic responses and adverse swelling, which may result in nerve compression.[10] Recently, Daristotle et al. developed a surgical sealant by incorporating nanoscale-to-microscale silica particles into the polymer blend of PEG and poly(lactic-*co*-glycolic acid).[398] The incorporation of nano-to-microscale silica particles endowed the surgical sealant with better flexibility, wet tissue adhesion, higher burst pressure, and enhanced hemostatic efficiency, without causing evident increase of cytotoxicity/local inflammation. These results suggest that the strategy of incorporating nanoscale/microscale inorganic particles into organic polymer systems may represent a universal approach to enhance the mechanical properties and hemostatic performance of the organic polymer systems. In another study, Xia et al. reported a hybrid hydrogel composed of PEG and HA stabilized via disulfide bonds and thiourea–catechol coupling for treating upper gastrointestinal hemorrhage.[399] The hybrid hydrogel displayed rapid gelation rate, sufficient mechanical property, and robust blood coagulation capacity. Furthermore, the hybrid hydrogel not only staunched upper gastrointestinal hemorrhage in pigs, but also could stay adherent and achieved sustained hemostatic effect at the wound site for 48 h, indicating the huge potential of the hybrid hydrogel as a hemostatic agent for controlling upper gastrointestinal bleeding. In addition, Bu et al. reported a tetra-PEG hydrogel sealant based on the reaction between tetra-armed poly(ethylene glycol) succinimidyl succinate and tetra-armed poly(ethylene glycol) amine for hemorrhage control.[400] The resulting hydrogel displayed high mechanical strength, strong tissue adhesion, rapid gelation rate, controllably dissolvable and quickly degradable properties, satisfactory hemostatic capability, and outstanding biocompatibility, indicating its potential to function as an effective hemostatic agent for controlling visceral hemorrhage in vivo.

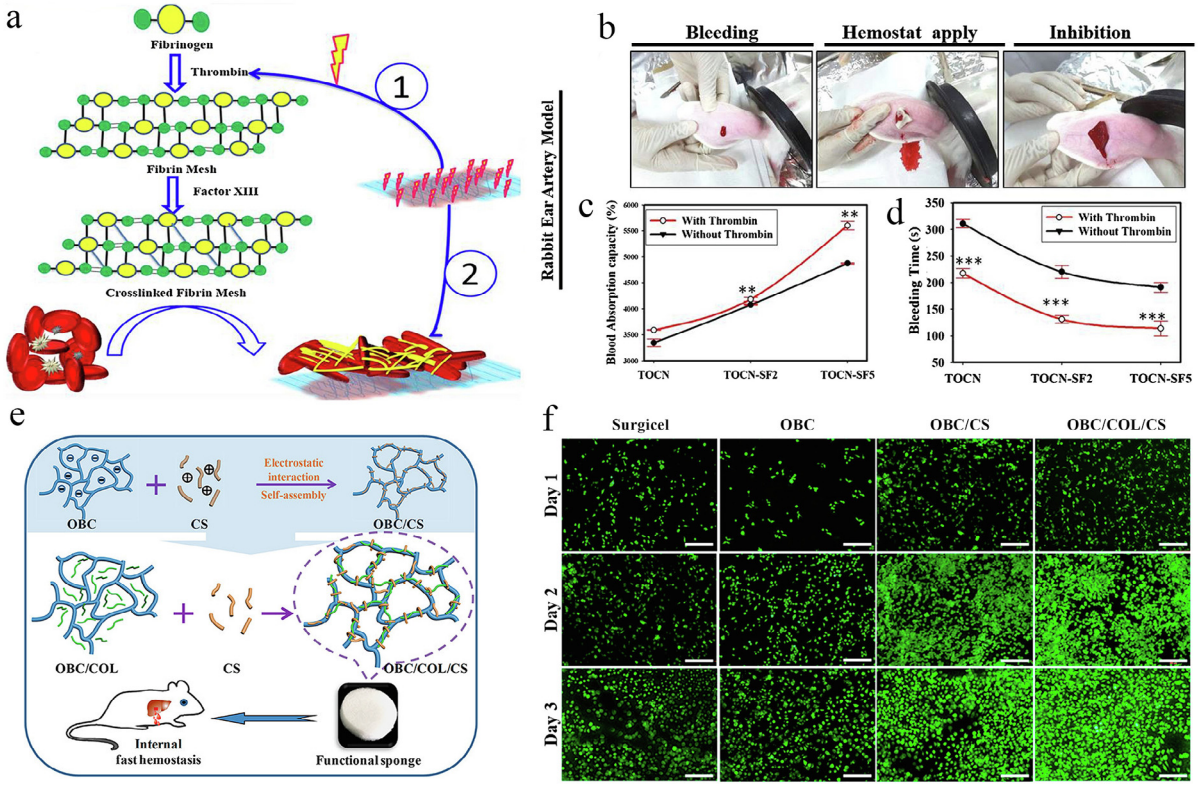

Fig. 17. (a) Scheme illustrating the use of TOCN-SF-Th scaffold for hemostasis via the following two mechanisms: (1) active hemostasis via thrombin and (2) passive hemostasis via the TOCN-SF structure. (b) Representative images of treating rabbit ear artery bleeding with TOCN-SF-Th scaffold. (c) Blood absorption and (d) bleeding time evaluation results of various scaffolds with and without thrombin. (a–d): Reprinted with permission from Ref. [382]. Copyright 2019, Elsevier B.V. (e) Schematic diagram showing the fabrication of OBC/CS and OBC/COL/CS and the hemostatic application of OBC/COL/CS. (f) Fluorescence imaging results of calcein AM-stained L929 fibroblasts cultured on different samples (Surgicel, OBC, OBC/CS, and OBC/COL/CS) after 1, 2, and 3 days. Scale bars: 200 μm. (e and f): Reprinted with permission from Ref. [364]. Copyright 2020, American Chemical Society.

Besides PEG, hyperbranched polyglycerol can also be adopted to develop hemostatic materials.[401] Hyperbranched polyglycerol is structurally associated with PEG and it possesses a macromolecular architecture with a high degree of branching based on glycerol. Compared to PEG, hyperbranched polyglycerol demonstrates superior hydration capacity and biocompatibility, and it is expected to be an ideal substitute for PEG.[402,403] Wen et al. synthesized and characterized a library of functionalized hyperbranched polyglycerols, which were modified with cationic quaternary ammonium groups and zwitterionic sulfabetaine ligands.[401] The quaternary ammonium groups could interact with the negatively charged erythrocyte membrane, therefore causing erythrocyte aggregation, and they also had the ability to enhance the adhesion and activation of platelets. The zwitterionic ligands and hyperbranched polyglycerol backbone could reduce the cytotoxicity of the cationic moieties to avoid adverse hemolysis and also absorb a large quantity of wound fluids due to their favorable hydration property. This research illustrates the feasibility to prepare hemostatic materials using hyperbranched polyglycerols.

4.3.2. Poly(vinyl alcohol) (PVA)

The PVA belongs to a class of nontoxic and water-soluble synthetic polymers that have been widely applied in implantable medical devices and drug delivery.[404] The PVA sponge placed in the wound site can induce local compression to achieve physical hemostasis.[405] However, for complicated or severe bleeding, the hemostatic ability of PVA sponge is too weak to hinder bleeding quickly and efficiently. As a result, researchers began to focus on combining PVA with other hemostatic materials (such as CS, gelatin, and so on) to improve its hemostatic capability.[405–408] For example, Huang et al. fabricated a composite hemostatic cryogel composed of carboxymethyl CS, dopamine, and PVA via combining cryo-polymerization reaction and foaming reaction to control lethal noncompressible hemorrhage.[407] The PVA sponge could cause physical hemostasis via forming a barrier at the wound site and the introduced carboxymethyl CS and dopamine could significantly improve the hemostatic performance of the PVA sponge via promoting chemical hemostasis. In addition, the cryogel displayed high compression strength and great shape memory performance and efficiently hindered bleeding in the lethal liver defect hemorrhage model of coagulopathic rabbit and the noncompressible liver defect bleeding model of rabbit. Besides, Yang et al. used gelatin and norbornene anhydride-modified PVA to prepare composite sponges with excellent water absorption ability and rapid expansion property via a foaming method, physical/chemical crosslinking reactions, and lyophilization.[408] The prepared sponges could notably reduce blood loss and decrease hemostatic time in liver defect noncompressible hemorrhage model of Sprague–Dawley rat. PVA has also been adopted together with other materials to prepare hydrogels with hemostatic function. For instance, Ni and co-workers combined PVA with the polycationic polymer, i.e., poly(*N*,*N*-dimethylethylenediaminephazene) modified with phenylboronic groups, to prepare an antibacterial, self-healing, and injectable hydrogel.[409] The hydrogel could not only tightly adhere to the surface of a wet tissue via hydrogen bonding, π–π, and cation–π interactions, but also had the ability to accelerate wound closure and hemostasis.

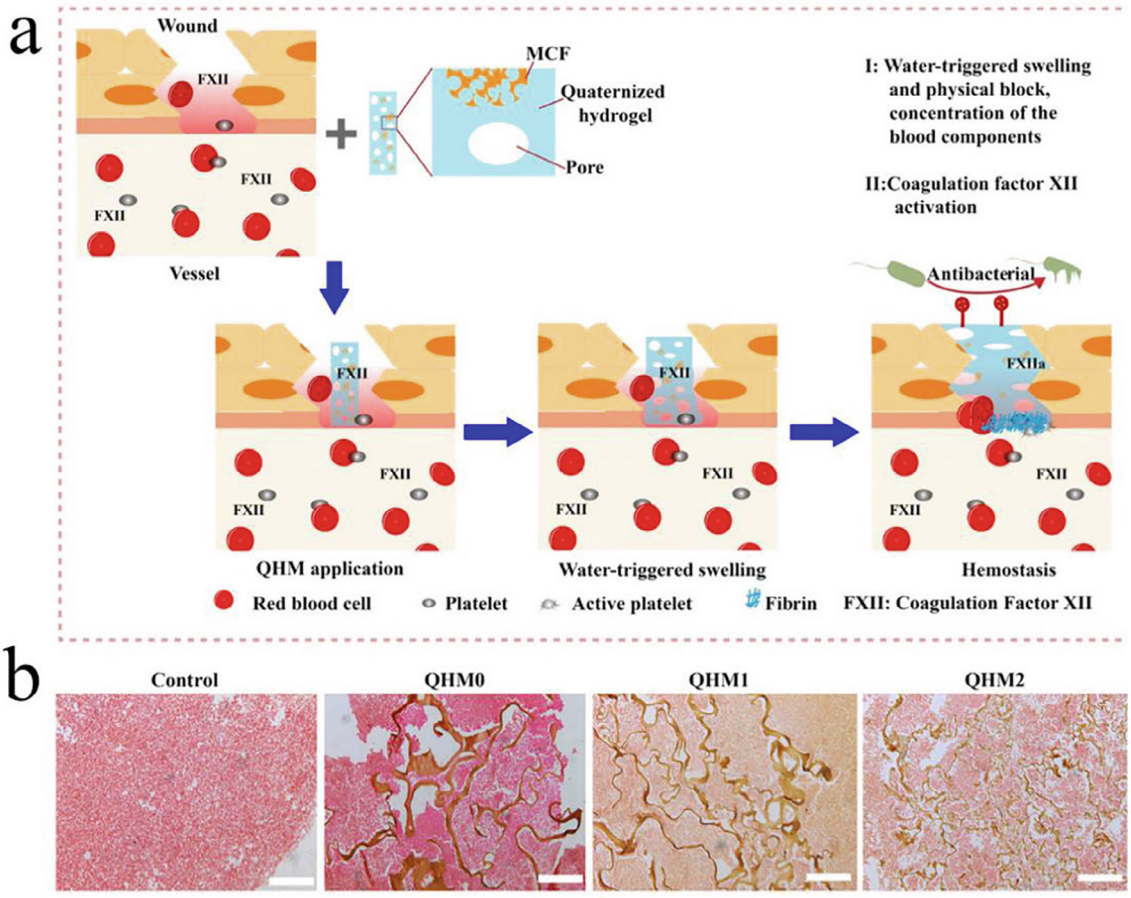

Fig. 18. (a) Scheme showing the hemostatic and antibacterial mechanisms of the QHM hydrogel sponge. (b) H&E staining results of the blood clots. Scale bar: 100 μm. (a and b): Reprinted with permission from Ref. [387]. Copyright 2019, American Chemical Society.

