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Review article

Smart design in biopolymer-based hemostatic sponges: From hemostasis to multiple functions

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ABSTRACT

Uncontrolled hemorrhage remains the leading cause of death in clinical and emergency care, posing a major threat to human life. To achieve effective bleeding control, many hemostatic materials have emerged. Among them, nature-derived biopolymers occupy an important position due to the excellent inherent biocompatibility, biodegradability and bioactivity. Additionally, sponges have been widely used in clinical and daily life because of their rapid blood absorption. Therefore, we provide the overview focusing on the latest advances and smart designs of biopolymer-based hemostatic sponge. Starting from the component, the applications of polysaccharide and polypeptide in hemostasis are systematically introduced, and the unique bioactivities such as antibacterial, antioxidant and immunomodulation are also concerned. From the perspective of sponge structure, different preparation processes can obtain unique physical properties and structures, which will affect the material properties such as hemostasis, antibacterial and tissue repair. Notably, as development frontier, the multi-functions of hemostatic materials is summarized, mainly including enhanced coagulation, antibacterial, avoiding tumor recurrence, promoting tissue repair, and hemorrhage monitoring. Finally, the challenges facing the development of biopolymer-based hemostatic sponges are emphasized, and future directions for *in vivo* biosafety, emerging materials, multiple application scenarios and translational research are proposed.

1. Background

Severe trauma claims the lives of over 5.8 million people worldwide annually, yet about 40 % of them are caused by uncontrolled bleeding or its consequences [1,2]. It has been reported that in civilian and battlefield Settings, massive blood loss from the junction of limbs, torso, and non-compressible injuries can lead to severe pre-hospital death, as well as hemorrhagic shock, coagulopathy, multiple organ failure, life-threatening sepsis, and acidosis. Bleeding accounts for a third of all deaths in civilian emergency care, and a staggering more than half on the battlefield. Importantly, these deaths could have been prevented by effective hemostasis, which highlights the urgent need for effective hemostatic measures to mitigate this lethal threat to human life [3]. Many methods of hemostasis have been created (e.g., transfusion of blood products, tourniquet, suture/anastomosis, electrotome hemostasis), which undoubtedly play a key role in emergency treatment and surgical procedures. However, the poor effects, high price, harsh operating environment, secondary tissue damage and other drawbacks make their application limited to a certain occasion, can not be widely promoted [4].

As an important field in medicine and materials science, biomaterial-based hemostasis strategy is attracting extensive research interest. Its

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development can be roughly divided into three stages: i) Assisted stage: In this initial stage, people mainly rely on physical pressure to stop bleeding, and use gauze and cotton balls to assist. This method has been commonly used in daily life and clinical medicine even to this day [5]; ii) Enhanced stage: With the progress of technology, the research gradually focus on improving the hemostatic property of material itself through many physical and physiological ways; iii) Functional stage: Besides efficient hemostatic performance, frontier research emphasizes the added value after completing the hemostatic task. Given that in many clinical settings, hemostatic materials are often not removed immediately after hemostasis, researchers explore how to give these materials more functions, such as antibacterial, drug release, tissue repair, and so on. This multi-functional design aims to solve problems in clinical practice, being an important trend for the future development of hemostatic materials [6].

In the design of hemostatic materials, the component and structure profoundly affect the properties and functions of materials. Biopolymers are a class of natural materials derived from animals and plants, mainly including polysaccharides and polypeptide [7]. These natural substances exhibit a number of remarkable characteristics that differ from synthetic polymers. Inherent biocompatibility is the most prominent feature, crucial in biomedical applications [8]. Biopolymers can coexist harmoniously with tissues without causing excessive inflammation, and can be safely biodegraded *in vivo*. In addition, these biopolymers exhibit unparalleled bioactivity and can be used in many biomedical fields [9]. Polysaccharides such as cellulose, chitosan, and alginate have unique structural properties that make them ideal for use in drug delivery and wound dressings. Similarly, collagen served as the most abundant protein in the body is widely used in medical cosmetology, wound healing and tissue engineering [10]. Many forms (e.g., sponge, hydrogel, powder and film) of hemostatic materials have been developed to control bleeding, which deeply affects their characteristics, functions and applications [11]. Due to the high porosity, sponges can quickly absorb blood and expand to seal the bleeding site especially in irregular, deep and incompressible wounds. Moreover, hemostatic sponge can react faster with the blood depend on its high specific surface area. Compared with the other types, the effect of sponge structure on its properties is particularly prominent, and this is closely related to the preparation process, which will be described below [6,10,12].

Hemostatic sponges are convenient to carry and use, widely used in clinical, especially in obstetrics and gynaecology, dentistry and otorhinolaryngology surgery. These applications demonstrate the versatility and importance of hemostatic sponges in the medical field. For example, Food and Drug Administration (FDA)-approved XStat™ has been successfully used for penetrating injuries at the junction of the trunk and limbs. DSI-sponge is used in surgical procedures to control bleeding from capillaries, veins and small arteries, offering attractive options for hemostasis when traditional methods have failed. In addition, the hemostatic sponge is also important to prevent post-operative adhesions such as in nose and uterus surgery [6,11].

Therefore, based on the above considerations, we reviewed the recent research progress of biopolymer-based hemostatic sponges, emphasizing the deep influence of material composition and structure on the functionalization (Fig. 1). The key process of physiological hemostasis is overviewed first, laying a foundation for the design of hemostatic materials. Then, starting from the material components, the latest progress of polysaccharide and polypeptides in hemostasis were introduced, specially highlighting their potential in the functional designs. As for the structure, we introduced the processes commonly used in sponge preparation and characteristic. In particular, the functional

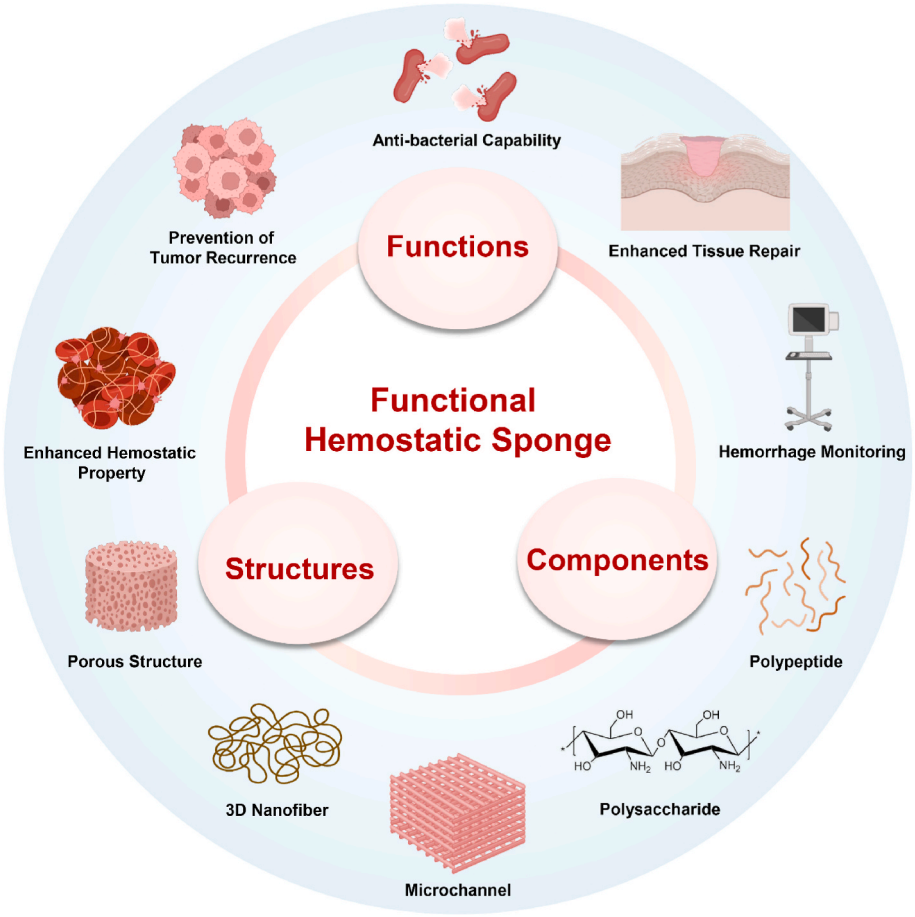

Fig. 1. The functions, structures and components of functional hemostatic sponges based on the biopolymers.

applications of hemostatic materials in enhancing coagulation, antibacterial, avoiding tumor recurrence, promoting tissue repair, and bleeding monitoring were summarized.

2. The fundamentals of hemostasis

The starting point of hemostatic materials design is how to promptly stop bleeding, and this process is the physiological response of the body originally. Hence, the researchers initially need to understand how blood clotting occurs under physiological conditions, and in this way, the hemostatic materials can be designed and optimized more reasonably. Under normal circumstances, people will stop bleeding on their own within a few minutes after efficient control. We must recognize that physiological hemostasis is a rapid and complex process, and thus far, all the steps and substances involved in this process have not been fully elucidated [6,13].

Based on current research, the process of hemostasis can be briefly summarized as two stages: primary hemostasis (involving vasoconstriction and platelet plugs formation) and secondary hemostasis (involving the clotting cascade and blood clot formation) [14] (Fig. 2). In primary hemostasis, after being damaged, blood vessels constriction occurs and blood flow decreases due to the traumatic stimulus response and muscle activity. Then, in a very short time (1–2 s), platelets (PLTs) recognize and adhere to the injury site, mediated by its receptor-ligand interaction with subendothelial collagen. The surface of PLTs is rich in glycoproteins that bind to collagen in different ways. Under low shear conditions, glycoprotein (GP) Ia/IIa and GP VI can directly bind to collagen, while under high shear conditions, this is not enough. At this point, the binding of GP Ib/IX/V to collagen is required, and the necessary condition for this is von Willebrand factor (vWF) as a bridge. Subsequently, PLTs occur significant morphological changes, forming an irregular polypseudopodia structure, increasing the aggregation effect. And the GP IIb/IIIa undergo a conformational transition and can bind to fibrinogen, thereby joining adjacent PLTs. Activated PLTs release a variety of substances such as adenosine diphosphate (ADP), and they stimulate the temporary synthesis of thromboxane A2 (TXA2). These substances have a clear effect on promoting PLTs aggregation, thus forming a positive feedback. Finally, the connected PLTs form platelet plugs to seal the wound and achieve the primary purpose of hemostasis [15].

For the secondary hemostasis, the main task is blood clotting, which is a three-stage enzymatic reaction process (prothrombinase complex formation, thrombin activation, fibrin production) involving many clotting factors. They are activated successively in a certain sequence, known as the coagulation cascade. Initially, the first stage can be divided into intrinsic and extrinsic coagulation pathway, which differ in the coagulation factors and triggering conditions. Extrinsic pathway is triggered by tissue factors (Factor III, F III) outside the blood. The intrinsic pathway is triggered by negatively charged foreign bodies (i.e., glass and collagen), and the involved clotting factors are all derived from the blood. The complexes (F IIIa – F VIIa and F VIIa – F IXa complex, respectively, a stands for activation) can activate F X, and further form prothrombinase complex on the surface of PLTs phospholipid membrane, which called the common pathway [16]. In response, thrombin (F IIa) is rapidly activated. It is worth noting that the extrinsic pathway only contributes 5 % of thrombin, but it greatly promotes the intrinsic pathway. Therefore, F III act as initiators, and intrinsic pathway are very important for strengthening the coagulation response. Under the action

