

Review

Not peer-reviewed version

---

# Chitosan-Based Biomaterials for Hemostatic Applications: A Review on Recent Advances

---

Daniela Gheorghita , [Horatiu Moldovan](#) , [Alina Robu](#) , [Ana-Iulia Bita](#) , [Elena Grosu](#) , [Aurora Antoniac](#) , [Iuliana Corneschi](#) , [Iulian Antoniac](#) <sup>\*</sup> , [Alin Danut Bodog](#) <sup>\*</sup> , [Ciprian Ionut Bacila](#)

Posted Date: 22 May 2023

doi: 10.20944/preprints202305.1508.v1

Keywords: hemostasis; topical hemostatic agents; chitosan-based composites; blood-material interaction



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Review

# Chitosan-Based Biomaterials for Hemostatic Applications: A Review on Recent Advances

Daniela Gheorghită<sup>1</sup>, Horațiu Moldovan<sup>2,3,4</sup>, Alina Robu<sup>1</sup>, Ana-Iulia Bița<sup>1</sup>, Elena Grosu<sup>1</sup>, Aurora Antoniac<sup>1</sup>, Iuliana Corneschi<sup>1</sup>, Iulian Antoniac<sup>1,4,\*</sup>, Alin Dănuț Bodog<sup>5,\*</sup> and Ciprian Ionuț Băcilă<sup>6</sup>

<sup>1</sup> Faculty of Material Science and Engineering, University Politehnica of Bucharest, 313 Splaiul Independentei, District 6, 060042 Bucharest, Romania, daniela.mgm@gmail.com (D.G.), alinarobu2021@gmail.com (A.R.), anaiulia.bit@gmail.com (A.I.B.), elena\_grosu@yahoo.com (E.G.), antoniac.aurora@gmail.com (A.A.), iulicorneschi07@gmail.com (I.C.), antoniac.iulian@gmail.com (I.A.)

<sup>2</sup> Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, 050474 Bucharest, Romania, h\_moldovan@hotmail.com (H.M.)

<sup>3</sup> Department of Cardiovascular Surgery, Clinical Emergency Hospital Bucharest, 014461 Bucharest, Romania

<sup>4</sup> Academy of Romanian Scientists, 54 Splaiul Independentei, 050094 Bucharest, Romania

<sup>5</sup> Faculty of Medicine and Pharmacy, University of Oradea, 10 P-ta 1 December Street, 410073 Oradea, Romania, alinbodog@gmail.com (A.D.B.)

<sup>6</sup> Faculty of Medicine, Lucian Blaga University of Sibiu, 10 Victoriei Boulevard, 550024 Sibiu, Romania, ciprian.bacila@ulbsibiu.ro (C.B.)

\* Correspondence: antoniac.iulian@gmail.com (I.A.); alinbodog@gmail.com (A.D.B.)

**Abstract:** Hemorrhage is a detrimental event present in traumatic injury, surgery, and disorders of bleeding, that can become life-threatening if not properly managed. Moreover, uncontrolled bleeding can complicate surgical interventions, altering the outcome of surgical procedures. Therefore, to reduce the risk of complications and decrease the risk of morbidity and mortality associated with hemorrhage, it is necessary to use an effective hemostatic agent that ensures immediate control of bleeding. In recent years, there have been increasingly rapid advances in developing novel generation of biomaterials with hemostatic properties. Nowadays, a wide array of topical hemostatic agents is available, including chitosan-based biomaterials that have shown outstanding properties such as: antibacterial, antifungal, hemostatic, analgesic activity, in addition to their biocompatibility, biodegradability, and wound-healing effects. This review provides an analysis of chitosan-based hemostatic and discusses the progress made in their performance, mechanism of action, efficacy, cost, and safety in recent years.

**Keywords:** hemostasis; topical hemostatic agents; chitosan-based composites; blood-material interaction

## 1. Introduction

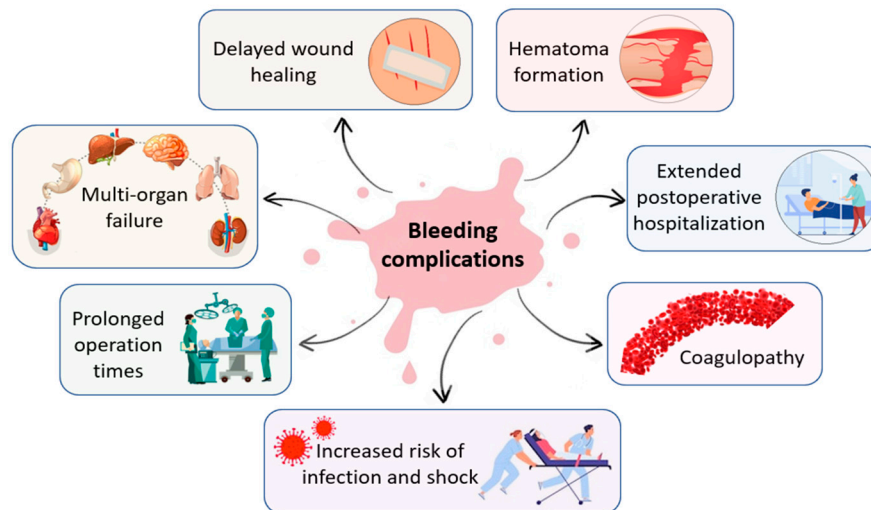
### 1.1. Hemorrhage in Surgical and Trauma Setting

Hemorrhage is a life-threatening condition that represents the first most common cause of death in combat casualties and the second amongst the civilians, as a result of traumatic injury. Hemorrhage refers to excessive blood loss that occurs due to unsuccessful formation of platelet plug at the site of injury [1,2].

In traumatic injuries, bleeding represents a leading cause of potentially preventable death. Moreover, trauma-induced coagulopathy is a complication attributed to trauma that describes abnormal clotting processes in which blood clots are not formed properly. Coagulation abnormalities are associated with internal bleeding and require proper management to restore circulating blood volume and reduce the risk of worsening trauma-induced coagulopathy [1,3]. Efficient bleeding management in the first hour of post-injury is the key to minimize the deleterious side effects of uncontrolled bleeding [2,4].

Additionally, many complex surgical interventions, such as cardiovascular, cranial, spinal, orthopedic and liver surgeries present a high incidence of uncontrolled bleeding that require hemostatic intervention [5–10]. In the intraoperative environment, uncontrolled bleeding can cause a

wide array of complications for both surgeons and patients that may lead to adverse intraoperative or perioperative outcomes, including prolonged operation times and postoperative hospitalization, delayed wound healing, increased risk of infection and shock, hematoma formation, multi-organ failure, coagulopathy and increased morbidity and mortality [2,10–16]. Figure 1 presents the complications of uncontrolled bleeding.



**Figure 1.** Main complications of uncontrolled bleeding in intraoperative environment.

During surgery, it is important to achieve rapid and effective hemostasis to retain visualization of the surgical field, maintain patients' hemodynamic equilibrium, reduce procedure and anesthesia time, as well as the occurrence of complications. Bleeding that is not effectively controlled can cause important blood loss volumes, which may require blood transfusions or blood-related products, thus exposing the patient to the numerous complications associated with transfusions: immunologic reactions, infection, immunosuppression, thereby complicating the operative procedure and increasing the risk of morbidity and mortality [17–19].

Preventing excessive blood loss during surgery equates to significantly decreasing the risk of major perioperative complications. Therefore, the risk of surgical re-intervention decreases, the patient needs shorter hospital length of stay which in turn may result in lower hospitalization costs. An appropriate management of such cases is critically important and thus, a major consideration for surgeons aiming to avoid these adverse effects [15,19,20].

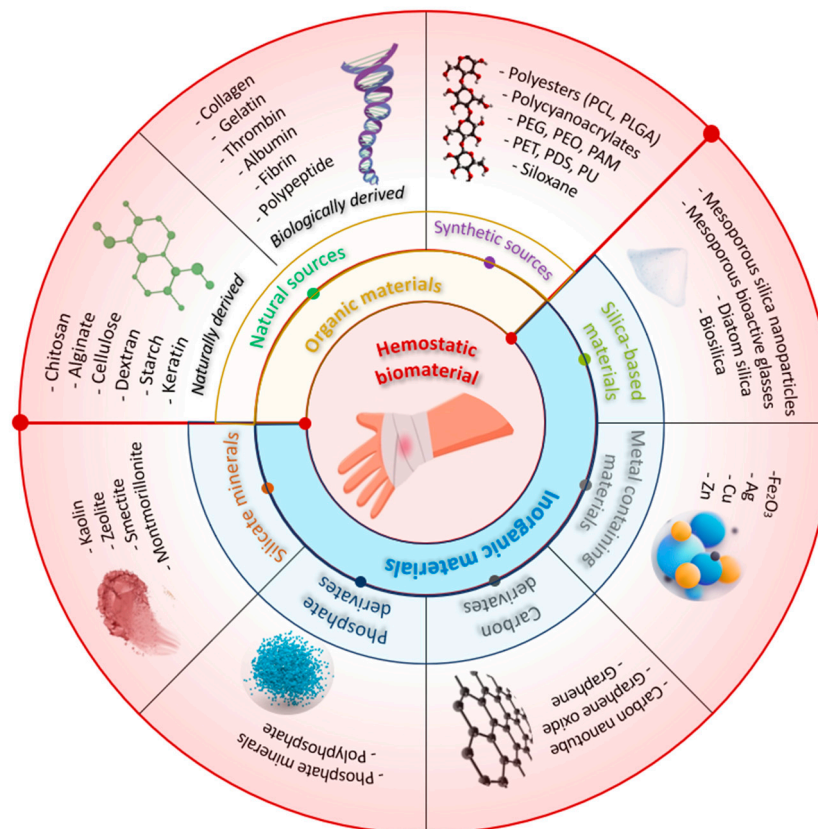
### 1.2. Achieving Hemostasis

Hemostasis represents the body's natural and physiological reaction to injury and the first step in wound healing. It is a vital process that involves multiple interlinked steps in order to stop the bleeding by forming a stable clot. The mechanism of hemostasis works like a multifaceted response to prevent and stop blood loss that occurs due to disruption of the vessel walls [1,21].

Conventional techniques for achieving hemostasis in surgery setting include a variety of mechanical techniques (e.g. sutures, ligatures, vascular clips, bone wax) and thermal techniques (e.g. electrocautery). To further aid in achieving hemostasis, adjunctive topical hemostatic products are also employed in conjunction with these primary techniques. Topical hemostatic agents play an important role in surgery environment as well as in the first-aid treatment, controlling blood loss and minimizing the risk of associated complications and the consequent mortality and morbidity [2,22].

Topical hemostatic agents can be categorized based on the raw materials used into two types: organic-based and inorganic-based hemostatic products [23]. Organic based hemostatic agents have two sources: natural source that comprises both naturally derived (carbohydrate based) and biologically derived (protein based) materials, and synthetic source. Figure 2 illustrates schematically multiple topical hemostatic materials used to control hemorrhage. Polysaccharides such as chitosan, alginate, cellulose, dextran, starch and keratin are currently the most commonly used natural polymeric hemostatic materials that are widely available. While biologically derived hemostatic

materials (e.g. collagen, gelatin, thrombin) facilitate platelet aggregation and activation achieving rapid hemostasis, their high cost, risk of immune reactions and poor mechanical properties have limited their widespread use [24]. Synthetic hemostatic agents are represented by polyesters (Polycaprolactone (PCL), poly (lactic-co-glycolic acid) (PLGA)), Poly(ethylene glycol) (PEG), polycyanoacrylates, Polyurethane (PU), siloxane, Polyethylene oxide (PEO), Polyacrylamide (PAM), polyethylene terephthalate (PET), Polydioxanone (PDS). These agents are widely used in various hemostasis operations because of their low immunogenicity, relatively high stability, and the ability to customize their chemical properties to enhance their clinical performance. However, the production cost of synthetic polymers is usually higher than that of natural polymers, and their poor biodegradability and potential cytotoxicity may impede their use in clinical practice [25].



**Figure 2.** Schematic illustration of multiple external hemostatic materials for hemorrhage control.

Several inorganic materials have been developed to accelerate blood coagulation, including silicate minerals, silica-based materials, metal containing materials, phosphate, and carbon derivatives. Inorganic hemostatic materials are often cheaper than organic materials, and they are physically and chemically stable, easy to produce and transport, and carry no risk of bloodborne disease. However, most inorganic materials are not bioabsorbable and need to be removed after used.

Some types of natural mineral clays (silicate minerals) have been found to have hemostatic properties and are used in medical applications to promote hemostasis. Kaolin is a type of clay that is commonly used in medical applications to promote hemostasis. It has a large surface area and can absorb water and blood, which helps to promote clotting. Montmorillonite is a type of clay that has a layered structure and a high cation exchange capacity. It is often used in hemostatic dressings and can promote clotting by absorbing blood and concentrating platelets. Zeolites are microporous, crystalline aluminosilicates that have unique properties, including a high surface area and the ability to selectively adsorb molecules [26–28].