4.3.3. Poly(acrylic acid) (PAA)

PAA, a synthetic polymer of acrylic acid, can be used to prepare superabsorbent polymers, which can accelerate the cessation of bleeding by rapidly absorbing blood.[410–413] Peng et al. developed a self-gelling and wet adhesive hemostatic powder (PEI/PAA/QCS powder) consisting of PAA, polyethyleneimine (PEI), and quaternized CS.[410] The PEI/PAA/QCS powder could quickly absorb blood to concentrate clotting factors and then instantly form an adhesive hydrogel, performing as a highly pressure-resistant physical barrier to halt hemorrhage. For bleeding in the heart, liver, femoral artery, and tail vein of rats and noncompressible hemorrhage in the liver and spleen of pigs, the hemostatic powder displayed excellent hemostasis effect. In another study, Ito et al. prepared a water-swellable PAA/poly(vinylpyrrolidone) complex film by a solid/solution interface complexation method.[412] The complex film could instantaneously form soft hydrogel at the wound site by absorbing body fluids/blood, and then adhered closely to the surface of wound to rapidly prevent bleeding. Besides, Bain et al. grafted PAA onto a thermoplastic elastomer (a polystyrene–polybutadiene–polystyrene triblock copolymer) via free radical polymerization to develop a tough and rapidly swelling hydrogel for bleeding control.[413] The obtained graft copolymer was able to swell rapidly and absorb much more water than the most advanced gauze-based hemostatic dressing. Moreover, the formed hydrogel exhibited sufficient toughness in the swollen state, and consequently it could be removed from the wound site without breaking or leaving debris after treatment. The above studies demonstrate the potential of PAA for the fabrication of hemostatic materials. However, it should be noted that the residual monomers may induce potential biological toxicity, which needs to be taken into account in future research.

4.3.4. Polyesters

Polyesters are a class of polymers and each repeat unit of their main chain contains the ester functional group. So far, diverse polyester materials have been applied to construct hemostatic agents. For example, polycaprolactone (PCL) is appropriate for being used for fabricating nanofiber wound dressings since it holds the properties of biodegradability and nonantigenicity in humans.[414] Additionally, PCL has several additional properties, e.g., high blend compatibility, low cost, low melting temperature, and FDA approval, which make it an ideal material for a variety of biomedical applications.[415,416] In recent years, some researches regarding PCL-based hemostatic materials have been carried out.[417,418] Park and co-workers added $CaCO_3$ to the PCL solution to prepare PCL/$CaCO_3$ fibers via electrospinning and then coated the resulting nanofibers with β-CS solution through ultrasonic spraying.[417] It was revealed that the PCL/$CaCO_3$ nanofibers coated with β-CS had the highest coagulation ability among all the tested samples, which was attributable to the ability of $CaCO_3$ to expedite the blood coagulation and the capacity of β-CS to notably improve the surface wettability of the fiber. Because PCL is biodegradable, and both $CaCO_3$ and β-CS are biologically safe materials, it may be unnecessary to worry about the operation for removing threads after surgery when the nanofibers are applied as wound dressings. Furthermore, the size and thickness of the PCL/$CaCO_3$ nanofibers coated with β-CS could be well tuned to be fit for the wound area. In another example, an injectable superelastic nanofiber rectangular matrix (“peanut”) was developed by Chen et al.[418] The nanofiber mats were prepared by electrospinning using PCL, expanded through a gas-foaming technique, and then subjected to gelatin coating and crosslinking with glutaraldehyde followed by thrombin immobilization to finally obtain the nanofiber peanuts. The nanofiber peanuts were further compressed into pellets and wrapped with water-soluble polymers (e.g., polyvinylpyrrolidone). The experimental results confirmed that the compressed nanofiber peanuts could be packed into a syringe for injection and could re-expand to their original shape in air, water, and blood within 10 s, which was important for them to exert a tamponade effect for activating hemostasis. In addition, the nanofiber peanuts had a stronger water/blood absorption capacity and a higher whole blood clotting efficiency compared with the commercial products. Further experiments showed that they had good hemostatic effect in a porcine liver injury model. In addition to PCL, poly(lactide-*co*-glycolide) (PLGA) has also been applied to prepare hemostatic agents. PLGA is a well-established biocompatible and biodegradable polymer approved by FDA, and has been extensively utilized as surgical sutures, drug vehicles, and implants.[419,420] Liu et al. developed PLGA-HA fibrous fragments (PLGA-HA FFs) via the techniques of electrospinning, ammonia dissociation, and surface grafting for hemostasis.[421] As indicated by the authors, the PLGA-HA FFs did not affect the coagulation cascade and realized hemostasis only in a physical way. They could absorb abundant water from the blood, thus concentrating coagulation factors, adhering platelets and RBCs, and then resulting in a primary thrombus formation. Further, in this work, the antibiotic azithromycin was loaded on the PLGA-HA FFs to endow them with immunoregulation and antiinfection properties.

Polyurethane-based wound dressings have also drawn the attention of many researchers due to the good biocompatibility, acceptable mechanical property, and suitable flexibility of polyurethane.[422,423] In 2017, Liu et al. fabricated a hemostatic polyurethane-urea foam (PUUF) wound dressing by using PEG, 4,4-diaminodicyclohexylmethane, and 4,4-methylenebis (cyclohexyl isocyanate) as raw materials.[424] The porous PUUF showed a strong water uptake ability, and compared with the commercial polyurethane dressing CaduMedi, the PUUF wound dressing showed superior blood coagulation performance. Both PUUF and CaduMedi could facilitate wound healing, causing full reepithelialization within only 13 days, but PUUF was milder and resulted in slighter inflammatory response relative to CaduMedi. Besides, Beaman et al. developed a hemostatic dressing based on a polyurethane shape memory polymer foam, which displayed rapid shape recovery ability to fill the wound area.[425] The foam considerably reduced blood loss as compared with QuikClot Combat Gauze and XStat (the two commercially available hemostatic dressings) in a noncompressible and lethal liver injury model of porcine.

4.3.5. Cyanoacrylates

Cyanoacrylates can change from monomers to polymers when encountering water and then bond the adjacent surfaces.[426] Accordingly, cyanoacrylates can be used for sealing wounds and avoiding blood leakage.[427,428] Luo et al. employed an electric field-modified electrospinning technique to afford cyanoacrylate fibers which could be in situ deposited onto the liver resection site to impede hemorrhage within only 10 s.[427] Of note, owing to the potential toxicity, the internal use of cyanoacrylates is sometimes not suitable.[226]

4.3.6. Other synthetic hemostatic polymers

Poly(2-oxazoline)s (or POx) are favorable polymers for biomedical uses due to their good cytocompatibility, versatile synthesis, and satisfactory excretability. POx hold some important merits when used as hemostatic materials. For example, the introduction of functional side chains/end groups to POx can be easy via cationic ring opening polymerization. Furthermore, with the help of this polymerization technique, it is possible to accurately regulate the degree of side-chain functionalization and polarity of the obtained polymers.[429] As a typical application example of POx, Boerman et al. prepared a nonbioactive synthetic hemostatic product via coating *N*-hydroxysuccinimide ester-functionalized poly(2-

oxazoline)s (POx-NHS) on a gelatin patch.[430] The resulting product could seal wounds and impede bleeding during surgery due to the formation of covalent crosslinks among blood proteins, tissue, gelatin, and POx-NHS. The authors proved that the hemostatic performance of POx-NHS-coated patch was better than that of the clinical product Tachosil, which achieved hemostasis only via activating the natural coagulation cascade, in the bleeding model of heparinized pigs.

Polyvinylpyrrolidone is a type of water-soluble and physiologically acceptable polymer that can be quickly transformed into a hydrogel.[431] Li et al. prepared curcumin-loaded mesoporous silica-incorporated nanofiber mats through blend electrospinning of polyvinylpyrrolidone and curcumin-loaded MSNs for hemostasis.[432] The curcumin imparted reliable antimicrobial effect to the nanofiber mats and the MSNs were applied as an effective drug carrier. In vitro and in vivo experimental results demonstrated that the hybrid nanofiber mats could effectively inhibit the growth of methicillin-resistant *Staphylococcus aureus*. Furthermore, the in vivo hemostasis tests showed that the hybrid nanofiber mats were able to be rapidly transformed into hydrogels while they were in contact with the blood, and subsequently activated the coagulation system to stanch bleeding. Besides polyvinylpyrrolidone, in a recent study, Zhang et al. mixed a biocompatible poly (*N*-hydroxyethyl acrylamide) (PHEAA) polymer with TA to yield a supramolecular coacervate hydrogel (TAHE hydrogel) and obtained the TAHE hydrogel powder via lyophilization followed by grinding. (Fig. 19a–c).[433] TA could crosslink macromolecules and bond with the substrates via hydrophobic interaction/multiple hydrogen bonding interactions. PHEAA contained secondary amide groups and hydroxyl groups in the side chains, and the two kinds of functional groups could act as hydrogen bonding donors/hydrogen bonding acceptors, contributing to enhancing the hydrogen bonding interaction with TA molecules and improving the adhesion of hydrogels. In Zhang's work, the TAHE hydrogel exhibited not only strong adhesion to various substrates, but also self-healing and antibacterial properties and superb hemostatic ability. The hemostatic function of TAHE powder was assessed in the rat liver hemorrhage model. As displayed in Fig. 19d, TAHE powder or TA treatment could quicken the hemostasis process. In addition, as demonstrated by Fig. 19e, TAHE powder and TA could also substantially decrease the blood loss from 1.26 g in the control group to 0.48 and 0.27 g, respectively. Besides, as illustrated in Fig. 19f, the TAHE powder could absorb plasma to cause blood cell aggregation; it also became sticky after absorbing blood and thus adhered to the bleeding site to form a physical hemostatic barrier. This work emphasizes that it is feasible to prepare hydrogels with robust adhesion to soft tissues or hemostasis potency via the introduction of TA into the synthetic polymer systems.

5. Intravenously administered hemostats

Intravenously administered hemostats have gained considerable attention due to their capability to treat wounds without contacting the hemorrhage sites. By contrast, the topical hemostats are unable to treat invisible or inaccessible wounds. Currently, intravenously administered hemostats are still the primary choice for improving the survival of battlefield casualties and civilians with serious truncal/junctional bleeding and traumatic brain wounds.[434–436] Nevertheless, intravenously administered hemostats are more challenging to be developed and the safety requirement of intravenously materials is higher than that of topical hemostats. They are supposed to be equipped with moderate coagulation ability, which means that they need to activate coagulation but not cause serious thrombosis/symptoms.