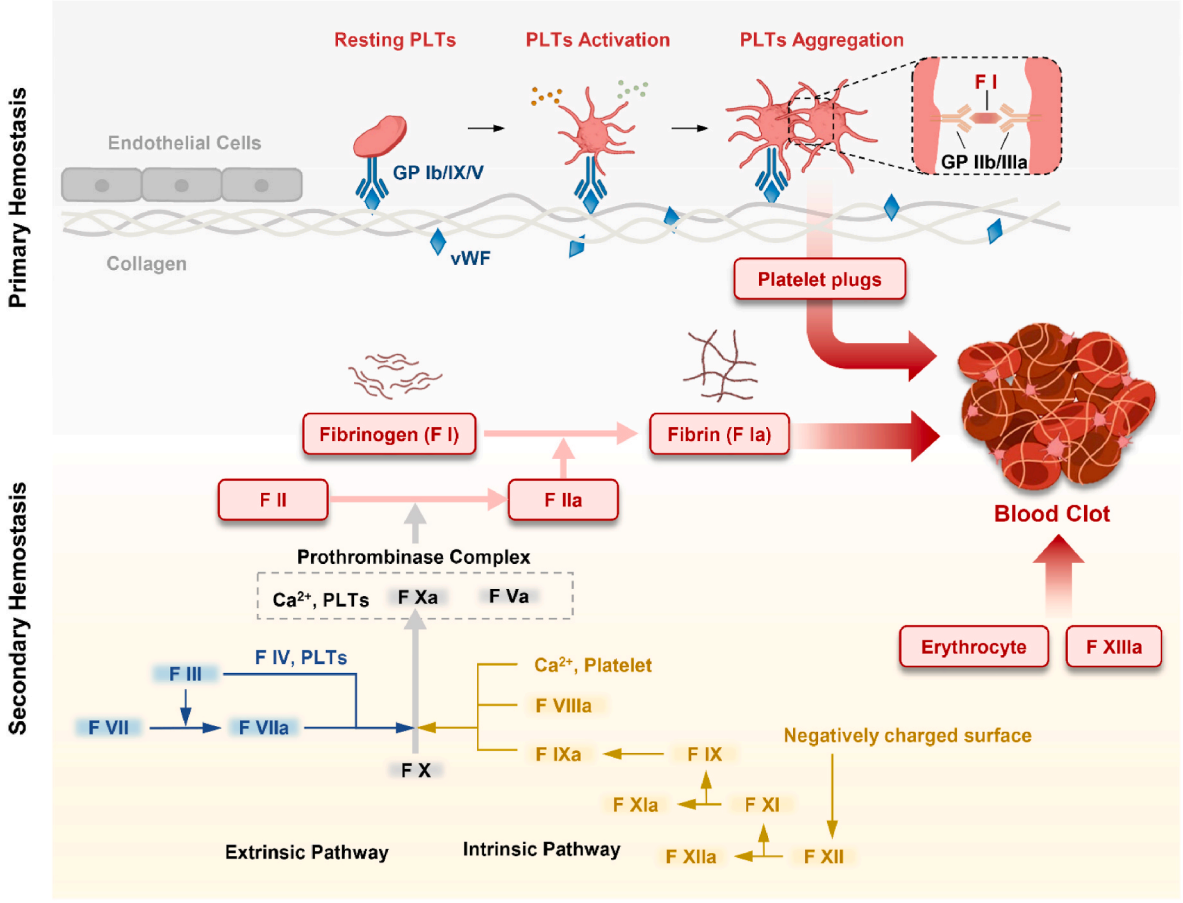

Fig. 2. Schematic illustration of the physiologic hemostasis process including primary hemostasis (platelet plugs formation) and secondary hemostasis (the clotting cascade and blood clot formation).

of thrombin, soluble fibrinogen is transformed into insoluble fibrin, which collaborates with platelet plug, erythrocyte, and F XIIIa to form a firm blood clot, achieving the purpose of hemostasis. Importantly, there is no clear division between primary and secondary hemostasis, they occur almost in parallel and can be mutually reinforcing [3].

The physiological hemostasis is a complex process with a variety of cells, proteins and ions. From a cellular point of view, the importance of PLTs is not in doubt, and the strengthening effect of erythrocytes on blood clots is also recognized [17,18]. For the protein, it is important to enhance intrinsic/extrinsic coagulation pathway and induce thrombin formation. Procoagulant Ca^{2+} ions (F IV) participate in the whole process of physiological hemostasis. All of them be used as design targets for functional hemostatic materials.

In terms of the physical mechanism of hemostasis, it can be summarized as concentration effect, adhesion sealing and charge stimulation: 1) Concentration effect: With the help of the large surface area and porosity of the material, the concentration of pro-coagulant components in the blood, such as PLTs, erythrocytes, coagulation factors, etc., is an effective and commonly used mechanism, and is important in sponge- and powder-type materials [11]; 2) Adhesion sealing: Through reasonable design, the material forms a strong adhesion with the tissue to achieve wound closure and prevent blood flow. The tissue adhesive can adapt to the irregular shape of the wound and is convenient to use [7,19]; 3) Charge stimulation: Most proteins and cell surfaces in the blood are negatively charged. Positive-charged materials can trap and activate them via electrostatic interactions, speeding up the coagulation process. Meanwhile, many studies still show that negative-charged materials can also promote clotting by activating intrinsic pathway [6].

3. Component design of hemostatic sponge

The material component serves as one of the pivotal factors influencing the performance of hemostatic materials, thereby being of paramount importance in their design. Primarily, two major categories exist: polysaccharides (i.e., cellulose, chitosan, dextran, alginate, hyaluronic acid, and starch) and polypeptides (i.e., collagen/gelatin, keratin, and silk fibroin) (Fig. 3). Each material has unique advantages in physical properties, hemostatic mechanism, bioactivity and so on, providing a variety of options for the design of hemostatic materials (Table 1).

3.1. Cellulose-based material

Cellulose is the most abundant natural polymer compound on earth and is the main component of plant cell walls. Typically, cotton and gauze have always played an important role in the medical field, and its soft, absorbent properties make them a common choice for emergency hemostasis [20,21]. Recently, Fan et al. successfully prepared fibrous-network cellulose sponges with high water absorption and rapid shape recovery by using surfactants and foaming agents. After being combined with chitosan, the cellulose sponge not only retains the own characteristics but also enhances the mechanical properties and pro-coagulant ability [22]. Additionally, the application of nanocellulose in hemostasis has attracted increasing attention. It has high crystallinity and usually be employed to enhances the excellent mechanical properties of sponges [23]. On the other hand, cellulose's inherent high crystallinity poses notable barrier in its application as a hemostatic material. This characteristic hinders the biodegradability *in vivo*, thus elevating the potential risk, especially for those surgical scenarios where hemostatic materials do not need to be removed [24]. The new cellulose-based hemostatic materials are gradually emerging.

Cellulose contains a large number of hydroxyl groups. Compared with the secondary hydroxyl groups on C_2 and C_3, the primary hydroxyl group on C_6 has lower steric resistance and higher reactivity. Oxidizing agents (2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), H_2O_2, NaClO) can introduce aldehyde, ketone, and carboxyl groups into cellulose to obtain oxidized cellulose (OC) [25]. OC not only inherits the biocompatibility of the cellulose, but also overcomes the insolubility problems. This enables the cellulose hemostatic material to rapidly absorb blood in the body, forming a stable gel-like substance, effectively sealing the bleeding point and achieving the effect of rapid hemostasis. OC hemostatic materials have been clinically applied. For example, Surgicel®

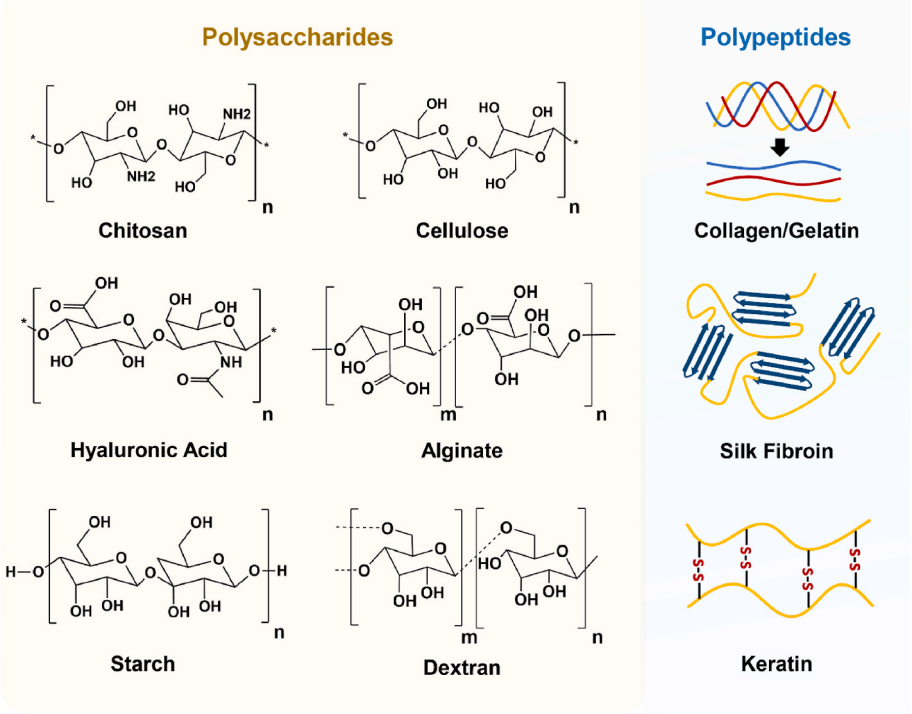

Fig. 3. The chemical structure of main biopolymers: polysaccharides (chitosan, cellulose, hyaluronic acid, alginate, starch and dextran) and polypeptides (collagen/gelatin, silk fibroin, keratin).

Table 1
Component design for functional biopolymer-based hemostatic sponges.

Materials	Source	Hemostatic mechanism	Characteristics	Reference
Cellulose	Produced by plants, algae, and delignified wood fibers	Concentration effect; Negative charge; Complexation with Fe^{3+}; Platelet activation and aggregation	Mechanical durability; High water absorption; Widely sourced; Poor biodegradation and solubility	[28,100, 159]
Chitosan	Derived from shrimp, crab, squid, and certain fungi	Positive charge; Erythrocyte aggregation; Platelet adhesion	Antibacterial properties; Biocompatibility; Poor solubility	[34,35, 159,160]
Hyaluronic Acid and Alginate	Commonly found throughout connective, epithelial and neural tissues; Extracted from seaweed	Concentration effect; Negative charge; Activating intrinsic pathway	Biocompatibility; Biodegradability; Insufficient chemical stability	[37,161]
Dextran	Microbial fermentation	Concentration effect; Erythrocyte aggregation; Platelet adhesion;	Adhesive ability; Biocompatibility; Easy chemical modification; Low mechanical strength	[51,58, 162]
Starch	Grains, root plants, legumes, etc	Platelet aggregation; Concentration effect;	High water absorption; Biocompatibility; Biodegradability; Widely sourced; Non-immunogenic; Low mechanical strength	[63,64]
Collagen and Gelatin	Protein in a mammal's body	Platelet adhesion and activation; Activating intrinsic pathway	Biodegradability; Biocompatibility; Bioactivity; Heterogeneity; Immunogenicity risk	[67,72]
Silk Fibroin	Commonly obtained from Bombyx mori cocoons	Platelet adhesion and activation; Enhanced binding of platelets and fibrinogen	Easy chemical modification; Biocompatibility Insufficient chemical stability	[16,155]
Keratin	Commonly found in hair, nails, wool, etc.	Platelet adhesion; Activating intrinsic and extrinsic pathways; Promoting fibrin clotting	Biocompatibility; Biodegradability Heterogeneity; Complex components	[91,161]

(Johnson & Johnson), which is mainly composed of oxidized regenerated cellulose, has become one of the most commonly used auxiliary hemostatic agents [26,27].

Carboxymethyl Cellulose (CMC) is another water-soluble cellulose derivative commonly used in the field of hemostasis, with excellent water absorption and swelling ability. Due to its high liquid absorption capacity, it is very conducive to concentrating substances in the blood, and CMC based hemostatic agents dissolve in the blood, resulting in an increase in blood viscosity and accelerated thrombosis. On the other hand, it has been reported that CMC acts as a bridge for fibrin polymerization [28]. Aldehydeated cellulose has also been developed, showing the biodegradability and enhanced chemical activity. A cryogel containing aldehydeated cellulose and dopamine has been reported with photothermal antibacterial (*S. aureus* and *E. coli* kill rate more than 90 %) [29]. In general, cellulosic materials have a long history in the design of hemostatic materials, and various functional designs continue to give them new vitality.

3.2. Chitosan-based material

Chitosan, a natural polymeric polysaccharide derived from chitin (commonly found in the shells of crustaceans and the exoskeletons of insects), boasts unique properties and bioactivities. It is the second most abundant polysaccharide after cellulose [19,30]. Remarkably, chitosan stands as the only biopolymer with positive charge, endowing it with inherent antibacterial and hemostatic activity. The negative-charged bacterial cell surface could electrostatically interact with chitosan, altering the membrane permeability and disrupting bacterial metabolism [31,32]. Using the positive charge, chitosan can also promote PLTs adhesion and aggregation [10]. Moreover, recent studies have also shown that the coagulation mechanism of protonated chitosan (quaternated, alkylated and catechol chitosan) is also reflected in the interaction with coagulation factors. The protonated chitosan recruits them and assembles high-abundance plasma proteins into an initial protein network by electrostatic action [33].

