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Biopolymers as Topical Haemostatic Agents: Current Trends and Technologies

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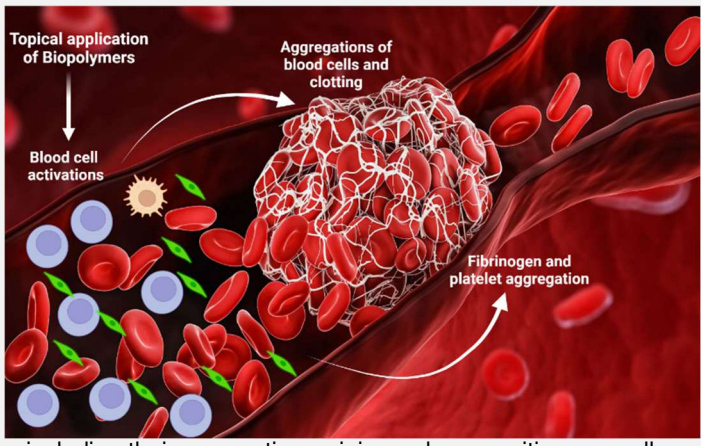
ABSTRACT

Hemostasis refers to the harmless practice of any surgical procedure or any other chronic ulcer which immediately requires therapy to prevent substantial blood loss and mortality from extreme hemorrhage in surgery/emergency conditions. Various natural, semi-synthetic as well as synthetic biopolymers are available with excellent hemostatic activity and further offer biodegradable and biocompatible nature with the live cells. Now a day's biopolymers have become the most significant hemostatic agents used in emergency operations and surgical procedures. However, to date, there is no comprehensive report evaluating natural hemostatic materials based on biopolymers. Therefore, this current review attempts to combine the most advanced methods and secondly reviews various biopolymers including their preparation, origin, and composition, as well as safety and biodegradability. Insights on the various commercially available products based on biopolymers exhibiting hemostatic activity are well discussed. Thus, the paper summarizes the latest research work on commonly used biopolymers as the most widely used materials and provides an orientation for further research and development in this field.



Keywords: Biopolymers, chitosan, sodium alginate, topical hemostatic agent

1. Introduction

In recent years, tissue injury and wound healing has become a major concern which leads to mortality and financial burden. Apart from external agents, our body has its defense mechanism to prevent excessive blood loss after an injury, and the mechanism is known as hemostasis. Hemostasis is a Greek word and is a combination of two words hemostasis in which haemo means blood and stasis means motionlessness of blood. Hemostasis describes as a process of formation of a thrombus in the walls of damaged blood vessels and preventing excess blood flow by preserving blood in a fluid state [1]. The process is characterized by a series of events that eventually lead to the inhibition of excess blood loss by the formation of a complex interaction between the vascular system, plasma proteins, and cellular components [2].

Hemostasis preceded by hemolysis which is an irregular loss of circulating red blood cells is a serious health condition [3]. Patients usually develop symptoms such as anemia, chest pain, shortness of breath, and fatigue when red blood cells are pathologically destroyed [4]. The trend of hemostats has been changing for centuries. During ancient times, Egyptians used materials such as pollen, silk, and lint as antiseptics in case of wounds. As time passed in 1960, George Winter published a paper demonstrating that silicone dressings can be used to maintain the wound bed moist in improving the re-epithelialization and healing of wounds. Multitudinous antiseptics were launched during

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the early 1990s [5]. Some examples of biopolymers include alginate (sorbsan, kaltostat, convatec, and pharma-plast), pectin (duoderm, convatec), and collagen. These biomaterials are the need of the hour in a health-conscious society and help in upgrading wound treatment. Over, the past 40 years, many biomaterials have been tested (in-vivo and in-vitro) and have shown significant results [6–11]. Although high-quality materials are available in the market (Table 1), their efficiency, environmental safety, high cost, and physical properties limit their widespread use. [12]. For composite hemostatic materials, potential problems including non-biodegradability and cytotoxicity should be examined before the impersonal use [13]. In addition, inorganic materials generally cause inflammation and thermal injuries due to their poor biodegradability and exothermic reactions when applied in clinical fields [14].

The present review provides a detailed role of the most prominent biopolymers included in wound dressings as a hemostatic agents along with their mode of application. Remarkable examples include collagen, chitosan, alginates, and poly (alkylene oxide). In addition, recent advances in clinical applications and other future ideas regarding biopolymers are also discussed. The review deals with the concept, state-of-the-art, and perspectives of hemostatic polymers.

2. Fundamentals of hemostasis

Hemostasis progresses through a series of interdependent stages and is divided into primary and secondary phases. Primary hemostasis consists of vasoconstriction and platelet plug formation and occurs immediately after tissue damage. Secondary hemostasis arises by the initiation of coagulation factors i.e. Serine protease, tissue factor, expressing cells and the development of insoluble fibrils **Figure 1** [15]. The two phases show overlapping effects with tight regulation to limited coagulation at the site of injury. In this section, we elaborate on the body's Hemostasis mechanism and various processes that take place along with it.

Hemostasis is a compound physiological process that occurs through the collaborative action of three events:

(i) Stypsis or vasoconstriction.

(ii) Formation of a platelet plug.

(iii) Formation of the coagulation cascade.

The above processes come in progression as mentioned below.

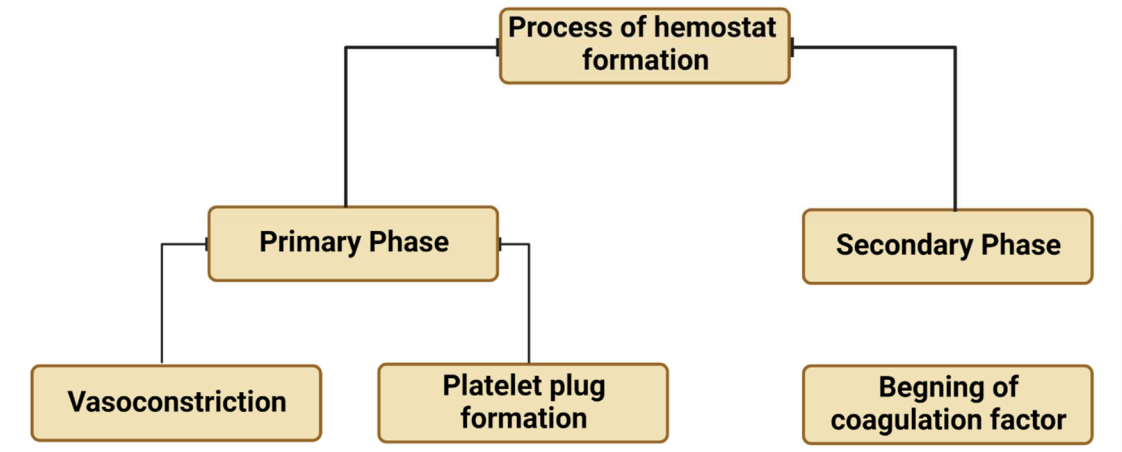

Figure 1. Depicts the process of hemostat formation.

2.1. Vascular spasm

Vasoconstriction is the primary response to the injury by the cells of vascular smooth muscles. These muscular cells have an endothelium layer that releases intravascular stimuli to control blood vessel contraction. A simple monolayer is a line between a capillary lumen (Vascular endothelium). These cells together span a wide area of 3000 m^2 and comprise to form diffuse tissues in an adult of almost 720 g. It is 1ocated at the boundary of flowing blood as well as the vessel barrier and contains sugar-proteins such as glycocalyx, glycoproteins, and proteoglycans. Glycocalyx acts

as the adhesion molecule contributing to the coagulation system. The vascular endothelium is a vascular tone regulator and active endocrine organ and aids in blood coagulation, thrombus formation, cellular adhesion, cellular proliferation, inflammation, and nutrient delivery to the flowing blood [16]. The vascular endothelium present in the brain is different as brain endothelial cells lack a basic aperture and are placed together by tight junctions. These types of cells have a minimum pinocytotic activity [17]. In addition, these brain endothelium cells make up the anatomical site of the blood-brain barrier. These endothelium cells further help in brain-specific thrombosis and hemostasis [18]. In vascular spasms, two surfaces are present thrombogenic and non-thrombogenic. The non-thrombogenic surface is provided with the production of coagulation inhibitors, fibrinolysis activators, and various other factors like nitric oxide, prostaglandins; endothelium-derived hyperpolarizing factor, proteinoids, and angiotensin II. Heparin sulfate is also produced which acts as a cofactor for the activation of thrombomodulin as well as an anti-thrombin [19]. On the contrary, the subendothelial Willebrand factor, thrombospondin, collagen, vitronectin, and laminin are involved in platelet adhesion as shown in **Figure 2** [20].

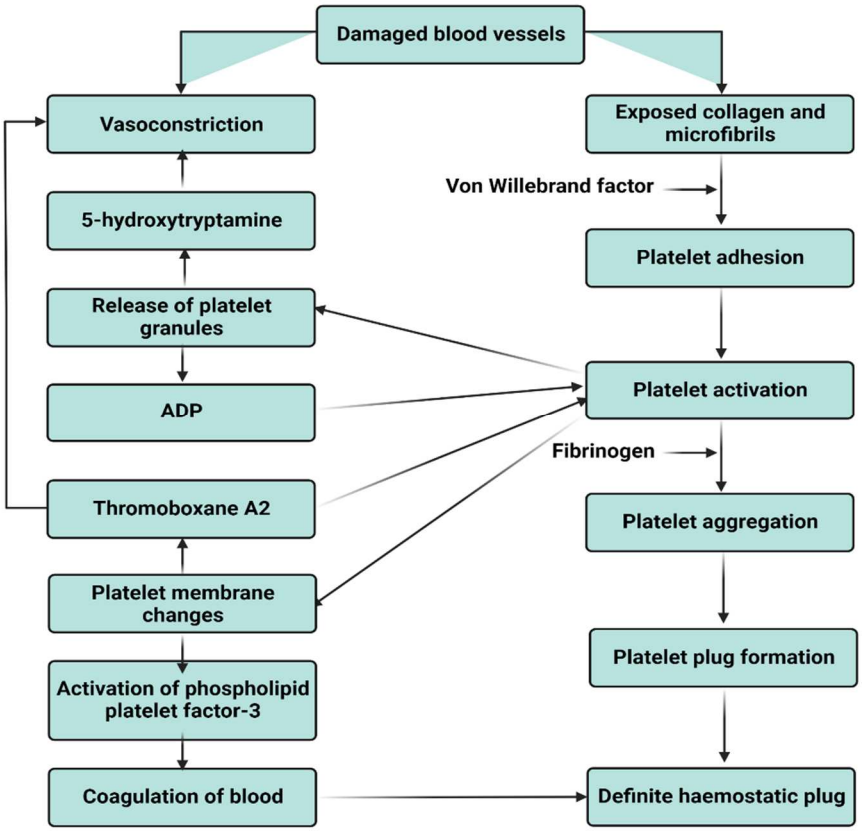

Figure 2. The flow chart represents the events during the formation of the hemostatic plug-in natural process of coagulation.