5.1. Fibrin- and coagulation factor-related hemostats

The researches on intravenously administered hemostatic agents can be mainly divided into two types—those using the strategies of mimicking the role of platelets and those using approaches that can adjust the components involved in the clotting cascade and modulate the formation of final fibrin clots. For the latter, the most apparent method is to intravenously administer coagulation factors/fibrinogen. The fibrinogen-based hemostatic products include fibrinogen concentrate and cryoprecipitate (composed of fibrinogen, von Willebrand factor, FVIII, and FXIII), which can aid in raising fibrinogen levels.[3] Adding exogenous fibrinogen is an efficacious means to antibleeding. Nevertheless, there are quite a few downsides of this strategy. First, fibrin is susceptible to fibrinolysis, which may cause bleeding again.[437] Second, the production costs of both isolated and recombinant fibrinogen are too high, not to mention the fact that isolated fibrinogen requires extra steps to remove blood-borne pathogens.[438,439] Finally, the transfusion of blood products is sometimes forbidden by some religions.[440] Based on all these drawbacks, some researchers have made great efforts to develop synthetic polymers that are able to accelerate clot formation or enhance adhesion of blood clots.[441–443] To give an example, Chan et al. constructed a synthetic hemostatic polymer PolySTAT with a linear poly(hydroxyethyl methacrylate) backbone which was grafted with $\sim$ 16 fibrin-binding peptides (Fig. 20a).[441] During fibrin polymerization, PolySTAT could noncovalently bind to manifold fibrin monomers to construct a stable crosslinked fibrin network. Under the conditions of simulated trauma-induced coagulopathy, the rotational thromboelastometry (a clinical tool for monitoring coagulation in blood samples) results indicated that PolySTAT was capable of speeding up clot formation, improving the maximal firmness of the clot, and impeding clot lysis. As presented by this research, manipulating fibrin clot structure via physical crosslinking with the help of a synthetic polymer is conducive to clot formation and may become a feasible transfusion approach for coagulopathy treatment. In another research, to increase the adhesive strength of clots, Chan and co-workers prepared Q-PEG, an 8-armed PEG conjugated to a glutamine-containing peptide.[442] The prepared Q-PEG could crosslink with spermidine in the presence of FXIIIa, and then form a composite clot with fibrin (Fig. 20b). The adhesion of the composite clot to blood vessel/collagen was significantly enhanced. The authors found that the addition of Q-PEG, spermidine, and additional FXIII zymogen into normal human plasma raised the adhesive strength of blood clots. After Q-PEG, spermidine, and additional FXIII zymogen were supplemented to fibrinogen-deficient whole blood, the adhesive strength of the formed clot increased from < 0.06 kPa to 1.9 ± 0.14 kPa. By contrast, the formed clot in fibrinogen-deficient whole blood without any addition were nonadhesive. Therefore, this study presents a strategy to construct advanced hemostatic agents capable of increasing the adhesive strength of the formed blood clots for treating fibrinogen deficiency in trauma-induced coagulopathy. Moreover, in 2018, Welsch and co-workers prepared PEG-PLPs (PLPs: platelet-like particles) from microgels which were composed of fibrin-targeting single domain variable fragment antibodies and polymers carrying PEG side chains (obtained from the polymerization of methacrylic acid and oligo ethylene glycol methacrylate).[443] PEG-PLPs showed the capability to boost the formation of fibrin network in vitro via the robust adhesion to the emerging fibrin clot as well as the noncovalent crosslinking of nascent fibrin fibers.

In addition to the above methods of promoting fibrin clot formation or increasing fibrin clot adhesion, inhibiting fibrinolysis provides another approach to promote coagulation. The antifibrinolytic approaches which suppress plasmin or the binding of plas-

min to fibrin have been employed in clinical settings.[13,444,445] Aprotinin, tranexamic acid, and aminocaproic acid are the most widely administered antifibrinolytic pharmaceuticals and have exhibited the ability to minimize blood transfusion needs in surgery.[5,446,447]

There are also some hemostatic products which can regulate the level of coagulation factors, instead of modulating directly the level of fibrin, to achieve hemostasis, including fresh frozen plasma abundant in manifold coagulation factors (FII, FV, FVII, FIX, and FX).[448–450] prothrombin complex concentrates (highly purified concentrates of coagulation factors including FII, FVII, FIX, and FX),[451] and a range of recombinant coagulation factors, such as the commercially available recombinant FVIII preparations for the treatment of hemophilia A and the recombinant FIX for the treatment of hemophilia B, as well as the most famous recombinant coagulation factor product, namely the recombinant FVIIa, which could accelerate thrombin generation.[452–456] Unfortunately, the infused coagulation factors suffer from rapid clearance in vivo and being inactivated by alloantibodies, which considerably hampers their clinical applications.[457] A series of bioengineering technologies have been employed to overcome these bottlenecks. To prolong their circulation time, the coagulation factors are usually encapsulated within nanocarriers like liposomes.[458] Besides, PEGylation or sialylation can increase the enzymatic stability, extend the half-life, and avoid the renal excretion of these infused coagulation factors.[459,460] Another applicable approach to prolong the half-life of a coagulation factor is fusing it to another type of protein with longer half-life (like the fragment crystallizable region of immunoglobulin).[461]

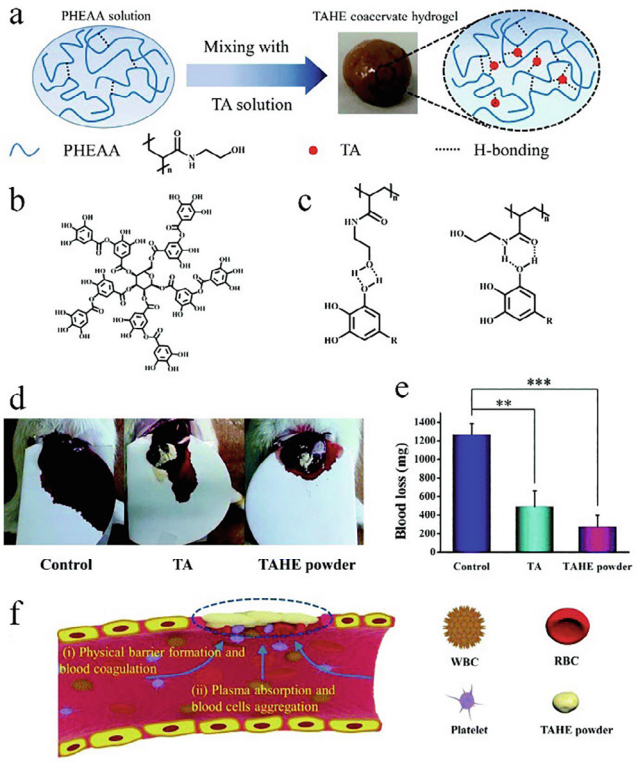

Fig. 19. (a) Scheme illustrating the preparation of the TAHE hydrogel. (b) Molecular structure of TA. (c) Possible hydrogen bonds formed between PHEAA and TA. (d) Photographs showing the hemostastic performance of TA or TAHE powder in a liver bleeding model of rat. (e) Blood loss results corresponding to (d). (f) Schematic diagram depicting the hemostatic mechanism of TAHE powder. (a–f) Reprinted with permission from Ref. [433]. Copyright 2020, Royal Society of Chemistry.

Up to now, with the vast development of nanotechnology, some researchers have begun to focus on how to use nanoparticles to effectively deliver components that can lead to the activation of coagulation factors to realize the target of hemostasis. To give an example, Donovan et al. encapsulated granular platelet-sized polyphosphate nanoparticles (polyP NPs) into liposomes to form procoagulant nanodrugs called artificial dense granules (ADGs), which were similar to human platelet dense granules in not only structure but also functionality (Fig. 20c).[462] The ADGs revealed good procoagulant property—detergent solubilization via Tween 20 or degradation of the lipid capsule by phospholipase C enabled the ADGs to release the polyP NPs which could cause autoactivation of FXII to accelerate blood clotting. Collectively, ADGs could decrease the coagulation time of plasma in the presence of phospholipase C. Based on these results, the authors believed that it is feasible to utilize ADGs as a promising procoagulant nanomedicine for antibleeding application.

5.2. Platelet-related hemostats

Another research direction of intravenously administered hemostats is to develop platelets or platelet substitutes for hemorrhage control. Platelets play a key role in the hemostasis process. However, the short shelf life of platelets (5 days at room temperature) to a great extent limits their clinical applications.[463,464] Some strategies have been proposed to increase the platelet shelf life, including cryopreservation, storing the platelets in platelet additive solutions at 4 °C, pathogen-reduction technology, and the use of platelet activation inhibitors.[465–469] The freeze-drying process has also been applied in the preservation of platelets. The lyophilized platelets are quickly available with minimal preparation work in the trauma setting where platelet transfusion is sometimes inaccessible.[470] To avoid damage to the morphology and function of platelets during the freeze-drying process, various stabilizing techniques have been adopted.[464] For instance, lyophilized human platelets (Stasix) are prepared using a stabilization technique which covalently crosslinks surface membrane lipids and proteins (via e.g., paraformaldehyde) to maintain the platelet-like properties of the lyophilized platelets.[470,471] Another solution is the development of thrombosome (a lyophilized platelet-derived hemostat using trehalose for its stabilization).[472,473] The thrombosome is able to adhere to the surface of collagen under the flow condition, promote clot formation, and cause the production of more thrombin. Besides, it can remain stable at room temperature over a long period of time.[464] In addition to their short shelf-life, platelets also have other serious problems, including limited portability and availability, a high risk of bacterial contamination, and the need for antigen matching.[474–477] To settle these issues, researchers began to focus on "donor-independent" platelet technologies, namely generating clinically available platelets from the cultured megakaryocytes or the earlier precursor cells in vitro or infused megakaryocytes which can release platelets in vivo. Compared with donor-derived platelets with large variability in quality and potential risks of immunologic reactions, bacterial contamination, and other transfusion-transmitted infections, these "donor-independent" platelets may not only become more consistent and safer, but also decrease the necessity of human donation.[478–480] Moreover, in these years, infusible platelet membranes and platelet-derived microparticles have also been developed to serve as platelet substitutes for procoagulation.[481,482] As an example, Jung et al. prepared natural platelet-derived vesicles, which were unfilled, spherical, and homogenous in size (~150 nm), through sonication in a hypotonic solution (Fig. 21a).[482] The platelet-derived vesicles secreted less inflammatory cytokines in comparison with activated platelets, and could thus restrain macrophage activation and

subsequent phagocytosis, favorable for preventing easy elimination of the platelet-derived vesicles by activated macrophages. Fig. 21b illustrated that platelets could interact with thrombin to form aggregates, and release pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α. Nevertheless, it was possible for the platelet vesicles to form aggregates in the presence of calcium chloride and thrombin with no cytokine secretion as a consequence of their empty interior. Furthermore, the hemostatic effect of platelet vesicles was better than that of platelets in the tail transection bleeding model of mouse. As presented in Fig. 21c, when injected with a buffer solution or a platelet suspension, the hemorrhage time was 90.9 ± 13.9 and 85.7 ± 20.8 s, respectively. In sharp contrast, the hemorrhage time reduced to 46.2 ± 26.3 s in the platelet vesicle group.

Over these years, to overcome the aforementioned defects of natural platelets, the investigations concerning "synthetic platelet substitutes" have also drawn the interest of many researchers. [477,483,484] The synthetic platelet substitutes have some significant advantages compared with blood-based transfusion products, such as unlimited supply, relatively low cost, and simpler handling and storage.[484–486] Generally, synthetic platelet substitutes are usually equipped with moieties that are conducive to platelet-mimetic adhesion/aggregation, to facilitate platelet aggregation as well as platelet plug formation.[483] Several moieties, such as platelet surface glycoproteins, full-length fibrinogen, fibrinogen-derived Arg-Gly-Asp (RGD) peptides, etc., have been adopted to decorate albumin microparticles, polymeric NPs, liposomes, and even erythrocytes to foster platelet aggregation and adhesion.[483,484,487–497] To give an example, the Lavik's group developed two types of synthetic platelets, one is PLGA–poly-L-lysine (PLL)–PEG-glycine–arginine–glycine–aspartic acid–serine (GRGDS) (PLGA–PLL–PEG-GRGDS) NPs and the other is poly(lactic acid)–PEG-GRGDS (PLA–PEG-GRGDS) NPs.[493,494] The RGD peptide in the two NPs could bind to the receptors on activated platelet surface, thus assisting the aggregation of these activated platelets. Besides, the PLGA–PLL–PEG-GRGDS NPs decreased hemorrhaging in a femoral artery injury model of rat. The PLA–PEG-GRGDS NPs were stable at a high temperature of 50 °C for 7 days and were effective at stemming bleeding and improving survival within 1 h in a liver injury model of rat. Later, they prepared a polyurethane–PEG-GRGDS nanocapsule, which caused faster clot formation than the control group and no reduction of the maximum clot firmness.[495] Moreover, the polyurethane–PEG-GRGDS did not lead to the activation of complement in the blood, thus avoiding the induction of complement-mediated infusion reactions, which may trigger symptoms including severe inflammatory responses, shock, and even death. The polyurethane–PEG-GRGDS has a noticeable advantage in safety and represents an important intravenous hemostatic nanodrug. In another example, Zhang and co-workers prepared intravenous NPs (CPG-NPs-2000) with PEG-2000 as the spacer, CS succinate as the core, and the GRGDS peptide as the targeting hemostatic motif.[496] CPG-NPs-2000 possessed good aqueous dispersity, excellent thermal stability, and good clearance profile. In a liver trauma rat model, CPG-NPs-2000 presented dramatic hemostatic ability compared with saline, tranexamic acid, and CS succinate NPs. This work highlights that CPG-NPs-2000 may be used as an effectual intravenous hemostatic agent for severe internal bleeding. In 2019, He et al. synthesized biocompatible and cuboidal γ-cyclodextrin metal–organic frameworks (MOFs), whose surface was modified with the GRGDS peptide to form the final product termed GS5-MOF, for targeting injured vessels and controlling hemorrhage.[487] The GS5-MOF NPs displayed the ability to specifically adhere/aggregate to the activated platelets at the injured blood vessels and exhibited superb hemostatic effect with a reduction of blood loss and bleeding time by 90 % in vivo.