To improve the hemostasis effect, researchers innovate functional design from both physical and physiological aspects. Physical enhancement of hemostasis is mainly to improve the bio-adhesion [7, 34]. For example, a tris(hydroxymethyl) methyl glycine-modified chitosan derivative (CTMG) was prepared, which is rich in hydrogen bonds and significantly improves the solubility of chitosan in water. In addition, the hydrogel forms a strong adhesion to the tissue surface through hydrogen bonding and electrostatic interaction. Compared with single function hemostatic sponge, CTMG gel sponge has rapid hemostatic, enhanced wound healing and antibacterial effect [35]. Some chemical modifications are also used to enhance physiological pro-coagulant activity. Alkylation is a kind of coagulation promoting chemical modification commonly used at present. Hydrophobic alkyl groups are reported to be anchored to cell membranes, thereby enhancing cell adhesion [5]. An N-alkylated chitosan complex sponge (ACGS) was prepared by freeze-drying method, which has the ability to promote the adhesion and aggregation of erythrocytes and PLTs [36]. Furthermore, the remarkable biocompatibility of chitosan also provides hope for tissue repair after hemostasis. Shi's research group reported that an expandable chitosan cryogel should have an effective hemostatic effect on non-compressible bleeding and severe fatal bleeding. In addition, using the biodegradability and biocompatibility of chitosan, in situ tissue regeneration was successfully induced [12]. The connected pores in the sponge can promote the expansion of cells and provide a suitable growth environment for tissue repair. In the future, with the in-depth research on the properties of chitosan and the advancement of modification technologies, the application prospects of functional chitosan-based hemostatic sponges will become even broader.

3.3. Anionic polysaccharide-based material

Anionic polysaccharides such as hyaluronic acid (HA) and alginate are capable of ionizing negatively charged ions or groups in aqueous solution. They are rich in carboxyl groups and have good water solubility, which can form hydrogen bonds or other interactions. As reported, the anionic polysaccharide can interact with F XII through electrostatic interaction, which can rapidly activate intrinsic pathways [16]. The HA-polyurethane composite sponge was reported, significantly reducing activated partial thromboplastin time (APTT) but having no effect on prothrombin time (PT), demonstrating that the hydrogel could activate an intrinsic pathway through the negative charge of HA

[37].

Although they have similar effects on the clotting process, they still have their own unique functions. As one of the main components of extracellular matrix (ECM), HA plays an important role in many medical applications such as moisturizing skin, lubricating joints and tissue filling [38]. It has been approved by FDA for use in many medical products and treatments [39,40]. Besides reliable biocompatibility, HA has unique bioactivities including immunoregulation, pro-angiogenesis, cell recruitment, and pro-regeneration properties. In particular, it promotes wound healing by up-regulating the expression of IL-1β, IL-8, VEGF, MMP-9, and MMP-13 [41,42]. Alginate, mainly derived from the cell wall of brown algae, is a linear anionic polysaccharide, connected by β-D-mannouronic acid (M) and α-L-glucuronic acid (G) residues via 1, 4-glucoside bonds [43]. Alginate can combine with Ca^{2+} ions via ionic bonds to form an "egg-box" structure. Alginate sponge has high gelling property, which can exchange with Na^{+} ions in the blood to form sodium alginate covering the wound, and the exchanged Ca^{2+} ions enter the blood to activate the coagulation cascade [44].

Another advantage of anionic polysaccharides is that they provide a molecular basis for chemical modification, which facilitates functionalization and customized design. Guo's group obtained adipic dihydrazide-modified hyaluronic acid (HA-ADH) by amidation reaction, which can be cross-linked with oxidized dopamine via Schiff base. The results showed that the cryogel owned stable mechanical properties, antioxidation, high swelling rate and photothermal antibacterial property, being a promising hemostatic material and wound healing dressing [45]. Similarly, hydrazided HA (HHA) was prepared by Qian et al., realizing hydrazide-metal coordination crosslinking [46]. Using sodium periodate as an oxidizing agent, the cis-dihydroxyl group in alduronic acid unit can be oxidized to aldehyde group, interacting with amino groups of proteins to achieve tissue adhesion and protein adsorption [47]. In addition, catechol grafting, methacryloyl and adenosine 5′-diphosphate (ADP) modification of HA have been reported [48–50]. In summary, based on the inherent biocompatibility, absorbability and procoagulant activity of anionic polysaccharide, combined with functional designs, it becomes one of the ideal choice of hemostatic sponge.

3.4. Dextran-based material

Dextran, also known as glucans, is a branched poly-α-D-pyranoglucoside derived from microbes, notable for its complex polysaccharide structure, abundance of hydroxyl groups facilitating chemical modification, and significant water absorption capability, which contribute to its pronounced potential for hemostasis. Liu et al. designed an efficient in situ wet-adhesive dextran derivative sponge for rapid hemostasis [51]. Dextran could convert into poly-dextran aldehyde (PDA) using sodium periodate. The aldehyde groups on the PDA surface can react with tissue proteins to form Schiff base bonds, making it adhere firmly to the tissue, significantly enhancing its hemostatic capability. However, this study did not explore what happens after the hemostasis.

It should be noted that wound healing process is often a complex and long-term process, with hemostasis being just the first step. The ideal hemostatic agent should not only focus on quickly hemostasis but also cause no reaction harmful to the tissue repair, such as the oxidative stress, prolonged inflammation, bacterial infection, and hampered cell activity [52]. β-glucans are distinguished by their unique triple-helical conformation. This structural specificity grants them remarkable bioactivities, such as potent immunostimulatory properties, antioxidant capabilities, anti-infection abilities [53,54]. The activation of the dectin-1 receptor on macrophages by yeast β-glucan, which promotes the differentiation of macrophages towards the pro-healing M2 phenotype [55]. However, the inherent poor solubility due to triple-helix conformation limit the further application of β-glucans [56].

Carboxymethylation has been identified as an effective method to enhance the solubility of polysaccharides, thereby increasing their biological effectiveness [57]. Zhou et al. developed a wet-adhesive carboxymethylated yeast β-glucan (CMYG) hemostatic sponge possesses multifunctional properties such as free radical scavenging, antibacterial, and anti-inflammatory effects, significantly promoting the wound healing [58]. The study showed that CMYG retained the core benefits of β-glucan while presenting enhanced solubility and biological activity, making it a promising material for developing hemostatic agents and wound healing products.

3.5. Starch-based material

Starch, owing to its low cost, superior water absorption properties, excellent biocompatibility, and good degradability, has demonstrated broad application prospects in hemostasis [59]. In particular, commercial starch-based hemostatic powders such as Aristas® and PerClot® have obtained approval from the FDA, thereby solidifying their position as safe and efficacious options in medical settings [60,61]. Nevertheless, the hemostatic mechanism of traditional starch-based materials is mainly to physically concentrate blood components or increase blood viscosity, and lack of physiological procoagulant activity.

The hemostatic starch has witnessed a variety of functional modifications to improve hemostatic effect, underscoring its versatility and potential for future advancements. Initially, Ca^{2+} ions loading on oxidized starch enhanced the clotting activity and degradation of the starch [62]. Further, Liu's group developed a borate-modified thiol starch sponge (St-SP) for hemostasis. This modification endows St-SP with unique self-gelling and self-healing properties. Specifically, the boronic acid groups react with the vicinal diol structures in starch to form stable borate ester bonds. St-SP successfully achieved complete hemostasis of irregular wounds on rabbit liver without any external pressure, which is significantly better than PerClot sponge [63]. Furthermore, Huang et al. designed a starch-based sponge (SQG) with shape memory for rapid hemostasis in penetrating wounds. Carboxylated starch (SC) is prepared through the esterification reaction of succinic anhydride with starch, which could form a stable network structure with polyethylene glycol diglycidyl ether (PEGDE) via chemical crosslinking. This structure not only enhances the mechanical stability of the sponge but also provides excellent shape memory characteristics [64].

The importance of antibacterial is gradually recognized in emergency hemostasis. For this, Xu's group used the large area of microporous starch microspheres to prepare cationic microspheres by surface modification of cationic antibacterial tannic acid (QTA). Besides effective hemostasis, it also showed antibacterial properties against gram-positive and gram-negative bacteria [65]. Moreover, by reacting high amylose starch with 3-chloro-2-hydroxypropyltrimethyl ammonium chloride (CHPTAC), positively charged quaternized starch (QS) is obtained. The introduction of positive charges not only significantly improves the antimicrobial capabilities of starch but may also enhance the coagulation through interaction with negatively charged cellular components in the blood, such as erythrocytes and PLTs [64]. And interestingly, this modification also facilitates further chemical design. Liu and colleagues achieved a convenient layer-by-layer assembly using the positive charge of QS and the negative charge of tannins to form absorbable microparticles (MQ_xT_y) with a multilayered structure [66].

3.6. Collagen/gelatin-based material

Collagen is integral to both structural integrity and physiological hemostasis [67]. It facilitates PLTs adhesion, activation, and aggregation at injury sites, thereby initiating coagulation cascades essential for maintaining hemostasis. The I domain of GP IIb/IIIa could recognize and bind collagen on GFOGER, GLOGER, GROGER, GLOGEN, etc sequences, leading to promoted platelet adhesion and activation. It has also been reported that hydroxyproline may be the key to platelet adhesion and activation [68,69]. During the tissue repair process, collagen can

promote cell growth and proliferation [70]. Fish skin collagen has attracted much attention. Wang et al. successfully developed a sponge made from tilapia collagen for effectively controlling acute wound bleeding, demonstrating the outstanding efficacy in promoting PLTs activation and achieving coagulation [71]. To improve the wound healing after hemostasis, Chang et al. developed a functional hemostatic material of fish-skin collagen scaffold crosslinked with NaCl in situ. This material maintains the natural double-layer structure of fish skin (a porous dermal collagen layer and a fat-rich epidermal layer). By loading exosomes extracted from rat adipose-derived stem cells, it obtains stronger hemostatic capability and wound healing effect [72]. In addition, ECM-based materials with collagen as the main component are also of interest due to exciting bioactivities such as angiogenesis, immunomodulation, stem/progenitor cell recruitment [73,74]. Nevertheless, in general, ECM-based hemostatic materials are rarely reported. Recently, a kidney decellularized ECM sponge has been developed, which not only achieved rapid hemostasis for renal hemorrhage but also demonstrated superior wound healing [75].

The potential allergen issues with biological collagen make its safety uncertain. To this, many studies hydrolyzed it into the gelatin, and some commercial gelatin-based hemostatic products such as FloSeal® and Gelfoam® have been approved [76,77]. Notably, the overquick degradation rate and poor mechanical properties limit the application of gelatin. Crosslinking is an effective method, in which the choice of crosslinking agent is very important. Traditional crosslinkers such as glutaraldehyde have safety risks, and advanced researches are aimed at finding biosafe and functional crosslinkers [78,79]. Du and colleagues created a biodegradable rapid hemostatic sponge (GPZ) through the dual dynamic bond crosslinking among Zn^{2+} ions, protocatechualdehyde (PA), and gelatin. The dynamic Schiff base bond formed between PA and gelatin can gradually hydrolyze under physiological conditions. The addition of Zn^{2+} ions not only promotes the sponge stability, but also accelerate the enzyme-mediated decomposition [80]. Green tea-derived polyphenolic, epigallocatechin gallate (EGCG), has shown remarkable crosslinking with many materials. Xie's group crosslinked small intestinal submucosa (SIS) with EGCG to improve its mechanical properties and hydrophilicity. More importantly, this crosslinking strategy enhanced the osteogenic, antioxidant, antibacterial, and immunomodulatory capacity of SIS [81,82].