If trauma, injury, or inflammation causes damage to the vascular endothelium, Von Willebrand Factor is released along with Collagen and the factor in tissue spreads on the endothelial cell surface. Collagen stimulates the site-adherence platelet. Cytoplasmic granules containing serotonin, adenosine diphosphate, and A2 are released by platelets which increase the vasoconstriction effect. Fibrinolysis is also regulated by the endothelium layer. The first step to vascular repair is, therefore, initiated [21].

2.2. Platelet plug formation

The platelet plug or platelet thrombus is an accumulation of platelets formed in response to blood vessel injury. After the accumulation of platelets at the site of injury, their sticky nature allows them to adhere to each other as shown in **Figure 2**.

In a healthy adult, the platelet count is about 150 and 400 billion per liter which is produced by megakaryocytes in the bone marrow. Platelets form a thrombus through the progression of adhesion, beginning, and release of intracellular organelles, and finally aggregating them in a common mass [22]. Secondly, these platelets release phospholipids which promote coagulation by the formation of fibrin and thrombin.

2.2.1. Adhesion

When the endothelium layer is damaged, collagen is exposed by glycoprotein receptor complexes. GP1b/V/IX and GPVI commence platelet aggregation and clot formation in cooperation with collagen and Von Willebrand Factor. Collagen and Von Willebrand Factor molecules are released from platelets by the process of de-granulation. De-granulation describes as the process of physiological change in the dimensions of platelets due to the release of alpha and dense granules. Platelets derive growth factors; fibrinogen and Von Willebrand Factor are released from alpha granules whereas from dense granules adenosine triphosphate and serotonin are released [23]. The adenosine diphosphate released from the dense granules binds to the receptors on the Platelets membrane as shown in **Figure 2.** Von Willebrand Factor and thrombospondin are cell adhesion ligands and act as an intermediate in strengthening the aggregation between endothelial collagen and platelet surface receptors. Von Willebrand Factor plays two important roles, firstly it attaches to the GPIb component of the GbI/V/IX glycoprotein complex, and secondly, it contributes eloquently to platelet-platelet contacts. The glycoproteins, when attached to the superficial surface of platelets, initiate the binding of the platelet monolayer to collagen at the site of injury.

2.2.2. Activation

Under normal circumstances, blood flows freely throughout the body without the accumulation of platelets and can lead to the formation of undesirable thrombosis. Furthermore, when platelets attach to the damaged vascular endothelium layer, their activation occurs through several stimuli. Von Willebrand Factor and collagen are responsible for GPIb / GPVI ligand involvement. This attachment leads to the discharge of dense granule contents *i.e.,* Thromboxane A2 and adenosine diphosphate. This activation activates the GPCR -mediated second-stage activation and enhances the endogenous activation of platelet-specific activator integrin and glycoprotein GPIIb-IIIa [24]. Concluding that the termination pathway for all agonists is activated by glycoprotein GPIIb-IIa because it acts as a primary receptor for platelet aggregation and adhesion. Other activators include collagen and thrombin. The enzymatic cleavage of two sites on prothrombin by factor X leads to the formation of thrombin. Thrombin promotes platelet activation and aggregation by activation of protease-activated receptors on the cell membrane [25].

2.2.3. Secretion

In this step de-granulation from both dense bodies and alpha, granules take place. The role of calcium is essential to provide a free surface for the assembly of various coagulation factors.

2.2.4. Aggregation

As soon as platelets get in contact with the injury site, they begin to interact with each other for the formation of platelet cumulative. Thromboxane A2 and adenosine diphosphate help in the enlargement of platelet aggregate. Platelet aggregation is mainly mediated by the integrin GPIIb/IIIa. After the activation of platelets, a conformational change occurs to make it able to bind to the extracellular ligands, Von Willebrand Factor, and fibrinogen. Thrombin triggers the binding of adhesive platelet with Von Willebrand Factor and fibrinogen. adenosine diphosphate catalyzes the aggregation allowing fibrinogen to link two adjacent platelets [26]. Moreover, GPIIb/IIIa is also accomplished by cooperating with the platelet cytoskeleton, thus regulating changes in figures as well as contraction of the thrombus formed as shown in **Figure 2** [27].

A balance between prostacyclin and thromboxane A2 helps in the inhibition of excess platelet activation and aggregation, preventing the extension of a clot, and thus providing a localized platelet aggregation action.

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2.3.Coagulation

Coagulation is a setup of serine protease enzyme and their co-factors that interact with a phospholipid surface to form a clot made of fibrin [28]. In this, a rapid molecular reaction takes place by the rapid assembling of co-factors, enzymes, and substrates. The coagulation cascade is a series of steps having extrinsic and intrinsic pathways as shown in **Figure 3**. Coagulation involves a change of solvable fibrinogen into insoluble fibrin strands to strengthen the platelet aggregation (secondary hemostasis). Secondary hemostasis is based on coagulation factor activation and its outcome in a cohort of insoluble fibrin fibers. Recent Studies have shown that coagulation is based on the expression of tissue factors. The clotting process is subdivided into three distinct phases *i.e.* amplification, propagation, and initiation [29].

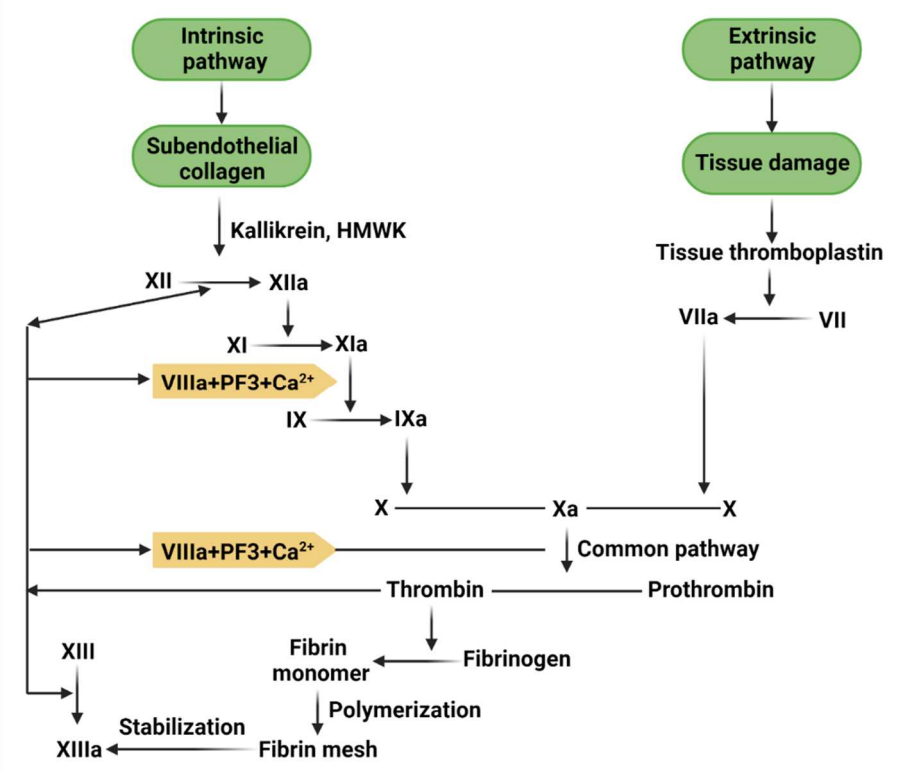


Figure 3. The intrinsic and extrinsic pathway results in the activation of various coagulation factors responsible for the coagulation of blood.

2.3.1. Initiation

On Damage to blood vessels, tissue factor cells are exposed to blood and their expression leads to the initiation phase [30]. After exposure of tissue factor cells to blood, it binds to factor VII and factor VIIa. The binding of factor

VII is less as compared to factor VIII. But factor VII binding is important as it leads to the activation of prothrombin, which results in the formation of thrombin. Furthermore, the tissue factor/ FVII complex converts IX to IXa and factor X to Xa as shown in Fig. 3. The phase of initiation can even take place when there is no injury and this can be controlled by the action of anti-thrombin and tissue factor pathway inhibitor [31]. The two other cells involved in the initiation of coagulation are monocytes and endothelial cells. Both of these cells involve several signal transduction pathways, regulating tissue factor induction either positively or negatively [32].

2.3.2. Amplification

After the generation of thrombin in the initial phase, it gets attached to the receptor GPIb of platelets. This complex formation leads to the formation of cleavage of protease-activating protein-1 (PAR-1). As a result, De-granulation and platelet activation occur [33]. All the factors e.g., Thrombin Triggers factors V, VIII, and IX are shown in **Figure 3**. However, Blood coagulation can also occur on different cell surfaces such as smooth muscle cells [34].