Recently, Gao and co-workers fabricated an injectable hemostat (called polymer peptide interfusion), i.e., the HA polymer conjugated with a von Willebrand factor-binding peptide and a collagen-binding peptide.[497] The polymer peptide interfusion could not only selectively bind to activated platelets, but also facilitate the accumulation of activated platelets at injury sites to promote the clot formation. As demonstrated in the mouse tail vein laceration model, the groups treated with the polymer peptide

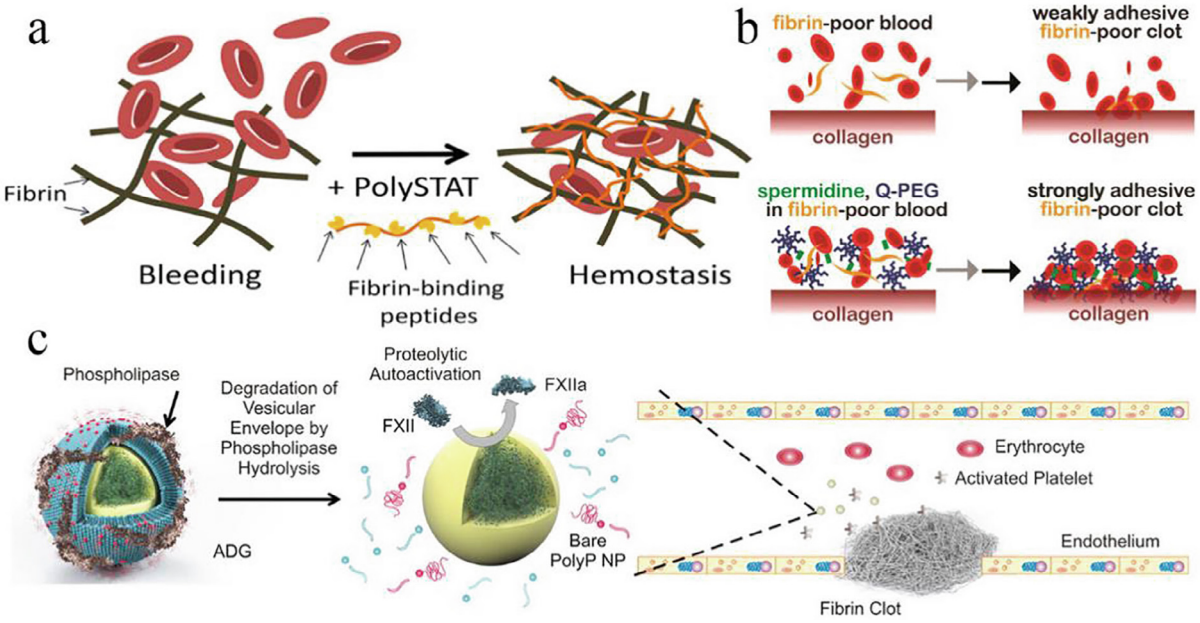

Fig. 20. (a) Scheme depicting the hemostatic mechanism of PolySTAT. Reprinted with permission from Ref. [441]. Copyright 2016, American Chemical Society. (b) Scheme displaying the role of Q-PEG and spermidine in facilitating the adhesion of the fibrinogen-deficient whole blood clot to collagen surface. Reprinted with permission from Ref. [442]. Copyright 2016, American Chemical Society. (c) Scheme showing the degradation of the lipid envelope of an ADG and the release of polyP NPs to cause FXII autoactivation. Reprinted with permission from Ref. [462]. Copyright 2016, American Chemical Society.

interfusion displayed a reduction of > 97 % for blood loss and bleeding time. In the inferior vena cava trauma model of rat, a 284 % increase of the survival time was found. Moreover, the authors confirmed that the polymer peptide interfusion could be stably stored for several months (at room temperature) after lyophilization. It is expected that the polymer peptide interfusion may hold the potential to be used as an effective clinical intravenous hemostat.

5.3. Other emerging intravenously administered hemostats

5.3.1. Procoagulant phospholipids

It is worth mentioning that a procoagulant phospholipid surface is also needed for clot formation during hemostasis and the studies involving procoagulant phospholipids have attracted the attention of some researchers. The negatively charged procoagulant phospholipids provide substrates for the assembly of characteristic enzyme complexes related to the clotting cascade, consequently accelerating hemostatic processes.[498] The procoagulant phospholipids can originate from cell-derived microparticles (that are small membrane vesicles released from platelets, erythrocytes, leukocytes, endothelial cells, etc.).[499] For instance, Jy and coworkers fabricated a red cell microparticle for use as a hemostatic agent, which contained procoagulant phospholipids.[500] The red cell microparticles held the ability to substantially decrease blood loss in bleeding models of rats and rabbits. In another investigation, Slatter et al. demonstrated the procoagulant effect of hydroxyeicosatetraenoic acid-phospholipids, which are enzymatically oxidized phospholipids derived from innate immune cells.[501] The hydroxyeicosatetraenoic acid-phospholipids not only boosted coagulation in FVIII-, FIX-, and FX-deficient human plasma, but also avoided blood loss in the model of murine hemophilia A. This work validates that the procoagulant phospholipids can enhance the action effect of coagulation factors in vitro and in vivo, which is able to compensate for the deficiency of coagulation factors in patients and ameliorate defective hemostasis. Consequently, the procoagulant phospholipids hold great promise for use as a robust hemostatic agent for hindering hemorrhage in patients with genetic/acquired bleeding disorders.

5.3.2. Positively charged intravenous hemostatic nanoparticles

As mentioned earlier, positively charged molecules have the ability to cause the aggregation of platelets, and therefore the NPs prepared from positively charged molecules may have potential hemostatic effect and can function as potent intravenous hemostatic agents. Cheng et al. fabricated a series of positively charged NPs via the cholic acid-assisted self-assembly of PEI.[502] It was shown that the assembled NPs caused the activation and aggregation of platelets in in vitro studies. The assembled NPs had the potential to serve as not only a local hemostat but also an intravenous hemostat. This local hemostatic effect was verified in liver and femoral artery bleeding models of rabbit and rat, and the tail transection model of mouse. Additionally, intravenous injection of the NPs remarkably prevented the femoral artery hemorrhage in rats.

6. Other hemostats

Carbon dot is generally believed as a quasi-0D carbon-based nanomaterial with a diameter usually below 20 nm and possesses intrinsic fluorescence property.[503,504] Carbon dots have a variety of favorable properties like easy synthesis and functionalization, ultrasmall size, high aqueous dispersity, excellent optical properties, and exceptional biocompatibility.[505–508] To date, carbon dots have found a variety of biomedical applications such as biosensing, bioimaging, drug delivery, and anticancer/antimicrobial applications.[509–515] In addition to the above applications, some researchers have made efforts to investigate the hemostatic activity of carbon dots.[516,517] For example, Luo et al. prepared a type of carbon dots with good water dispersity from the aqueous extracts of *Cirsium setosum* Carbonisata, which has been used as an antihemorrhagic drug for many years in traditional Chinese medicine.[516] The as-prepared carbon dots possessed a nearly spherical shape and were uniform in size with low toxicity. Furthermore, the carbon dot-treated mice had an appreciably shorter bleeding time than the normal saline-treated mice in liver and tail hemorrhage experiments. The coagulation assays suggested that the carbon dots were able to activate the fibrinogen system and stimulate the extrinsic blood coagulation system to achieve hemostasis. Pollen Typhae Carbonisatus (PTC) is a kind of calcined herb drug which has also been employed as a hemostatic medicine for thousands of years. Yan and co-workers prepared water-dispersible carbon quantum dots (termed PTC-CQDs) from PTC.[517] The obtained PTC-CQDs with a size of 2–8 nm were capable of controlling hemorrhage in the mouse liver scratch and tail amputation models. The authors revealed that the antibleeding effect might be related to the capacity of PTC-CQDs to stimulate the fibrinogen system and blood coagulation system. These investigations propose a simple strategy to fabricate hemostatic carbon dots by using the water extract of medicinal herbs with antihemorrhagic activity. Nevertheless, the detailed hemostatic mechanism of the hemostatic carbon dots still remains unclear.

7. Conclusions and perspectives

Hemostasis is an extremely complex physiological process with an ultimate goal to form a blood clot, which can completely block the broken blood vessel and prevent blood flowing out. Unfortunately, for severe hemorrhage, it is challenging to impede bleeding quickly only by relying on the natural hemostatic process of the human body, and the hemostatic intervention is necessary to be provided for facilitating hemostasis. Various hemostatic materials are able to enhance hemostasis and reduce bleeding time/bleeding volume through diverse hemostatic mechanisms, including active hemostasis process and passive hemostasis process. The hemostasis is accelerated by activating the coagulation cascade in the active hemostasis, while the hemostasis is achieved in physical ways (such as compression, blockage, absorption of plasma, suture of bleeding sites, etc.) in the passive hemostasis process, without the participation of active components involved in coagulation cascade. The thrombosis may be caused in active hemostasis, while the hemostasis efficiency of a passive hemostatic way is usually quite low. Therefore, to settle serious bleeding problems, the combination of active and passive hemostasis may be a better choice.