3.7. Silk-based material

Silk is mainly composed of two structural proteins, silk fibroin (~75 %) and sericin (~25 %). The insoluble silk fibroin acts as the core structure to provide mechanical strength, while the sericin in out layer binds the silk fibroin fibers together to ensure the silk integrity [83]. Silk fibroin with unique mechanical properties, adjustable biodegradation, and cells functions regulation make it a good scaffold material for biomedical application [84]. In hemostasis mechanism, silk fibroin enhanced PLTs adhesion and aggregation, and significantly induced PLTs-fibrinogen interaction [85,86]. Notably, silk fibroin can form hydrogels and close the bleeding site, in which the β-sheet works the physical crosslinking point. However, this process is often very long (more than 10 min). Liu's group used a FDA-approved amino acid surfactant, ethyl lauroyl arginine hydrochloride (LAE), to reduce this time to less than 1 min (under body temperature), revealing the distinct pathway and thermodynamics of LAE-induced superfast gelation of silk fibroin. Based on this system, an injectable antibacterial hydrogel and an asymmetric hierarchical porous sponge have been prepared [87]. In addition, the function of silk fibroin can be improved by methylacrylylation, which gives it photo-responsiveness. Kim et al. reported a methacrylated silk fibroin sealant that not only retains the inherent biocompatibility but also introduces the capability of photo-crosslinking. This strategy is more controllable and faster than the gelation of silk fibroin itself. And a proof-of-concept was performed in laparoscopic surgery [88].

Sericin is the cortical protein of silk with good water solubility, biocompatibility, promoting cell adhesion and proliferation activity, antioxidant ability, which can be produced in large quantities with low cost from industrial waste produced during silk reeling. Sericin is a rising material in hemostasis field. Wang et al. reported a hemostatic and antibacterial sericin-methacryloyl/Ag cryogel (SMC@Ag) via freezing polymerization. Here, sericin was reacted with methacrylic anhydride and in-situ reduced Ag^{+} ions. The SMC@Ag revealed excellent hemostatic activity, which is due to promoting the activation of the clotting pathway and enhancing PLTs adhesion during coagulation. For pure sericin, this study suggests that similar to collagen, sericin acts as a substrate for PLTs to promote adhesion [89]. Certainly, the hemostatic mechanism of sericin still needs to be further verified and explored.

3.8. Keratin-based material

Keratin, a family of fibrous structural proteins, is the main protein that makes up hair, nails, horns and beaks [90]. It has many advantages, such as high natural abundance, low cost, good biocompatibility, and good biological activity. At present, KeraStat™, an injectable keratin hydrogel, has been approved. Recently, keratin-based functional designs and its hemostatic mechanisms have been explored. Shi's group prepared a wool keratin/zeolitic imidazolate framework 8 composite shape memory sponge, showing the better hemostatic performance than commercial sponge. The inherent thiol group in keratin improves the biocompatibility of sponges and formation of Zn-S bonds [91]. Human hair-extracted keratin has been widely studied with a variety of functions. As reported, in situ injection of human hair-derived keratin gel (K-gels) into the hematoma area after intracerebral hemorrhage surgery reduced hematoma volume. It was shown to improve treatment by preventing rebleeding after surgery and reducing brain damage, including apoptosis and neuro-inflammatory response [92]. However, there are still some disadvantages hindering the deeply study: uncontrolled amino acid composition and differences between batches.

Recombinant expression is a feasible method to further simulate the natural products [93]. Wang et al. expressed all 17 types (11 type I and 6 type II) of human hair keratin variants through recombination. Their hemostatic mechanism was further explored, and it was found that the content of α-helices in the protein sequence was proportional to the hemostatic activity of keratin, and tyrosine, phenylalanine and (or) glutamine residues at the N-termini of α-helices were directly involved in fibrinopeptide release and fibrin polymerization [94]. Moreover, it has been proved that recombinant keratin has a strong influence on the intrinsic pathway of blood coagulation, and also participates in the extrinsic pathway [95]. Besides the excellent hemostatic effect, we should also note the tissue repair properties of keratin. In wound healing process, keratin is thought to have a role in guiding the whole stage. It has an immunomodulatory effect and promotes the polarization of M2-type macrophages. In the subsequent stage, wound healing and epithelialization can be accelerated through the mediation of keratinocytes [96,97]. Taken together, these outstanding hemostatic and tissue repair bioactivities lay the foundation for the development of more functional keratin-based biomaterials.

4. Structural design of hemostatic sponge

The structural design of hemostatic sponges plays a crucial role in determining their physical properties, hemostatic efficacy and bioactivity. For instance, a design featuring low density and high elasticity enables these sponges to self-expand and conform to the wound upon application, thereby offering the requisite compressibility to facilitate physical hemostasis. Hemostatic sponges with interconnected microchannel structures possess superior liquid absorption, which are essential for achieving rapid hemostasis and material transportation. Additionally, 3D nanofiber structures endow hemostatic sponges not only outstanding hemostatic effects but also aid in wound healing. The

preparation process and characteristics of the different structures are listed in Table 2.

4.1. Porous structure

Introducing a porous structure into sponges can enhance their hemostatic performance. To achieve it, various strategies have been explored, including direct freeze-drying and the use of foaming agents to increase the liquid diffusion coefficient to accelerate shape recovery [98–102]. However, these sponges exhibit limited interconnectivity among their pores, which results in restricted blood absorption, significantly prolonged shape recovery time, and an inability to promote cell infiltration, tissue ingrowth, and vascularization [103–105]. Consequently, this hinders their hemostatic efficacy and the subsequent tissue repair process. Furthermore, increasing the porosity and pore size of sponges can improve their permeability and promote rapid shape recovery, but often at the expense of the mechanical strength of the sponge [106]. This compromise can impair the structural integrity and pressure retention capabilities of the sponges on the wound.

To develop hemostatic sponges with simultaneously enhanced permeability and mechanical properties, Jiang et al. proposed a novel secondary network compaction strategy and successfully fabricated superporous chitosan sponge (spCS) with enhanced permeability and mechanical properties for non-compressible hemostasis in pigs (Fig. 4a). Compared to the porous sponge (pCS) without secondary network compaction, the spCS possesses a high-interconnected porous network, larger pore size, and higher porosity (269 % higher than pCS), as well as enhanced network density (53 % higher than pCS). Furthermore, its fatigue resistance is improved (retains 95 % of the maximum stress after 100 cyclic compression at 85 % strain), enabling rapid water-triggered shape recovery (0.84s, 451 % faster than pCS) and blood-triggered shape recovery (4.0s, 410 % faster than pCS), and demonstrating procoagulant properties [107]. Compared to traditional methods, this temperature-assisted secondary network compaction strategy following phase separation-induced primary compaction successfully fabricated superporous sponges with highly-interconnected porous structures, enhanced blood absorption rate and capacity, and fatigue resistance.

4.2. Microchannel structure

To endow the sponges with a super liquid absorption capacity, Wang designed the capillary-mimicking structure via the ice segregation-induced self-assembly process, which remarkably strengthened the hemostatic ability of the materials [108]. The stem of *Euryale ferox* has longitudinally aligned channels that efficiently transport water and nutrients. Inspired by this, Xie et al. successfully prepared a bio-inspired QX/rGO sponge with anisotropic structure using directional freezing-casting and subsequent freeze-drying processes. Due to its bio-inspired structure and multiple interactions, this sponge exhibited excellent mechanical compressibility, significantly enhancing its blood absorption efficiency, making it suitable for hemostasis in noncompressible deep bleeding wounds [109]. Using 3D printed microfiber leaching technology, Du designed a hemostatic sponge with highly interconnected microchannels (Fig. 4b), showing high fluid absorption capacity and enhanced hemostatic efficiency. These studies suggest that the introduction of cylindrical microchannels into sponges can improve the hemostasis of sponges [110]. To investigate the relationship between the taper of microchannels and hemostatic performance of porous sponges, Cao et al. prepared gelatin methacryloyl-based sponges with designed conical microchannels and a disordered porous structure using the 3D printing method and freeze-drying technology (Fig. 4c). The results demonstrated that the taper and distribution of microchannels in the sponge affected the water and blood absorption properties, as well as the expansion ability. Once contacting with blood, the increasing taper of the conical microchannel gradually reduces the resistance of the sponge to the blood flow, thereby accelerating the blood absorption rate. In addition, the liver defect and perforation models confirmed that the hemostatic performance of sponge is positively correlated with the taper of the conical microchannels [111].

Table 2
Structure design for functional biopolymer-based hemostatic sponges.

Structure		Methods of preparation	Characteristics	Reference
Porous Structure	**Porous**	Lyophilization; Foaming technology	Porosity increase; High water absorption; Increased permeability; Limited connectivity	[98–100,102,104–106]
	Superporous	Secondary network compaction strategy; Lyophilization	Highly interconnected porous structure; Enhanced blood absorption; Increased fatigue strength; Fast shape memory	[107]
Microchannel Structure	**Conical microchannel**	3D printing sacrificial template method; Lyophilization	Microchannel taper regulates hemostasis; Complex preparation process	[111]
	Highly interconnected microchannel	3D printed microfiber leaching; Lyophilization	Superior liquid absorption capacity; Fast shape recovery property; Complex preparation process	[110]
	Capillary-mimicking microchannel	Ice segregation-induced self-assembly; Lyophilization	Superior liquid absorption capacity; Simple preparation process; Lack of process stability	[108]
	Biomimetic microchannel	Directional freeze-casting technique; Lyophilization	Anisotropic porous structure; High liquid absorption capacity; Enhanced elasticity under compression; Complex preparation process	[109]
3D Nanofiber Structure	**Layered 3D nanofibers**	Electrospinning and modified gas-foaming technology	3D dynamic microenvironment Special spinning solution	[114]
	Interconnected 3D nanofibers	Novel conjugate electrospinning strategy	Simple preparation process	[115]
	3D Nanofibrous Cellular-Structured	Sol-gel electrospinning technology; Calcination heat treatment technology; Reconstruction-homogenization technology; Lyophilization	Fast self-expanding ability; High elasticity/anti-fatigue property; High liquid absorption capacity; Tissue adhesive Complex preparation process	[116]

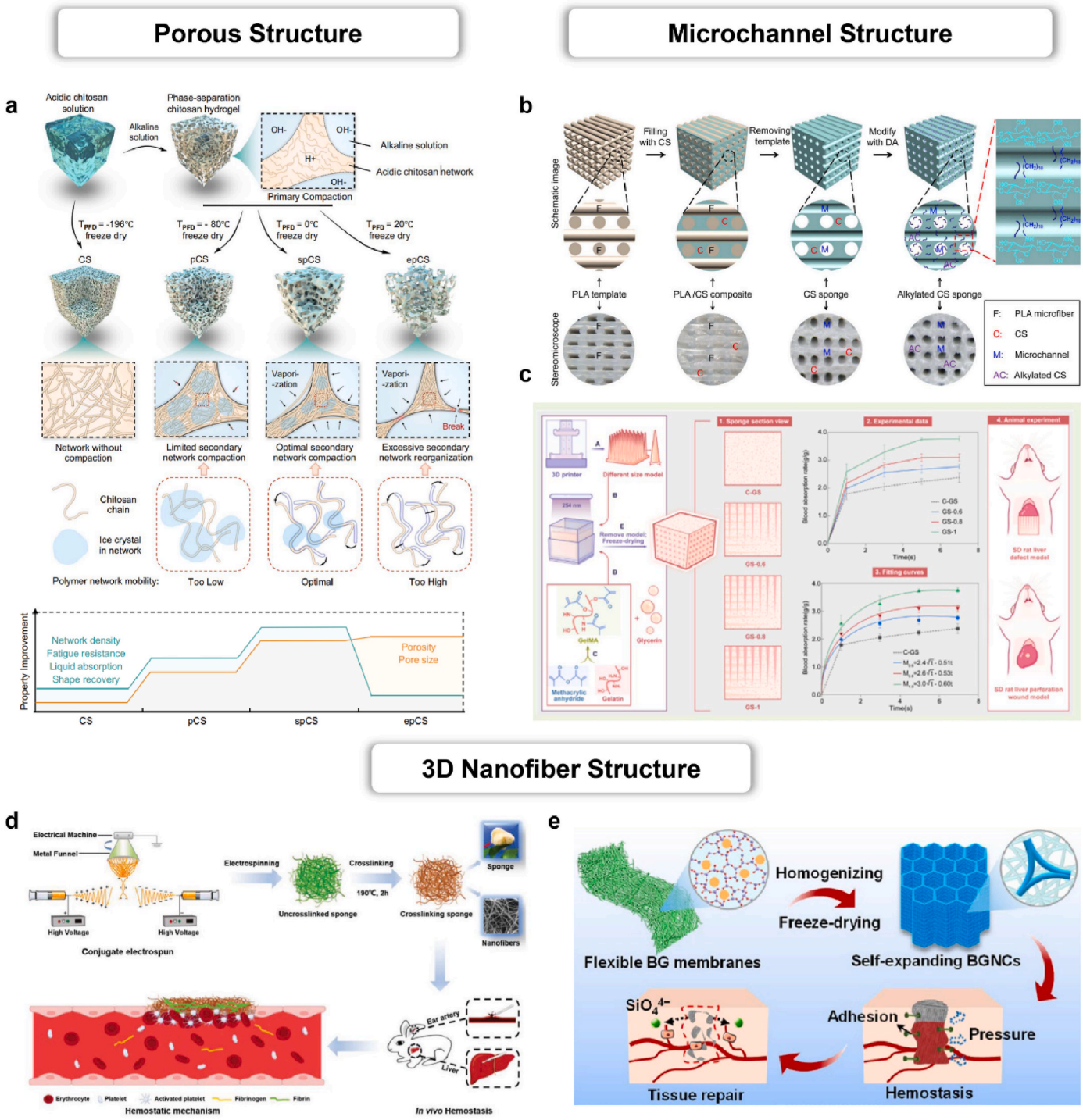

Fig. 4. The advanced structure of functional hemostatic sponge: a) Fabrication of the superporous chitosan sponge (spCS) by temperature assisted secondary network compaction (TA-2ndNC). Reproduced with permission from Ref. [107]. *Copyright @ 2024, Springer Nature*. b) Fabrication process illustration of the MACSs and images of the different sponges. Reproduced with permission from Ref. [110]. *Copyright © 2021, Springer Nature*. c) Fabrication process of GelMA-based sponges with conical microchannels using 3D printing and freeze-drying. Reproduced with permission from Ref. [111]. *Copyright © 2023, American Chemical Society*; d) Fabrication process of 3D nanofiber gelatin sponge using a conjugate electrospinning strategy. Reproduced with permission from Ref. [115]. *Copyright © 2021, Wiley-VCH GmbH*; e) Fabrication process of self-expanding BGNCs achieving rapid hemostasis and promote wound healing. Reproduced with permission from Ref. [116]. Copyright © 2023, American Chemical Society.