Phosphates are a class of compounds that contain the element phosphorus. They have been studied for their potential use as hemostatic agents, particularly in the form of calcium phosphate materials. Hydroxyapatite is a common component of bone and has been shown to be effective in promoting hemostasis in surgical settings. Tricalcium phosphate is another calcium phosphate



material that has been studied for its hemostatic properties and has been shown to be effective in controlling bleeding in dental procedures.

Carbon derivatives are another class of compounds that have been investigated for their potential use as hemostatic agents. Carbon nanotubes are long, thin tubes made up of carbon atoms that have unique mechanical and electrical properties. Carbon nanotubes and graphene oxide have been shown to promote blood clotting and to enhance the effectiveness of other hemostatic agents [29,30].

Silica-based materials, including mesoporous silica, mesoporous bioactive glasses, diatom silica, and their composites, have recently been explored as a promising avenue in the field of hemostasis due to their negative charge and highly absorptive pores, which give them inherent hemostatic abilities. Diatom silica, for instance, is a nanostructured silica biomaterial with 3D porous structure with high porosity, and specific surface area, enabling it to absorb water, concentrate coagulation factors, and promote hemostasis. Mesoporous silica particles share similarities with natural mineral clays in that they can quickly absorb water and aggregate platelets, blood cells, and coagulation factors at the site of injury [31,32].

**Table 1.** Characteristics and hemostatic mechanism of different hemostatic materials and commercially available topical hemostatic agents.

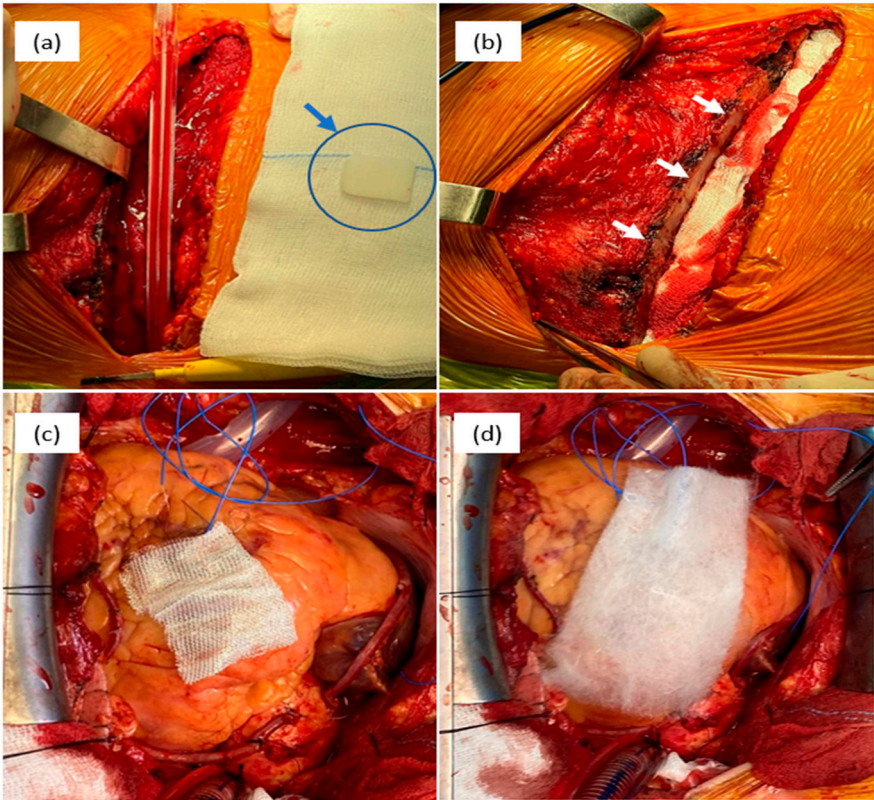
Materials and trademarks	Hemostatic mechanism	Characteristics	Ref.
Chitosan-based materials <i>ChitoFlex, Axiostat, PosiSep X, Celox, TraumaStat, HemCon.</i>	Positive surface charge enables it to bind with negatively charged blood components, promoting platelet activation and agglutination of blood proteins to facilitate fibrin clot formation, while also forming a strong physical barrier that adheres to wet tissues and seals wounds.	Biocompatible, biodegradable, antibacterial ability, stimulatory effect on tissue regeneration, hemostatic effect, cost-effective, easy to store and long shelf-life; suitable for patients with coagulopathy, although it may not be entirely effective in extensive bleeding wounds.	[33–37]
Cellulose-based materials <i>BloodSTOP, WoundClot, Surgicel, Suntouch, ActCel.</i>	Absorbs fluids, forms a physical barrier to prevent blood loss, exhibits anti-microbial activity, is bioabsorbable, and aids clotting by binding to calcium ions, initiating the clotting cascade through contact activation and decreasing pH at the wound site, leading to platelet activation and aggregation.	Appropriate for achieving hemostasis in cases of capillary, arteriolar, venous, and bone bleeding, and is also biocompatible, non-immunogenic, and bactericidal, conforming well to the wound site. However, it may not be effective in managing severe bleeding.	[2,38–41]
Starch-based materials <i>PerClot, EndoClot</i>	Absorbs water from the blood, leading to the formation of a gel-like matrix that can adhere to tissue and promote the aggregation of platelets and activation of clotting factors, ultimately resulting in the formation of a stable fibrin clot that can help to stop bleeding.	Reduces bleeding and the need for transfusions, minimizes the risk of blood infections and has no known immune or allergic reactions or toxic side effects. Should not be used in blood vessels to avoid the risk of embolism and is suitable for minor injuries. It is easy to use, lightweight, has a long shelf life, is inexpensive.	[42–47]
Collagen-based materials <i>Avitene, Helitene, Hemopad, Helistat, Collastat, Instat, CoStasis, D-stat.</i>	Forms a physical matrix, triggers the process of coagulation cascade and induces the activation of platelets, leading to the release of clotting factors like thrombin and fibrinogen.	Promotes tissue regeneration and repair, and possesses characteristics such as biocompatibility, cell adhesion, biodegradability, non-toxicity, and low antigenicity. Effective in heparinized patients, not suitable for use in patients with thrombocytopenia.	[2,20,33,48,49]

		Applicable for treating various types of wounds and injuries, but caution must be taken when used in restricted areas or near nerve structures due to the potential risk of compressive complications. It is a cost-effective solution that remains stable at room temperature, non-toxic, and non-antigenic. Furthermore, it has a strong adsorption capability, can stick to the wound surface, and can increase its volume up to twice its original size by absorbing fluids. Exhibits excellent hemostatic and adhesive properties,	
Gelatin-based materials <i>Gelfoam, Surgifoam, Gelfilm, Gelita-spon.</i>	Triggers the activation and aggregation of platelets, expedites the formation of clots, and provides structural support to the clot formed by enhancing thrombin generation and subsequently propagating the coagulation cascade.		[23,50–53]
Fibrin-based materials <i>Artiss, Tissel, Evicel, Tissucol, TachoSil.</i>	Major protein component of blood clots, is formed as the final step in the coagulation cascade, serving as a scaffold for tissue repair and providing cues for cell behavior during injury healing.	biocompatibility, and can be used for severe bleeding and patients with coagulation disorders but is not recommended for application on blood vessels. It also aids in tissue regeneration following injury due to its fast polymerization dynamics and ease of tunability. Presents bactericidal and bacteriostatic effects, non-toxic, non-carcinogenic, and good histocompatibility, with considerable hemostatic ability and can be applied in anastomosis, wound hemostasis, wound adhesion, and tendon repair, however, it may result in vascular embolization and release of toxic substances. Favorable biocompatibility, minimal cytotoxicity, and excellent hemostatic properties, commonly utilized in surgical settings to reduce bleeding and facilitate wound healing with a low occurrence of unfavorable consequences.	[54–57]
Polycyanoacrylates-based materials <i>Dermabond, Omnex, Glubran, Histoacryl, GLUture.</i>	Rapidly polymerize upon contact with fluids to create a mechanical barrier or plug that occludes the bleeding vessel or tissue, resulting in hemostasis.		[52,58–60]
PEG-based materials <i>Coseal</i>	Upon contact with tissue fluids to form a gel-like matrix, which adheres to the tissue and provides a mechanical barrier to prevent bleeding.		[48,61–64]
Polyurethane-based materials <i>Bioclusive, Opsite Flexigrid, Tegaderm, Allevyn, Tegaderm (3M Science), TissuGlu (Cohera Medical, Inc.), ResQFoam (Arsenal Medical, Inc.), Nanosan-Sorb (SNS Nano Fiber Technology)</i>	It triggers activation and aggregation of thrombocytes, initiating both coagulation cascade.	Polyurethane dressings can maintain a moist wound environment by allowing the transmission of moisture, oxygen, and air while blocking fluids and bacteria, and provide thermal insulation, promoting autolytic debridement; their high absorbency is due to a hydrophilic contact surface, microporous foam, and hydrophobic backing. Maintains its shape and firmness when exposed to blood,	[51,65–67]
Zeolite and kaolin powder based materials	Has a hygroscopic action, which allows it to quickly absorb water from blood to concentrate coagulation factors; it	Ease of use, stability, no biological toxicity or disease transmission, provide deep tissue access, are inert,	[26,48,68–70]

<i>Quikclot, Woundstat Combat Gauze</i>	can also release Ca <sup>++</sup> in blood and activate FXII to trigger the intrinsic coagulation pathway, and potentially induce contact activation of platelets.	and do not elicit an immune response. Not bioabsorbable and are less effective for arterial bleeding or coagulopathic patients. Their success is dependent on the patient's blood clotting activity. May cause thrombotic complications if particles enter the bloodstream.
PEG – Polyethylene glycol; PU – Polyurethane; FXII – Coagulation factor XII;		

Metal-containing materials have been effectively utilized in the field of hemostasis due to their demonstrated procoagulant activity. Silver nanoparticles have been shown to have antimicrobial properties, which may be useful in preventing infections at the site of bleeding and promote blood clotting. Copper nanoparticles have been shown to have antibacterial properties and promote blood clotting in both in vitro and in vivo experiments. Similar to copper nanoparticles, zinc nanoparticles have been found to promote blood clotting and prevent bleeding when applied to a wound. Several studies showed that zinc nanoparticles significantly accelerated blood clotting in vitro and demonstrated antibacterial activity [71–76].

However, more research is needed to fully understand their mechanisms of action and to optimize their use in hemostasis. It is also important to consider potential safety concerns associated with the use of these materials in medical applications, including the potential for toxicity or immunological reactions [77–81]. Numerous materials possess inherent properties that assist with the coagulation process and can effectively act as hemostatic agents. However, complex clinical requirements are not always met by the hemostatic efficiency of these materials.



**Figure 3.** Intraoperative aspect of different hemostatic materials used in cardiovascular surgery: Bone wax – (a) physical aspect of bone wax (blue arrow) and (b) sternum aspect after application of bone wax (white arrows); (c) Cellulose-based materials type Surgicel Original and (d) Cellulose-based materials type Surgicel Fibrillar.

Although the desired properties of an ideal local hemostatic agent may differ depending on the surgical specialty, certain characteristics are generally valued, including immediate and effective bleeding control, good safety profile (non-toxic, non-immunogenic), as well as ease of preparation and administration [17].

The process of blood clotting involves a complex interplay of biological, chemical, and physical reactions. In various blood clotting mechanisms, chitosan has demonstrated its effectiveness in hemostasis by virtue of its porous structure. By working in tandem with two or more hemostatic mechanisms, the hemostatic efficacy of chitosan can be further enhanced [82].

## 2. Chitosan Properties and Hemostasis Efficiency

Chitin is a white, hard, inelastic, nitrogenous, natural polysaccharide [molecular formula:  $(C_8H_{13}O_5N)_n$ ] which was extracted in 1911 from mushrooms and has been identified as the second most abundant polysaccharide found in nature after cellulose [2,83,84]. Chitin represents the strengthening material to the cell walls of fungi, exoskeletons of crustaceans (e.g. shrimps, lobsters, crabs), insects and fish scales [83,85,86]. Chitin and its derivatives are used in various sectors such as: chemistry, cosmetics, medicine, agriculture as well as in the textile and paper industry [85].

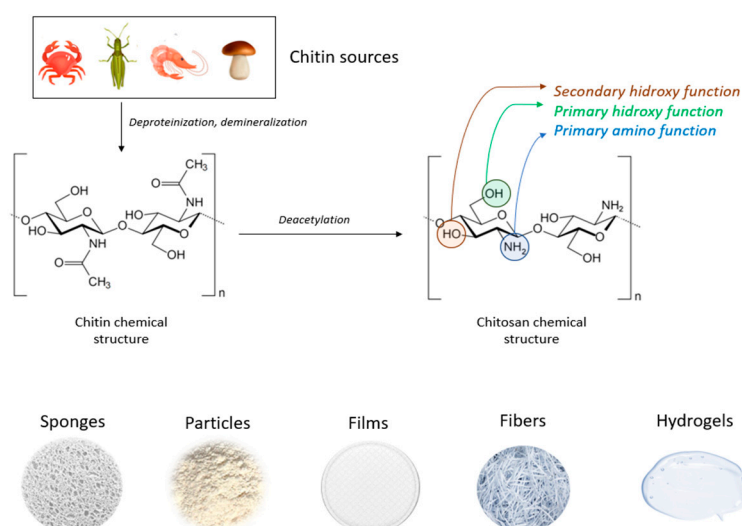
For biomedical applications, chitin is usually converted through enzymatic or chemical deacetylation to its most well-known derivative, chitosan [83]. Chitosan can have varying degrees of deacetylation and is classified as a copolymer of  $\alpha$ -(1 $\rightarrow$ 4) glucosamine  $(C_6H_{11}O_4N)_n$  containing a varied number of N- acetyl groups [84,85]. Chitosan is a weak base insoluble in  $H_2O$  and organic solvent, but soluble in acidic solutions (pH<6.5) [83,87]. Due to its increased versatility and biological properties, much of the research has been conducted on chitosan. In vitro studies have demonstrated that chitosan exhibits superior cytocompatibility when compared to chitin [85].