To achieve more efficient bleeding control, researchers are constantly committed to improving existing hemostatic materials and developing diverse new hemostatic materials via several different strategies. For example, the shape, surface morphology, size, and internal structure of the materials can be adjusted to improve the physical properties such as water absorption ability of the material to enhance their hemostatic capacity. Besides, chemical modification of the hemostatic materials also represents a viable solution to improve their hemostatic performance. For instance, carboxymethylation of polysaccharides (such as starch) is conducive to improving the water solubility and hemostatic efficiency of the polysaccharides. The biological strategy is also a promising strategy to facilitate the development of hemostats. It is possible to achieve appreciable success via using/imitating key biological components in the natural hemostatic process or to design hemo-

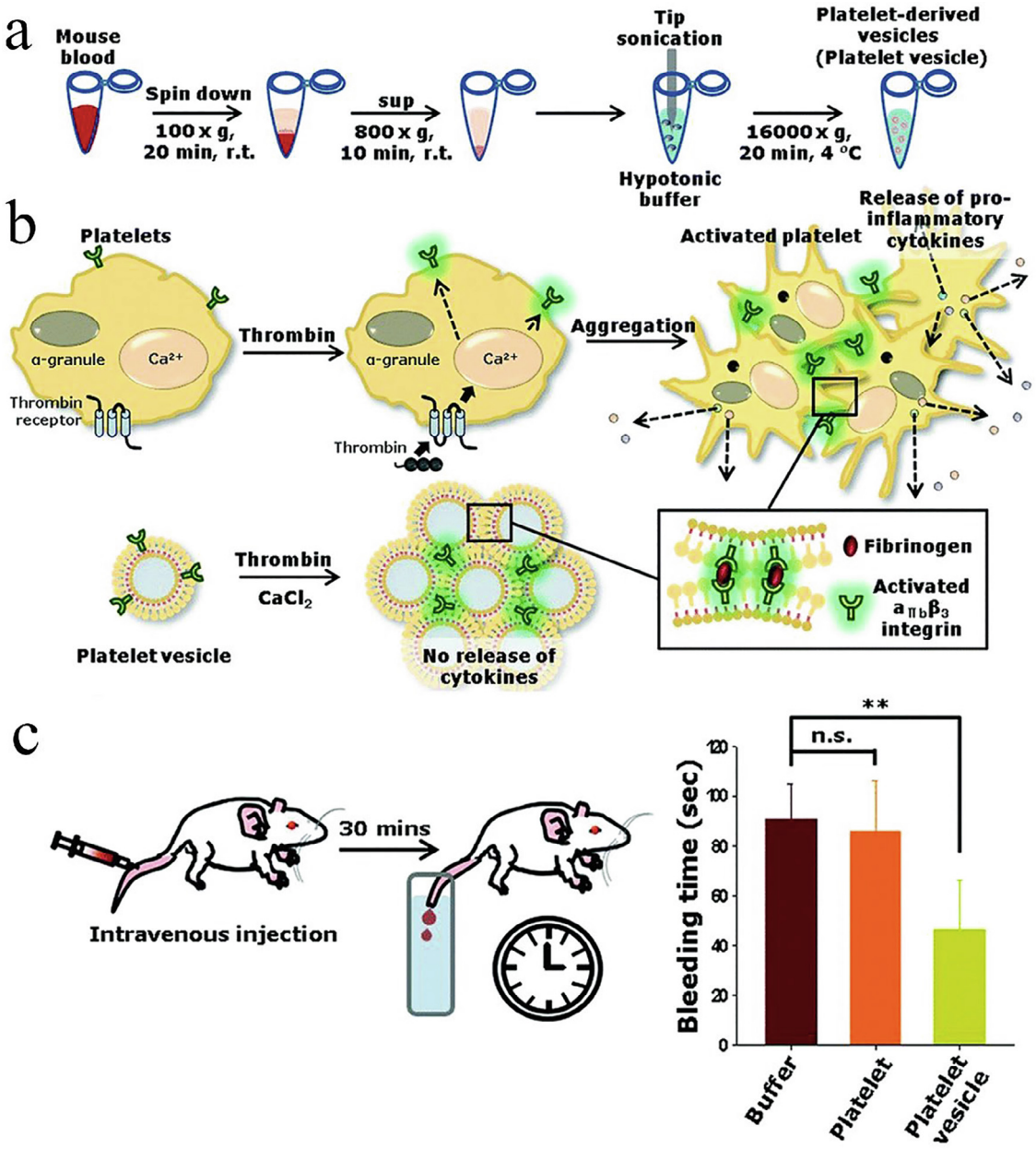

Fig. 21. (a) Synthesis of platelet-derived vesicles. (b) Scheme depicting the release of proinflammatory cytokines from aggregated platelets or platelet vesicles (r.t. = room temperature). (c) Scheme illustrating the experimental design for hemostatic effect evaluation and bleeding time of the mouse tail transection models after treatment of various samples. (a–c): Reprinted with permission from Ref. [482]. Copyright 2019, Royal Society of Chemistry.

static agents with bionic properties such as excellent adhesion. In addition to the above three methods, the combination of two or more materials with different physical, chemical, and biological properties to construct composite hemostatic materials is an extremely general and effective strategy, which has been adopted in a number of studies related to hemostatic materials. There is a broad array of hemostats, including external inorganic/organic hemostatic agents and intravenous hemostatic agents. The features of different types of hemostatic materials and a few representative examples showing the recent investigations on various hemostatic agents are summarized in Table 2 (external hemostatic materials) and Table 3 (intravenous hemostatic agents).

External inorganic hemostatic agents include silicate minerals, silica, MSNs, biosilica, phosphate minerals, polyphosphates, carbon sponges, metal NPs, metal ions, etc. Some types of silicate minerals have procoagulant capacity, low price, and usually have stable physical and chemical properties, which provide great convenience for silicate minerals to be developed into effective hemostatic materials with long storage life. Zeolite is one of the most classical hemostatic agents, but its application is severely limited by deleterious thermal injury. Kaolin-based hemostatic agents can not only prevent bleeding by activating the coagulation cascade, but also effectively avoid the thermal injury problem. Smectite, rectorite, halloysite, and other mineral materials with coagulation activity have also been applied in hemostasis. Notably, the hemostat WoundStat composed of smectite may cause severe damage to patient health and has been forbidden by the FDA since 2007. [518] Powdered MSNs with large surface area, high porosity, and abundant negative charges show a strong capacity to control bleeding. However, the systemic embolism and the subsequent

debridement problem caused by the dispersion of powdered MSNs in the blood should be taken into account. These problems also hamper further clinical applications of most powdered hemostatic materials.[519] Carbon sponges have the ability to absorb a large amount of plasma and concentrate coagulation factors and blood cells to accelerate hemostasis, but their potential biological toxicity needs to be further elucidated to ensure the safe use of the material. To solve a series of problems existing in the application of inorganic hemostatic agents, combining them with other materials, especially organic polymer materials, may represent a practical strategy. For example, the hemostatic properties of the composites prepared by the combination of kaolin and CS are notably improved due to their synergistic hemostatic effect.[76] Besides, the hemostatic CS-nBG hydrogel also takes full advantage of the merits of nBG and CS, while avoiding their shortcomings, making the CS-nBG hydrogel particularly effective for bleeding control. [109]

Organic hemostatic agents for external use mainly include some kinds of peptides/proteins, polysaccharides, and synthetic polymers. Peptide/protein hemostatic materials mainly contain collagen, gelatin, keratin, fibrin, SF, self-assembling peptides, glutaraldehyde-crosslinked albumin, and thrombin. Peptides/proteins usually display natural biocompatibility and excellent biodegradability. Therefore, peptides/proteins with hemostatic property are promising candidates for the development of hemostatic materials. A number of peptide/protein-based composite hemostatic materials have been developed to accelerate blood coagulation. The combination of protein materials with some natural polysaccharides, inorganic particles, and other types of materials promotes the development of composite materials with satisfactory physical, chemical, mechanical, and biological properties, and even endow the composites with a variety of functions such as antiinfection, wound healing, and tissue adhesion. Unfortunately, it remains a daunting challenge to avoid inherent defects of peptides/proteins (e.g., fibrin and collagen) during hemostasis. For example, fibrin-based hemostatic adhesives carry a risk of disease transmission due to the presence of plasma-derived components and may induce allergic reaction, and the purity and predictability of performance are important issues that should be considered during the preparation of animal-derived collagen.[520,521] Furthermore, the thermal stability and high price of peptide/protein materials hinder their practical application as hemostatic materials. Polysaccharide-based hemostatic materials have also attracted particular attention owing to their significant advantages, including rich sources, low price, good stability, low immunogenicity, and excellent biocompatibility/biodegradability. Polysaccharide materials have many properties including linear/branched structures, low/intermediate/high molecular weights with varying polydispersities, monofunctional or multifunctional performance, etc. The various structures and properties of polysaccharides offer huge biological advantages for their biomedical applications.[522] Additionally, to meet a wide range of demands, the physical and chemical properties of polysaccharide materials can be tuned by various chemical modification approaches, making them more suitable for diverse biomedical applications such as hemostasis and antibiosis. As mentioned earlier, the carboxymethylation of starch is beneficial to enhancing its hemostatic performance. Alkylation enables CS to anchor onto the cell plasma membrane, thereby inducing blood cell coagulation and promoting bleeding cessation. Besides, the introduction of quaternary ammonium group can not only facilitate platelet aggregation and help to adsorb plasma proteins and fibrinogen to accelerate hemostasis, but also effectively kill a variety of bacteria. The introduction of catechol groups or pyrogallol groups into polysaccharide-based hemostatic materials can endow them with strong tissue adhesion property, contributing to the development of hemostatic adhesives. In addition to introducing functional groups by chemical modification, incorporating hemostatic active components (such as Ca^{2+}, SiO_2, laponite, thrombin, recombinant batroxobin, tranexamic acid, serotonin, and some peptides with hemostatic function, etc.) into polysaccharide materials also exemplifies a feasible and effective strategy to enhance the hemostatic potency of polysaccharide materials. Similarly, adding antibacterial components, including antibacterial peptides, antibiotics, AgNPs, etc., into polysaccharide materials is able to effectively reduce the risk of wound infection and simultaneously realize hemostasis to achieve better wound care. Besides polysaccharide materials, synthetic polymer materials like PEG, hyperbranched polyglycerol, PVA, PAA, PCL, PLGA, polyurethanes, and cyanoacrylates usually display poor biological activity and is unable to directly activate the coagulation cascade. They usually staunch bleeding by sealing/blocking the wound or absorbing a large amount of blood to concentrate coagulation factors and blood cells. To improve the hemostatic activity of these materials, they can be chemically modified with functional groups that can promote hemostasis, such as quaternary ammonium group. Furthermore, the combination of synthetic polymers and natural polymers through crosslinking, blending, and grafting represents a feasible and universal method, which helps to improve the biological activity of synthetic polymers, avoid the poor mechanical property of natural polymers, and provide convenience for the development of biomedical materials with excellent hemostatic performance. Adding inorganic hemostatic components such as Ca^{2+} and mesoporous silica into synthetic polymer systems is also conducive to improving their hemostatic efficiency.

Although external hemostatic agents are rapidly developing, they are inadequate to treat internal injuries with noncompressible bleeding or some wounds that cannot be reached by external hemostatic agents. As a result, intravenous hemostatic agents are indispensable for bleeding control. This kind of hemostatic agents should bear the following features: they are able to activate the coagulation cascade to accelerate coagulation, but should not activate excessive coagulation to avoid inducing serious thrombosis and life-threatening symptoms such as stroke or infarction. Some natural hemostatic components, such as platelets, coagulation factors, and fibrin, have been used for hemostasis via intravenous infusion. However, big hurdles have been met in their clinical applications. The platelets with poor portability and availability are inconvenient to store; coagulation factors for infusion encounter rapid in vivo clearance and are easy to be inactivated by alloantibodies; fibrin may bring the risk of virus transmission and is susceptible to fibrinolysis, which may cause rebleeding. In addition, these natural hemostatic components also suffer from some limitations like high cost and prohibited transfusion of blood products by some religions. To avoid the shortcomings of these natural hemostatic components, researchers began to pay particular attention to the development of synthetic hemostatic agents for intravenous injection. Compared with natural hemostatic components, intravenous synthetic hemostatic agents are more convenient to store, can be easily designed according to specific needs, and can effectively avoid the risk of viral infection. Synthetic intravenous hemostatic agents should be featured with targeting ability and can specifically take effect the injury site. Researchers have to make significant efforts to investigate the reasonable construction of synthetic intravenous hemostatic agents, and need to consider carefully the biocompatibility including the systemic metabolism of the agents.

It is worth noting that based on the main active components and distinctive characteristics of various hemostatic materials, they are divided into different categories in this review, but the boundaries between various hemostatic materials are actually not so clear, since there are many hemostatic materials containing two or more hemostatic components. Currently, increasing

Table 2
Summary of external hemostatic materials.