2.3.3. Propagation

All coagulation factors in the activated state are placed on the surface of the platelets. The initial stage is the formation of a tenase complex that causes the FX to activate FIXa, FVIIIa, and calcium. FXa forms the Va complex with calcium on the surface of the platelet. This is known as the complex of prothrombinase [35]. The amount of thrombin formed during amplification is insufficient. This deficiency is corrected by the prothrombinase complex which directly converts prothrombin to thrombin and thrombin to thrombin burst. The thrombin burst leads to the formation of the steady clot by the following process:

(i) Cleavage of fibrinopeptides A and B form fibrinogen forming fibrin. The process allows the polymerization of fibrin stands with activated FXIII at recognized sites.

(ii) Thrombin cleaves PAR-4 producing additional de-granulation and clot retraction [36].

2.4. Fibrinolysis

Clot Dissolution or fibrinolysis acts as a mechanism of clotting and repairing, comprising a series of enzymatic steps that are closely regulated. Fibrinolysis is designed to remove intravascular fibrin and restore blood flow but this system also participates in cell migration and angiogenesis [37]. The active serine protease plasmin is tinged to tissue plasminogen factor with plasminogen comprising an eminent role as shown in **Figure 4**. When bound to the fibrin surface, tissue plasminogen factor activity is increased. Plasmin hydrolyses arginine and lysine binds in its major substrates [38]. Fragments X and Y are generated by the Cleavage of fibrin and fibrinogen which hinder the polymerization of thrombin and fibrin, correspondingly. The inhibition of tissue plasminogen factor by PAI-1, plasmin by a 2-antiplasmin, and excessive fibrinolytic contribute to fibrinogen intake and hemorrhage [39].

As will be discussed in the next section, hemostatic agents accomplish their role by intensifying one or more of the above processes. Specifically, they can:

(i) Strengthen the natural stypsis by inducing vasoconstriction.

(ii) Stick to the tissue tightly to create a mechanical barrier.

(iii) Hasten the production of the coagulation cascade.

(iv) Absorb water from blood accumulating the platelets and coagulation factors at the injury site.

(v) Disintegrate the plasma proteins and induce platelet activation and aggregation, therefore forming thrombi at the injury site. **Table 1** summarizes which of these processes is followed by each class of biopolymers along with their structures.

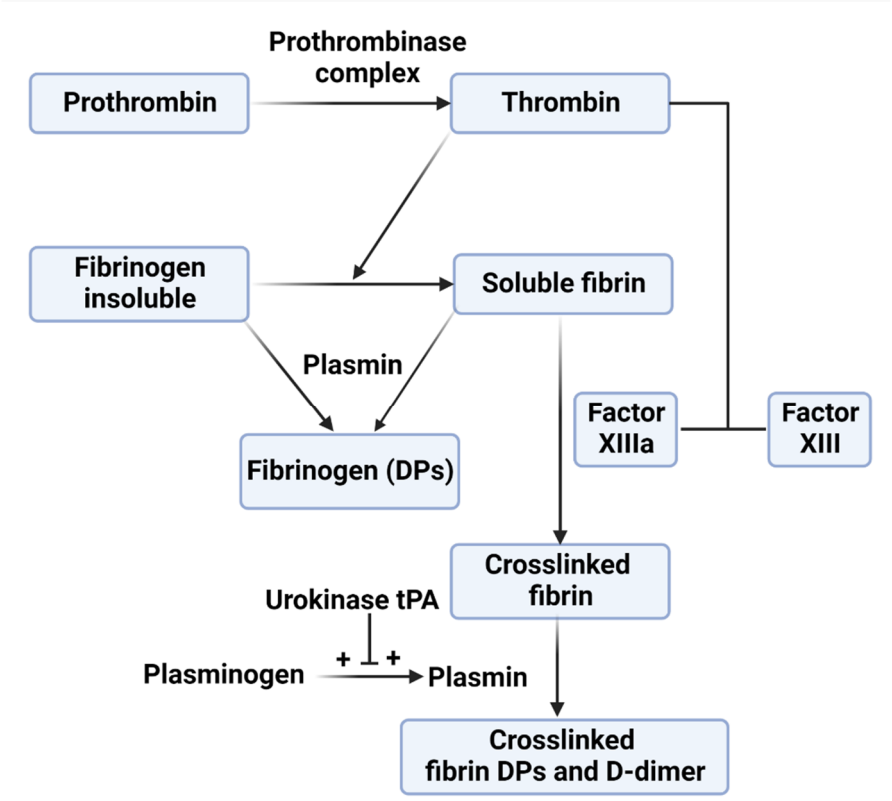
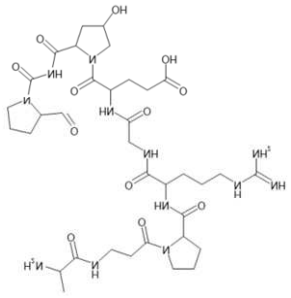
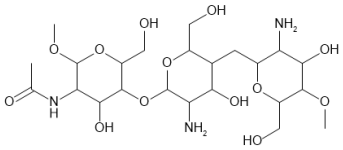
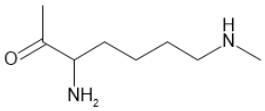
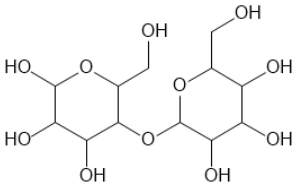
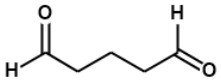
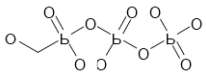
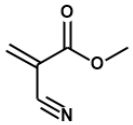
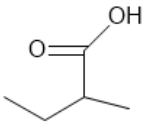
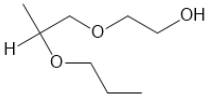
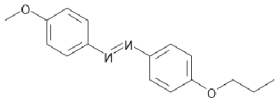
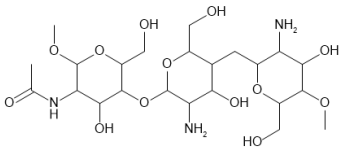
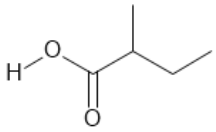
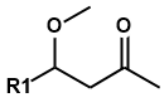
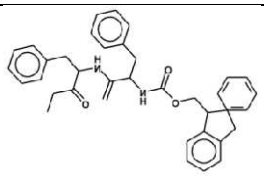
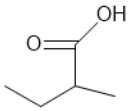
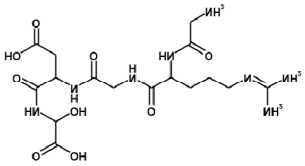
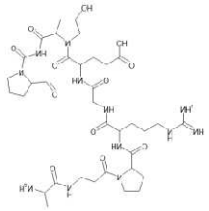
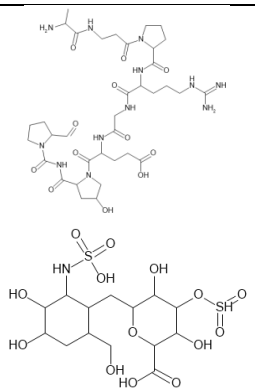
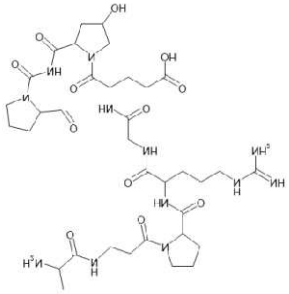
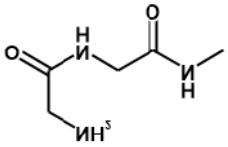


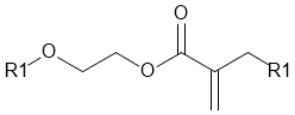
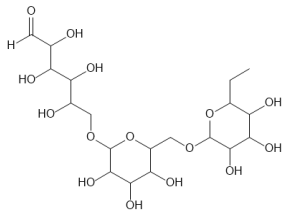
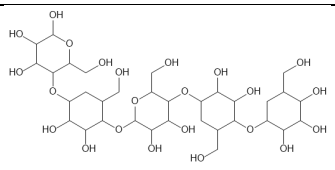
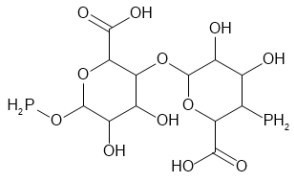
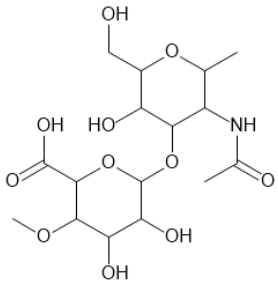
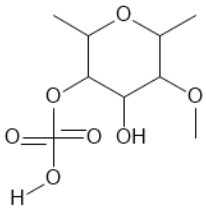
Figure 4. The flow chart represents the process involved in fibrinolysis.

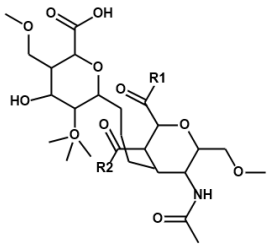
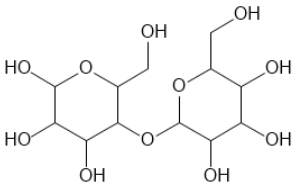
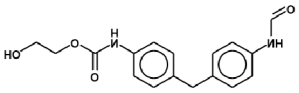
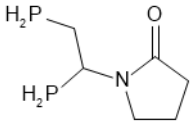
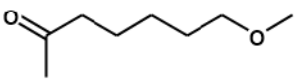
Table1. Role of various biopolymers used as a hemostatic agent and its mechanism of action.