Chitosan is a biopolymer that has captured the attention of researchers and industries alike due to its unique physical and chemical properties, remarkable macromolecular framework and biological activities. These attributes distinguish it from synthetic polymers, making it an exciting and promising material for applications in fundamental science, applied research, and industrial biotechnology [88].

Significant attention is directed towards its potential medical and pharmaceutical applications due to its remarkable properties, such as biocompatibility, biodegradability and non-toxicity, which make it very valuable in the biomedical field [85,89]. Chitosan is a biocompatible substance that does not trigger an immune response, making it compatible with living tissues. Chitosan also possesses several other distinctive properties, including hemostatic and antithrombogenic properties, the ability to form polyoxysalts, create films and demonstrate molecular adsorption properties [83]. Figure 2 illustrates how chitosan is obtained and its main properties. Several studies have shown that chitin and chitosan are both biocompatible and biodegradable biopolymers, present antimicrobial properties and enhance blood coagulation [87,90].

The bacteriostatic and fungistatic properties of chitosan-based materials are particularly useful for wound treatment. In addition to their antimicrobial properties, chitosan and its oligosaccharides can stimulate cell growth. Chitosan-based materials such as non-wovens, nanofibers, composites, films, and sponges have been shown to promote wound healing and dermal regeneration. As a result, chitosan's primary commercial applications in the biomedical field are related to wound healing [91].



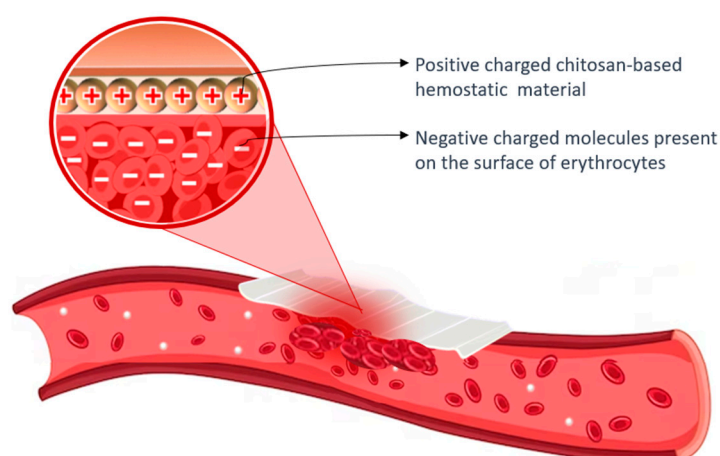


**Figure 4.** Chemical structures of chitin and chitosan and chitosan main forms.

Due to its versatility, chitosan has proven to be a valuable material for a variety of practical applications in numerous fields such as medicine, chemistry, cosmetics, biotechnology, agriculture, chromatography, as well as textile and fiber industries [92].

Chitosan has tremendous potential in the medical and biomedical fields, with applications ranging from pharmaceutical formulations and drug delivery (including antibiotics, vaccines, anti-inflammatory agents, peptides, proteins, and growth factors) to antimicrobial treatments, burns, wound healing, gene delivery and therapy, regenerative medicine, and tissue engineering (for tendon, cartilage, ligament, bone, liver, neural, and skin regeneration). Additionally, chitosan has potential applications in cancer treatment, therapy, and diagnostics, as well as in dentistry, dermatology, ophthalmology, biosensors, bio-imaging (such as magnetic resonance imaging), support for immobilized enzymes, and veterinary medicine [85,91,93]

Chitosan fibers are distinct from other fibers in that they carry a positive charge, giving them cationic properties that enable them to interact electrostatically with negatively charged molecules. This cationic nature of chitosan also allows it to bind with the anions on bacterial cell walls, thereby impeding their entry into the cell. This microbicidal action of chitosan is crucial in the wound healing process [93]. Figure 5 presents the hemostatic mechanism of chitosan-based material.



**Figure 5.** Hemostatic mechanism of chitosan based material: The aggregation of erythrocytes occurs due to the interaction between positively charged chitosan and negatively charged molecules present on the surface of erythrocytes.

While many naturally occurring polysaccharides, such as agar, dextran, pectin, carrageenan, cellulose, agarose and alginic acid are neutral or acidic in nature, chitosan stands out as an example

of a highly basic polysaccharide. Chitosan's most distinctive property is its cationic nature and its unique behavior in solution, which is also of great importance for its medical applications. This biopolymer is the only naturally occurring cationic polymer known to exist in nature [91,94].

Chitosan's cationic properties play a significant role in inducing hemostasis, as the surfaces of platelets and erythrocytes carry negative charges due to the presence of phosphatidylcholine, phosphatidylethanolamine, and sialic acid groups, respectively. It is noteworthy that the majority of the biological and chemical applications of chitosan rely on its cationic properties and its versatility as a biomaterial [91].

Upon contact with blood, chitosan has been demonstrated to stop bleeding by absorbing water and converting it into an adhesive element that adheres to the damaged tissue [85]. In fact, a scientific research has shown that a chitosan dressing was able to effectively control an arterial hemorrhage in dogs [95]. Several animal model studies have demonstrated that chitosan-based dressings are effective hemostatic agents, even in coagulopathic conditions. Moreover, they are more cost-effective compared to other alternatives [84]. Chitosan has been demonstrated to be a highly effective hemostatic agent in various formulations such as gels/hydrogels, powders, membranes and films, dressings, sponges, foams, and microspheres.

3. Current Trends on Chitosan Based Hemostatics

There is a growing demand for biomaterials that can perform multiple functions, including hemostasis, antibacterial activity, stimulation of cell division and differentiation, and acceleration of tissue healing. Chitosan, by itself, is unable to absorb excessive bleeding and has limited antibacterial activity in solution. To overcome these limitations, researchers have recently blended chitosan with gelatin, sodium hyaluronate, and silver nanoparticles to enhance its absorption capacity and antibacterial activity [82]. The composite dressing was found to possess high porosity, allowing it to absorb a significant amount of blood while also promoting hemostatic activity through platelet aggregation and activation. Additionally, the dressing exhibits antibacterial properties against *E.coli* and *S.aureus*. The incorporation of ibuprofen drugs, nano zinc oxide, gallic acid, and cinnamaldehyde has further enhanced the antimicrobial and hemostatic properties of chitosan-based materials [82].

A study conducted by Pan et al. [96] demonstrated that the incorporation of zinc alginate in chitosan microspheres resulted in the activation of coagulation factor XII and the initiation of the intrinsic coagulation cascade. This led to the production of thrombin and fibrin clot, as well as the acceleration of blood coagulation time, clotting, and clot propagation, in addition to fibrin clot formation.

Combining chitosan with alginate, cellulose, silk, and *Bletilla striata* polysaccharide has been shown to induce hemostatic activity by reducing hemostasis time and minimizing blood loss. This approach can effectively manage bleeding complications during surgical procedures in diabetic patients [97,98].

**Table 2.** Different forms of Chitosan-based materials for hemostatic application and their characteristics findings.

Forms	Composition	Characteristics	Ref.
Dressing	CS, Aluminum chloride	The microporous structure of the dressing is irregular, which allows it to absorb the maximum amount of blood and promote clot formation.	[35]
	Carrageenan, CS	The composite dressing's greater swelling, larger surface area, and mesoporous structure result in superior hemostatic activity by promoting increased adhesion of blood cells and platelets.	[99]
	CS, Calcium Alginate	Biocompatibility, antibacterial, moisture retention, healing promotion, and noncytotoxicity characteristics make chitosan-calcium alginate dressing a superior option for wound care.	[100]
Hydrogel	CS, PEG	The combination of biodegradability, self-adhesiveness, self-healing ability, stretchability, antibacterial properties, and biocompatibility makes it a promising material for emergency hemostasis, particularly for joint and limb injuries. The hydrogel showed strong adhesion to various substrates (PTFE, pigskin, and glass tubes) and provided long-term stability when applied to bleeding wounds in both static and dynamic humid environments.	[101]

	Hydroxybutyl-functionalized CS	The material possesses thermosensitive characteristics, strong adhesion ability, effective hemostasis, appropriate mechanical properties, self-healing capability, easy removal as needed, antioxidant properties, as well as photothermal and intrinsic antibacterial activity. [102]
	FCMCS, PDA, PAM	The hydrogel exhibited a variety of functions including tissue adhesion, biocompatibility, self-healing, and antibacterial properties. It also maintained its mechanical characteristics while offering broad-spectrum antibacterial activity. [103]
	CMCS, OHA	The material exhibits favorable biodegradability and biosafety profiles, and possesses strong hemostatic and sealing capabilities, making it a promising candidate for clinical hemostatic sealant applications. [104]
Sponge	Cs, AgNPs	The chitosan/Ag nanocomposite sponges demonstrated outstanding antibacterial activity against <i>Staphylococcus aureus</i> and <i>E. coli</i> in the antibacterial test. They also displayed good mechanical properties and noncytotoxicity, with cell viability values exceeding 90%. [105]
	CS, Cellulose	The sponge demonstrates favorable biocompatibility and hemostatic capability, making it a promising option for prompt hemostasis in cases of severe bleeding. [106]
	CS/PVA-PD-FeO NPs	The sponge demonstrated high porosity and water absorption properties, as well as significant antibacterial activity. It facilitated gaseous exchange, absorbed wound exudate, and inhibited microbial growth in diabetic wounds. Therefore, it can be inferred that the chitosan composite sponge's antioxidant, antidiabetic, and antibacterial properties can contribute to the healing of diabetic wounds. [107]
	CS/ AgNPs /Alginate	The material demonstrated notable absorbency and a significant antimicrobial impact, particularly in assays involving <i>Bacillus cereus</i> and <i>Staphylococcus aureus</i> . [108]
	CS, SIP	The material exhibits a strong ability to absorb fluids, as well as significant procoagulant effects, making it effective in promoting wound healing. [109]

CS – Chitosan; PEG – Polyethylene glycol; CMCS – Carboxymethyl chitosan; PDA – Polydopamine; PAM – Polyacrylamide; FCMCS – Fungal mushroom-derived carboxymethyl chitosan; OHA – Oxidized hyaluronic acid; AgNPs – Silver nanoparticles; PD – aqueous leaves extract of *Pinus densiflora*; FeO – Iron oxide; PVA – Poly vinyl alcohol; SIP – Squid ink polysaccharide.

Hemostatic dressings are designed to support or collaborate with the body's innate clotting mechanism to control bleeding. It has been reported that chitosan-based dressings can expedite hemostasis, even in the presence of coagulopathy [110,111].

Santosh S. Biranje et.al. conducted a study in which a porous chitosan nanoparticulate dressing was prepared using the lyophilization method for potential use in wound healing. The chitosan dressing exhibited high porosity, improved swelling properties, controlled biodegradation, and biocompatibility, as well as accelerated hemostatic activity. These results suggest that chitosan-based dressings have immense potential for use in wound healing applications [99].