Material	Hemostatic mechanism	Feature	Form	Animal model	Efficacy	Reference
Zeolite	Absorb blood and concentrate blood components; activate coagulation cascade	Good water absorption capacity; long-term physical and chemical stability; cheap and biocompatible, but may cause serious burn due to thermal release of zeolite after absorbing plenty of water	mCHA-C	Rabbit lethal femoral artery injury model	Less blood loss and lower active component leakage than CG	[65]
			Z-CGS	Rat artery injury model	High procoagulant activity	[72]
Kaolin	Absorb liquid and accelerate the activation of FXII	Thermally, chemically, and mechanically stable, low-risk as an allergen, and low-cost	CSMS-K	Rat liver laceration and tail amputation models	Decreased blood loss and hemostatic time	[76]
			Hemostatic membrane constructed by kaolinite-incorporated polyvinylpyrrolidone electrospun fibers	A tail amputation model and a liver and spleen injury model of rat	Excellent hemostatic effect	[77]
Smectite	Absorb water, activate intrinsic clotting pathway	High absorption, swelling, plasticity, and viscosity	Gelatin–laponite hydrogel	A standardized liver bleeding model of rat	Decreased blood coagulation time	[87]
			Blend composition of thiolated gelatin/GelMA with polydopamine-functionalized laponite nanoplates	—	Decreased blood coagulation time	[88]
REC	Stimulate coagulation cascade	With negative charge, but the rectorite dispersed in blood may trigger thrombosis	Hemostatic nanocomposite of REC and CS	In vitro porcine skin model	Skin adhesion and hemostasis	[93]
			Chitin nanogel/REC nanocomposite	Rat tail incision	Good hemostatic activity	[94]
Halloysite	Foster blood coagulation	Biocompatibility and good blood coagulation capability	CHNFs	—	Shorter plasma coagulation time/whole blood coagulation time than QuikClot Combat Gauze	[99]
Bioglass	Activate coagulation factor XII, accelerate coagulation cascade, and steady the formation of fibrin clots	May cause cell damage/inflammatory responses	CS-nBG hydrogel	In vivo major organ injury model	Faster blood clot formation	[109]
			Ga-MBG/CHT scaffold	—	Improved capability to promote thrombus generation and platelet adhesion/aggregation	[116]
MSNs	Absorb water, activate clotting factor XII and other coagulation proteins	Mesoporous structure, large surface area, highly ordered pore structure, and alcoholic hydroxyl groups; may bring about systemic embolization	MSN@U	Rat liver laceration model	Shortened hemostasis time	[123]
			MSN–GACS	Femoral artery and liver injury models of rabbit	Better hemostatic efficacy and lower cardiovascular toxicity than CG	[124]
			AgNP-MSG	Rat liver injury model	Quick hemorrhage control and great antibacterial effect	[125]
Biosilica	Activate the cofactors HWK–kininogen and prekallikrein and coagulation factors XI and XII	Hierarchical porous structure, satisfactory blood compatibility, and negligible cell toxicity	Ca-biosilica	Rat tail amputation model	Better hemostatic effect than Quickclot	[128]
			CDDs	—	Quick hemostasis	[131]
			Hydroxybutyl CS and diatom-biosilica sponge	—	Accelerated blood clotting	[132]

(*continued on next page*)

Table 2 (*continued*)

Material	Hemostatic mechanism	Feature	Form	Animal model	Efficacy	Reference
Phosphate mineral	Elevate blood coagulation cascade and ameliorate the platelet adhesion	—	Porous microspheres fabricated by hydroxyapatite-*graft*-poly(D, L-lactide) nanocomposites	—	Excellent hemostatic performance	[133]
			Hemostatic aerogel combining hydroxyapatite nanowires and PVA	Rat liver and rabbit femoral artery models	Effective prevention of bleeding	[134]
			CS hydrogel with nano whitlockite	Sprague–Dawley rat femoral artery and liver injury models	Decreased blood loss compared with CS hydrogel	[135]
Polyphosphate	Enhance coagulation factor V activation, stabilize fibrin clot, and promote feedback activation of factor XI by thrombin	Rapid degradation and dissolution	Polyphosphate-conjugated hyaluronan hydrogel	Mouse liver hemorrhage model	Comparable hemostatic ability relative to fibrin glue	[141]
Carbon aerogels (sponge)	Rapidly absorb plasma	Low density, porous structure, and high specific surface area, but potential thrombosis, hemolysis, and cytotoxicity	Graphene–kaolin composite sponge	Rabbit artery injury model	Staunching bleeding in around 73 s	[151]
			BGCS	Rat tail amputation model	Halting bleeding within 50 s	[153]
			N-Alkylated CS/GO composite sponges	Rabbit femoral injury model	Better coagulation efficacy than Celox	[154]
AgNPs	Accelerate thrombin generation and activate platelets	—	CGSH/Ag50	Rabbit liver and ear injury models	Rapid control of bleeding, antibacterial activity, promotion of full-thickness wound healing	[164]
Ce	Promote platelet aggregation	—	Composite sponge comprised of Ce-containing MBG and CS	—	Better hemostatic effect than gelatin sponge	[165]
Collagen	Induce platelet aggregate formation and combine with thrombin to stimulate platelets and foster clotting factor release	Good biodegradability and biocompatibility, and low antigenicity	Recombinant collagen sponge	Rabbit liver injury model	Effectively promoting blood coagulation	[173]
			CPNFs-Col sponge	Rabbit hepatic trauma and ear artery models	Activated intrinsic coagulation cascade pathway	[174]
			Collagen/OMCC sponges	Rabbit ear artery and hepatic trauma models	Rapid hemostatic efficacy	[175]
Gelatin	Activate platelet aggregation	Good biocompatibility, great biodegradability, and low antigenicity, but weak absorption capacity	HA/gelatin hydrogel	Rat liver-bleeding model	Rapidly absorbing blood	[179]
			Gelatin/dopamine cryogels	Mouse tail amputation and liver trauma models, rat liver incision model, and rabbit liver cross incision model	Better hemostatic effect compared with normal gauze/gelatin sponge	[180]
			Cryogel based on gelatin and Ag NPs	Noncompressible liver hemorrhage model of rat	Lower blood loss than gelatin sponge	[181]
			GelMA-based photocrosslinkable hydrogel	Cardiac penetration holes of pig hearts or incision wounds of pig carotid arteries	Sealing injured cardiac walls and arteries	[187]
			Hemostatic bioadhesive gel containing reptilase and GelMA	Rat tail cut and liver incision models	Causing rapid hemostasis	[189]
			Hydrogel consisting of GelMA, adenine acrylate, and $CuCl_2$	Mouse liver injury model	Good antibacterial and hemostatic effects	[190]

Table 2 (*continued*)

Material	Hemostatic mechanism	Feature	Form	Animal model	Efficacy	Reference
Keratin	Adhere and activate platelets; decrease plasma coagulation lag time and amplify fibril lateral assembly	Good cellular attachment, biocompatibility, and biodegradability	Expandable sponge based on polyacrylamide and keratin	Rat penetrating liver hemorrhage and swine femoral artery transection hemorrhage models	Effectual hemostasis	[200]
			Kerateine nanoparticles	Rat tail amputation and liver puncture models	Considerably reducing coagulation time	[197]
Fibrin	Related to the polymeric fibrin network formation	Great blood clotting ability, but with low strength and risk of contamination with viruses	Chitin–fibrin gel with tigecycline-loaded gelatin nanoparticles	Liver (oozing) and femoral artery (pressured) bleeding models of Sprague–Dawley rats	Causing rapid blood clotting and preventing bacterial infection	[209]
SF	Seal the wound	Low cost, various sources, tunable mechanical properties, and excellent biocompatibility and biodegradability	TA-SF-diclofenac potassium hydrogel	Rat tail truncation model and animal tooth extraction model	Strong wet-adhesion ability, satisfactory hemostatic property, and outstanding anti-inflammatory effect	[214]
			CSH	Rabbit liver hemorrhage model	Elevated blood clotting, declined blood loss, and accelerated reepithelialization/ revascularization	[215]
Self-assembling peptides	Form nanofiber barriers and concentrate blood components	Self-assembly characteristic, inherent biocompatibility, and degradability	RADA16-I nanofiber-based bandage	Porcine skin wound	Accelerating hemostasis	[221]
			RATEA16	Rabbit liver wound model	Achieving complete bleeding cessation within around 40 s	[218]
			I_3QGK	Rat liver wound	Rapidly impeding hemorrhage	[224]
CS	Nonspecifically bind to cell membranes; promote platelet activation and blood protein agglutination to facilitate fibrin clot formation	Low cost, abundant sources, trouble-free storage and long shelf-life, good biocompatibility/ biodegradability, antibacterial ability, and stimulatory to tissue regeneration	CS@ZnAlg microspheres	Rat liver laceration and tail amputation models	Enhanced hemostatic activity than CSMS	[245]
			Squid ink polysaccharide-CS sponge loaded with Ca^{2+}	Rabbit ear artery, femoral artery, and liver hemorrhage models	Causing decreased hemorrhage volume than gelatin sponge/CS dressing	[249]
			CS-loaded cyclodextrin hydrogel	Acute liver punch models of rat, rabbit, and pig	Shorter hemostasis time compared with commercial dressing	[254]
			Dodecyl-modified CS-coated microneedle patch	Rabbit liver, spleen, and kidney hemorrhage models	Excellent hemostatic effect	[261]
			TMC/AgNPs	Mouse liver injury model	Hemostasis and antiinfection	[265]
			Dry cryogels based on polydopamine-crosslinked CS	Mouse liver trauma, rat standardized circular liver section, and rabbit liver defect hemorrhage models	Superior hemostatic effect compared with gelatin sponge and Combat Gauze	[277]
			Catechol-conjugated CS hydrogel	Rabbit ilium bone defect model	Causing quick hemostasis	[278]
			CS/TA/SF hydrogel	Bleeding in liver hole, liver cut, heart hole, and tail cut of rats, bleeding in the ear artery, femoral artery, liver cut, and cardiac puncture of rabbits	Causing rapid and effective hemostasis	[284]

(*continued on next page*)

ic activity, which is beneficial for avoiding the inherent defects of a single hemostatic component and potentiating the hemostatic performance in different application

Table 2 (*continued*)

Material	Hemostatic mechanism	Feature	Form	Animal model	Efficacy	Reference
Dextran	Absorb blood to concentrate clotting factors, RBCs, and platelets, accelerating clot formation	Good water solubility, good biocompatibility/ biodegradability, and low cost; reduce immunogenicity of enzymes/proteins	Sponges made of crosslinked HA and cationized dextran	Mouse liver hemorrhage model	Effectively stemming bleeding	[292]
			Aldehyde dextran sponge	Femoral artery, ear vein, and liver injuries of rabbits	Notably decreased blood loss	[293]
			Hydrogel dressing consisting of OD and hydrophobically modified CS	Rat liver hemorrhage model	Satisfactory hemostatic/ antibacterial capability and wound healing effect	[297]
			OD/EPL hydrogel	Rat liver injury model	Comparable hemostatic performance relative to commercial fibrin glue	[298]
			Poly(DEX-GMA/AAc) microgel particle	Ear artery, ear vein, liver artery, and femoral artery hemorrhage of rabbits	Decreased hemostasis time and blood loss	[299]
Alginate	Facilitate the concentration of platelets and RBCs, and activate clotting factors	Relatively low cost, mild gelation, and exceptional biocompatibility; but weak mechanical strength and poor chemical stability	Sodium alginate/gelatin sponge	Mouse liver injury model	Exceptional hemostatic activity	[315]
			Hydrogel based on catechol- and aldehyde-modified alginate and adipic dihydrazide-modified poly (L-glutamic acid)	Rat liver bleeding model	Quickly and effectively controlling hemorrhage	[316]
			Silver nanocluster-decorated alginate/SiO_2 nanofiber composite scaffold	Rabbit femoral vascular injury model	Halting bleeding in 10 s	[317]
HA	Physical hemostasis	Excellent biocompatibility; able to promote dermal regeneration	Hybrid hydrogel combining HA-AEMA and mPEG-MA hybrid hydrogel and CLNs	Mouse liver hemorrhage model	Quickly stemming bleeding and accelerating wound healing	[325]
			Cryogel dressings obtained from adipic dihydrazide-modified HA and dopamine	Deep noncompressible liver hemorrhage of rat	Good antibleeding and antibacterial performance	[326]
			Serotonin-conjugated HA hydrogel	Liver hemorrhage in hemophilic mouse	Higher hemostatic activity than fibrin glue	[327]
Starch	Rapidly absorb plasma, concentrating blood cells and coagulation factors	Low cost, wide sources, and good hydrophilicity/biocompatibility/degradability; free of animal or human blood components and proteins	Ca^{2+}CPSMs	Mouse tail amputation model	Satisfactory hemorrhage control	[338]
			Microparticles composed of plant polyphenols and starch	Cancellous-bone-defect model of mouse	Good hemostatic effect and markedly accelerated bone repair	[340]
Cotton	Pack the wounds and absorb water	Softness, low-skin-irritating property, and good breathability, but limited hemostatic capacity and nonnegligible risk of adhesion with wounds	Carboxymethylated cotton fabric	Rat liver injury model	Less hemostatic time	[353]
			Modified cotton fabric with Janus-like property	Rat carotid artery bleeding and liver injury models	Better hemostatic capability than cotton fabric	[354]
Oxidized cellulose	Absorb liquid, act as a physical barrier to block blood flow, and stimulate platelet aggregation	Antibacterial property, biocompatibility, biodegradability, and comparatively low cost	SSAD-CS	Noncompressible torso liver hemorrhage model of rat	More effective hemostatic performance than gelatin sponge	[377]
			Janus sponge based on CNFs and organosilanes	Femoral artery and carotid artery injury models of rat	Decreased blood loss and prolonged survival time	[379]
			TOCN-SF-Th	Rabbit ear artery bleeding model and rat liver avulsion and tail amputation models	Decreased blood loss and bleeding time	[382]
			QHM	Lethal rabbit liver defect bleeding model	Decreased blood loss compared with commercially available hemostats	[387]