4.3. 3D nanofiber structure

As a new types of wound dressings, nanofibers have attracted much attention. Compared to traditional fibers, nanofibers are finer, softer, and have a larger specific surface area. Due to their similarity to natural ECM, large specific surface area, and porous structure, electrospun nanofibers provide an ideal biomimetic environment for wound healing [112]. However, the highly compact 2D geometry of traditional nanofiber membranes leads to poor connectivity, low absorptivity, small pore diameter, and low porosity [113], limiting their applications in hemostatic sponges. Zhang et al. successfully prepared a 3D nanofiber sponge with a layered structure by combining electrospinning and modified

gas-foaming technology to expand 2D nanofiber membranes into the 3D. This structure increases the interfacial interaction between the sponge and blood cells, thereby accelerating hemostasis. Through fine-tuning of the structure, the 3D nanofiber sponge acquires properties beneficial to wound healing, such as good elasticity and high permeability and fluid absorption ratio [114]. Xie et al. proposed a novel conjugate electrospinning strategy to fabricate an ultralight 3D gelatin sponge composed of continuous interconnected nanofibers. This unique fluffy nanofiber structure endows the sponge with low density, high surface area, compressibility, and ultrastrong liquid absorption capacity (Fig. 4d). Moreover, the conjugate electrospinning technique does not require special spinning solutions and collectors, is compatible with most commercial electrospinning machines, and features low production cost, high output, and suitability for industrial production [115]. Furthermore, Lu et al. designed and prepared self-expanding cryogels based on flexible bioactive glass nanofibers. The unique 3D nanofiber cellular structure is constructed by the continuous interpenetrating fibrous structure and the flexible BG nanofiber membranes with low fiber packing density, which can be folded without breaking (Fig. 4e). Thanks to this structure, these cryogels exhibit high absorption capacity (3169 %), fast self-expanding ability, near-zero Poisson's ratio, injectability, high compressive recovery at a strain of 80 %, robust fatigue resistance (almost no plastic deformation after 800 cycles at a strain of 60 %), and good adhesion with diverse tissues [116]. Hence, the internal architecture of hemostatic sponges plays a crucial role in their efficacy for hemostasis and facilitating wound healing. Through the optimization of their internal structural design, the development of more efficacious hemostatic materials can be achieved.

5. Functionalization of hemostatic sponge

The functionalization of hemostatic materials has gradually become the development trend, focusing on the additional functions of the hemostatic sponge in addition to hemostasis. Here, we summarized five points: enhanced hemostatic property, anti-bacterial capability, prevention of tumor recurrence, enhanced tissue repair and hemorrhage monitoring. Their mechanisms and typical applications are listed in Table 3.

5.1. Enhanced hemostatic property

The primary objective of a hemostatic sponge should be to promptly and effectively halt bleeding in order to save lives. Enhancing its hemostatic efficacy remains an ongoing pursuit. The impact of composition and structure on the hemostatic effectiveness for hemostatic sponge has been reviewed earlier in the article. Furthermore, it is imperative to acknowledge other functional designs such as bio-adhesion, surface modification, and other advanced structure are also important for improving hemostatic property.

5.1.1. Bio-adhesion design

Bio-adhesives have experienced flourishing development in many fields boasting numerous advantages including easy to operate, reduced infection risk, and minimum additional injury and patient discomfort [2,9,29]. The strong adhesive force between hemostats and bleeding tissues without the need for long-term press is particularly suitable for controlling non-compressible bleeding from penetrating injuries and solid organs such as the liver, kidney and spleen. However, a major challenge is achieving efficient adhesion in the presence of fluids such as water and blood [117,118]. A prominent advantage of hemostatic sponges lies in their rapid liquids absorption, facilitating the removal of interfacial water and providing favorable conditions for wet adhesion. Zhang's group modified the chitosan with tris(hydroxymethyl) methyl glycine to bring abundant hydroxyl groups, showing strong water-mediated bio--adhesive. When hydrated, the sponge underwent a transformation into a hydrogel state. The plentiful hydroxyl groups within the sponge can electrostatically interact with functional groups on tissue surfaces, enabling the tight adhesion [35]. Additionally, research has developed an aldehyde dextran sponge with excellent liquid adsorption and bio-adhesion properties, which stems from the aldehyde groups reacting with tissues through Schiff base reactions [51]. Besides the non-covalent/covalent interactions, the researchers proposed that the

Table 3
Functional design of biopolymer-based hemostatic sponges.

Functional Design	Strategy	Material and Mechanism	Reference
Enhanced Hemostatic Property	Bio-adhesion Design	CTMG: Electrostatic interaction	[35]
		PDA sponge: Schiff base reaction	[51]
		QCS/PDA cryogel: Enhanced macro-porous structure	[34]
	Surface and Structural Design	MACS: Procoagulant alkylation modification	[110]
		PCMC/CCS: Enhanced mechanical properties	[120]
		Janus structure P-CS1N1-1‰ CO: hydrophobic coating	[121]
		J-ZGS: one-side pro-coagulant properties	[122]
		ACPs: Micronization and tissue adhesion	[123]
Anti-bacterial Capability	Antibacterial Agents Load	TMC/AgNPs sponge: AgNPs introduction	[126]
		WK/ZIF-8: ZIF-8 introduction	[91]
		GA-CS: Anti-infective activity of gallic acid	[128]
		PQC: Antibacterial quaternization chitosan	[129]
		GC-EPL cryogel: Antimicrobial polypeptides EPL	[133]
	Photothermal/ Photodynamic Strategy	OD/CC-PDA5: Mussel-inspired PDA load	[98]
		CH/Au@sMX: MXene load	[138]
		SEF cryogel: Fe^{3+}/EGCG-based metal phenolic networks formation	[139]
		CS-ZnO/Ce6 sponge: photosensitizer Ce6 load	[141]
	Advanced Structural Design	Ch-(TA/CaII)5: TA/Ca surface coating	[142]
		Janus OCAQ cryogel: Asymmetric hydrophobic modification	[143]
Prevention of Tumor Recurrence	Anti-tumor Agents Load	Sandwich-like CFSC sponge: Cisplatin load	[145]
	Combined strategy	CPDS: Combination photothermal effect and lenvatinib load	[147]
		QH/ZDH cryogel: Combination sonodynamics and chemotherapy	[148]
Enhanced Tissue Repair	Interconnected microchannel	HA-PU cryogel: Promoting cell infiltration	[37]
	Antioxidant Property	CS/Ag/TA cryogel: Effective oxidation resistance of TA	[152]
	Pro-healing effect	DHGT + PHMB + TiO_2 NPs sponge: Multiple bioactivities of TiO_2	[50]
	Biodegradation	Ssponge: Degradation rate appropriate for tissue repair	[78]
Hemorrhage Monitoring	Capacitance change	All-in-one theranostic platform: SF between two AgNW electrode	[155]
	Conductivity change	TACC: Excellent conductivity due to carbon nanotubes	[157]

porous structure provides increased surface area for contact with tissue to enhance bio-adhesion [34]. Simultaneously, it's important to recognize that the robust adhesion poses challenges during removal and dressing change. On-demand removal needs attention in designing the adhesive hemostatic sponge.

5.1.2. Surface and structural design

During the process of hemostasis, rapid blood absorption of sponge facilitates direct contact with blood. Consequently, enhancing the hemostatic effect can be achieved through surface modification using procoagulant functional groups. In addition to the bio-adhesive groups mentioned above, hydrophobic long-chain alkyl groups could effectively insert into the cell membrane and capture cells [36,119]. Du et al. prepared a chitosan hemostatic sponge with a highly interconnected microchannel structure, followed by alkyl modification using dodecyl aldehyde. The authors confirmed that hydrophobic alkyl chains further promote procoagulant activity, with the hemostatic effect ultimately validated in lethal normal/heparinized rat and pig liver puncture wound models [110]. Moreover, this functional modification is also used in hemostatic gauzes designs [5].

The Janus structure was designed to enhance hemostatic effect, and it should be noted that researchers can achieve this goal via different strategies. Proper mechanical enhancement can make the hemostatic sponge exert compression on the surrounding tissue and resist high blood pressure. For this, a two-layer hemostatic patch containing carboxymethyl cotton and catechol grafted chitosan (CCS) was prepared. The abundant cotton fiber in carboxymethyl cotton enhances the materials' mechanical properties [120]. Liu's group also reported a hemostatic sponge with asymmetric structure, but the purpose was different with the above. Initially, a directional freeze-drying method is employed to create an oriented pore structure in the sponge, known to enhance liquid absorption rates compared to irregular pore structure. Moreover, one-side hydrophobic properties facilitated by polydimethylsiloxane coating to prevent unnecessary blood loss resulting from excessive blood absorption [121]. Another design embedded pro-coagulant zein nanoparticles on one side of the sponge to enhance the hemostatic performance [122]. Moreover, the application of hemostatic sponges extends beyond large bulks. To achieve improved repair for irregular wounds, researchers have developed powder-type cryogel (ACPs) based on chitosan and polyacrylic acid. Upon blood absorption, the material can crosslink to form an integrated unit, providing strong bio-adhesion [123].

5.2. Anti-bacterial capability

In harsh environment, especially battlefield, infection has become one of the most serious complications following gunshot injuries and burns, with mortality rates second only to hemorrhagic shock. It is of utmost importance that hemostatic materials can prevent infections. Moreover, bacterial infection is a prominent obstacles to wound healing, prolonging the inflammatory response. Therefore, the development of novel antibacterial hemostatic materials has become an urgent need.

5.2.1. Antibacterial agents introduction

Many antibacterial agents have been applied for hemostatic sponges to confer antibacterial properties with the materials, which can be mainly divided into metal-based, natural, and photothermal antibacterial agents. Metal ions such as Ag^{+}, Cu^{2+}, and Zn^{2+} ions are acknowledged for their antibacterial properties [31]. For instance, silver nanoparticle (AgNPs) was introduced into the gelatin cryogel, processing a good killing effect against methicillin-resistant *S. aureus* (MRSA) and *P. aeruginosa* and removing mature biofilms [124]. However, revealed by recent studies, it is worth noting that the cumulative toxicity of AgNPs to the body is recognized when it is released in large quantities over short time [125]. To solve it, Wu et al. prepared thiol-modified chitosan (TMC) sponge, where AgNPs can be crosslinked with thiol groups and immobilized in the TMC sponge, showing good antibacterial activity and slow release rate of AgNPs (14.35 % after 14 days) [126]. Besides, the antibacterial properties of pH-responsive zeolitic imidazolate framework-8 (ZIF-8) were investigated because it can consistently release Zn^{2+} ions, especially under acidic conditions. Shi's group reported a multifunctional shape-memory wool keratin/ZIF-8 (WK/ZIF-8) composite sponge. The continuous release of Zn^{2+} ions realizes the purpose of antibacterial by destroying the fluid membrane of bacteria and Zn^{2+} ions can induce the activation of clotting F XII, accelerate the production of thrombin and fibrin, and thus promote hemostasis [91].