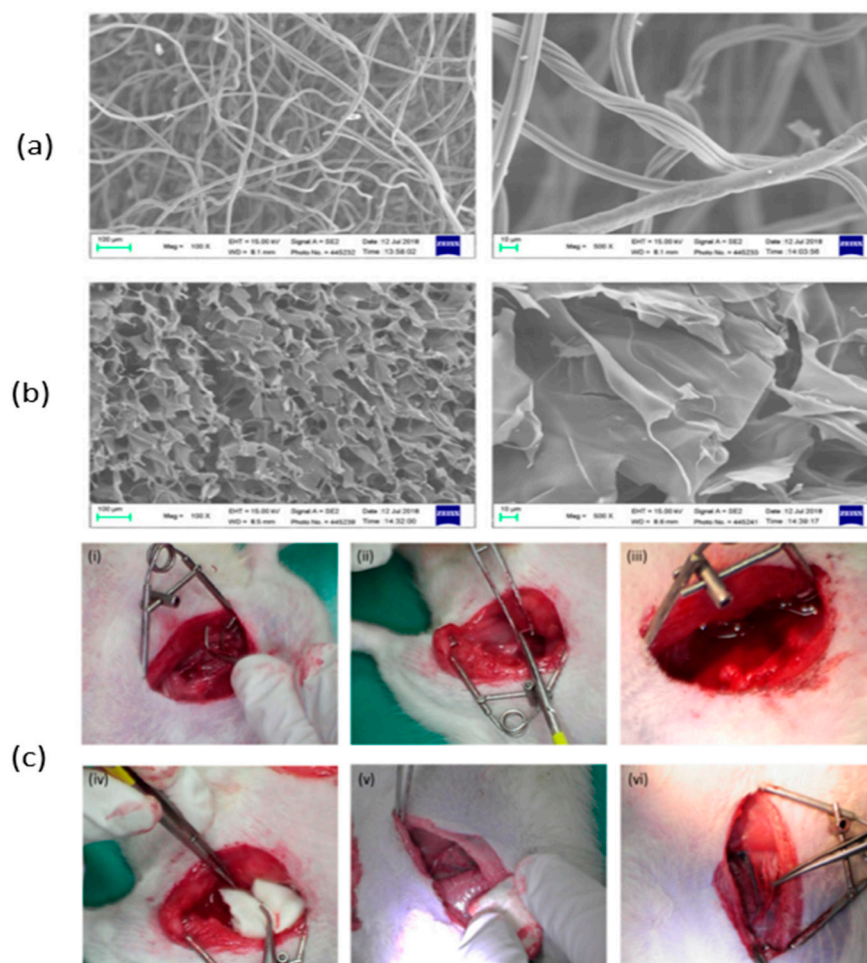
In their study, Wang et al. obtained chitosan/polybutylenes succinate (CS/PBS) nanofiber membranes with varying CS contents of 0%, 20%, 40%, 60%, 80%, and 90%, using the electrospinning technique. The results of the research demonstrated that the CS/PBS fiber membrane with different CS contents exhibited distinct characteristics such as varying fiber diameter, wettability, liquid absorption, moisture permeability and blood clotting performance. The membrane with a CS content of 90% demonstrated the most favorable properties for wound dressing, making it the most suitable option [112].

In a study developed by Buriuli et.al., a dressing was obtained from chitosan and pectic acid, using sonication and freeze-drying methods. The dressings featured a porous structure, exceptional water and blood absorption, strong hemostatic performance and had a lightweight and flexible structure, making them a promising material for potential use as a hemostatic agent [110].

Akram et.al. obtained a Chitosan/calcium phosphate (CCP) hemostatic dressing that was found to be effective in controlling blood loss and reducing blood clotting time to only 15 seconds.

Moreover, the CCP-based hemostatic dressings were found to be effective in controlling bacterial infections [113].

According to Wang et al., chitosan fiber (CF) dressing exhibited stronger hemostatic properties compared to regular gauze-type surgical dressing. In an animal model of femoral artery hemorrhage and in patients with surgical wounds, CF dressing reduced the hemostasis time and effectively controlled blood loss and absorption [114]. Figure 6 presents scanning electron microscopy (SEM) analysis of chitosan-based dressings and rat femoral artery hemorrhage model that was used to evaluate the dressings. The surface of the CF dressing appeared to be evenly fibrous, with fibers measuring approximately 10  $\mu\text{m}$  in diameter as shown by SEM in Figure 6(a). On the other hand, the Chitosan sponge exhibited a highly porous surface, with pore diameters ranging from around 50-100  $\mu\text{m}$  (Figure 6(b)). These dressings were both characterized by large surface areas and interconnected networks, with the CF dressing having the highest surface area among the two. In this study, a rat femoral artery hemorrhage model was employed to assess the effectiveness of the dressings. This model simulates a severe injury to the groin region, which results in partial damage to the femoral artery and life-threatening bleeding that cannot be managed by standard dressings (Figure 6(c)).

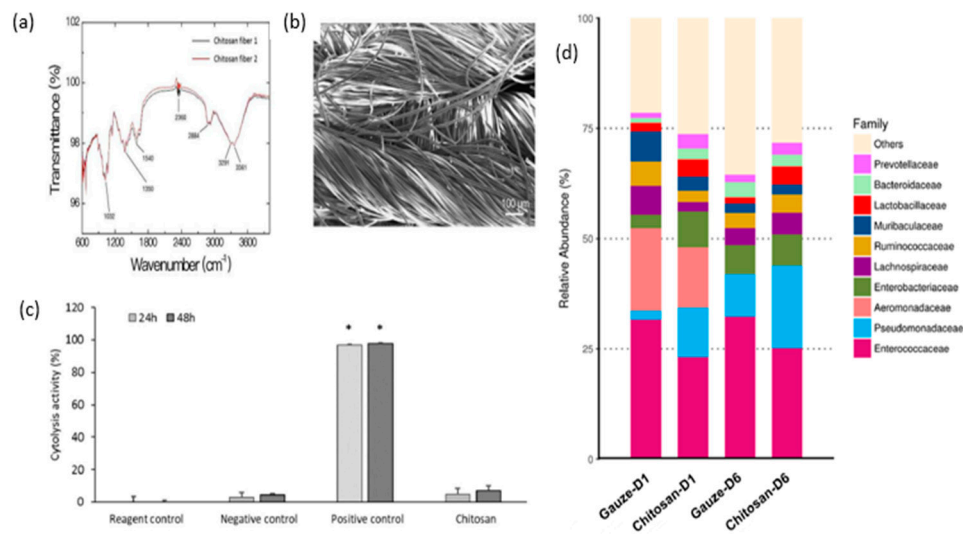


**Figure 6.** SEM analysis of (a) Chitosan fiber, (b) Chitosan sponge and (c) in vivo assessment of hemostatic efficacy of dressings tested on a rat femoral artery hemorrhage model. [114].

The findings of C.-H.Wang et.al. showed that chitosan dressing outperforms regular gauze-type surgical dressing in terms of antimicrobial and procoagulant properties when applied to surgical wounds in patients. The study suggests that chitosan dressing not only possesses antimicrobial and procoagulant properties, but also has the potential to promote wound healing by introducing beneficial microbiota [115]. Figure 7 presents some results after Characterization of the chitosan dressing including Fourier-transform infrared spectroscopy (FT-IR) results, Scanning electron microscopy (SEM) observation, cytotoxicity activity measurement and relative abundance of most predominant bacteria identified in wound-contact up to 6 d post-surgery. Fourier-transform infrared



(FTIR) spectroscopy analysis, as presented in Figure 7(a) demonstrated characteristic transmittance bands of chitosan dressing. Scanning electron microscopy (SEM) analysis shown in Figure 7(b) demonstrated that the chitosan dressing had a uniform fibrous structure and a significantly large surface area. The chitosan dressing showed a high level of biocompatibility as it was able to significantly inhibit cytolysis (Figure 7(c)), similar to the negative control represented by Dulbecco's modified Eagle's medium (DMEM) and phosphate-buffered saline (PBS). The study utilized 16S rRNA-based sequencing on the Illumina MiSeq platform to analyze the microbial community in the wound affected by the dressing treatments. Figure 7 (d) illustrates the effect of wound dressings on the relative abundance of bacterial population at the family level. The results showed that the chitosan dressing was able to suppress the growth of Enterobacteriaceae members (from 8.1% in 1 day to 7% in 6 days postsurgery) while promoting the growth of Pseudomonadaceae members by 7.6% up to 6 days postsurgery compared to the regular gauze dressing.



**Figure 7.** Characterization of the chitosan dressing: (a) Fourier-transform infrared spectroscopy results; (b) Morphology observations using scanning electron microscopy; (c) Cytolysis activity measurement for biocompatibility evaluation (\*  $p < 0.05$ ; 24 and 48 h incubation); (d) Relative abundance of most predominant bacteria identified in wound-contact chitosan and regular gauze dressings up to 6 days post-surgery (D1 = day 1, D6 = day 6) [115.]

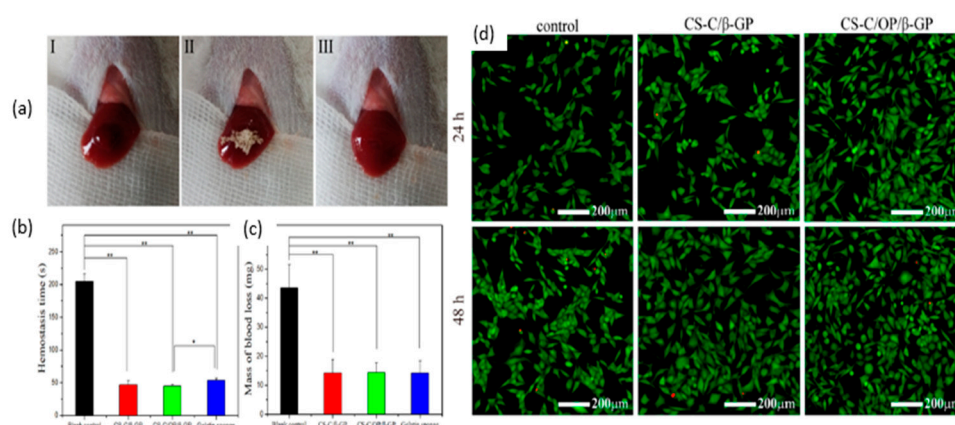
### 3.2. Hydrogel

Hydrogels have gained attention for clinical applications due to their ability to maintain a moist environment and seal tissue during hemostasis, thanks to their high-water content. They are composed of hydrophilic polymers cross-linked in a three-dimensional network that closely resemble the extracellular matrix, allowing them to absorb substantial amounts of water. The ability of hydrogels to swell is attributed to the presence of hydrophilic groups (-OH, -CONH-, -CONH<sub>2</sub>, and -SO<sub>3</sub>H) within the polymeric components of the gels [116,117].

In a study conducted by Qiao et al. (2021), a supramolecular hydrogel was developed by combining chitosan with silk fibroin and using tannic acid as a crosslinker. The resulting hydrogel exhibited a strong wet adhesion capacity and demonstrated rapid hemostatic activity in various arterial and visceral bleeding models. These findings suggest that the use of supramolecular hydrogels could be a promising strategy for achieving hemostasis in clinical applications [23].

Zhang et al. prepared chitosan-based thermo-sensitive hydrogel loading oyster peptides (CS-C/OP/β-GP) using catechol-modified chitosan (CS-C) as the matrix material and β glycerol phosphate (β-GP) as a thermo-sensitive agent. According to the findings, the coagulation time and blood coagulation index of the CS-C/OP/β-GP hydrogel were superior to those of a commercially available gelatin sponge when tested in vitro [118]. Moreover, the platelet adhesion and erythrocyte adsorption rates of the CS-C/OP/β-GP hydrogel were significantly higher, showing an increase of 38.98% and 95.87%, respectively, when compared to the gelatin sponge. Furthermore, it was observed that the use of CS-C/OP/β-GP hydrogel reduced the hemostasis time in mouse liver injury by 19.5% and

decreased the mass of blood loss in the mouse tail amputation model by 18.9%. Safety evaluations also revealed that the CS hydrogel was non-cytotoxic to L929 cells, and the hemolysis rates were under 5% at concentrations of up to 1 mg/mL, indicating favorable biocompatibility. These findings suggest that CS hydrogel has the potential to be a reliable medical dressing for hemostasis, making it a promising candidate in this field. Figure 8 shows the application of samples in the hemostasis of liver injury (a), liver hemostasis time (b), liver blood losses (c) and Calcein-AM/PI double staining for L929 cells (d). Figure 8 (d) illustrates that there was no notable variation between the control group and the samples after 24 hours. However, CS-C/ $\beta$ -GP and CS-C/OP/ $\beta$ -GP exhibited intense green fluorescence when compared to the control group after 48 hours. Upon visual inspection of the samples, it was observed that aside from a few dead cells, the majority of the cells retained their normal spindle shape, and there was a higher cell density and uniform distribution. These findings suggest that L929 cells were able to grow and develop normally in the presence of CS-C/OP/ $\beta$ -GP.



**Figure 8.** Hemostasis in a liver injury model (I: bleeding; II: hemostasis; III: aspect of wound after hemostasis) (a) Time of hemostasis (b) Mass of blood loss (c) and Calcein-AM/PI double staining for L929 cells (d) [118].

G.Patil et. al. obtained a novel chitosan-based hydrogel that was loaded with SiNPs and  $\text{AlCl}_3$  and demonstrated its effectiveness as a hemostatic dressing for non-compressible bleeding. The hydrogel composite exhibited improved platelet aggregation and calcium store activation, leading to faster hemostasis. Additionally, the soft texture of the hydrogel allowed for easy application and was determined to be safe [119].

In recent years, the application of nanotechnology in the biomedical field has led to the development of new tools. For instance, incorporating silver nanoparticles (AgNPs) into chitosan-based hydrogels has been proposed as a means of introducing a bactericidal and bacteriostatic agent [120]. According to a report by Vijayakumar and colleagues in 2019, chitosan-AgNPs hydrogels demonstrated superior antibacterial activity when compared to uncoated hydrogels. The in vitro antibacterial activity of the hydrogels was evaluated against wound infections caused by methicillin-resistant *S. aureus* and *P. aeruginosa*. The results showed that chitosan-AgNPs hydrogels exhibited an effective antibacterial action [120].