Table 2 (*continued*)

Material	Hemostatic mechanism	Feature	Form	Animal model	Efficacy	Reference
PEG	Seal blood vessels to promote hemostasis	Good biocompatibility, nonimmunogenicity, and structural flexibility; but possible allergic responses and adverse swelling	Hydrogel composed of PEG and HA	Rat model of arterial hemorrhage and pig model of acute gastrointestinal bleeding	Rapid gelation rate, sufficient mechanical property, and robust blood coagulation capacity	[399]
			Tetra-PEG hydrogel sealant	Rabbit liver bleeding and porcine spleen bleeding models	Satisfactory hemostatic capability	[400]
PVA	Achieve physical hemostasis by local compression	Nontoxic, water-soluble synthetic polymers	Hemostatic cryogel composed of carboxymethyl CS, dopamine, and PVA	Lethal liver defect hemorrhage model of coagulopathic rabbit and noncompressible liver defect bleeding model of rabbit	High compression strength, great shape memory performance, and strong hemostatic ability	[407]
			Hydrogel comprised of PVA and polycationic polymer	Hemorrhagic liver model of rat	Strong adhesion to the wound surface and ability to accelerate hemostasis/wound closure	[409]
PAA	Quickly absorb blood	—	Hemostatic powder containing PAA, PEI, and quaternized CS	Bleeding at the heart, liver, femoral artery, and tail vein of rats and noncompressible hemorrhage in liver and spleen of pigs	Excellent hemostatic performance	[410]
PCL	—	Biodegradability, nonantigenicity in humans, high blend compatibility, and low cost	Injectable superelastic nanofiber rectangular matrix	Porcine liver injury model	Good hemostatic effect	[418]
PLGA	—	Good biocompatibility and biodegradability; with FDA approval	PLGA-HA FFs	Rat liver laceration model	Safe and effective hemostasis	[421]
Polyurethane	—	Good biocompatibility, mechanical property, and flexibility	PUUF wound dressing	—	Superior blood coagulation performance	[424]
			Hemostatic dressing based on a polyurethane shape memory polymer foam	Noncompressible lethal porcine liver injury model	Rapid shape recovery ability and reduced blood loss compared with QuikClot Combat Gauze and XStat	[425]
Cyanoacrylate	Seal wound to stop bleeding	Potential toxicity	Cyanoacrylate fibers	Liver resection model of rat	Hindering hemorrhage within 10 s	[427]

Abbreviations: mCHA-C: mesoporous chabazite-type zeolite-cotton; CG: Combat Gauze; Z-CGS: zeolite/crosslinked graphene sponge; CSMS-K: chitosan/kaolin composite porous microspheres; GelMA: gelatin methacrylate; REC: rectorite; CS: chitosan; CHNFs: cellulose–halloysite hemostatic nanocomposite fibers; CS-nBG: chitosan-nanobioglass; Ga-MBG/CHT: 1 % Ga-mesoporous bioactive glass/chitosan; MSN@U: urushiol-functionalized mesoporous silica nanoparticle; MSN–GACS: mesoporous silica nanoparticle–glycerol-modified *N*-alkylated CS; AgNP-MSG: silver nanoparticle-incorporated mesoporous silica granule; Ca-biosilica: calcium-doped biosilica; CDDs: CS/dopamine/diatom-biosilica composite beads; PVA: poly(vinyl alcohol); BGCS: *Bletilla striata* polysaccharide/graphene oxide (GO) composite sponge; CGSH/Ag50: chitosan/gelatin/sodium hyaluronate dressing with Ag NPs; MBG: mesoporous bioactive glass; CPNFs-Col sponge: collagen sponge reinforced with CS/calcium pyrophosphate nanoflowers; OMCC: oxidized microcrystalline cellulose; HA: hyaluronic acid; SF: silk fibroin; TA-SF-diclofenac potassium hydrogel: tannic acid-silk fibroin-diclofenac potassium hydrogel; CSH: cellulose/silk fibroin hydrogel; RADA16-I: CH_3CO-RADARADARADARADA-$CONH_2$; RATEA16: CH_3CO-RATARAEARATARAEA-$CONH_2$; CS@ZnAlg: chitosan@zinc alginate; CSMS: chitosan microsphere; TMC/AgNPs: thiol-modified CS/AgNPs sponge; CS/TA/SF: chitosan/tannic acid/silk fibroin; RBCs: red blood cells; OD: oxidized dextran; EPL: ε-poly-L-lysine; poly(DEX-GMA/AAc): polymerized glycidyl methacrylate derivative dextran/acrylic acid; HA-AEMA: aminoethyl methacrylate hyaluronic acid; mPEG-MA: methacrylated methoxy polyethylene glycol; CLNs: chlorhexidine diacetate-loaded nanogels; Ca^{2+}CPSMs: calcium ion-exchange crosslinked porous starch microparticles; SSAD-CS: skin secretion of *Andrias davidianus*@cellulose nanocrystal/cellulose nanofiber sponge; CNFs: cellulose nanofibers; TOCN-SF-Th: thrombin-loaded 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-oxidized cellulose nanofiber (TOCN)–silk fibroin scaffold; QHM: quaternized hydroxyethyl cellulose/mesocellular silica foam hydrogel sponge; PEG: polyethylene glycol; tetra-PEG: tetra-armed poly(ethylene glycol); PAA: poly(acrylic acid); PEI: polyethyleneimine; PCL: polycaprolactone; PLGA: poly(lactide-*co*-glycolide); PLGA-HA FFs: poly(lactide-*co*-glycolide)-hyaluronic acid fibrous fragments; PUUF: polyurethane-urea foam.

Table 3
Summary of various intravenous hemostatic agents.

Strategy	Traditional product	Problems	Emerging product	Effect	
Modulating the components involved in clotting cascade or the formation of fibrin clots	Fibrinogen-based hemostatic products	Fibrin is susceptible to fibrinolysis, causing rebleeding; high cost; need to remove blood-borne pathogens; may be forbidden by some religions	PolySTAT	Helping construct a stable crosslinked fibrin network	[441]
	Fresh frozen plasma	Risk of transmitting infection; may cause allergic reactions and anaphylaxis	Q-PEG	Increasing the adhesive strength of clots	[442]
	Coagulation factor products	Suffer from rapid clearance in vivo and may be inactivated by alloantibodies	PEG-PLPs	Boosting fibrin network formation in vitro	[443]
	Aprotinin, tranexamic acid, and aminocaproic acid	–	ADGs	Causing autoactivation of FXII	[462]
Platelet-related products	Platelets	Short shelf life, limited portability and availability, high risk of bacterial contamination, and the need for antigen matching	"Donor-independent" platelet technologies	More consistent and safer, decreasing the necessity of human donation	[478–480]
	Freeze-dried or lyophilized platelets	–	Natural platelet-derived vesicles	Better hemostatic effect than platelets	[482]
	–	–	Synthetic platelet substitutes	Facilitating platelet aggregation and platelet plug formation, unlimited supply, relatively low cost, and simpler handling and storage	[483,484,487–497]

Abbreviations: ADGs: artificial dense granules; PolySTAT: a synthetic polymer with a linear poly(hydroxyethyl methacrylate) backbone grafted with ~ 16 fibrin-binding peptides; Q-PEG: an 8-armed PEG conjugated to a glutamine-containing peptide; PEG-PLPs: platelet-like particles from PEG side-chain microgels with fibrin binding moieties.

scenarios.

In recent years, owing to the rapid emergence of new hemostatic materials, it is necessary to establish an objective and effective evaluation system to comprehensively assess the hemostatic effect of these materials. Such an evaluation system is supposed to contain in vitro and in vivo evaluation methods. Some in vitro tests have been employed to evaluate the hemostatic efficacy of materials qualitatively and quantitatively. First of all, the clotting formation on the tested material in contact with blood should be observed directly. The cell adhesion, platelet adhesion and activation, and fibrinogen adsorption on the sample need to be further observed clearly via various imaging techniques (e.g., SEM). Besides, the coagulation effect of the samples can be primarily reflected via the photometric detection of free hemoglobin and the calculation of BCI. To assess the thrombus generation after the contact between the material and blood, thrombin-antithrombin-III complex serves as an indicator for thrombin generation and can be measured via enzyme linked immunosorbent assay (ELISA).[523] Moreover, the plasmatic thrombin generation can be determined via a commercialized thrombin generation test. Thrombelastogram (TEG) technology can also be adopted to provide a robust and low-cost snapshot of the hemostatic performance of a hemostat. TEG analyzes the viscoelastic changes during the clotting process and represents an important graphic means to assess the dynamic development of thrombus formation and can also be used to evaluate the blood clot strength. Besides, several important coagulation-related time indexes (containing whole blood clotting time, plasma clotting time, APTT, and PT) also serve as screening tools to estimate the procoagulant activity of diverse hemostats. To accurately predict the hemostatic effects of various materials, it is essential to choose suitable in vitro test methods with regard to the properties/intended use of the material along with the physiological condition of the patient. The method of in vitro evaluation is simple and fast, which can quickly help researchers judge the hemostatic ability of materials to determine the most effective material for further research. However, there are still some discrepancies between the in vitro and in vivo hemostatic evaluation results of materials, and an accurate judgment of the treatment effect of hemostatic materials still requires the reasonable construction of in vivo models. The available in vivo models are diverse, comprising controlled and uncontrolled bleeding, compressible and incompressible hemorrhage, regular and irregular bleeding, polytrauma or specific organ (such as liver, spleen, and heart), in different animals (consisting of small rodents, large mammals, as well as non-human primates). The common trauma models for mouse consist of ear, tail, and liver bleeding and the models of rat contain liver laceration, spleen bleeding, artery injury, tail amputation, etc. The mice and rats are cost-effective and easily available, however, there are some dissimilarities in physiology and hemodynamics between humans and rodents, causing discrepant outcomes between humans and mice/rats. Rabbit is one of the most viable and popular candidates for in vivo models used to evaluate the hemostatic efficiency of materials. Many injury models can be constructed on rabbits, including but not limited to ear injury, lethal artery injury, spleen hemorrhage, kidney hemorrhage, liver defect, and cardiac puncture. A series of hemostatic materials have also been tested on pigs to treat liver and spleen injuries, skin wounds, cardiac penetration, or carotid artery bleeding. The cardiovascular system parameters and size of pigs are similar with those of humans and the wound healing process of pigs is comparable to that of humans; nonetheless, the pig models are expensive and require skilled operation. The great physiological similarity between primates and humans makes the experimental results produced from the primates most similar to those obtained from humans. Consequently, the experiments carried out on non-human primates are important for pre-

Table 4
Summary of clinical trials of promising hemostat products in recent years.