Antibacterial natural polymers and polypeptides are being used progressively in hemostatic sponges due to their good biocompatibility and non drug resistance. Chitosan and its derivatives own broad-spectrum inhibition for bacteria and fungi, particularly *E. coli* and *S. aureus*. The antibacterial mechanism is due to the cationic nature, which interacts with positively charged components on the bacterial cell membrane and further disrupt it [127]. Therefore, chitosan is one of the important raw materials for preparing antibacterial hemostatic sponge. Tang et al. prepared a composite sponge composed of hydrophobically modified chitosan (HM-CS) and gallic acid modified chitosan (GA-CS). The sponge has outstanding antibacterial performance, and the modification of chitosan by GA further improves it. The anti-infective activity of GA is derived from its polyphenol groups, which can interact with enzymes involved in cell wall synthesis and change the permeability of bacterial membranes [128]. Besides the polyphenol groups, quaternization is also a common method to enhance the antimicrobial properties, which also destroy the cell membrane and cause the components leakage (Fig. 5a and b) [129,130]. In addition, the antibacterial polypeptides can be expanded to construct hemostatic sponges, such as antimicrobial peptides (AMPs). They are the important active substances for the body to resist the invasion of external pathogens and play an important role in the innate immune system [131]. As a typical AMPs, ε-poly lysine (EPL), which is polymerized from 25 to 35 lysine residues, has broad-spectrum antibacterial activity against many microorganisms such as gram-positive/negative bacteria, yeast and fungi and non drug resistance. The biosafety of EPL has been recognized and approved by the FDA in 2003 [132,133].

5.2.2. Photothermal/photodynamic strategy

Photothermal therapy (PTT) is a promising antibacterial technology that uses a photothermal agent (PTA) to convert light energy into heat energy. PTT has the advantages of non-invasiveness, high efficiency, and low drug resistance [134]. According to the chemical composition, PTA is commonly divided into noble metal materials, metal compound materials, carbon materials, organic materials and so on [135]. For example, mussel-inspired polydopamine (PDA) is a kind of biomaterial which is self-polymerized by covalent bond, hydrogen bond and π-π interaction of dopamine under alkaline conditions. Because of the excellent biocompatibility, high photothermal conversion efficiency, hydrophilicity and easy modification, it has received considerable attention [28,136,137]. Sun et al. prepared a PDA-mixed hemostatic, capable of hemostasis, preventing bacterial infection and promoting healing. The near infrared irradiation (NIR) energy absorbed by PDA is effectively converted into heat energy. After 4 cycles of NIR irradiation, the sterilization efficiency of OD/CC-PDA5 was still higher than 90 % [98]. Furthermore, other PTT platforms like metal-phenolic networks and MXene have been developed to enhance the antibacterial properties of hemostatic sponges (Fig. 5c and d) [138,139]. Although PTT strategy has many advantages and extensive research, it should also be noted that the antibacterial effect of the material is closely related to the photothermal temperature. When the temperature rises to 50 °C, it can effectively inhibit infections caused by drug-resistant bacteria. However, local hyperthermia (over 50 °C) will cause irreversible damage to normal tissue and hinder tissue healing.

Photodynamic antimicrobial therapy (PDAT) is also a new antibacterial strategy that has attracted much attention in recent years. PDAT is

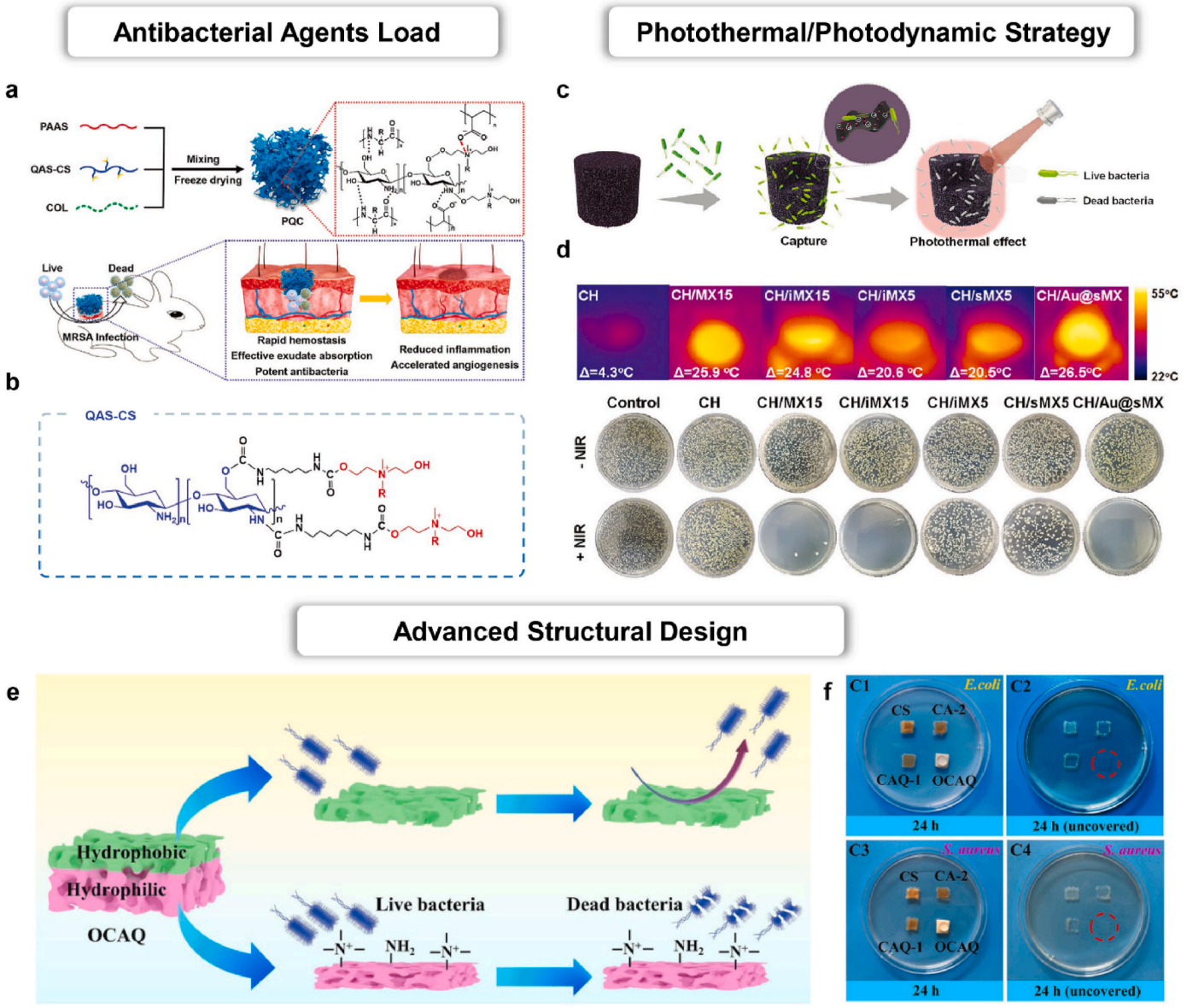

Fig. 5. The anti-bacterial capability of functional hemostatic sponges: a) Schematic diagram for the preparation of composite polymer sponges and their application as a novel multifunctional dressing for MRSA-infected wound healing; b) The molecular structure of QAS-CS (quaternary ammonium salt-conjugated chitosan). Reproduced with permission from Ref. [129]. *Copyright © 2021, Wiley-VCH GmbH.* c) Schematic illustration of the antibacterial mechanism of the composite sponges; d) Infrared thermographs of the composite sponges irradiated by a NIR laser and antibacterial effect on *S. aureus* without/with NIR irradiation. Reproduced with permission from Ref. [138]. *Copyright © 2022, Wiley-VCH GmbH.* e) Schematic illustration of antibacterial mechanism and f) antibacterial effect of OCAQ. Reproduced with permission from Ref. [143]. *Copyright © 2023, Elsevier.*

a method of using photosensitizers such as chlorin e6 (Ce6) to produce reactive oxygen species (ROS) under appropriate excitation light source irradiation, causing oxidative damage to biomolecules (lipids, proteins and nucleic acids, etc.), thus killing pathogenic microorganisms [140]. Miao's group reported a novel chitosan antibacterial sponge (CS-ZnO/Ce6) combining zinc oxide particles (ZnO) and Ce6. The sponges showed instant and sustained antibacterial effect induced by Ce6 and ZnO, respectively. Upon 660 nm light irradiation, Ce6 can generate abundant singlet oxygen ($^1O_2$) to immediately inactivate bacteria, and the existence of ZnO can ensure the long-term bacterial inhibition of sponges and prevent further infection, as well as promote wound healing [141].

5.2.3. *Advanced structural design*

Besides incorporating substances, the design of the structure could be another aspect of enhancing antibacterial properties, such as the coating design and Janus structure. In view of high surface area, the hemostatic sponge could be used to carry functionalized drugs. Tan et al. constructed a porous cryogel, and its surface was modified with tannic acid (TA) and Ca^{2+} ions to form TA/Ca surface coating. After swiftly being absorbed by sponge, the blood rapidly and thoroughly interfaces with the TA/Ca layer. As F IV, Ca^{2+} ions accelerate multiple processes of the coagulation cascade, promoting the formation of the fibrin network. And TA possesses natural antibacterial activity, including causing membrane permeability disruption. This is a good example of utilizing the structural optimization design based on the inherent characteristics of the sponge [142].

Besides improving hemostatic properties as described above, the Janus structure empowers the material with antibacterial properties. Fang et al. prepared both hydrophobic and hydrophilic Janus sponges by using octadecanol to modify the one side of sponges. The functionalized outer layer serves as a safeguard by hydrophobic and anti-fouling

properties, thus effectively preventing blood outflow and bacterial invasion (Fig. 5e and f) [143]. As a passive defense, hydrophobic design can prevent bacterial colonization and prevent bacterial wound invasion, but it cannot actively kill bacteria. Therefore, hydrophobic design and antibacterial drugs are used in combination. Researchers prepared a multifunctional Janus polyurethane sponge (Janus-PU) by coating near-infrared (NIR)-responsive and superhydrophobic nanoparticles (F-ZnO@AgNPs) on one side of the sponge. Besides superhydrophobic property, the AgNPs own the broad-spectrum antibacterial activity. Furthermore, ingeniously, the synergistic combination of Janus structure and strong photothermal effect endows Janus-PU with NIR-controlled unidirectional exudate removal, thereby achieving the optimal moist environment for wound healing. This material has been proven to accelerate the healing of diabetic chronic wounds infected with MRSA [144].

5.3. Prevention of tumor recurrence

Surgical removal is the primary treatment for most early-stage solid tumors, such as hepatocellular carcinoma and breast cancer. However, due to the high incidence of tumor recurrence and metastasis, the long-term prognosis is discouraging. For example, the 5-year postoperative recurrence rate of liver cancer is up to 50–70 %. Although there are different views on its causes, the inevitable intraoperative bleeding and residual tumor cells lead to the increasing circulating tumor cells, making early recurrence and metastasis of solid tumors more likely after resection.

Hemostatic sponges have currently been extended to prevent tumor recurrence and metastasis, which not only achieve prompt hemostasis but also can adsorb shed and residual tumor cells at the surgical margin. As the recognized preferred scheme, researchers have incorporated anti-tumor drugs into the material. To effectively utilize the drugs, the structure of the sponge has been elaborately designed. Zhang et al. innovatively prepared a sandwich-like composite sponge, where the outer sponge can rapidly hemostasis while adsorbing shed tumor cells. Simultaneously, the inner nanofiber can continuously release cisplatin, effectively killing them (Fig. 6a and b) [145]. The sandwich-like structure is widely adopted by many researchers, and curcumin, doxorubicin and triptolide were loaded to play anti-tumor role [44,146].