### 3.3. Sponge

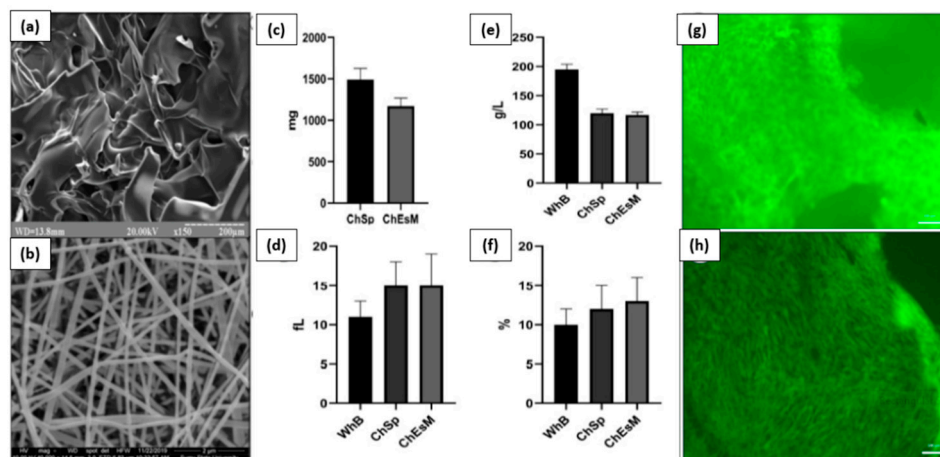
Typically, sponges have a porous structure, which makes them permeable to gas exchange, flexible, and able to absorb exudates from skin lesions [121].

Kim and colleagues [122] developed a chitosan-catechol sponge with the aim of improving hemostasis in patients with coagulopathy. They conducted a detailed analysis of the hemostatic mechanism of the sponge and proposed a synergistic mechanism based on the combined action of catechol and cationic charges. This mechanism was found to promote rapid coagulation, even in cases of coagulopathic blood, and was therefore considered promising for clinical application [19]. Upon contact with blood, the chitosan-catechol sponge would form a barrier layer by interacting with the proteins in the blood, which helps to prevent bleeding. However, native chitosan has limited film-forming ability since it is not able to dissolve in neutral conditions, which can result in a decrease in its hemostatic efficacy compared to catechol-conjugated chitosan.

In 2020, Wu and colleagues developed a sponge that serves multiple functions including fast hemostasis and long-term antimicrobial activity [123]. This was achieved by modifying chitosan with mercaptosuccinic acid and using sulfhydryl groups (-SH) to immobilize AgNPs. The introduction of -SH improved the activity of tissue factor (TF) which initiates the coagulation cascade, and also reduced cytotoxicity by slowing down the release rate of AgNPs. Furthermore, the immobilized AgNPs were able to enhance the strength of the formed bleeding clot by serving as action sites for amino, mercapto, and carboxyl groups.

Fan et.al. obtained a chitosan/cellulose composite sponge that displayed a high water absorption capacity and mechanical strength [106]. Furthermore, this newly developed sponge also demonstrated inhibitory effects on the growth of *E. coli*, *S. aureus*, and *P. aeruginosa* bacteria. Tests conducted on the chitosan/cellulose composite sponge showed that it had good coagulation ability and demonstrated rapid hemostasis in vivo, as it was able to stop bleeding from a rat leg artery injury in just 34 seconds.

V. Deineka et al. conducted a study to evaluate the biocompatibility, hemostatic efficacy, and tissue-regeneration performance of a Ch-PEO (Chitosan-Polyethylene Oxide) copolymer that was prepared using the electrospinning technique [124]. The Chitosan electrospinning membranes (ChEsM) were fabricated from chitosan and polyethylene oxide (PEO) powders to produce a highly porous material with adequate hemostatic properties. The study analyzed the structure, porosity, density, antibacterial characteristics, in vitro degradation, and biocompatibility of ChEsM and compared them with a conventional chitosan sponge (ChSp). In vitro, both materials showed significant biocompatibility and hemostatic efficacy. However, ChEsM exhibited weaker antibacterial properties compared to ChSp. In vivo studies validated the superior biocompatibility and satisfactory hemostatic performance of ChEsM, with close interaction with host tissues and cells. The in vivo model demonstrated a faster biodegradation rate of ChEsM and enhanced liver healing. Figure 9 presents Scanning electron microscopy images of chitosan sponge and chitosan electrospinning membrane, blood sorption and hematological parameters as well as live/dead staining with FDA/PI after 48h of cell cultivation [124].



**Figure 9.** Scanning electron microscopy image of ChSp (a) and ChEsM (b); blood sorption (c) and hematological parameters: platelet (e), platelet distribution width (d) and mean platelet volume (f) after interacting with blood; ChSp (g) and ChEsM (h) live/dead staining with FDA/PI after 48 h of cell cultivation [124].

Bal-Ozturk and colleagues conducted a study in which they fabricated and characterized chitosan/alginate/zinc oxide (CHI/AA/ZnO) nanostructured hydrogel sponges for potential use as a hemostatic agent in biomedical applications. The hydrogel sponges containing ZnO demonstrated a good bacteriostatic effect on *S. aureus* in antibacterial experiments, with the antibacterial properties increasing as the amount of ZnO in the polymer network increased [125].

In a study developed by Lin et.al., a Chitosan-Graphene Oxide Hemostatic Sponge was obtained with porous structure that allows it to quickly absorb plasma in blood. The sponge also stimulates interfacial reactions with erythrocytes and platelets. Compared to commercial gauze sponges, this

hemostatic sponge demonstrated improved hemostatic efficiency and holds great potential for use in hemostatic applications, wound treatment, and targeted drug delivery in clinical settings [121].

Zheng et al. developed a novel AuNPs (gold nanoparticles) corn stalk/chitin composite sponge (CCAu). Investigations showed relevant properties, including hemostasis, antibacterial effects, and wound healing promotion. In both in vitro and in vivo tests, the CCAu sponge demonstrated excellent hemostatic ability and biocompatibility, as well as effective antibacterial activity against *S. aureus* and *E. coli*. Additionally, the sponge was found to accelerate wound healing by promoting cell migration, angiogenesis, and collagen deposition [126].

#### 4. Conclusion and Future Perspectives

Uncontrolled bleeding is a significant factor that can impact a patient's recovery and quality of life after surgery. Managing blood loss during surgery can significantly reduce the risk of major perioperative complications. In cases of traumatic injuries, prompt and effective hemostasis is critical to prevent excessive blood loss, which can lead to shock and potentially fatal outcomes. Effective blood management strategies, including the use of appropriate hemostatic agents, can significantly reduce morbidity and mortality associated with traumatic injuries.

Chitosan's exceptional biochemical properties make it an important polymeric biomaterial for use in biomedical applications that require hemostatic properties. It can be processed into various products, such as scaffolds and nanoparticles, that are increasingly being used in the rapidly growing field of nanomedicine. Chitosan-based composite materials can be optimized in various forms to achieve a fast hemostasis. In order to obtain these composite materials, chitosan can be blended with other functional components, such as pain relievers, anti-inflammatory agents, and wound healing materials, to obtain multi-functional CS-based composite hemostatic materials.

Currently, there is no hemostatic product on the market that can be considered an ideal hemostatic product, but this ideal could be achieved using composite materials obtained by combining different hemostatic materials with different mechanisms of hemostasis that can lead to synergistic effects and thus, a faster hemostasis.

It is anticipated that the field of nanotechnology will continue to improve hemostatic materials by improving key properties and incorporating new functionalities. The ultimate goal is to design a hemostatic material with optimal properties that can induce rapid and effective clotting under a variety of bleeding conditions, such as patients with blood deficiencies or injuries of different sizes and shapes. To achieve this, it is important to continue developing a deeper understanding of the interactions between different nanomaterials and blood.

As medical services continue to advance, the demand for high-performance hemostatic materials is increasing. The fabrication of novel hemostatic materials that are efficient, safe, and easy to transport has become a critical research area. Despite advances in surgical techniques and procedures, uncontrolled bleeding remains an important complication that contributes to poor clinical outcomes, remaining one of the leading causes of morbidity and mortality in trauma, childbirth, and complex surgeries.

**Author Contributions:** Conceptualization, H.M. and I.A.; methodology, D.G., H.M., E.G., and I.A.; software, D.G., A.R., A.I.B, and I.C.; validation, D.G., H.M., A.R., A.I.B., E.G., A.A., I.C., I.A., A.D.B, and C.I.B.; formal analysis, A.D.B., and C.I.B.; investigation, D.G., A.R., A.I.B., A.A., and I.C.; resources, I.C., C.I.B., and A.D.B.; data curation, H.M., and I.A.; writing—original draft preparation, D.G., E.G., and A.A.; writing—review and editing, D.G., E.G., and A.A.; visualization, D.G., A.R., A.I.B., E.G., A.A., I.C., A.D.B, and C.I.B.; supervision, H.M., and I.A.; project administration, H.M.; funding acquisition, I.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by a grant from the Romanian Ministry of Education and Research, CCCDI-UEFISCDI, project number PN-III-P2-2.1.-PED-2019-5236, within PNCDI III. In addition, financial support from the Competitiveness Operational Program 2014-2020, Action 1.1.3: Creating Synergies with RDI Actions of the EU's HORIZON 2020 framework program, and other international RDI programs, MySMIS code 108792, the Acronym Project "UPB4H", financed by the contract 250/11.05.2020, is gratefully acknowledged.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.



**Data Availability Statement:** Data reported in this manuscript is available upon official request from corresponding authors.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Malik, A.; Rehman, F.U.; Shah, K.U.; Naz, S.S.; Qaisar, S. Hemostatic Strategies for Uncontrolled Bleeding: A Comprehensive Update. *J Biomed Mater Res B Appl Biomater* **2021**, *109*, 1465–1477.
2. Mohamed, E.; Fitzgerald, A.; Tsuzuki, T. The Role of Nanoscale Structures in the Development of Topical Hemostatic Agents. *Mater Today Nano* **2021**, *16*.
3. Moore, E.E.; Moore, H.B.; Kornblith, L.Z.; Neal, M.D.; Hoffman, M.; Mutch, N.J.; Schöchl, H.; Hunt, B.J.; Sauaia, A. Trauma-Induced Coagulopathy. *Nat Rev Dis Primers* **2021**, *7*, doi:10.1038/s41572-021-00264-3.
4. Yesudasan, S.; Averett, R.D. Recent Advances in Computational Modeling of Fibrin Clot Formation: A Review. *Comput Biol Chem* **2019**, *83*, 107148, doi:10.1016/j.compbiolchem.2019.107148.
5. Pariza, G.; Mavrodin, C.; Antoniac, I. Dependency between the Porosity and Polymeric Structure of Biomaterials Used in Hernia Surgery and Chronic Mesh-Infection. *MATERIALE PLASTICE* **2015**, *52*, 484–486.
6. Brătilă, E.; Comandasu, D.; Milea, C.; Berceanu, C.; Vasile, E.; Antoniac, I.; Mehedintu, C. Effect of the Surface Modification of the Synthetic Meshes Used in the Surgical Treatment of Pelvic Organ Prolapse on the Tissue Adhesion and Clinical Functionality. *J Adhes Sci Technol* **2017**, *31*, 2028–2043, doi:10.1080/01694243.2017.1294358.
7. Iliuta, L.; Rac-Albu, M.; Rac-Albu, M.-E.; Andronesi, A. Impact of Pulmonary Hypertension on Mortality after Surgery for Aortic Stenosis. *Medicina (B Aires)* **2022**, *58*, 1231, doi:10.3390/medicina58091231.
8. Crișan, R.-M.; Băcilă, C.I.; Morar, S. The Role of Psychological Autopsy in Investigating a Case of Atypical Suicide in Schizophrenia: A Case Report with a Brief Review of Literature. *Egypt J Forensic Sci* **2022**, *12*, 30, doi:10.1186/s41935-022-00291-5.
9. Iliuta, L. Predictors of Persistent Severe Diastolic Dysfunction after Aortic Valve Replacement in Aortic Stenosis Compared with Aortic Regurgitation. *Eur Heart J* **2012**, *33*, 667–668.
10. Costache, V.S.; Moldovan, H.; Arsenescu, C.; Costache, A. Aortic Valve Surgery of the 21st Century: Sutureless AVR versus TAVI. *Minerva Cardiology and Angiology* **2018**, *66*, doi:10.23736/S0026-4725.17.04558-3.
11. Dobritoiu, F.; Moldovan, H.; Oncica, R.; Vasile, G.; Nechifor, E.; Copaescu, C. Giant Cavernous Hemangioma of the Right Atrium - A Rare Case and Literature Review. *Chirurgia (Bucur)* **2020**, *115*, 267, doi:10.21614/chirurgia.115.2.267.
12. Costache, V.S.; Meekel, J.P.; Costache, A.; Melnic, T.; Solomon, C.; Chitic, A.M.; Bucurenciu, C.; Moldovan, H.; Antoniac, I.; Candea, G.; et al. Geometric Analysis of Type B Aortic Dissections Shows Aortic Remodeling After Intervention Using Multilayer Stents. *Materials* **2020**, *13*, 2274, doi:10.3390/ma13102274.
13. Renkens, K.L.; Payner, T.D.; Leipzig, T.J.; Feuer, H.; Morone, M.A.; Koers, J.M.; Lawson, K.J.; Lentz, R.; Shuey, H.; Conaway, G.L.; et al. *A Multicenter, Prospective, Randomized Trial Evaluating a New Hemostatic Agent for Spinal Surgery*; Vol. 26;.
14. Moldovan, H.; Ciomaga, I.; Nechifor, E.; Tigănașu, R.; Badea, A.; Dobra, I.; Nica, C.; Scarlat, C.; Gheorghîță, D.; Antoniac, I.; et al. A Rare Case of Left Ventricular Malignant Peripheral Nerve Sheath Tumour—Case Report and Review of the Literature. *Medicina (B Aires)* **2022**, *58*, 1404, doi:10.3390/medicina58101404.
15. Moldovan, H.; Antoniac, I.; Gheorghîță, D.; Safta, M.S.; Preda, S.; Broască, M.; Badilă, E.; Fronea, O.; Scafa-Udriște, A.; Cacoveanu, M.; et al. Biomaterials as Haemostatic Agents in Cardiovascular Surgery: Review of Current Situation and Future Trends. *Polymers (Basel)* **2022**, *14*, 1189, doi:10.3390/polym14061189.
16. Han, W.; Wang, S. Advances in Hemostatic Hydrogels That Can Adhere to Wet Surfaces. *Gels* **2022**, *9*, 2, doi:10.3390/gels9010002.
17. Dang, N.C.; Ardehali, A.; Bruckner, B.A.; Parrino, P.E.; Gillen, D.L.; Hoffman, R.W.; Spotnitz, R.; Cavoors, S.; Shorn, I.J.; Manson, R.J.; et al. Prospective, Multicenter, Randomized, Controlled Trial Evaluating the Performance of a Novel Combination Powder vs Hemostatic Matrix in Cardiothoracic Operations. *J Card Surg* **2020**, *35*, 313–319, doi:10.1111/jocs.14376.
18. Agarwal, R.; Niezgoda, J.; Niezgoda, J.; Madetipati, N.; Gopalakrishnan, S. Advances in Hemostatic Wound Dressings: Clinical Implications and Insight. *Adv Skin Wound Care* **2022**, *35*, 113–121, doi:10.1097/01.ASW.0000790488.72494.57.