Study title	Condition	Hemostat	Phase	NCT number
PeproStat as a Topical Agent Used to Stop Bleeding in Patients Undergoing Surgery	Bleeding	PeproStat	Phase 2	NCT03131336
Determine the Efficacy of TT-173. Reducing the the Total Blood Loss Associated with Total Knee Arthroplasty (HESTAT)	Degenerative osteoarthritis	TT-173	Phase 2/3	NCT02687399
Traumastem versus Surgicel for the Secondary Treatment of Local Bleeding in Patients Undergoing Hepatic Resection (TSFHR)	Liver hemorrhage	Traumastem	Phase 3	NCT03489070
Seraseal for Endoscopic Hemostasis	Gastrointestinal hemorrhage	Seraseal/Fastact hemostatic agent (combined activated factors IIa, VIIa, IXa, Xa)	Phase 4	NCT02349490
The Bioseal Vascular Study	Cardiovascular bleeding; vascular bleeding; hemorrhage	Bioseal fibrin sealant	Phase 4	NCT02094885
Efficacy and Safety of Sangustop as Haemostatic Agent versus a Carrier-Bound Fibrin Sealant During Liver Resection (ESSCALIVER)	Hemorrhage	Sangustop	Phase 4	NCT00918619
Hemostasis Pad Using Chitosan after Invasive Percutaneous Procedures	Coronary artery disease; puncture	EzClot (hemostasis pad)	Phase 4	NCT02954029
Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot Polysaccharide Hemostatic System (CLOT)	Blood loss; surgical use	PerClot polysaccharide hemostatic system	Not applicable	NCT02359994
ACCEL Absorbable Hemostat	Hemorrhage	ACCEL absorbable hemostat powder	Not applicable	NCT04728087
Effectiveness of BioFoam Surgical Matrix to Improve Hemostasis During Liver Resection (BioFoam)	Hemorrhage	BioFoam surgical matrix	Not applicable	NCT02612220
A Prospective, Multi-Center, Single-Arm Study of the Veriset Hemostatic Patch in Controlling Bleeding in Soft Tissue	Nonemergent, soft tissue procedures, performed via an open approach	Veriset hemostatic patch	Not applicable	NCT01719172
Performance and Safety of the Surgical Hemostatic Agent "HEMOCOLLAGENE" in Patients Requiring Oral Surgery	Oral hemorrhage	HEMOCOLLAGENE	Not applicable	NCT05171231
Efficacy of a Collagen Hemostatic Dressing after Tooth Extraction	Tooth avulsion	Hemostatic dressing ETIK COLLAGENE	Not applicable	NCT05174858
A Study to Assess the Safety and Performance of SurgiClot in the Treatment of Cancellous Bone Bleeding	Cancellous bone bleeding	SurgiClot hemostatic dressing	Not applicable	NCT02509208
Studying Safety & Efficacy of Axiostat Dressing in Acute Hemorrhage Due to Trauma-Comparative Study	Bleeding	Axiostat	Not applicable	NCT03035695
EndoClot for Hemostasis and Preventing Post-procedure Bleeding after Endoscopic Mucosal Resection (EMR)	Endoscopic hemorrhage	EndoClot	Not applicable	NCT01496781
Surgicel Snow in Gynecological Surgery	Laparoscopic hysterectomy	Surgicel snow	Not applicable	NCT02908841
Prospective Clinical Trial of the Hemopatch Topic Hemostatic in Cardiac Surgery	Bleeding	Hemopatch	Not applicable	NCT02133378

All the data are from https://clinicaltrials.gov/.

clinical investigation purposes. For various in vivo bleeding models, coagulation time, blood loss, wound healing, and survival rate are the vital indicators to evaluate the hemostatic activity of materials. Compared with in vitro evaluation methods, the results of in vivo research are often more reliable, while the establishment of in vivo models requires higher costs and more complicated operations. Hence, the in vitro and in vivo evaluation methods need to be integrated to conduct a comprehensive estimation of the hemostatic properties of the prepared materials.

To meet the clinical demands, there are several important directions for the future development of hemostatic materials:

The design, development, and application of hemostatic materials should be target-oriented, that is, different hemostatic materials and hemostatic measures should be adopted for different bleeding accidents in consideration of the difference of bleeding volume, emergency degree, bleeding organ, and the physical condition of the bleeding patient. First, in terms of the emergency degree of a bleeding accident, simple, handy, and low-cost hemostatic materials are well suitable for dealing with slight/local bleeding with low blood flow rate. Nonetheless, for deep/irregular wounds where incompressible and severe hemorrhage with high blood flow rate occurs, rapid and effective hemostatic materials must be adopted. Unfortunately, until now, the researches on hemostatic materials that can effectively prevent fatal incompressible bleeding are still insufficient. It is necessary to devote more attention to the field and strive to develop a variety of novel hemostatic materials that can rapidly stem the bleeding of deep, irregular, or incompressible wounds. The development of hemostatic hydrogels is an important and prevalent strategy to manage intractable hemorrhage. Hemostatic hydrogels should be equipped with excellent wet adhesion, suitable mechanical strength, capacity to perfectly fit within and adhere firmly to the irregular injured site with large/fast blood flow. Besides, after successful bleeding control, the hydrogels should either be completely degraded or remain intact and could be easily removed to avoid secondary bleeding and infection arising from forced tearing. Hence, it is vital to adjust the adhesive ability of hemostatic hydrogels so that they can adapt to different demands during and after hemostasis. In other words, the hemostatic hydrogels should firmly adhere to the wet tissue surface to take effect during hemostasis. After the completion of hemostasis, the adhesive ability of the hemostatic materials should be adjusted to an appropriate level for easy removal of the materials. In addition, it is essential to select appropriate hemostatic materials for the different bleeding organs. For instance, for upper gastrointestinal hemorrhage, especially for those involved in recurrent hemorrhage, widespread and diffuse hemorrhage, or those happen in patients with complicated anatomy, the hemostatic materials should have the ability to adhere tightly to the wet and smooth surface of gastrointestinal mucosa and to achieve long-term effective hemostasis, which raises high demands for hemostatic materials.[399] The bone hemorrhage and bone defects induced by trauma or bone tumor resection usually have irregular/incompressible injury areas, and massive body fluid may also occur in these injury sites. Hence, the corresponding hemostatic materials need to be able to stem irregular and incompressible bleeding and have strong wet adhesion capacity. To guarantee biocompatibility, the hemostatic materials should be absorbable following bone wound healing to avoid obstructing bone regeneration. Besides, the physical condition of a patient should also be taken into account when managing hemorrhage, including coagulation dysfunction and potential allergic reactions to some materials. For patients with coagulation dysfunction, there are some effective strategies including employing specific single-factor concentrates to replace the deficient coagulation factors, using prothrombin complex concentrates, systemic antifibrinolytics (e.g., tranexamic acid, ε-aminocaproic acid, etc.), procoagulant phospholipids, or synthetic hemostatic polymers (including PolySTAT and Q-PEG) which are capable of accelerating clot formation, refining clot firmness, or hindering clot lysis. Along with intravenous hemostatic agents, some local hemostatic agents can also be adopted to treat the bleeding wounds in patients with coagulation dysfunction, but these hemostatic agents are often required to stop bleeding not via activating the coagulation cascade, but through physical ways: including sealing the wound, providing a physical barrier to concentrate RBCs, or other ways independent of fibrinogen and thrombin in the blood. Moreover, for those patients with possible allergic reactions, the hemostatic materials should not cause severe allergic responses to avoid posing a threat to the health of the patients.

Some new technologies can be applied in the research of various hemostatic materials. The rapid development of nanotechnology in recent years provides choices for the design of hemostatic materials. Some porous nanomaterials (such as nanoclay, nBG, MSNs, etc.) present a good ability to absorb blood. And the smaller pore size than the cell size helps them combine well with the blood cells to further promote hemostasis.[524] Some metal NPs are also believed to possess good procoagulation ability. A broad array of other nanomaterials (including nanofibers, nanogels, nanotubes, carbon dots, etc.) can also be regarded as good choices for bleeding control. In addition to acting as hemostatic agents, nanomaterials are also expected to be engineered into a general platform to deliver diverse hemostatic, antibacterial, antioxidant, and other bioactive components to achieve multiple biological functions. When novel technologies are adopted to develop hemostatic materials, the safety of materials should not be ignored. It is necessary to give preference to the materials approved by FDA to avoid side effects on human body, including thrombosis, embolism, inflammation, allergic reaction, etc.

The hemostatic materials with dual or multiple functions provide tremendous advantages in practical applications. Hemostasis is often closely related to the process of wound healing. Thus, imparting diverse biomedical functions, including antibiosis, wound healing promotion, and pus drainage, to the hemostatic materials is quite essential in their practical applications and contributes to realizing hemostasis and promoting wound healing at the same time. The hemostatic materials can also be endowed with the identification and monitoring functions of the bleeding sites. Some optical materials can be combined with the hemostatic components to realize the visualization of bleeding positions. For example, Jin et al. developed an optically anisotropic hemostatic coacervate through nonionic self-coacervation between cholesteryl liquid crystal and TA.[525] When the bleeding site was treated with the hemostatic coacervate, a ‘‘polyphenol-blood barrier” could be formed to promote bleeding cessation, followed by a bright green light emission of the delaminated liquid crystal from the hemostatic coacervate. The optically anisotropic hemostatic coacervate achieved clear visualization and identification of the hemostasis process and exhibited promising potential to prevent hemorrhage in clinical settings, especially minimally invasive surgery. The combination of sensors and hemostatic materials also provides great convenience for the monitoring of hemorrhagic wound areas. Moreover, the addition of tracers to hemostatic materials contributes to rapid and accurate identification and diagnosis of unknown internal bleeding areas via some standard clinical imaging technologies like endoscopy, ultrasonographic visualization, X-ray computed tomography, near-infrared imaging, etc. To give an example, Gkikas et al. combined hemostatic polymeric NPs with three kinds of tracers, i.e., biotin-functionalized NPs, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindodicarbocyanine perchlorate (DiD, a fluorescent dye), and gold NPs, to achieve identification of internal bleeding with immunohistochemistry, near-infrared fluorescence imaging, and X-ray computed tomography,

respectively.[526] The applicability of multifunctional hemostatic materials in the practical situations should also be considered. Many multifunctional hemostatic materials have the properties of rapid hemostasis and antiinfection. However, the two properties are often verified in two different situations or experiments. For the bleeding accidents in real life, whether the multiple functions can be realized perfectly at the same time remains challenging. Furthermore, the preparation process of multifunctional materials is often complicated and troublesome. The researchers are supposed to try to choose suitable preparation approaches and then continuously optimize the approaches to develop simple, low-cost, and "green" preparation technologies to facilitate the large-scale production of the hemostatic materials.

In addition, although there are numerous researches on hemostatic materials, the clinical translation of these hemostatic materials is seriously insufficient. Some recently ongoing clinical trials of potential hemostats have been summarized in Table 4. It is necessary to speed up the clinical translation of hemostatic materials to help patients with bleeding problems.

In the near future, more significant efforts are expected to be made to develop more effective and safer hemostatic agents for bleeding control. We sincerely hope that this review may inspire more researchers to devote themselves to improving the hemostatic performance of the existing hemostatic materials and propose more feasible construction strategies to develop new hemostatic materials.

Data availability

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the Natural Science Foundation of Jiangsu Province (BK20211510), National Natural Science Foundation of China (21673037), and Nantong Municipal Science and Technology Project (MS22020010).

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