Sr. No.	Biopolymers based Haemostatic agents	Molecular structure	Mechanism of action (As hemostatic agent)	Ref.
1.	Collagen/ Gelatin		Tissue adhesion and barrier formation Acceleration of coagulation cascade	[39]
2.	Chitosan		Vasoconstriction Artificial clot formation and blood gelation Tissue adhesion and barrier formation	[39]
3.	Polylysine gel		Vasoconstriction Artificial clot formation and blood gelation Tissue adhesion and barrier formation Acceleration of coagulation cascade	[39]

4.	Oxidized Cellulose		Artificial clot formation and blood gelation The low pH promotes antimicrobial effect	[39]
5.	BSA/ Glutaraldehyde		Artificial clot formation and blood gelation Tissue adhesion and barrier formation	[39]
6.	Polyphosphates		Acceleration of coagulation cascade	[39]
7.	Poly(cyanoacrylates)		Tissue adhesion and barrier formation	[39]
8.	Poly (acrylic acid)		Water absorption Artificial clot formation and blood gelation	[39]
9.	Poloxamers		Tissue adhesion and barrier formation	[39]
10.	PEO-b-PDHA		Tissue adhesion and barrier formation	[39]
11.	PEO/Chitosan gel		Tissue adhesion and barrier formation Vasoconstriction Artificial clot formation and blood gelation	[39]
12.	SAP		Tissue adhesion and barrier formation Vasoconstriction Artificial clot formation and blood gelation Water absorption	[39]
13.	PLA/PCL		Tissue adhesion and barrier formation Vasoconstriction Artificial clot formation and blood gelation	[39]

14.	RADA16-1 peptide		Artificial clot formation and blood gelation	[39]
15.	Acrylic cationic hydrogels		Tissue adhesion and barrier formation Acceleration of coagulation cascade	[39]
16.	GRGDS- tagged 1		Artificial clot formation and blood gelation	[39]
17.	Gelatin		Physical matrix for the initiation of clot	[40]
18.	Gelatin and Thrombin		Combination of effects of gelatin and thrombin	[40]
19.	Micro-fibrilar Collagen		Platelet adhesion and activation	[41]
20.	Fibrin sealants		Thrombin and fibrinogen are combined at the time of application. Thrombin degrades fibrinogen into fibrin and initiates clot formation.	[41]

21.	Polyethylene glycol		The PEG macromers get bonded with growth factors like epidermal growth factors. favors epithelialization possesses good barrier properties and oxygen permeability, two polyethylene glycols polymers mix and react at the wound site	[42]
22.	Dextran		It is resistant to both protein adsorption and cell adhesion allowing cell adhesion to be achieved by specific derivatization with extracellular matrix (ECM)–based peptides	[43]
23.	Beta-glucans		Strongly inhibits adipogenic differentiation, supports wound healing, and significantly lowers skin irritation	[44]
24.	Alginates		They are capable of absorbing 20 times their weight, allowing a moist wound environment and preventing microbial contamination	[45]
25.	Hyaluronic acid		Facilitates the movement of cells within the extracellular matrix providing a substrate for cell migration and proliferation thus enhancing dermal repair. Biodegradation of Hyaluronic acid produces by-products that also aid in epithelial cell proliferation and migration. It also plays an even more significant role in angiogenesis and the inflammatory response, further supporting cellular growth	[46]
26.	Fucoidan		Because of its interaction with growth factors such as basic fibroblast growth factor and transforming growth factor-β	[47]

27.	Chondroitin sulfate		Acts as a surrogate ECM, serving as a repository for cytokines and growth factors, important bio-entities for the healing process, and they provide structural frameworks for fibroblasts during epithelial regeneration	[48]
28.	Keratin		It has a high water intake capacity and can be used as dressing material at the wound site to prevent loss of biological fluid to the environment and to minimize wound exudate	[49]
29.	Polyurethanes		Favor's epithelialization	[50]
30.	Polyvinylpyrrolidone		It serves as a blood substitute and blood detoxifier	[51]
31.	Polycaprolactone		Mimic the fibrous structure of the extracellular matrix and act as suitable templates to treat over-bleeding.	[52,53]

3. Current biopolymers-based hemostatic agents

Amid the hemostatic materials, biopolymers are naturally derived polymers. Biopolymers have the advantages of biocompatibility, biodegradability, and plethora in source as well as no immune response. Also, biopolymers have single material composition and are easy to produce. Statically, these materials include stimulation of platelet or camouflage, coagulation factors, functional analogs of coagulation factors, porosity, surface area, different charges on the surface, swelling ratio, degradation patterns, fluid absorption, and strong adhesion [54]. Broadly, based on physiological conditions biopolymers can be classified into three different forms.

3.1. Absorbable polymers

Absorbable polymers are specially designed to degrade under physiological conditions. These polymers are also known as bio-erodible or bio-absorbable polymers (BAPs). These biopolymers are used in multiple bio-medical applications including Gene therapy, dental and medical devices, orthopedic devices, elastomeric films, encapsulation, and medical device coatings [55]. Poly-a-hydroxy aliphatic esters (BAPs) are innovative bioabsorbable polymers that are commonly used as implantation materials (orthopedics, drug distribution, skulls, and sutures). The food and drug agency FDA has licensed polylactic acid (PLA), polyglycolic acid (PGA), and polydioxanone (PDO) for human therapeutic use. Under optimal circumstances, a BAP may promote bone healing while steadily metabolizing the body, thereby reducing the need for a second surgery, which may be required while implanting a metal alloy. Polymeric drug delivery system avoids drug degradation and can also ensure drug release by adjusting drug to polymer ratio, molecular weight, and polymer structure. Bio-absorbent implants can be built for fracture implants, drug delivery, ligament replacement, and other medical uses [56].

3.2. Biological polymers

They are large molecules with similar chain-like smaller molecules. Smaller molecules are monomers. Combining small organic polymers may form giant molecules or polymers. Combining tiny organic molecules, they may shape giant molecules or polymers. These molecules are also called macromolecules. In living organisms, natural polymers are used to create tissue and other components [57]. Biomimetic polymer processing has also been applied to the development of linear and soluble materials that are self-assembled into bio-like structures. In an extensive series of publications, Percec and colleagues showed that discotic liquid crystal polymers may combine to form supramolecular structures varying from basic wedges to discs, rods, and more complicated columnar types [58–60].

The molecular setup of nature has been organized to produce new products that are real blends of natural and artificial polymers. Tirrell and colleagues developed a path to modified biopolymers by introducing synthetic small molecules into synthetic polypeptides such that the resulting products represent the basic characteristics of naturally occurring proteins along with enhanced functional properties. This is achieved by incorporating monomer units of amine and carboxylic acid groups, along with advanced features accepted by bacterial systems. Theoretically, this technique can be applied to any bacterial protein development as long as the host's aminoacyl tRNA synthetases may use the artificial amino acid as a substrate [61,62].

3.3. Synthetic polymers

Many polymers are now in operation at the biological interface, and in many instances, this is because their properties are either biomimetic naturally, or equivalent to their natural equivalents. For example, 2-hydroxyethyl methacrylate, when copolymerized with cross-linkers, and other monoacrylates exhibit desirable characteristics such as water retention, aqueous swell-ability, and controllable mechanical characteristics. This allows 2-hydroxyethyl methacrylate to be used as biomedical hydrogels and in contact lenses. These synthetic hydrogels share natural counterparts' excellent features but do not experience disadvantages such as deterioration and poor long-term storage. Poly(ethylene glycol), which has become a versatile biocompatible polymer in pharmaceutical and formulation chemistry, is also becoming increasingly relevant in drug delivery applications, as it may result in more successful pharmaceuticals encapsulating small molecular drugs in this polymer or combining PEG with therapeutic peptides, proteins and antibodies [63,64]. Indeed, in drug distribution applications, synthetic polymers might have more easily crossed boundaries into the biopolymer region. Synthetic polymers may improve therapeutic efficacy by safety before transmission to the target site, simply through enhancing the stabilization of a medication formulation, or through regulating the active compound's release kinetics and/or plasma supply. In the existence of carrier proteins such as albumins, this can be called analogous: moreover, synthetic polymers may often serve as more complex molecular chaperones, much as they do in biology. Of particular concern in the biological field are situations where synthetic polymers may steer a drug to a specific target location or interfere with a biological process instead of a natural polymer. To achieve this, synthetic polymers must have tightly specified structures and practical group positioning, and the materials and techniques by which this can be achieved are now well known [65].

With the development of technology, many medical researchers have used biopolymers as topical hemostatic agents. Chitosan, oxidized cellulose, sodium alginate, hyaluronic acid, dextran, and gelatin are examined for solicitation on hemostats due to their excellent performance from swelling rate to high drainage capacity [66].

Table 2 and **Table 3** summarize the list of marketed products along with their applications and mechanism of action.

Table 2. Various marketed products for the management of Haemostasis.

Sr. No.	Marketed Hemostatic agent	Clinical Applications	Ref.
1	AVITENE	Used to accelerate clot formation and effectively enhance platelet aggregation	[67]
2	HELITENE	It is indicated in surgical procedures as an adjunct to Hemostasis when control of bleeding by conventional techniques is ineffective	[67]
3	INSTAT MCH	It is indicated in surgical procedures as an adjunct to Hemostasis when control of bleeding by conventional techniques is ineffective	[67]
4	GELFOAM	Sterile compressed sponge intended for application to bleeding surfaces	[68]
5	SURGIFOAM	Sterile, water-insoluble, malleable, gelatin-absorbable sponge	[68]
6	SURGICEL	It is made of an oxidized cellulose polymer and is used to control post-surgical bleeding	[69]
7	OXYCEL	Used in minor anorectal surgery	[69]
8	GELITACEL	Used in situations where wrapping and draping is essential	[69]
9	INTERCEED	It is a knitted fabric composed of a modified cellulose that swells and eventually gels after being placed on the injury site and eventually forms a barrier that gets slowly absorbed after some days	[69]
10	HEMCON	Reduces bleeding time in dental extraction patients	[70]
12	CLO-SUR	Used in aortic-suture lines and lung surgery	[71]
13	BIOGLUE	It is a dual-action sealant hemostat	[72]
14	BIOFOAM	It gets polymerized quickly in connection with tissue fluid, excellent tensile strength	[72]
15	HISTOACRYL	Atraumatic wound closure, low exothermic reaction, and water-resistant barrier	[73]

Table 3. Summary of traded hemostatic products along with their specific mechanism of action