19. Moldovan, H.; Gheorghita, D.; Antoniac, I.; Gheorghe, D.; Fiori, F.; Mohan, A.; Raftu, G.; Ionel, C.; Costache, V. Bioadhesives Used in Cardiovascular Surgery. *Revista De Chimie* **2018**, *69*, 2799–2803.
20. Park, S.M.; Kang, D.R.; Lee, J.H.; Jeong, Y.H.; Shin, D.A.; Yi, S.; Ha, Y.; Kim, K.N. Efficacy and Safety of a Thrombin-Containing Collagen-Based Hemostatic Agent in Spinal Surgery: A Randomized Clinical Trial. *World Neurosurg* **2021**, *154*, e215–e221, doi:10.1016/j.wneu.2021.07.012.
21. Scridon, A. Platelets and Their Role in Hemostasis and Thrombosis—From Physiology to Pathophysiology and Therapeutic Implications. *Int J Mol Sci* **2022**, *23*.
22. Moldovan, H.; Antoniac, I.; Gheorghita, D.; Safta, M.S.; Preda, S.; Broască, M.; Badilă, E.; Fronea, O.; Scafa-Udriște, A.; Cacoveanu, M.; et al. Biomaterials as Haemostatic Agents in Cardiovascular Surgery: Review of Current Situation and Future Trends. *Polymers (Basel)* **2022**, *14*.
23. Wang, L.; Hao, F.; Tian, S.; Dong, H.; Nie, J.; Ma, G. Targeting Polysaccharides Such as Chitosan, Cellulose, Alginate and Starch for Designing Hemostatic Dressings. *Carbohydr Polym* **2022**, *291*.
24. Li, L.; Du, Y.; Yin, Z.; Li, L.; Peng, H.; Zheng, H.; Yang, A.; Li, H.; Lv, G. Preparation and the Hemostatic Property Study of Porous Gelatin Microspheres Both in Vitro and in Vivo. *Colloids Surf B Biointerfaces* **2020**, *187*, 110641, doi:10.1016/j.colsurfb.2019.110641.
25. *Biologically Responsive Biomaterials for Tissue Engineering*; Antoniac, I., Ed.; Springer New York: New York, NY, 2013; Vol. 1; ISBN 978-1-4614-4327-8.
26. Zheng, Y.; Wu, J.; Zhu, Y.; Wu, C. Inorganic-Based Biomaterials for Rapid Hemostasis and Wound Healing. *Chem Sci* **2022**, *14*, 29–53.
27. Baharlouei, P.; Rahman, A. Chitin and Chitosan: Prospective Biomedical Applications in Drug Delivery, Cancer Treatment, and Wound Healing. *Mar Drugs* **2022**, *20*.
28. Mecwan, M.; Li, J.; Falcone, N.; Ermis, M.; Torres, E.; Morales, R.; Hassani, A.; Haghniaz, R.; Mandal, K.; Sharma, S.; et al. Recent Advances in Biopolymer-Based Hemostatic Materials. *Regen Biomater* **2022**, *9*.
29. Feng, Y.; He, Y.; Lin, X.; Xie, M.; Liu, M.; Lvov, Y. Assembly of Clay Nanotubes on Cotton Fibers Mediated by Biopolymer for Robust and High-Performance Hemostatic Dressing. *Adv Healthc Mater* **2023**, *12*, 2202265, doi:10.1002/adhm.202202265.
30. Shakiba-Marani, R.; Ehtesabi, H. A Flexible and Hemostatic Chitosan, Polyvinyl Alcohol, Carbon Dot Nanocomposite Sponge for Wound Dressing Application. *Int J Biol Macromol* **2023**, *224*, 831–839, doi:10.1016/j.ijbiomac.2022.10.169.
31. Patil, G.; Torris, A.; Suresha, P.R.; Jadhav, S.; Badiger, M. V.; Ghormade, V. Design and Synthesis of a New Topical Agent for Halting Blood Loss Rapidly: A Multimodal Chitosan-Gelatin Xerogel Composite Loaded with Silica Nanoparticles and Calcium. *Colloids Surf B Biointerfaces* **2021**, *198*, 111454, doi:10.1016/j.colsurfb.2020.111454.
32. Sun, X.; Fang, Y.; Tang, Z.; Wang, Z.; Liu, X.; Liu, H. Mesoporous Silica Nanoparticles Carried on Chitosan Microspheres for Traumatic Bleeding Control. *Int J Biol Macromol* **2019**, *127*, 311–319, doi:10.1016/j.ijbiomac.2019.01.039.
33. Guo, Y.; Wang, M.; Liu, Q.; Liu, G.; Wang, S.; Li, J. Recent Advances in the Medical Applications of Hemostatic Materials. *Theranostics* **2023**, *13*, 161–196.
34. Behrens, A.M.; Sikorski, M.J.; Kofinas, P. Hemostatic Strategies for Traumatic and Surgical Bleeding. *J Biomed Mater Res A* **2014**, *102*, 4182–4194.
35. Koumentakou, I.; Terzopoulou, Z.; Michopoulou, A.; Kalafatakis, I.; Theodorakis, K.; Tzetzis, D.; Bikiaris, D. Chitosan Dressings Containing Inorganic Additives and Levofloxacin as Potential Wound Care Products with Enhanced Hemostatic Properties. *Int J Biol Macromol* **2020**, *162*, 693–703, doi:10.1016/j.ijbiomac.2020.06.187.
36. Sultankulov, B.; Berillo, D.; Sultankulova, K.; Tokay, T.; Saparov, A. Progress in the Development of Chitosan-Based Biomaterials for Tissue Engineering and Regenerative Medicine. *Biomolecules* **2019**, *9*.
37. Patil, G.; Torris, A.; Suresha, P.R.; Jadhav, S.; Badiger, M. V.; Ghormade, V. Design and Synthesis of a New Topical Agent for Halting Blood Loss Rapidly: A Multimodal Chitosan-Gelatin Xerogel Composite Loaded with Silica Nanoparticles and Calcium. *Colloids Surf B Biointerfaces* **2021**, *198*, doi:10.1016/j.colsurfb.2020.111454.
38. Uranues, S.; Fingerhut, A.; Levin, E.; Spazierer, D.; Rahimi, N.; Baumgartner, B. Effectiveness of Hemopatch® versus Surgicel® Original to Control Mild and Moderate Liver Bleeding. *BMC Surg* **2022**, *22*, doi:10.1186/s12893-022-01747-0.

39. Ponsen, A.C.; Proust, R.; Soave, S.; Mercier-Nomé, F.; Garcin, I.; Combettes, L.; Lataillade, J.J.; Uzan, G. A New Hemostatic Agent Composed of Zn<sup>2+</sup>-Enriched Ca<sup>2+</sup> Alginate Activates Vascular Endothelial Cells in Vitro and Promotes Tissue Repair in Vivo. *Bioact Mater* **2022**, *18*, 368–382, doi:10.1016/j.bioactmat.2022.01.049.
40. Kliuk-Ben Bassat, O.; Schwartz, D.; Zubkov, A.; Gal-Oz, A.; Gorevoy, A.; Romach, I.; Grupper, A. WoundClot® Hemostatic Gauze Reduces Bleeding Time after Arterial Venous Fistula Decannulation. *Blood Purif* **2021**, *50*, 952–958, doi:10.1159/000514934.
41. Mena-Álvarez, J.; Quispe-López, N.; Zubizarreta-Macho, Á.; Rico-Romano, C.; Rodero-Villanueva, R.; Fernández-Aceñero, M.J. Histological Analysis of Different Local Haemostatic Agents Used for Periapical Surgery: An Experimental Study with Sprague-Dawley Rats. *Australian Endodontic Journal* **2019**, *45*, 357–364, doi:10.1111/aej.12332.
42. Rao, K.; Gomati, A.; Yuen Hao Tong, E.; W Ah-See, K.; Shakeel, M. Use of PerClot® in Head and Neck Surgery: A Scottish Centre Experience. *European Archives of Oto-Rhino-Laryngology* **2021**, *278*, 1965–1969, doi:10.1007/s00405-020-06247-6.
43. Zhang, Y.B.; Wang, H.J.; Raza, A.; Liu, C.; Yu, J.; Wang, J.Y. Preparation and Evaluation of Chitosan/Polyvinylpyrrolidone/Zein Composite Hemostatic Sponges. *Int J Biol Macromol* **2022**, *205*, 110–117, doi:10.1016/j.ijbiomac.2022.02.013.
44. Capella-Monsonís, H.; Shridhar, A.; Chirravuri, B.; Figucia, M.; Learn, G.; Greenawalt, K.; Badylak, S.F. A Comparative Study of the Resorption and Immune Response for Two Starch-Based Hemostat Powders. *Journal of Surgical Research* **2023**, *282*, 210–224, doi:10.1016/j.jss.2022.09.022.
45. Huang, W.; Wu, J.; Huang, Z.; Zhang, D.; Chen, F.; Liu, C. A Self-Gelling Starch-Based Sponge for Hemostasis. *J Mater Chem B* **2022**, *11*, 1331–1343, doi:10.1039/d2tb02224a.
46. Karimi BCDEF, N.; Amooee ACEF, A.; SafiDahaj BDEF, F. Comparison of the Effect of PerClot® Powder and a Chitosan Derivative on Postoperative Intra-Abdominal Adhesions in Rat Animal Models., doi:10.5604/01.3001.0015.5982.
47. Goldis, A.; Goldis, R.; Chirila, T. V. Biomaterials in Gastroenterology: A Critical Overview. *Medicina (Lithuania)* **2019**, *55*.
48. Guo, Y.; Cheng, N.; Sun, H.; Hou, J.; Zhang, Y.; Wang, D.; Zhang, W.; Chen, Z. Advances in the Development and Optimization Strategies of the Hemostatic Biomaterials. *Front Bioeng Biotechnol* **2023**, *10*.
49. Cziperle, D.J. Avitene™ Microfibrillar Collagen Hemostat for Adjunctive Hemostasis in Surgical Procedures: A Systematic Literature Review. *Medical Devices: Evidence and Research* **2021**, *14*, 155–163, doi:10.2147/MDER.S298207.
50. Zhong, Y.; Hu, H.; Min, N.; Wei, Y.; Li, X.; Li, X. Application and Outlook of Topical Hemostatic Materials: A Narrative Review. *Ann Transl Med* **2021**, *9*, 577–577, doi:10.21037/atm-20-7160.
51. Ghimire, S.; Sarkar, P.; Rigby, K.; Maan, A.; Mukherjee, S.; Crawford, K.E.; Mukhopadhyay, K. Polymeric Materials for Hemostatic Wound Healing. *Pharmaceutics* **2021**, *13*.
52. Pereira, B.M.; Bortoto, J.B.; Fraga, G.P. Topical Hemostatic Agents in Surgery: Review and Prospects. *Rev Col Bras Cir* **2018**, *45*.
53. Salama, N.M.; Tabashy, R.H.; Mahmoud, I.H.; Rahman, A.E.R.M.A. El; Mohamed, D.N.E.; Kassas, H. El Does Gelfoam Slurry Embolization Post-Pulmonary Biopsy Reduce Risk of Pneumothorax? A Prospective Randomized Control Study. *Egyptian Journal of Radiology and Nuclear Medicine* **2023**, *54*, doi:10.1186/s43055-022-00950-6.
54. Sekyi-Djan, N.; Chapple, C.; Hammond-Kenny, A.; Hilger, A. The Use of ARTISS Fibrin Sealant in Thyroid Surgery: Case Series and Review of the Literature. *British Journal of Surgery* **2022**, *109*, doi:10.1093/bjs/znac056.021.
55. Somani, S.N.; Moshirfar, M.; Shmunes, K.M.; Ronquillo, Y.C. Comparison and Application of Commercially Available Fibrin Sealants in Ophthalmology. *Ocular Surface* **2020**, *18*, 418–426.
56. Jolly, K.; Gupta, K.K.; Egbuji, O.; Naik, P.P.; Ahmed, S.K. Endoscopic Transsphenoidal Surgery Reconstruction Using the Fibrin Sealant Patch Tachosil®. *Br J Neurosurg* **2021**, doi:10.1080/02688697.2021.1905771.
57. Carretta, A.; Epskamp, M.; Ledermann, L.; Staartjes, V.E.; Neidert, M.C.; Regli, L.; Stienen, M.N. Collagen-Bound Fibrin Sealant (TachoSil®) for Dural Closure in Cranial Surgery: Single-Centre Comparative Cohort Study and Systematic Review of the Literature. *Neurosurg Rev* **2022**, *45*, 3779–3788, doi:10.1007/s10143-022-01886-1.