In addition, the therapy combines chemotherapy and other methods has received extensive attention from researchers. For example, PTT in combination with chemotherapy has many advantages, which can overcome the low selectivity of single chemotherapy and multi-drug resistance. Furthermore, PTT can also increase the accumulation of drug-carrying nanoparticles at the tumor site and enhance the sensitivity of tumor cells to chemotherapy drugs. Mu and colleagues reported a novel photothermal chitosan/PDA sponge possessing multiple strategies for preventing tumor recurrence (Fig. 6c and d) [147]. The rapid blood absorption serves as the first crucial defense line against tumor cell extravasation. Secondly, outstanding photothermal conversion performance (above 45 °C *in vivo*) can rapidly eliminate occult lesions through thermal ablation. Thirdly, it's noteworthy that mild PTT induction activates immunity and improves the tumor immune microenvironment by promoting the maturation of dendritic cells and the proliferation of

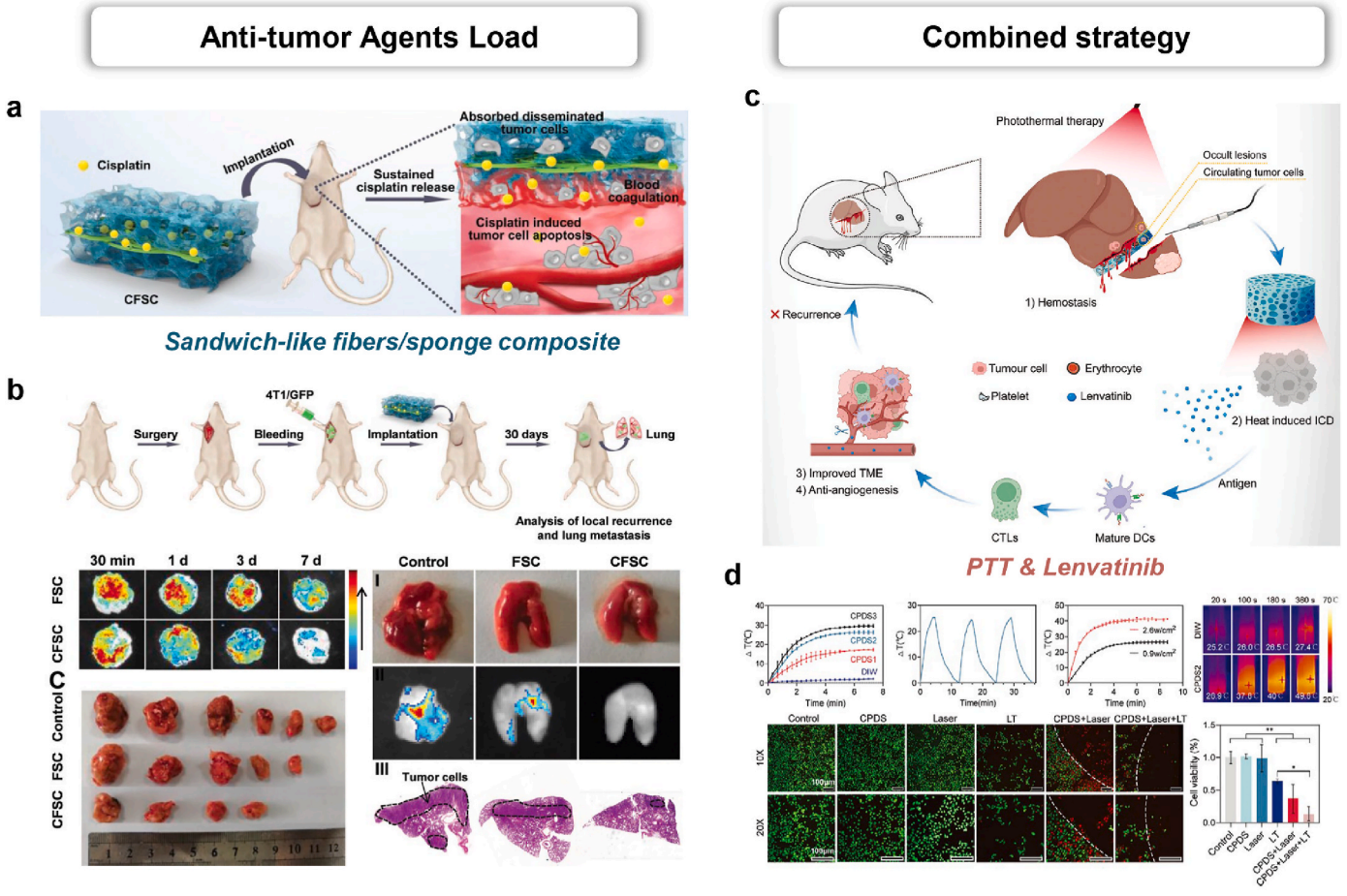

Fig. 6. The anti-tumor capability of functional hemostatic sponges: a) CFSC promotes blood coagulation and induces apoptosis of disseminated and residual tumor cells; b) In vivo efficacy evaluation of CFSC on a subcutaneous postoperative 4T1/GFP recurrence and metastasis model. Reproduced with permission from Ref. [145]. *Copyright © 2018, Wiley-VCH GmbH.* c) Schematic illustration of CPDS-mediated immunotherapy inhibits tumor recurrence; d) CPDSs have good photothermal conversion efficiency and tumor-killing effect in vitro. Reproduced with permission from Ref. [147]. *Copyright © 2023, Wiley-VCH GmbH.*

cytotoxic T lymphocytes. Moreover, the authors combined it with chemotherapy using lenvatinib, significantly enhancing the anti-tumor efficacy. Combined strategy of sonodynamics and chemotherapy, Guo's group developed the hematoporphyrin monomethyl ether (HMME)-loaded dopamine-modified ZIF-8 (ZDH), significantly killing cancer cells via ultrasound-generating ROS and pH-responsive releasing HMME [148]. In short, with the development of hemostatic materials and the progress of tumor therapy, their application in preventing tumor recurrence and metastasis has attracted more attention in recent years.

5.4. Enhanced tissue repair

Advanced hemostatic materials pay more and more attention to tissue repair after hemostasis [149]. Hemostatic sponges have large specific surface area and designable pore structure, endowing them with notable advantages in liquid absorption, material transport, cell migration and proliferation [12]. Therefore, hemostatic sponge has the potential to act as a wound dressing and facilitate wound healing. Considering the impact of structure on hemostasis and tissue repair, Wang et al. prepared the homo-compositional hydrogel and cryogel including modified polyurethane and HA. The cryogel has a larger pore structure and higher water/blood absorption rate compared to the hydrogel, thereby achieving more effectively hemostasis. Moreover, the authors further pointed out that the cryogel showed the marginally higher wound healing rate compared to the hydrogel group (Fig. 7a and b) [37]. Another study compared the difference in tissue repair following hemostasis between sponge with dense structure (ACS) and interconnected microchannel (MACS-2). The results revealed that infiltrated cells were primarily located at the edges of ACS with dense structure. Nevertheless, the substantial cells infiltrated the interior of MACS-2, secreting abundant ECM to form neo-tissues [110]. All these indicate that the structure of hemostatic sponge can regulate the tissue repair process.

Wound repair is a complicated process involving many factors [32,82]. Herein, we summarize the studies of plant-derived polyphenols and metal ions in enhancing the healing ability of hemostatic sponges. During the wound healing process, the intricate wound environment like recurrent bleeding and bacterial infection could induce excessive oxidative stress, triggering a robust inflammatory response and impeding wound healing. Polyphenols are rich in phenolic hydroxyl groups, which demonstrate excellent antioxidant and anti-inflammatory abilities [150,151]. Xu et al. prepared a multifunctional chitosan-based cryogel including silver and TA. Due to TA, the cryogel could eliminate over 95 % of ROS, and TA can undergo oxidation to form quinone, which

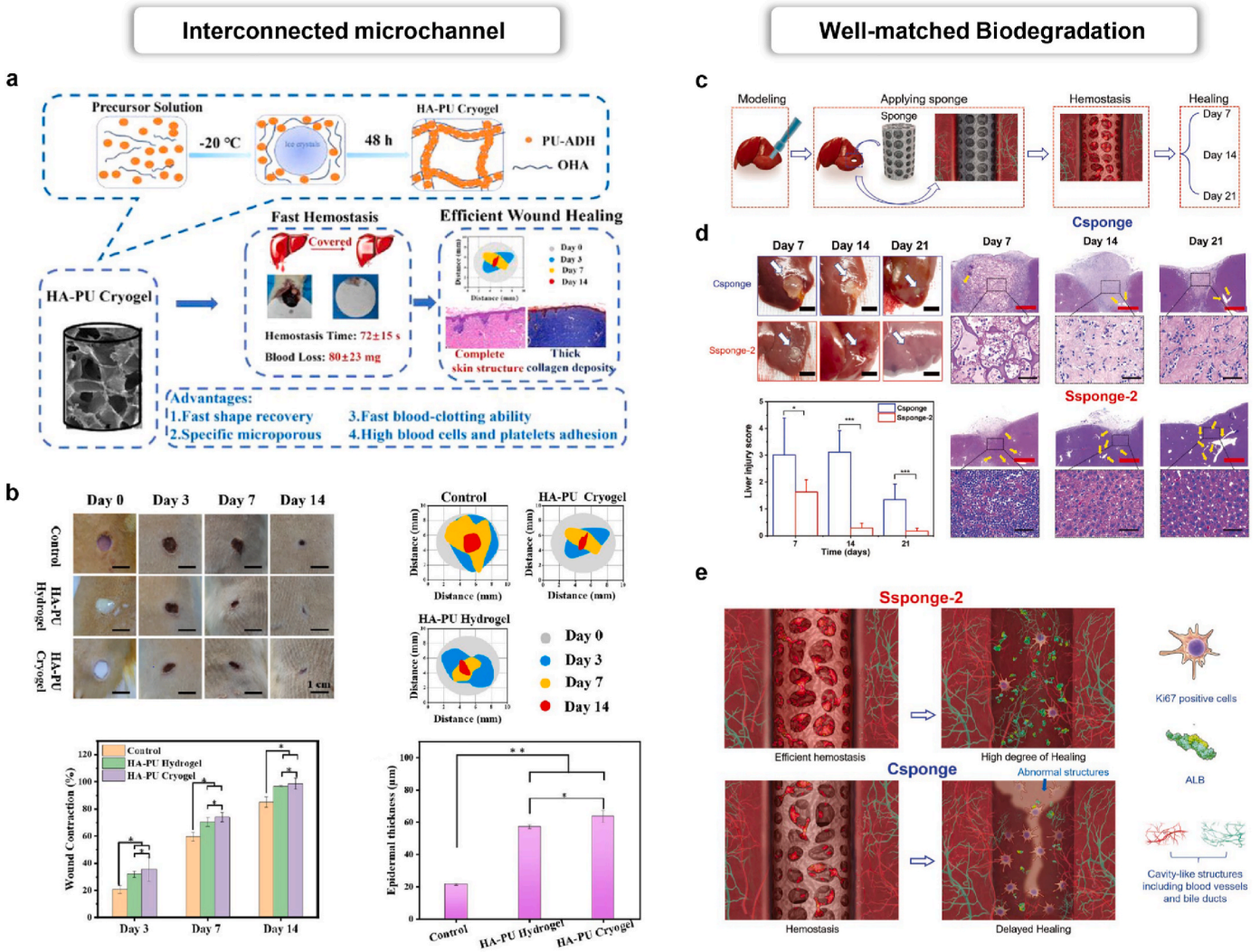

Fig. 7. The enhanced tissue repair of functional hemostatic sponges: a) The preparation and applications (hemostasis and wound healing) of the HA-PU cryogel; b) Wound healing assessment of HA-PU hydrogel and cryogel in rat full-thickness skin defect. Reproduced with permission from Ref. [37]. *Copyright © 2022, American Chemical Society*. c) Schematic showing the procedure of the liver regeneration model; d) In vivo liver regeneration performance of Ssponge; e) Scheme showing that Ssponge-treated livers possessed a better healing effect. Reproduced with permission from Ref. [78]. *Copyright © 2022, Wiley-VCH GmbH*.

could serve as a crosslinker with amino groups in chitosan [152]. Meanwhile, the presence of phenol hydroxyl groups makes TA easy to bind to other substances through non-covalent interactions, especially hydrogen bonds and ionic coordination [113]. Some metal ions have also been reported to be bioactive, especially for promoting cell proliferation, migration and functional expression. For instance, Zn^{2+} ions not only inhibit bacterial growth but also enhance the keratinocyte migration during the wound healing [80,153]. And Li et al. verified the role of TiO_2-loaded sponges in burn wound. The results indicated that the addition of TiO_2 accelerated the re-epithelialization, collagen deposition, and angiogenesis in the skin tissue [50]. As mentioned earlier, these substances often have more than one function. Therefore, they have identified a promising direction for the multi-functionalization of hemostatic sponges.