Sr. No.	Hemostatic agent	Composition	Mechanism of Action	Form	Ref.
1.	Quick Clot	Zeolite	Rapidly adsorbs water in an exothermic reaction to concentrate clotting factors	Granular	[74]
3.	Rapid deployable Hemostat	Marine Algae derivative	Cross-links RBCs	Dressing	[75]
4.	ChitoFlex	Chitosan (double sided)	Cross-linking of RBCs for the formation of mucoadhesive barrier	Roll	[75]
5.	Combat gauze	Kaolin	Activates intrinsic pathway of coagulation	Gauze	[75]
6.	Celox	Chitosan	Cross-linking of RBCs for the formation of mucoadhesive barrier	Granular	[75]

7.	Celox-A	Chitosan	Cross-linking of RBCs for the formation of mucoadhesive barrier	Granular	[76]
8.	Omnistat	Chitosan	Cross-linking of RBCs for the formation of mucoadhesive barrier	Granular	[76]
9.	Recothrom	Thrombin	Activates platelets and catalyzes the conversion of fibrinogen to fibrin	Hemostatic solution	[76]
10.	Tisseel	Fibrin	Mimics the final coagulation cascade step by forming a clot	sealant	[77]
11.	WoundStat	Smectile	Adsorbs fluid to form clay-like material, Activates intrinsic pathway	Granular	[78]
12.	ChitoGauze	Chitosan	Cross-linking of RBCs for the formation of mucoadhesive barrier	Z-fold	[78]
13.	Modified Rapid Deployable Hemostat	Lyophilized matrix of acetylated poly-*N*-acetyl glucosamine containing nanofibers	Induces Vasoconstriction, RBC, and platelet activation	Dressing	[79]
14.	Salmon Thrombin-Fibrinogen	Lyophilized salmon, thrombin, and fibrinogen	This leads to polymerization in fibrin clot	Lyophilized salmon, thrombin, and fibrinogen sealed in water-soluble dextran	[79]
15.	Floseal	Gelatin	Gelatin granules absorb the blood and swell (20% within 10 min) to form a tamponade	Hemostatic matrix	[79]
16.	Costasis	Collagen	Platelet activators	Hemostatic spray	[80]
17.	CoSeal	Polyethylene glycol	Forms a direct mechanical barrier to blood flow	sealant	[80]

3.3.1. Chitosan

Chitosan is a natural, eco-friendly, polymeric biodegradable material [81]. Hemostatic agents help quick and efficient hemostasis to control blood loss during a major hemorrhage [82]. The hemostasis, bacteriostatic and fungistatic behavior of chitosan can also be exploited in wound care. As a hemostat, chitosan helps to coagulate naturally and obstructs the nerve endings, thereby, decreasing the pain sensation. The polymer gradually depolymerizes to release fibroblast proliferation of N-acetyl-β-D glucosamine, ensures proper deposition, and induces an increased level of hyaluronic acid at the bleeding site.

For bleeding control; numerous hemostatic, biological and non-biological agents are used [83]. There are several disadvantages associated with the use of biologically active agents i.e., handling and the potential for transmission of diseases, to achieve hemostasis according to their origin, non-biological drugs, such as chitin and chitosan, have become increasingly popular as hemostatic drugs because they are not dependent on the native coagulation waterfalls for the regulation of bleeding. Chitosan and Chitin are close-range linked materials. Chitin is a polysaccharide that

exhibits cellulose similarity, the only dissimilarity is the presence of an $–NH_2$ or acetyl amine group instead of the -OH groups at the 2 and 2 carbon. Chitin is called chitosan when deacetylation exceeds 50 percent. Chitosan is soluble in an aqueous acidic solution due to free amine moieties [84].

The description of the web properties of chitosan dates to the early 1980s [85]. The antihemorrhagic mode of chitosan is still not entirely understandable even after thirty years of research. Chitosan and Polylysine are the main functional classes. Both materials are expected to have similar hemostatic activity. Scientific studies indicate chitosan is not directly involved in the cascade of coagulation, that is including collagen, gelatin, and oxidized cellulose [86]. By its positive protonated $–NH_2$ groups, chitosan is interacting firmly with the negatively charged platelet membrane, contributing to thrombin formation. This argument is supported by the fact that mixing chitosan with organic acids enhances protonation and improves high hemostatic behavior. Yet, chitosan appears to be favorable in the mechanism of attracting various circulating plasma proteins that spread to the surface of the material, thereby fostering platelet adhesion [87]. Chitosan plays part in the process of wound healing through immune cell activation. Last but not least Chitosan seems to play a part in the injury cure phase via activation of macrophage, cell stimulation, proliferation, and structure of historical and architectural tissue [88]. Chitosan increases the rate of hemostasis by providing a smooth and sterilized area for the growth of cells, a continuous exchange of gases for blood coagulation, and the conversion of liquid blood into a gel state, thus promoting blood coagulation. Chitosan consists of 2-acetamide and 2-deoxy-D glucopyranose monomeric units [89].

HemCon® (patches and sheets), QuikClot® (gauze, pads, and sponge), and Clo-Sur® (pads) are marketed chitosan-based preparations. So far, the use of these dressings has not been associated with any harmful effects. Recent studies have shown that the HemCon® bandage is also healthy for allergic shellfish patients [90]. HemCon dressings also have an antibacterial barrier in addition to the provision of hemostasis against several microorganisms like MRSA (Methicillin-resistant Staphylococcus aureus), VRE (Vancomycin-resistant Enterococcus). Zhao and colleagues recently prepared a simple preparation of chitosan / Polylysine hydrogels with excellent hemostatic properties as shown in **Figure 5**, without toxicity in cells L929. The authors attributed the antihemorrhagic behavior of the drug to a collaborative effect of chitosan's intrinsic hemostatic property and hydrogels ' strong adhesion (four times higher than commercial fibrin sealants) [91]. Dowling and co-workers have shown in recent years that hydrophobic-modified chitosan can perform reversible hemostatic action [92]. The content was designed by the reaction of 4-octadecyl benzaldehyde to the 'NH2' groups of chitosan resulting in a bottle of a copolymer-like brush. The author claims that the hydrophobic segments of their changed chitosan integrate into the blood cell membrane, as fibrin self-assemblies itself in a meshwork that converts liquid blood into a gelled clot, creating a 3D network that gels the blood. After alpha-cyclodextrin has been applied, the meshwork becomes disrupted and the blood clot is re-liquidated [93]. Preliminary tests on models for animal injuries showed an anti-hemorrhage effect that is equivalent to the effect of fibrin glues on hydrophobically modified chitosan.

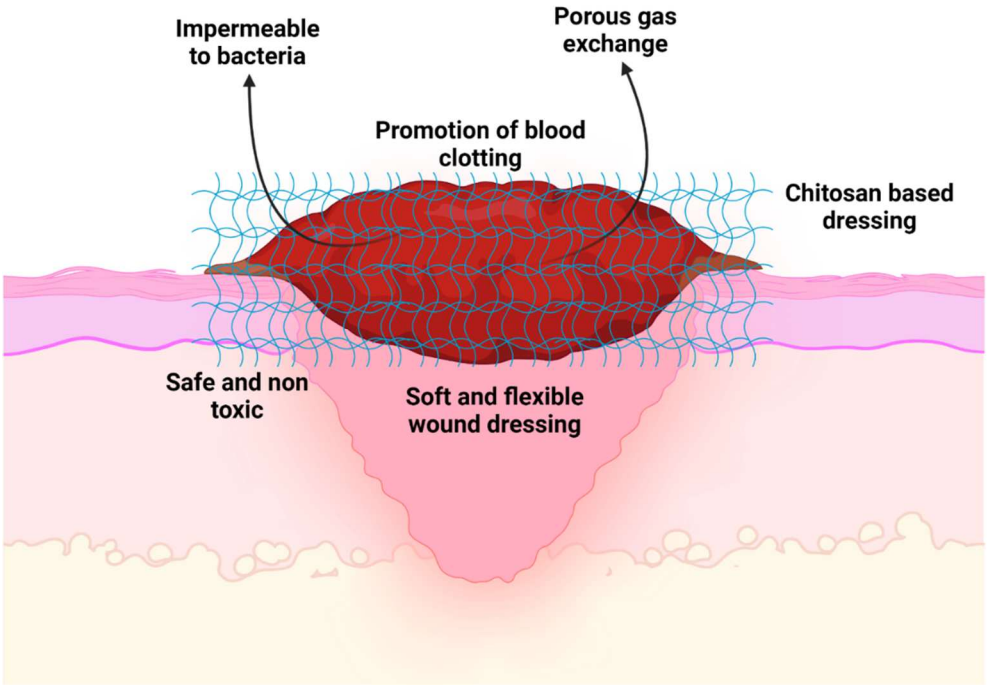


Figure 5. Depicting the molecular basis of chitosan as a soft, flexible, non-toxic, and hemostatic agent.

Many trade-approved hemostatic agents are extracted from chitin and chitosan [94]. Chitosan bandages are even used in the army, as they can heal rapid hemorrhage. Various factors and qualities of chitosan derivatives have made them a significant biodegrading marine polysaccharide *i.e.,* Biocompatibility, biodegradability, anti-bacterially, renewability, additive immune, bio-adhesive, anti-thrombogenic, non-toxic, polycationic, film-forming, non-allergenic, antifungal, hydrate agent and many more. Han and co-workers have recently produced super-molecular hydrogel chitosan [95], which is widely used as an anti-gastritis agent. Through radiation mediated cross-linking at ambient temperature, these co-workers prepared hydrogen verities for the treatment of wounds using the aqueous solution for gelatin and carboxymethyl cellulose [96,97]. In an experiment performed by souyma *et al.,* 33% of cells were plated with Dialdehyde hyaluronic acid and the remaining 67% was gelated. It leads to cell loss being reduced and cell encapsulation enhancement [98]. After 20 days, it showed better seeding density with matrix synthesis. Another technique for improving the properties of chitosan hydrogel is by preparing chitosan composites [99].