58. Eichinger, J.K.; Oldenburg, K.S.; Lin, J.; Wilkie, E.; Mock, L.; Tavana, M.L.; Friedman, R.J. Comparing Dermabond PRINEO versus Dermabond or Staples for Wound Closure: A Randomized Control Trial Following Total Shoulder Arthroplasty. *J Shoulder Elbow Surg* **2022**, *31*, 2066–2075, doi:10.1016/j.jse.2022.04.014.
59. Mirzaei, Y.; Hagemester, K.; Tolba, R.H.; Steitz, J. Novel In Vitro Study to Assess Microbial Barrier Properties of Polyurethane-Based Tissue Adhesives in Comparison to the Gold Standard Dermabond®. *Biomed Res Int* **2022**, 2022, doi:10.1155/2022/5249214.
60. Gong, M.; Liu, Z.; Kong, J.; Zhao, B.; He, X.; Gu, J.; Su, H. Transcatheter Arterial Embolization Using N-Butyl-2 Cyanoacrylate Glubran® 2 for Acute Massive Pancreaticoduodenal Arterial Hemorrhage. *Front Mater* **2022**, *9*, doi:10.3389/fmats.2022.1003539.
61. Slezak, P.; Klang, A.; Ferguson, J.; Monforte, X.; Schmidt, P.; Bauder, B.; Url, A.; Osuchowski, M.; Redl, H.; Spazierer, D.; et al. Tissue Reactions to Polyethylene Glycol and Glutaraldehyde-Based Surgical Sealants in a Rabbit Aorta Model. *J Biomater Appl* **2020**, *34*, 1330–1340, doi:10.1177/0885328219900078.
62. Dhandapani, V.; Ringuette, V.; Desrochers, M.; Sirois, M.; Vermette, P. Composition, Host Responses and Clinical Applications of Bioadhesives. *J Biomed Mater Res B Appl Biomater* **2022**, *110*, 2779–2797, doi:10.1002/jbm.b.35113.
63. Keskin, E.; Aydın, H.A.; Kalayci, M.; Işık, E.; Özgen, U.; Şimşek, K.; Baklaci, D.; Gökçe, M. The Histopathological Effects of Reabsorbable Polyethylene Glycol Hydrogel (Coseal) on Epidural Fibrosis in an Experimental Postlaminectomy Model in Rats. *Turk J Med Sci* **2021**, *51*, 1512–1520, doi:10.3906/sag-2009-241.
64. Li, X.F.; Lu, P.; Jia, H.R.; Li, G.; Zhu, B.; Wang, X.; Wu, F.G. Emerging Materials for Hemostasis. *Coord Chem Rev* **2023**, 475.
65. Ohlinger, R.; Rutkowski, R.; Kohlmann, T.; Paepke, S.; Alwafai, Z.; Flieger, C.; Moller, S.; Lenz, F.; Zygmunt, M.; Unger, J. Impact of the Lysine-Urethane Adhesive Tissuglu® on Postoperative Complications and Interventions after Drain-Free Mastectomy. *Anticancer Res* **2020**, *40*, 2801–2812, doi:10.21873/anticancer.14253.
66. Yılmaz, G.; Özdenkaya, Y.; Karatepe, O.; Tanrikulu, Y.; Kamalı, G.; Yalçın, O. Effects of Polyurethane Membrane on Septic Colon Anastomosis and Intra-Abdominal Adhesions. *Ulusal Travma ve Acil Cerrahi Dergisi* **2021**, *27*, 1–8, doi:10.14744/tjtes.2020.41624.
67. Kim, K.; Siddiqui, Z.; Acevedo-Jake, A.M.; Roy, A.; Choudhury, M.; Grasman, J.; Kumar, V. Angiogenic Hydrogels to Accelerate Early Wound Healing. *Macromol Biosci* **2022**, *22*, 2200067, doi:10.1002/mabi.202200067.
68. Meng, F.C.; Lee, C.Y. Safety and Efficiency of Femoral Artery Access Closure Using QuikClot Combat Gauze in Patients with Severe Arterial Calcification of Access Sites. *Quant Imaging Med Surg* **2023**, *13*, 282–292, doi:10.21037/qims-21-1164.
69. Jia, Y. jun; Du, W. qiong; Zong, Z. wen; Jiang, R. qing; Zhong, X.; Ye, Z.; Li, T. shi; Yang, H. yang; Xiao, L. ping; Fan, J. Hemostatic Effects of Bio-Zeolite Gauze and QuikClot Combat Gauze on Major Bleeding in Rabbits Acutely Exposed to High Altitude. *Prehospital Emergency Care* **2022**, doi:10.1080/10903127.2022.2126912.
70. Ding, S.; Wei, X.; Yang, K.; Lin, S.; Tian, F.; Li, F. Ca-Ga Double Doping Strategy to Fabricate Hemostatic Mesoporous Silica Nanoparticles (MSN) with Antibacterial Activity., doi:10.1007/s12633-020-00692-y/Published.
71. Milić, M.; Vuković, B.; Barbir, R.; Pem, B.; Milić, M.; Šerić, V.; Fröhlich, E.; Vinković Vrček, I. Effect of Differently Coated Silver Nanoparticles on Hemostasis. *Platelets* **2021**, *32*, 651–661, doi:10.1080/09537104.2020.1792432.
72. Fernando, L.; Chen, W.-T.; Lai, C.-W.; Ye, F.-Y.; Lai, P.-S.; Lin, J.-J.; Yasuda, K.; Song, T.-T.; Song, J.-M. Biocompatibility and Antimicrobial Activity of Copper(II) Oxide Hybridized with Nano Silicate Platelets. *Surf Coat Technol* **2022**, *435*, 128253, doi:10.1016/j.surfcoat.2022.128253.
73. Milić, M.; Cvetić, Ž.; Bendelja, K.; Vuković, B.; Galić, E.; Ćurlin, M.; Dobrošević, B.; Jurak Begonja, A.; Vinković Vrček, I. Response of Platelets to Silver Nanoparticles Designed with Different Surface Functionalization. *J Inorg Biochem* **2021**, *224*, 111565, doi:10.1016/j.jinorgbio.2021.111565.
74. Metwally, W.M.; El-Habashy, S.E.; El-Nikhely, N.A.; Mahmoud, H.E.; Eltaher, H.M.; El-Khordagui, L. Nano Zinc Oxide-Functionalized Nanofibrous Microspheres: A Bioactive Hybrid Platform with



- Antimicrobial, Regenerative and Hemostatic Activities. *Int J Pharm* **2023**, 638, 122920, doi:10.1016/j.ijpharm.2023.122920.
75. Shefa, A.A.; Taz, M.; Hossain, M.; Kim, Y.S.; Lee, S.Y.; Lee, B.-T. Investigation of Efficiency of a Novel, Zinc Oxide Loaded TEMPO-Oxidized Cellulose Nanofiber Based Hemostat for Topical Bleeding. *Int J Biol Macromol* **2019**, 126, 786–795, doi:10.1016/j.ijbiomac.2018.12.079.
  76. Yang, C.M.; Lee, J.; Lee, S.Y.; Lee, H.; Chathuranga, K.; Lee, J.; Park, W. Silk Fibroin/Tannin/ZnO Nanocomposite Hydrogel with Hemostatic Activities. *Gels* **2022**, 8, 650, doi:10.3390/gels8100650.
  77. Carbonell-Blasco, P.; Martín-Martínez, J.M.; Antoniac, I.V. Synthesis and Characterization of Polyurethane Sealants Containing Rosin Intended for Sealing Defect in Annulus for Disc Regeneration. *Int J Adhes Adhes* **2013**, 42, 11–20, doi:10.1016/j.jadhadh.2012.11.011.
  78. *Bioceramics and Biocomposites*; Antoniac, I., Ed.; Wiley, 2019; ISBN 9781119049340.
  79. Iannitti, D.A.; Kim, C.; Ito, D.; Epstein, J. Impact of an Active Hemostatic Product Treatment Approach on Bleeding-Related Complications and Hospital Costs among Inpatient Surgeries in the United States. *J Med Econ* **2021**, 24, 514–523, doi:10.1080/13696998.2021.1916751.
  80. Pennington, Z.; Ehresman, J.; Westbroek, E.M.; Lubelski, D.; Cottrill, E.; Sciubba, D.M. Interventions to Minimize Blood Loss and Transfusion Risk in Spine Surgery: A Narrative Review. *Clin Neurol Neurosurg* **2020**, 196, 106004, doi:10.1016/j.clineuro.2020.106004.
  81. PRISADA, R.M. PERSPECTIVES TO DESCRIBE SURFACE PROPERTIES OF RAW PHARMACEUTICAL MATERIALS. A FRACTAL APPROACH ON THE WETTING OF POWDERS. *Farmacia* **2020**, 68, 354–361, doi:10.31925/farmacia.2020.2.23.
  82. Biranje, S.S.; Sun, J.; Shi, Y.; Yu, S.; Jiao, H.; Zhang, M.; Wang, Q.; Wang, J.; Liu, J. Polysaccharide-Based Hemostats: Recent Developments, Challenges, and Future Perspectives. *Cellulose* **2021**, 28, 8899–8937.
  83. Elieh-Ali-Komi, D.; Hamblin, M.R.; Daniel, E.-A.-K. Chitin and Chitosan: Production and Application of Versatile Biomedical Nanomaterials HHS Public Access; 2016; Vol. 4.
  84. Khan, M.A.; Mujahid, M. A Review on Recent Advances in Chitosan Based Composite for Hemostatic Dressings. *Int J Biol Macromol* **2019**, 124, 138–147.
  85. Al-Rooqi, M.M.; Hassan, M.M.; Moussa, Z.; Obaid, R.J.; Suman, N.H.; Wagner, M.H.; Natto, S.S.A.; Ahmed, S.A. Advancement of Chitin and Chitosan as Promising Biomaterials. *Journal of Saudi Chemical Society* **2022**, 26.
  86. Motelica, L.; Fica, D.; Fica, A.; Truşcă, R.D.; Ilie, C.I.; Oprea, O.C.; Andronescu, E. Innovative Antimicrobial Chitosan/ZnO/Ag NPs/Citronella Essential Oil Nanocomposite—Potential Coating for Grapes. *Foods* **2020**, 9, 1–26, doi:10.3390/foods9121801.
  87. Janvikul, W.; Uppanan, P.; Thavornnyutikarn, B.; Krewraing, J.; Prateepasen, R. In Vitro Comparative Hemostatic Studies of Chitin, Chitosan, and Their Derivatives. *J Appl Polym Sci* **2006**, 102, 445–451, doi:10.1002/app.24192.
  88. Tiplea, R.E.; Lemnaru, G.M.; Truşcă, R.D.; Holban, A.; Kaya, M.G.A.; Dragu, L.D.; Fica, D.; Fica, A.; Bleotu, C. Antimicrobial Films Based on Chitosan, Collagen, and ZnO for Skin Tissue Regeneration. *Biointerface Res Appl Chem* **2021**, 11, 11985–11995, doi:10.33263/BRIAC114.1198511995.
  89. Radu, E.R.; Pandele, A.M.; Tuncel, C.; Miculescu, F.; Voicu, S.I. Preparation and Characterization of Chitosan/LDH Composite Membranes for Drug Delivery Application. *Membranes (Basel)* **2023**, 13, doi:10.3390/membranes13020179.
  90. Okamoto, Y.; Yano, R.; Miyatake, K.; Tomohiro, I.; Shigemasa, Y.; Minami, S. Effects of Chitin and Chitosan on Blood Coagulation. *Carbohydr Polym* **2003**, 53, 337–342, doi:10.1016/S0144-8617(03)00076-6.
  91. Crini, G.; Lichtfouse, E. Sustainable Agriculture Reviews. 35, Chitin and Chitosan: History, Fundamentals and Innovations; ISBN 9783030165376.
  92. Spoială, A.; Ilie, C.I.; Dolet, G.; Croitoru, A.M.; Surdu, V.A.; Truşcă, R.D.; Motelica, L.; Oprea, O.C.; Fica, D.; Fica, A.; et al. Preparation and Characterization of Chitosan/TiO<sub>2</sub> Composite Membranes as Adsorbent Materials for Water Purification. *Membranes (Basel)* **2022**, 12, doi:10.3390/membranes12080804.
  93. Subramanian, A.; Krishnan, U.M.; Sethuraman, S. Skin Tissue Regeneration. In *Electrospinning for Tissue Regeneration*; Elsevier, 2011; pp. 298–316.
  94. Jiménez-Gómez, C.P.; Cecilia, J.A. Chitosan: A Natural Biopolymer with a Wide and Varied Range of Applications. *Molecules* **2020**, 25, 3981, doi:10.3390/molecules25173981.
  95. Szatmári, V. Chitosan Hemostatic Dressing for Control of Hemorrhage from Femoral Arterial Puncture Site in Dogs. *J Vet Sci* **2015**, 16, 517–523, doi:10.4142/jvs.2015.16.4.517.