Another important consideration is that hemostatic materials must be safely degradable *in vivo* particularly in clinical. For example, formaldehyde produced after the degradation of cyanoacrylate-based tissue adhesives is toxic and easy to cause itching, allergic reactions and other adverse reactions *in vivo* [154]. Furthermore, during tissue repair, the degradation rate of the material should align with the tissue repair rate. Zhu et al.'s study corroborates this view. In their study, commercial gelatin sponges (Csponge) were compared with rapidly degrading gelatin-based sponges (Ssponge) in a liver defect model. On day 21 after surgery, the tissue healing area reached nearly 100 % treated with Ssponge, whereas it was approximately 70 % for livers treated with Csponge. This demonstrates that the slower degradation of Csponge impeded tissue healing (Fig. 7c–e) [78].

5.5. Hemorrhage monitoring

Active monitoring of postoperative bleeding is critical for patient safety and management, which is also unmet medical need and an urgent challenge to be solved in the research of hemostatic materials. Recently, Haghniaz and colleagues have developed a theranostic platform aimed at effective hemostasis and detecting bleeding. This platform is constructed by embedding silk fibroin between two conductive electrodes made of silver nanowires (AgNW). Importantly, this innovative platform functions as a capacitive sensor that can promptly distinguish between blood and other body fluids (i.e., serum and water) via capacitance (C) change. When bleeding occurs, blood infiltrates the silk fibroin sponge, markedly elevating its initial dielectric constant (ε), which is a physical quantity that has a positive correlation with C ($C \propto \varepsilon$),

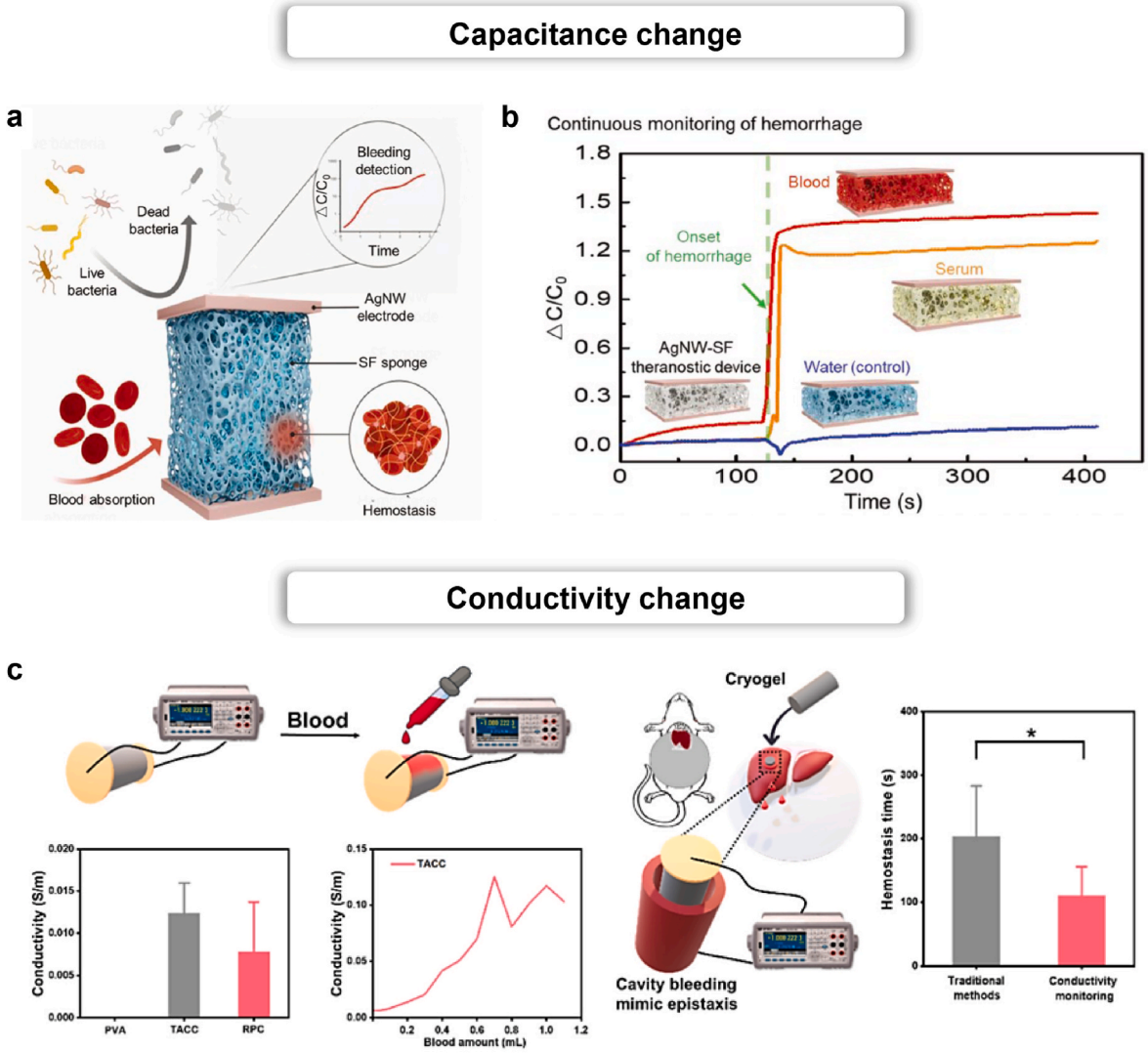

Fig. 8. The hemorrhage monitoring of functional hemostatic sponges: a) Illustration of the AgNW- silk fibroin theranostic device for intelligent hemorrhage management; b) Continuous monitoring of hemorrhage by capacitance change after absorption of blood versus serum and water. Reproduced with permission from Ref. [155]. *Copyright © 2023, Wiley-VCH GmbH.* c)The preliminary exploration of the bleeding monitoring performance of conductive TACC via conductivity change. Reproduced with permission from Ref. [157]. *Copyright © 2022, Elsevier.*

thereby inducing a corresponding change in *C* in reaction to the bleeding. Furthermore, the researchers looked at the impact of fluids other than blood on the detection of bleeding, including serum and water. Research suggested that the whole blood induces more pronounced changes in capacitance than serum. This can be attributed to the higher concentration of electrolytes in whole blood, including fibrinogen, coagulation factors, and hemoglobin (Fig. 8a and b) [155].

Another study focused on epistaxis, which is a very common bleeding problem in life and clinic. The bleeding problem is small but persistent, so its bleeding needs to be monitored [156]. Guo's team developed a smart cryogel with transversally aligned channels (TACC) using catechol-modified polyvinyl alcohol, quaternized chitosan, and carbon nanotubes. In comparison to random porous cryogel (RPC) and longitudinally aligned multilayered cryogel (LACC), TACC exhibited superior hemostatic performance and breathability. Moreover, its outstanding conductivity enables TACC to monitor bleeding effectively, which is also served as the crucial indicator to reflect the amount of blood absorbed. As blood absorption increases, the conductivity of TACC also increases. The authors established two models to investigate the bleeding monitoring performance: one is based on the scenario where the bleeding point is located at the bottom of the cryogel (i.e. blood permeating from bottom to top), and the other is based on the scenario where the bleeding point is located around the frozen cryogel (i.e. blood permeating from outside to inside) (Fig. 8c) [157].

As can be seen, current designs for bleeding monitoring rely on the electrical conductivity of materials, translating the amount of bleeding into changes in specific physical quantities such as capacitance and conductivity. Although the design of these materials is impressive, it is important to note that these work provides a proof-of-concept or in-vitro result. In-vivo and further systematic studies are warranted.

6. Conclusions and outlook

As a research hotspot of medicine and materials science, hemostatic materials have attracted wide attention in recent years. After long-term studies, the hemostatic effects of many substances have been identified, and a few of them have successfully entered clinical applications. We review the advanced research of biopolymer-based hemostatic sponges, focusing on the material component, structure and advanced function. However, it is also important to recognize that each material has inherent limitations that need to be further addressed with sound strategies. Below, we summarize the main issues and emerging trends in the field of hemostatic materials.

6.1. *In vivo* biosafety

As a key branch of biomaterials, the core requirement of hemostatic materials is biosafety, which is the basic premise to ensure the health and safety of patients. The primary responsibility is to control bleeding effectively, but we also need to pay close attention to the behavior and impact after hemostasis, especially in the case of applications that do not require removal from the body. Unfortunately, in many studies, the biocompatibility assessment of hemostatic materials and their long-term existence *in vivo* may lack comprehensive and in-depth discussion. This cannot fully reveal the material's stability, degradability, and potential impact on surrounding tissues in complex physiological environments, thus laying a hidden danger to the long-term health of patients. This also hinders the translational research of new hemostatic materials. Therefore, we urgently need to strengthen relevant research and follow internationally recognized standards and guidelines to conduct biosafety evaluation of hemostatic materials. This includes, but is not limited to, toxicity testing of materials, immune responses monitoring, histocompatibility observation after implantation, and analysis of possible degradation products.

6.2. *Emerging materials*

Biopolymers mentioned above are increasingly becoming the focus of research because of their unique biocompatibility and multiple functions. However, as basic research, the deeper mechanism needs to be systematically studied and summarized like the hemostatic mechanism of the material itself, the effect of physical properties and chemical modification on hemostasis. In addition, although current studies have tried to diversify the functions of hemostatic materials the actual feasibility and synergistic effects still need to be evaluated. For example, as the first step in tissue repair, how hemostasis affects the cellular behavior in the repair process needs to be clarified. A series of emerging materials, such as nanomaterials (plant-derived phenols, MXene, metal-organic frameworks (MOFs), bioactive polypeptide, etc.) and tissue/cell-derived materials (ECM materials, exosomes, etc.) have gradually emerged in the biomedical field, but the application in hemostasis is still insufficient. In the future, through rational functional design, these materials are expected to provide new strategies for bleeding control.

6.3. *Multiple application scenarios*

The clinical application scenario of hemostatic sponge needs further consideration. It is specially used for narrow, deep and irregular bleeding wounds due to its unique expanding and shape memory ability. Sponges can be used to their advantage when faced with open wounds, such as major surgery bleeding, car accident injuries, battlefield gunshot wounds. However, in this process, it should be noted that although physical expansion will play a role in local compression and hemostasis, long-term compression will lead to nerve death and local tissue necrosis, resulting in counterproductive effects. Moreover, with the development of clinical technology, non-invasive endoscopic technology has been applied more and more widely, and traditional bulk hemostatic sponge is difficult to adapt to it. Miniaturization facilitates endoscopic delivery for refined surgery. In addition, for the special structure of different organs and the special conditions of different patients (such as age and blood clotting function), different hemostatic sponges can be designed in combination with cash technology such as 3D printing to provide personalized treatment plans.

6.4. *Translational research*

Unlike basic research, which focuses on excellence in a single performance, translational research is placed under a more rigorous review framework, which requires not only a high standard of performance, but also a combination of factors to achieve overall optimization [158]. In the development of hemostatic materials, biosafety is the primary and uncompromising threshold. In addition to the safety and effect of the material itself, the standards formulation and market acceptance will affect their application. As a medical device, hemostatic sponges need to comply with relevant regulations and standards. However, there are differences in regulatory requirements for medical devices in different countries and regions, which increases the difficulty and cost of bringing products to market. The acceptance and use habits of new products by doctors, patients and medical institutions will affect their marketing effectiveness. Translational research has always been a critical and complex challenge. This requires us to consider multiple factors in research to promote the materials can be translated to benefit the majority of patients.

In summary, the latest advancements in biopolymer-based hemostatic sponges have showed the great potential in the medical field. Through the optimization of material composition, structural innovation, and functional design, hemostatic materials are advancing towards greater safety, efficiency and intelligence. It is reasonable to believe that in the near future, more functionalized novel hemostatic sponges will be developed and successfully applied to the clinic, bringing revolutionary changes to the medical field.

CRediT authorship contribution statement

Chen-Yu Zou: Writing – original draft, Visualization, Conceptualization. **Chen Han:** Writing – original draft, Visualization, Conceptualization. **Fei Xing:** Writing – original draft. **Yan-Lin Jiang:** Writing – original draft. **Ming Xiong:** Writing – original draft. **Jesse Li-Ling:** Writing – original draft. **Hui-Qi Xie:** Writing – review & editing, Writing – original draft, Conceptualization.

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.

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