In addition to this "screening effect," as described earlier, collagen is likely to promote hemostasis by stimulating the plates and factor XII, like the intrinsic pathways. BC (biological collagen) has been marketed under different designations, including AviteneTM (sheets, flours, and sponges for foaming), HelistatTM (sparrows), HeliteneTM (fibers, pads), and Instant MCHTM (microfibrillar) BC can yield immune/allergic responses to porcine proteins and an antigen reaction, albeit biocompatible and biodegradable [100].

This shares a similar action mechanism and drawbacks with collagen. Furthermore, its hemostatic properties are less pronounced than those of thrombin as a performance enhancer for reasons that are not yet entirely clear. Gelatin hemostats were sold in the form of Gelfoam® (sponge and residue) as well as Surgifoam ® (sponge and residue), to name a few [101].

In the absorption of body fluids, metabolites, exudates, and governing nutrients, the floating action of wound dressing plays an essential part [102]. Higher-degree dressing would have a greater pore size and a wider surface region, allowing for improved proliferation or attachment of the cell [103]. On comparison of swelling properties of chitosan with traditional cotton gauze and cotton absorbing pad, the Chitosan dressing showed a swelling potential of 645–700% while submerged in the simulated body fluid for 2 hours at 25 °C and then attained a balance.

The statistical research was performed using one-way ANOVA, accompanied by Bonferroni checking with GraphPad Prism 5.0 for windows (GraphPad Prism, US of San Diego). The b0.05 p-values are viewed as statistically

important while the b0.001 was deemed extremely important. Both data points were presented as a mean ± standard deviation to evaluate the porosity, density, swelling, and biodegradation behavior [104]. For wound healing, different types of chitosan were studied, including hydrogels, films, membranes, scaffolds, sponges, etc. [105].

3.3.2. Dextran

Dextran is a polysaccharide consisting of repeated units of d-glucopyranose (d-glucose) connection through linear α-1,6-glycosidic connections and derived from lactic acid bacteria (streptococcus mutants, Leucon Stoc men) that use sucrose. Dextran obtained from mushrooms, yeast, and oats, gained popularity in tissue engineering because dextranase was found in mammalian tissue, which could degrade enzymatically. Biocompatibility, biodegradability, and water-solubility of dextran molecules lead to their use in nanomedicine. Dextran is commercially synthesized using a biochemical process, emerging a cationic ring that opened up levoglucosan polymerization.

Polysaccharide has extensive functions in pharmaceuticals (drug delivery hemostatic materials because they exhibit magnificent adhesive capacity, promoting wound healing, pharmacological properties, and antiseptic), chemical, clinical, biosensor, binder receptor, and food industries (where it is used to separate, purify proteins, and produce modified drug delivery system). Normally used molecular weights of dextran (40,000-500,000 Da) contain several thousands of reactive hydroxyl groups per molecule. Dextran hydrogels were used to support vascularization and wound healing, as shown in **Figure 6** [106–112].

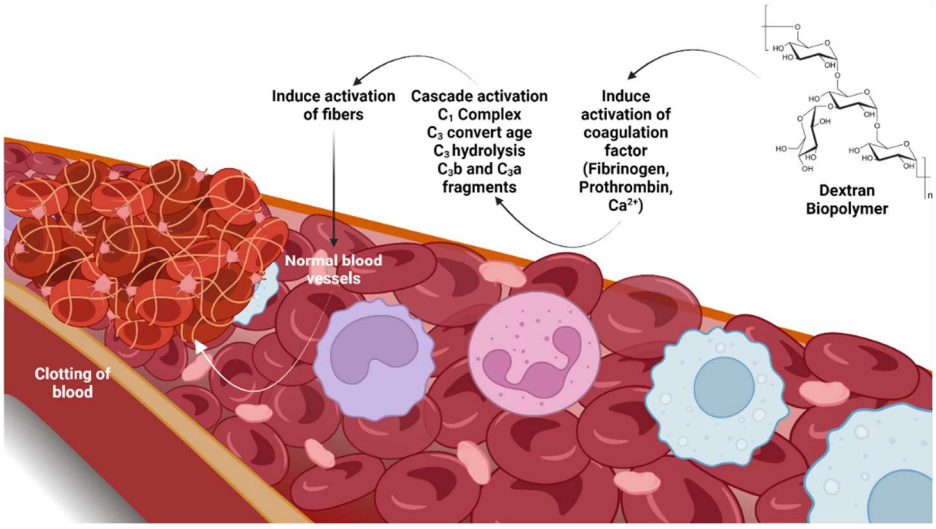


Figure 6. Role of dextran in promoting hemostasis and in activation of coagulation factors and repairs injured blood vessels.

3.3.2.1 Pharmacokinetic (PKA) profile of dextran

Pharmacokinetic characteristics determine all of the dextran characteristics such as molecular size, shape, flexibility, load, and lipophilic hydrophilic equilibrium (HLB). The pKa value varies with the molecular weight of dextran molecules when the dextran molecular weight is less than 70,000. Dextran loses polarity through the action of the GIT dextranase enzyme [113].

Liu *et al.* have investigated a unique type of dextran molecule known as "Herein" which comprises of poly-dextran aldehyde sponge with a pore size of 30-50μm. Poly-dextran aldehyde sponges significantly accelerate blood cell coagulation by aggregating acid-fast bacterial cells and inhibiting them. Also induces the activation of coagulation factors through the formation of the coagulation cascade. Later it was discovered that Aldehyde dextran has affected hemostasis characteristics and reduced blood loss from organ cells such as ear vein, femoral artery, and rabbit liver injury. The proper absorption and adhesion properties of the PDA sponge are further analyzed. The progression of hemostasis based on poly-dextran aldehyde sponges shows great biodegradability and negligible irritation of the skin [114]. The poly-dextran aldehyde sponge can achieve rapid adhesion, regardless of intestinal or vascular bleeding. The explicit hemostasis, by the complexity of the blood mechanisms of the major hemostatic components, was unclear. Three major phases of the process are involved in the stypsis, and platelet plug formation; then the coagulation cascades were activated, fibrin fibers were formed, fibrinolysis started, and wound healing. Therefore, to

acquire a profound perception of the hemostasis poly-dextran aldehyde sponge mechanism, a series of works on the adhesion of tissues, coagulation processes, absorption of whole blood and water plasma, red blood cells adhesion and aggregation, whole blood clotting kinetics, activation of the platelets, PT and aPTT test, effects on activity factors of coagulation and analyses of thromboelastogram, as per building. The poly-dextran aldehyde motility sponge for the integration of blood cells is also possible due to the structure of their pores. Blood and its components may accumulate very rapidly, beneficial for thrombus formation and coagulation factors in poly-dextran aldehyde sponge by capillary action. In short, the appropriate stable poly-dextran aldehyde sponges' networks likely played a crucial role in hemostasis.

Good biological compatibility has been a prerequisite for the use of hemostats; hemolytic capacity, skin irritation, cytotoxicity, and deterioration of poly-dextran aldehyde have been examined in detail. The hemostatic potential of poly-dextran aldehyde products with dissimilar aldehyde content, Celox, and Surgical, as well as blood containing TCTP (None, 0 percent) and Triton-X (TX-100, 100 percent), was set such as controls [115]. The hemolysis rates of all PDA groups in contrast to the TCTP group were very small, with a consensus of not more than 2.0 ± 0.11%, by the ASTM-F756 (American Society for Testing and Equipment) limits. However, the hemolysis of the Surgicel commercial group was up to 88.8 percent. In addition, were shown micrographs of RBCs corresponding to the hemolysis test. The morphology of RBCs in poly-dextran aldehyde was demonstrated. A typical healthy round was still present surface, supporting almost non-hemolytic poly-dextran aldehyde risks.

In 2008, Jared and co-workers, while experimenting on a heavy liver injury swine model presented the consequences of novel hemostatic dextran polymer dressing for survival under blood pressure conditions. They have used a standard laparotomy pad or laparotomy pass covered with dextran polymer called "Bloxx" for further animal studies. In three animals (out of six) it was found that laparotomies coated with dextran showed the least blood loss. The above observations showed that the use of "Bloxx" in lethal lever injury is effective and that bandage is acceptable to regulate blood loss in wounded persons [116]. Maria *et al.* described the hemostatic effect of dextran 70 (a form of dextran) and oxypolygelatin in clinically healthy dogs. The above clinical study on healthy dogs reveals that Dextran has a greater hemostatic effect and prolonged action than oxypolygelatin. Furthermore, molecular data reveals that there is a decrease in platelet aggregation in response to the conversion of ATP to ADP [117].

As per Micafl and co-workers, the interaction between dextran molecules, fibrinogen, and plasma membrane, results in a decreased capacity for the erythrocyte's flexibility and thus further did not involve in fibrinogen formation. Dextran's outcome is the formation of a loose adherent cap on the membrane of the erythrocyte and stronger adherence on the membrane of platelet cells. They were found to behave as a hemostatic agent by dextran [118].

According to studies, the polysaccharide dextran was widely used as a plasma volume expander for clinical purposes and it improved blood flow. Dextran showed a deep impact on red blood cell flexibility and the formation of rouleaux. It is confirmed that dextran was used to match the RBC membrane's binding characteristics and the chance of fibrinogen complexing. According to the above research, the impact of displaying dextran molecule on red blood cells and the component factor indicates distinct functions like red blood cells' antithrombic flexibility. The dextran molecule has a hemostatic impact and induces prolonged action in the hemostasis system as well. Various scholars also maintain the continuation of the study of dextran molecules [119].

The mechanism of the anticoagulant activity of dextran molecules with carboxylic and benzyl amide sulphonate groups was explored by multiple coagulation studies by Fischer *et al.* The derivatives indicate the action of heparin. Previously, dextran with an average molecular weight (m = 4500) was replaced in distinct proportions by groups of carboxylic and benzyl amide sulphonate [120]. The antithrombic activity of these components depends on the corresponding percentages of the monomer units loading each substituent. Molecule activity occurs through the impact of a supportive result between carboxylic and sulfate. All the potency of heparin-carrying functional groups showed anticoagulant activity. Serine proteases have been noted to catalyze heparin. They also financed the different behavior of dextran molecules depending on the chemical nature of the molecules and the associated functional group of the dextran molecular activity [121].