96. Pan, M.; Tang, Z.; Tu, J.; Wang, Z.; Chen, Q.; Xiao, R.; Liu, H. Porous Chitosan Microspheres Containing Zinc Ion for Enhanced Thrombosis and Hemostasis. *Materials Science and Engineering C* **2018**, *85*, 27–36, doi:10.1016/j.msec.2017.12.015.
97. Karahaliloğlu, Z.; Demirebilek, M.; Ulusoy, İ.; Gümüşkaya, B.; Denkbaş, E.B. Active Nano/Microbilayer Hemostatic Agents for Diabetic Rat Bleeding Model. *J Biomed Mater Res B Appl Biomater* **2017**, *105*, 1573–1585, doi:10.1002/jbm.b.33696.
98. Wang, C.; Luo, W.; Li, P.; Li, S.; Yang, Z.; Hu, Z.; Liu, Y.; Ao, N. Preparation and Evaluation of Chitosan/Alginate Porous Microspheres/Bletilla Striata Polysaccharide Composite Hemostatic Sponges. *Carbohydr Polym* **2017**, *174*, 432–442, doi:10.1016/j.carbpol.2017.06.112.
99. Biranje, S.S.; Madiwale, P. V.; Patankar, K.C.; Chhabra, R.; Dandekar-Jain, P.; Adivarekar, R. V. Hemostasis and Anti-Necrotic Activity of Wound-Healing Dressing Containing Chitosan Nanoparticles. *Int J Biol Macromol* **2019**, *121*, 936–946, doi:10.1016/j.ijbiomac.2018.10.125.
100. Zhao, W.Y.; Fang, Q.Q.; Wang, X.F.; Wang, X.W.; Zhang, T.; Shi, B.H.; Zheng, B.; Zhang, D.D.; Hu, Y.Y.; Ma, L.; et al. Chitosan-Calcium Alginate Dressing Promotes Wound Healing: A Preliminary Study. *Wound Repair and Regeneration* **2020**, *28*, 326–337, doi:10.1111/wrrr.12789.
101. Song, F.; Kong, Y.; Shao, C.; Cheng, Y.; Lu, J.; Tao, Y.; Du, J.; Wang, H. Chitosan-Based Multifunctional Flexible Hemostatic Bio-Hydrogel. *Acta Biomater* **2021**, *136*, 170–183, doi:10.1016/j.actbio.2021.09.056.
102. Shou, Y.; Zhang, J.; Yan, S.; Xia, P.; Xu, P.; Li, G.; Zhang, K.; Yin, J. Thermoresponsive Chitosan/DOPA-Based Hydrogel as an Injectable Therapy Approach for Tissue-Adhesion and Hemostasis. *ACS Biomater Sci Eng* **2020**, *6*, 3619–3629, doi:10.1021/acsbiomaterials.0c00545.
103. Rao, K.M.; Narayanan, K.B.; Uthappa, U.T.; Park, P.H.; Choi, I.; Han, S.S. Tissue Adhesive, Self-Healing, Biocompatible, Hemostasis, and Antibacterial Properties of Fungal-Derived Carboxymethyl Chitosan-Polydopamine Hydrogels. *Pharmaceutics* **2022**, *14*, doi:10.3390/pharmaceutics14051028.
104. Xia, L.; Wang, S.; Jiang, Z.; Chi, J.; Yu, S.; Li, H.; Zhang, Y.; Li, L.; Zhou, C.; Liu, W.; et al. Hemostatic Performance of Chitosan-Based Hydrogel and Its Study on Biodistribution and Biodegradability in Rats. *Carbohydr Polym* **2021**, *264*, doi:10.1016/j.carbpol.2021.117965.
105. Zhou, P.; Xia, Z.; Qi, C.; He, M.; Yu, T.; Shi, L. Construction of Chitosan/Ag Nanocomposite Sponges and Their Properties. *Int J Biol Macromol* **2021**, *192*, 272–277, doi:10.1016/j.ijbiomac.2021.10.011.
106. Fan, X.; Li, Y.; Li, N.; Wan, G.; Ali, M.A.; Tang, K. Rapid Hemostatic Chitosan/Cellulose Composite Sponge by Alkali/Urea Method for Massive Haemorrhage. *Int J Biol Macromol* **2020**, *164*, 2769–2778, doi:10.1016/j.ijbiomac.2020.07.312.
107. Sathiyaseelan, A.; Saravanakumar, K.; Mariadoss, A.V.A.; Wang, M.H. Antimicrobial and Wound Healing Properties of Feo Fabricated Chitosan/Pva Nanocomposite Sponge. *Antibiotics* **2021**, *10*, doi:10.3390/antibiotics10050524.
108. Gordienko, M.G.; Palchikova, V. V.; Kalenov, S. V.; Lebedev, E.A.; Belov, A.A.; Menshutina, N. V. The Alginate–Chitosan Composite Sponges with Biogenic Ag Nanoparticles Produced by Combining of Cryostructuration, Ionotropic Gelation and Ion Replacement Methods. *International Journal of Polymeric Materials and Polymeric Biomaterials* **2022**, *71*, 34–44, doi:10.1080/00914037.2020.1798439.
109. Huang, N.; Lin, J.; Li, S.; Deng, Y.; Kong, S.; Hong, P.; Yang, P.; Liao, M.; Hu, Z. Preparation and Evaluation of Squid Ink Polysaccharide-Chitosan as a Wound-Healing Sponge. *Materials Science and Engineering: C* **2018**, *82*, 354–362, doi:10.1016/j.msec.2017.08.068.
110. Buriuli, M.; Kumari, W.G.; Verma, D. Evaluation of Hemostatic Effect of Polyelectrolyte Complex-Based Dressings. *J Biomater Appl* **2017**, *32*, 638–647, doi:10.1177/0885328217735956.
111. Misgav, M.; Lubetzki, A.; Brutman-Barazani, T.; Martinowitz, U.; Kenet, G. The Hemostatic Efficacy of Chitosan-Pads in Hemodialysis Patients with Significant Bleeding Tendency. *Journal of Vascular Access* **2017**, *18*, 220–224, doi:10.5301/jva.5000707.
112. Wu, H.; Yan, S.; Wang, Y.; Zhang, C. Preparation and Properties of Electrospun Chitosan/Polybutylenes Succinate Nanofiber Membrane for Wound Hemostatic Dressing. *Journal of Industrial Textiles* **2022**, *52*.
113. Akram, A.M.; Omar, R.A.; Ashfaq, M. Chitosan/Calcium Phosphate-Nanoflakes-Based Biomaterial: A Potential Hemostatic Wound Dressing Material. *Polymer Bulletin* **2022**, doi:10.1007/s00289-022-04300-4.
114. Wang, Y.W.; Liu, C.C.; Cherng, J.H.; Lin, C.S.; Chang, S.J.; Hong, Z.J.; Liu, C.C.; Chiu, Y.K.; Hsu, S. Der; Chang, H. Biological Effects of Chitosan-Based Dressing on Hemostasis Mechanism. *Polymers (Basel)* **2019**, *11*, doi:10.3390/polym11111906.

115. Wang, C.H.; Cherng, J.H.; Liu, C.C.; Fang, T.J.; Hong, Z.J.; Chang, S.J.; Fan, G.Y.; Hsu, S. Der Procoagulant and Antimicrobial Effects of Chitosan in Wound Healing. *Int J Mol Sci* **2021**, *22*, doi:10.3390/ijms22137067.
116. Xie, M.; Zeng, Y.; Wu, H.; Wang, S.; Zhao, J. Multifunctional Carboxymethyl Chitosan/Oxidized Dextran/Sodium Alginate Hydrogels as Dressing for Hemostasis and Closure of Infected Wounds. *Int J Biol Macromol* **2022**, *219*, 1337–1350, doi:10.1016/j.ijbiomac.2022.08.166.
117. Elangwe, C.N.; Morozkina, S.N.; Olekhovich, R.O.; Krasichkov, A.; Polyakova, V.O.; Uspenskaya, M. V. A Review on Chitosan and Cellulose Hydrogels for Wound Dressings. *Polymers (Basel)* **2022**, *14*.
118. Zhang, D.; Hu, Z.; Li, S.; Zhang, L.; Lu, S.; Liang, F. Chitosan-Based Thermo-Sensitive Hydrogel Loading Oyster Peptides for Hemostasis Application. *Materials* **2020**, *13*, 1–16, doi:10.3390/ma13215038.
119. Patil, G.; Pawar, R.; Jadhav, S.; Ghormade, V. A Chitosan Based Multimodal “Soft” Hydrogel for Rapid Hemostasis of Non-Compressible Hemorrhages and Its Mode of Action. *Carbohydrate Polymer Technologies and Applications* **2022**, *4*, doi:10.1016/j.carpta.2022.100237.
120. Rodríguez-Acosta, H.; Tapia-Rivera, J.M.; Guerrero-Guzmán, A.; Hernández-Elizarraráz, E.; Hernández-Díaz, J.A.; Garza-García, J.J.O.; Pérez-Ramírez, P.E.; Velasco-Ramírez, S.F.; Ramírez-Anguiano, A.C.; Velázquez-Juárez, G.; et al. Chronic Wound Healing by Controlled Release of Chitosan Hydrogels Loaded with Silver Nanoparticles and Calendula Extract. *J Tissue Viability* **2022**, *31*, 173–179, doi:10.1016/j.jtv.2021.10.004.
121. Lin, X.; Shen, Y.; Wang, L. Multi-Scale Photoacoustic Assessment of Wound Healing Using Chitosan–Graphene Oxide Hemostatic Sponge. *Nanomaterials* **2021**, *11*, doi:10.3390/nano11112879.
122. Kim, K.; Ryu, J.H.; Koh, M.-Y.; Yun, S.P.; Kim, S.; Park, J.P.; Jung, C.-W.; Lee, M.S.; Seo, H.-I.; Kim, J.H.; et al. Coagulopathy-Independent, Bioinspired Hemostatic Materials: A Full Research Story from Preclinical Models to a Human Clinical Trial. *Sci Adv* **2021**, *7*, doi:10.1126/sciadv.abc9992.
123. Wu, Z.; Zhou, W.; Deng, W.; Xu, C.; Cai, Y.; Wang, X. Antibacterial and Hemostatic Thiol-Modified Chitosan-Immobilized AgNPs Composite Sponges. *ACS Appl Mater Interfaces* **2020**, *12*, 20307–20320, doi:10.1021/acsami.0c05430.
124. Deineka, V.; Sulaieva, O.; Pernakov, M.; Kornienko, V.; Husak, Y.; Yanovska, A.; Yusupova, A.; Tkachenko, Y.; Kalinkevich, O.; Zlatska, A.; et al. Hemostatic and Tissue Regeneration Performance of Novel Electrospun Chitosan-Based Materials. *Biomedicines* **2021**, *9*, doi:10.3390/biomedicines9060588.
125. Bal-Ozturk, A.; Karal-Yilmaz, O.; Akguner, Z.P.; Aksu, S.; Tas, A.; Olmez, H. Sponge-like Chitosan-Based Nanostructured Antibacterial Material as a Topical Hemostat. *J Appl Polym Sci* **2019**, *136*, doi:10.1002/app.47522.
126. Zheng, L.; Gu, B.; Li, S.; Luo, B.; Wen, Y.; Chen, M.; Li, X.; Zha, Z.; Zhang, H.T.; Wang, X. An Antibacterial Hemostatic AuNPs@corn Stalk/Chitin Composite Sponge with Shape Recovery for Promoting Wound Healing. *Carbohydr Polym* **2022**, *296*, doi:10.1016/j.carbpol.2022.119924.

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.