The experiments of Magnus et al. prove that dextran should not be prescribed to patients with von Willebrand's disease. Two patients with moderate degeneration of von Willebrand and two eligible individuals were administered intravenously, impairing the calculated coagulation factor VIII characteristics, i.e., declining antigen-related factor

VIII and co-factor rustication activity. For patients, who followed by an extended bleeding time, minimal to abnormally small concentrations were shown. Infusion factor VIII concentrates on the damage caused by reversed factor VIII and extended dextran bleeding time. The findings support the notion that dextran causes a faulty platelet feature in vivo by interfering with the molecular complex factor VIII [122].

Decorticated bone is a big cause of scoliosis operation blood loss. Present hemostatic strategies include compressed gauze and physical protection such as bone wax and other collagen materials. Compared to compressed gauze, we tested the protection and effectiveness of a novel fibrin-dressing (dextran-thrombin-fibrinogen) [123]. This dressing consists of lyophilized thrombin and fibrinogen trapped in an electrospun elastic nanofiber. The fibrin dressing is an efficient and secure way of managing bone blood loss in a backbone treatment model [124].

In compliance with C. Timothy Floyd, after a single 4-minute dressing procedure, optimal hemostasis was achieved at all injury sites in all research animals. Until surgery, bleeding was reported as discharge in 12 places and leaks in 8 places [125,126]. Medically, it is used to minimize blood viscosity as an antiplatelet and as a plasma volume expander in hypovolaemia. As of August 6, 2020, the dextran market is expected to grow at a rate of 4.2% in the upcoming decade. From 170 million USD in 2020, it will reach 220 million USD in 2024. The market spike is expected in the regions of North America, Europe, South America, and South Africa.

3.3.3. Sodium alginate

Sodium alginate is a native polysaccharide with the IUPAC name Sodium-3, 4, 5, 6-tetrahydroxyoxane-2-carboxylate derived from sodium salts of alginic acid and gum is separated from the cell walls of brown algae [127]. The gel can remain stable up to a temperature of 150 °C but long-term heat treatment can make the gel unstable. It is a thermostable hard and delicate gel that is influenced by calcium, much higher in the concentration of alginate and $Ca2^{+}$ when the gel is formed by force. Its appearance is clear and transparent and its mouth sensation is adhesive. Sodium alginate pH tolerance is good the pH of the gel remains below 3.7, so pH should be increased with the help of acidic ingredients [127]. Lemon juice and sodium citrate are frequently used to increase pH, but they should be used in modest amounts as they can increase saltiness. Sodium Alginate can tolerate up to 50% ethanol but sodium alginate is required to be hydrated before the addition of alcohol [127].

Due to its unique colloidal nature, alginate is a polymeric film that requires thickening, freezing, suspension, film-forming, gel creation, and emulsion resistance. Alginate's most dominant and incomparable property is its potential to react with versatile metal cations, especially calcium ions to make solid gels or insoluble polymers. Calcium gels are favorable for the manufacturing of new foods such as meat products, onion rings, spice fillings, crabsticks, and cocktail berries. Gels are also useful in food processing, and it is used in the biotechnology industries for the formulation of beads for binding of cells or catalyst. The efficiency of alginate to form a strong and insoluble gel in the presence of calcium ions can be put to use to enhance the properties of alginate film [127].

A variation of hydrogel has been developed with the help of derivatives (collagen, gelatin, alginate, fibrin, etc.) and biopolymers as an encapsulation system, microfluidic hydrogel, injectable material, cell deliver system, scaffolds, and as bio-ink for bioindication [125]. Alginate-fibrin hydrogel has demonstrated the capability to generate in vitro osteogenic demarcation in adipose stem cells which promotes the rapid release of stem cells, using the stem-cell encapsulation method which feeds mesenchymal stem cell bone chondrogenesis and supports caprine parenteral utricles in vitro improvement [128–130]. Whereas many research programs have demonstrated the benefits and use of hydrogels, such as collagen-alginate, fibrinogen alginates, and collagen-fibrinogen hydrogels. Collagen-fibrinogen-alginate preparation is conceivably a three-constituent hydrogel that incorporates the advantages of all three elements. Concentration range: 0.5-1% for specification and up to 1.5 % for other applications. Dispersion can be enhanced by mixing with sugar or other powder ingredients before addition to the fluid. Air bubbles are mostly trapped in the solution. To remove the air bubble, let it stay in the fridge for a few hours or you can situate it in a vacuum chamber [131–135].

Salts and ether of alginic acid are used as hydrogels in dental impression material, and absorbent material for surgical dressings (bandages). It is also used in the composition of microspheres and nanoparticles for analytical reagent kits and drug delivery systems. Sodium alginate is further used as a food additive, Emulsifier agent, gelling agent, and

thickener and also used as a stabilizer. Sodium alginate when given orally binds to mucous membranes and inhibits the absorption of various radioactive isotopes like radium Ra 226 and strontium Sr 90 in the intestine [136,137].

Wound healing is a complicated process that starts with hemostasis, inflammation, and removal of the element of the imperfect matrix, followed by tissue production and rearrangement [138]. In this analysis, PLGA (lactic-co-glycolic acid) and sodium alginate were aggregated and processed using electrospinning to achieve the desired physical and chemical properties of injury healing [139].

In the maxillofacial procedure, hemostatic agents are often used to assist a dry surgical area as well as to stop bleeding from tooth sockets. Altostrati is a hemostatic agent of non-woven fibers (Britain, Aldershot, UK). The fibers have been primarily developed for superficial injuries as wound bandages [140,141]. A series of these various sheets are composed of kaolinite crystals, which are arranged accordingly [142,143]. The primary property of kaolin is surface change; kaolin is essential to communicate with the solution of polymers and influences hemostasis. Kaolin is a strong touch pathway activator that rapidly forms clots in wounds. This was also used for many hemostasis tests as an activator [144,145].

When it comes into contact with blood, alginate fibers create a hydrophilic viscous gel that releases calcium ions to promote coagulation and platelet stimulation [146]. The affordability and high efficacy of alginate had led to its widespread usage for apicectomy as well as post-withdrawal bleeding. In such circumstances, many experimental studies have been performed for the biocompatibility of alginate-based hemostatic agents. Results are favored by studies conducted previously, using alginate-based material as hemostatic bandages for extraction sockets. There have also been numerous studies to determine the biocompatibility of hemostatic agent alginates in tooth sockets. The report shows that alginate fibers left in the tissue of humans are almost degradation-resistant, and may last for more than 6 months, which is significantly longer than that seen in dogs for an average of 12 weeks.

Two forms of alginate-based hemostatic agents such as tranexamic acid and kaolin occur in the gelatin-alginate hydrogel in high numbers. It is used to increase the adhesive strength in the hemorrhagic wound setting. Due to their hemostatic properties in local usage, they have been chosen for analysis. In contrast to gynecology, trauma, gastrointestinal bleeding, and angioneurotic pathological enema, it helps to reduce the loss of blood. Kaolin is a clay mixture with silicate and the formula superimposed 1:1 (Al_2O_3. $2SiO_2$.$2(H_2O)$) [147].

Cantered on their strong fibrinogenic adsorption rate, rapid water absorption, activated macrophage phagocytosis, promotion of platelets aggregations, facilitation of immune functions, preventing damage, and antimicrobial activity, these promising biopolymers are widely used in the field of hemostats for external application carboxymethyl chitosan and sodium alginate and collagen). However, all these properties could not be accomplished by single product content. Carboxymethyl chitosan is related to SA, for example, to maximize the development of porous spherical micro-particles. We have therefore engineered a hemostatic powder (carboxymethyl chitosan, sodium alginate, and composite collagen microspheres) to be used externally in a previous analysis. These microspheres display exceptional blood absorption properties with outstanding stacking interactions in comparison with the conventional hemostatic content. This property is especially necessary for the prevention of bleeding. The unique microsphere formation, gigantic surfaces, and material skeleton composition of the carboxymethyl chitosan, sodium alginate, and composite collagen microspheres permit this hemostatic agent to bind to the injury site and accumulate the plasma and create a barrier to facilitate blood coagulation. Carboxymethyl chitosan, sodium alginate, and composite collagen microspheres activate coagulation factors, because of their broad absorption ability to stimulate coagulation cascades and thrombin and to transform fibrinogen into a fibrin network, an effective method of hemostasis. In previous research, we noticed that carboxymethyl chitosan, sodium alginate, and composite collagen microspheres could boost platelet efficiency, demonstrate rapid biodegradability, and were in vitro non-cytotoxic. These milestones inspired us to pursue our studies on carboxymethyl chitosan, sodium alginate, and composite collagen microspheres in vivo, wound healing, and protection research. [148,149].

3.3.4. Gelatin

Gelatin is an eco-friendly polypeptide formed from collagen's temporary hydrolysis; a fibrous protein found in the body's connective tissues [150]. Gelatin, denatured collagen has demonstrated hemostatic efficacy in the surgical application and is usually used for fast coagulation in conjunction with thrombin. Because of its secure use in terms

of exceptional biocompatibility and biodegradability, it is usually used in internal bleeding. Collagen is present in connective tissues such as corneas, ligaments, teeth, tendons, dentin, and blood vessels. In the human body, at least 16 distinct types of collagens are found. The most important kinds are Types I, II, and III (or collagen I, II, and III), which create up about 80 to 90 percent of all the body's collagens. Type I collagen comprises three polypeptide spiral strands with a size of about 30 nm and a diameter of 1.5 nm [151]. Depending on the collagen origin and hydrolytic therapy techniques, there are several kinds of gelatin with distinct properties. For instance, pig-and-bovine-derived bacterial gelatin has been commonly used in regenerative medicine over the past several decades. Type I collagen's typical triple-strand framework consists of two α-strands and a β-chain [152,153]. Collagen has poor immunogenicity resulting from the determinant constructions of polypeptides in the three spiral bonds as well as the key molecular regions. In biomedical areas, this has significantly restricted its implementation.

Hait and his colleagues have come across effective patented characteristics of gelatin for mild to moderate bleeding. The first reports of gelatin's capacity to stop bleeding date back to the late 19thcentury. However, it wasn't until the 1940s that gelatin found commercial application. The first signs of gelatin's ability to stop bleeding were discovered in the late 19th century. It shares a common benefit and drawback function with collagen. It was used as a performance enhancer in conjunction with thrombin. Gelatin hemostats (sponge and powder) and Surgifoam ® (sponge and Pulver) have been sold for some years [154].

Besides this "sealing effect." collagen is also promoted by triggering the platelet and Factor XII. BC has been marketed under different names, as in the above-described touch and intrinsic routes, including Avitene™ (sheets, our, and foam), Helistat™ (sparrows), Helitene™ (ber form, pads), and Instant MCH™ (microfibrillar shape).

The normal molecular bonds present between different collagen fibers are shattered down into a shape during hydrolysis that is easier to rearrange [155]. The gelatin was ready to eliminate viral interference through alkali therapy. Hemostatic impacts, surgical processing, and tissue responses of the products, namely a two-layer layer of gelatin, TachoSil, and gelatin sponge, have been assessed using spleens from 21 animals. Its chemical structure is strongly comparable in many respects to that of its mother collagen. Photographic and pharmaceutical gelatin grades are usually derived from cattle teeth and pig skin. The gelatin polypeptide chain contains proline, hydroxyproline, and glycine. Glycine is accountable for chain closure. Conformation is restricted by the presence of proline. This is important for gelation properties. Type A gelatin has an isoelectric point of 9.0. It is obtained from acid hydrolysis of collagen, using sulphuric acid or HCL. Depending on the collagen, pre-treatment protocols are used before extraction. Type B gelatin is formed *via* alkaline hydrolysis of collagen using alkaline fluid (NaOH) with a 5.0 isoelectric point. In these cases, clusters of asparagine and glutamine amide are hydrolyzed into carboxyl groups in the collagen molecules, resulting in residues of aspartate and glutamate in gelatin molecules [156].

The two-layered gelatin blade and gelatin sponge had a superior hemostatic effect (completed 100% of weather conditions) as compared to TachoSil (0-17%). The gelatin matrix compresses the blood from wounds instantly, activates the autonomous elements in the build-up blood, and facilitates bleeding coagulation. Because of its exceptional hemostatic properties and functionality, the double-layer gelatin is a beneficial topical product and is associated with a lower risk of disease transmission and painful reactions. The two-layer gelatin layer was the most used surgical treatment among the assessed products [157].

3.3.5. Oxidized cellulose

The primary and secondary alcohol molecules found in oxidized cellulose can be transformed into groups of aldehyde, ketone, and carboxyl under oxidative conditions [158]. In this process, β-D10 1,4 glucosides bonds are also oxidized, resulting in a cellulose de-polymerization [159–161]. The degree and magnitude of oxidation depend on both the flora and fauna of the oxidizing agent and the conditions of oxidation. Such structural modifications express chemical, physical, and mechanical oxidized cellulose possessions which are significantly different from that of standard cellulose [162]. For example, oxidized cellulose in humans is entirely bioabsorbable, with both chemical and enzyme routes contributing to degradation. However, when used in the form of a gel, it is an effective enter sorbent and has pronounced antibacterial properties and hemostatic properties [163]. The latter is likely linked to the COOH groups which lower the pH, resulting in the unspecific accumulation of platelets and thus creating artwork of artificial coagulation. The structure of the oxidized cellulose strongly supports this theory. The lack of adequate mechanical

support for the clots can explain why some polyacids, e.g., Polycystic acids and polyprotic, are poorly anti-hemorrhagic, at least in part. While the reasons remain unknown, oxidized cellulose is stated to be less operative than collagen, particularly in irregular cavities or lacerations as well as excessive bleeding [164]. Oxidized cellulose can induce an antigen reaction like collagen and gelatin. The trade names of oxidized cellulose are Surgical™ (gauze and fleece), Oxycel™ (gauze and powder), and Gelitacel™ (gauze, fleece, and powder) [164].

Not many publications underline the economic value and high market expenses of using topical hemostatic agents during surgery [165]. A recent study demonstrated that the use of FloSeal was related to possible cost savings of $5.4 million across 600 patients attributed to a decrease in significant and minor injuries, procedure changes, transfusions, and time in the operating room. In the study of 25,048 operations (8,016 cardiac), 32 to 68% of patients suffered from uncontrolled bleeding, despite using haemostatic agent, and the cost was remarkably higher than controlled bleeding ($24,203 to $61,323 vs. $14,420 to $45,593 $p < 0,001$) [166]. Moreover, the costs for topical hemostatic agents have been substantially greater than that for regulated bleeding ($287 to $799 relative to $203 to $451, $p < 0.001$). The increased cost of hemostatic agents was perhaps attributed to combinations of various HAs used to stop bleeding, and the researchers suggest that new hemostatic agents are needed to improve clinical effectiveness and reduce the cost of the use of drugs.

Flowable thrombin-containing hemostatic agents have been a healthy and efficient substitute for preventing heart bleeding in gelatin sponges and oxidized cellulose (COR I, LOE A). Thrombin-containing and collagen-containing weathering agents are preferable to the weather conditions alone in microvascular bleeding during cardiac operations [165]. The application of commercially accessible fibrin sealants with viral inactivation is appropriate since they have been proven to be as successful as non-virally inactivated sealants and may lower the risk of viral transmission (COR IIa, LOE B). In pediatric cardiac surgery, the use of fibrin sealants in bleeding sites is especially successful in the case of coagulopathy (COR IIa, LOE B).

3.3.6. Inorganic polyphosphate

Inorganic polyphosphates are found in each cell of any living organism. Linear micro modules are made of high-energy phosphor-anhydride bonds that keep residues of orthophosphates [166]. A study stated that polyphosphates influence the osteobrin coagulation structure [166]. Polyphosphates have been integrated into coagulation clots which have increased turbidity and formed thicker slides. In the second study, it has been shown that polyphosphates are capable of triggering the coagulation factor XII [167]. The toxicity in the cell of blood or plasma is an issue with the use of inorganic phosphates as a hemostat".

4. Outlook, threats, and future perspectives

Although in recent decades many hemostats have been created and sold, hemorrhage remains a chief cause of morbidity and deaths [168]. Furthermore, hemorrhage may complicate any surgery. The main reason why the present generation is partially successful is that none of the hemostats is free from side-effects [169]. Fibrin glues are expensive & can convey viral or prion agents. Zeolites can contribute to thermal damage and can toxicate the eyes and lungs. Despite the significant improvements made over this time, there are still several issues with the use of hemostatic substances. Celox, QuickClot, QuickClot ACS+, HemCon, WoundStat, and TraumaDex are some of the FDA-approved hemostatic agents. Among these QuickClot, ACS+ and Celox are reported to be easily removed from the site of application but dressings like QuickClot face problems of poor biodegradation and thermal injury, whereas WoundStat consists of granules that can increase the risk of accumulation of residues in the lumen of blood vessels, difficult removal from site of application can also be seen.

Another example involves the HemCon patch, which is too small or not adaptable enough to cover the huge or deep lesion. Its square shape and rigid consistency make it perform well on flat surfaces in small spaces, this limitation is the greatest barrier to its use in extreme circumstances. The potential for the spread of infections due to the use of hemostatic agents can be another issue, a study on femoral artery damage model on pigs showed both major and minor changes, fibrin-gaseous pulmonary embolism, and shock symptoms 24 hours following treatment with ChitoGauze, CeloGauze, and CombatGauze.

Although it is important to investigate the mode of action of every class of polymers, some general structural-property relations in the discussions conducted in the previous sections can be established. Similar criteria can be used for the design of polymer hemostats in the following decade. To promote hemostasis; electrical charges must be present on the polymer chain. In particular, both negative and positive charges appear to trigger one or more clotting factors in one way or another and thereby increase the cascade of coagulation [169]. These can also stimulate the platelets and form unsolvable adducts with different blood proteins, resulting in "artificial" clots to help plug the wound. Last but not the least, the charges made polymers more hydrophilic and mucoadhesive, by creating hydrogen bonds from functional groups such as amine moieties and hydroxyl groups [167]. The polymer chemist will be required to project macromolecular structures to develop the next generation of polymer-like chitosan which is (i) biologically compatible and biodegradable, (ii) renewable building blocks can be developed through the green chemical route, (iii) easily recoverable and (iv) economical [170]. Current topical hemostats have flaws that limit their use to conditions with relatively low efficacy and necessitate additional modifications, preventing their usage in more widespread circumstances. There is currently no perfect dressing, and no hemostatic agent is likely to be preferable in every clinical circumstance. As a result, the development and improvement of such dressings still must be done. Additionally, most developed nations are the only places where hemostats are currently available for use. These products, which can save lives in both war and situations that occur in daily life, must be produced in underdeveloped regions of the world.

5. Conclusions

The choice of an excellent hemostat depends on the quantity of predictable or authentic hemorrhages encountered with any other conceivable hemorrhage diathesis in the patient's antiquity. Frequent, simpler straight steps (artery retraction, use of hemostat, and blood-vessel ligation) or hypotensive procedures can abate clinical or accidental bleeding. Biopolymers of varied pedigrees have been extensively studied because of their outstanding biocompatibility and bioactivity. Chitosan, alginate, collagen, hyaluronate, and cellulose are the most frequently used biopolymers based on their availability and cost, and thus they nowadays rule the present hemorrhage industry. Convergent scientific progress will outline the forthcoming nifty application of biopolymers as hemostatic products to satisfy the unmet needs of the world.

Author's contributions

Renu Kushwaha: Writing–Original draft; Sourav Sharma: Writing–Original draft, Writing–Reviewing and Editing, Figure preparation; Sandeep Kumar: Writing–Original draft, Writing–Reviewing and Editing; Arun Kumar: Writing–Original draft, Writing–Reviewing and Editing.

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