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METHODS AND INNOVATIVE APPROACHES FOR STOPPING MASSIVE HEMORRHAGE

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Summary

Uncontrolled hemorrhage can become a life-threatening injury in less than five minutes. The aim of this work is to make an overview of perspective technologies for creation of the gel for stopping massive hemorrhage. Biopolymers are natural compounds that comprise several polysaccharides and polypeptides. Because of their distinct molecular structure and bioactivity, they have piqued the curiosity of biomedical researchers and demonstrated a high potential for therapeutic change. Biopolymers have demonstrated superior biodegradability, dependable biocompatibility, and non-exothermic reactivity in first-aid hemostasis when compared to synthetic polymers and inorganic hemostatic materials. Given the growing importance of biopolymer functionalization, we examined the modification of polymers based on their functional designs, such as bioadhesion, charge stimulation, and the inclusion of procoagulant functional groups and ions. The numerous studies have demonstrated the excellent hemostatic effect, it is still necessary to further investigate how different kind of the materials affect the hemostatic process. The hemostatic materials' clinical transformation lags behind their basic research. In general, materials with few, basic components are better for transformation, but this has increased the need for careful planning in their design. Finally, the molecular structures and forms of hemostatic materials should receive more consideration during design. It is important to thoroughly investigate how the components interact with the coagulation process. It is anticipated that appropriate designs for hemostatic materials will enable rapid development from the lab to the patient bed.

Key words: *bleeding, biopolymers, hemorrhage, hemostatic material, hemostatic mechanisms, polysaccharides, polypeptides.*

Introduction. Uncontrolled hemorrhage can quickly become a life-threatening injury, necessitating an immediate response. Having specialized equipment readily available reduces the risk of death from severe bleeding significantly. The average blood volume in the human body is 65-70 mL per kilogram of body weight. There are three forms of bleeding: arterial bleeding, venous hemorrhage, and capillary bleeding. These are named for the blood artery from which the blood is drawn. Furthermore, bleeding can be superficial, such as from a tiny skin scrape, or inside, such as from an injury to an organ or bone. Massive bleeding is a potentially fatal emergency that can result in shock and death. If a person has a serious external bleed or fears internal bleeding, they must seek emergency medical attention. First aid can assist to stop the bleeding and avoid serious consequences or death. The most serious and urgent sort of bleeding is arterial bleeding. It can be caused by a penetrating injury, physical trauma, or organ or blood vessel damage. Because the blood is derived from the arteries, it differs from other forms of bleeding. Because it contains oxygen, blood, for example, is bright red. It also comes out in spurts and pulses that correspond to heartbeats. This is referred to as "massive" bleeding. Because the pressure from the beating heart prevents it from clotting or stopping as easily, it will be challenging to manage. A 20% or greater acute blood loss is intolerable to the human body and can result in hypovolemic shock, a potentially fatal condition. Uncontrolled hemorrhage necessitates the use of tourniquets and hemostatic dressings. While tourniquets have the reputation of causing permanent damage to the affected limb, studies have shown that commercial windlass-type tourniquets can be used for up to 2 hours with little risk of permanent damage. Many persons who get first aid training are instructed to utilize makeshift tourniquets. However, homemade tourniquets take far too long to make and are far less effective than commercial tourniquets. Furthermore, the bigger the limb, the greater the pressure necessary to occlude the injured blood artery. Up to 30% of the time, two tourniquets may be necessary. A little less than 5 minutes is all that is required for a fatal consequence. A tourniquet is not suited for injuries to the neck or torso. Wound packing with hemostatic gauze is required for these injuries. Individuals who have been trained to handle significant bleeding should have quick access to the necessary equipment to address this injury. Personal Protective Equipment, bandages for direct pressure, two commercial windlass-type tourniquets, and hemostatic gauze are also required. Individuals skilled in first aid should seek adequate training in its utilization in addition to the necessary tools. Severe bleeding and hypovolemic shock symptoms include chilly, wet skin that is pale or gray, an accelerated heart and respiratory rate, a weak pulse, and low blood pressure. The Prehospital External Hemorrhage Control Protocol shown below can be used as a guideline for the use of tourniquets and hemostatic gauze [7].

Even though the body has a strong coagulation mechanism, comprehensive hemostatic therapy is nevertheless

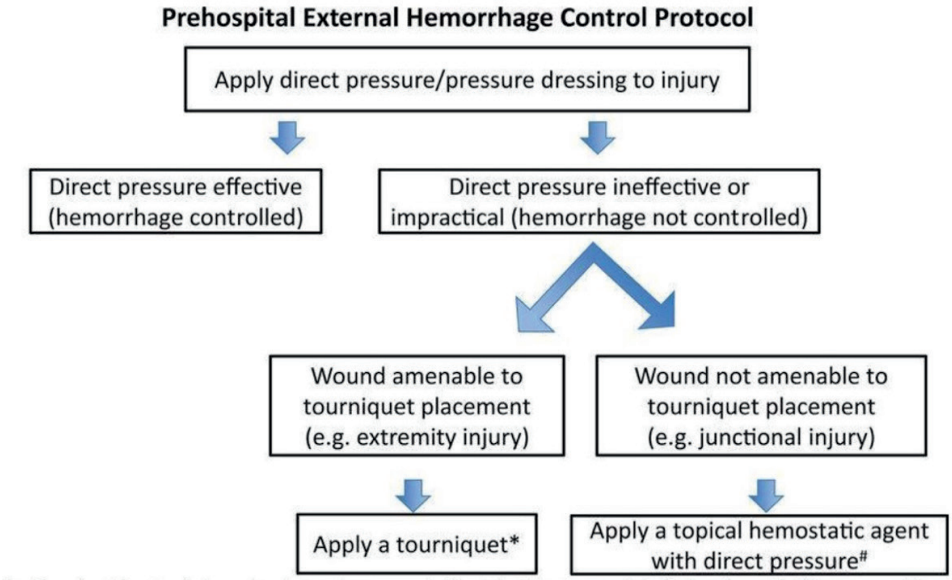

Figure 1. *Prehospital External Hemorrhage Control Protocol [7].*

** Use of tourniquet for extremity hemorrhage is strongly recommended if sustained direct pressure is ineffective or impractical; Use commercially - produced, windlass, pneumatic, or ratcheting device, which has been demonstrated to occlude arterial flow and avoid narrow, elastic, or bungee-type devices; Utilize improvised tourniquets only if no commercial device is available; Do not release a properly applied tourniquet until the patent reaches definitive care.*
#Apply a topical hemostatic agent, in combination with direct pressure alone is ineffective or impractical; Only apply topical hemostatic agents in a gauze format that supports wound packing; Only utilize topical hemostatic agents which have been determined to be effective and safe in a standardized laboratory injury model.

essential in the case of significant bleeding, particularly in pre-hospital care. Biopolymers are natural compounds that comprise several polysaccharides (e.g., chitosan, cellulose, and alginate) and polypeptides (e.g., gelatin, silk and fibroin). Because of their distinct molecular structure and bioactivity, they have piqued the curiosity of biomedical researchers and demonstrated a high potential for therapeutic change. Biopolymers have demonstrated superior biodegradability, dependable biocompatibility, and non-exothermic reactivity in first-aid hemostasis when compared to synthetic polymers and inorganic hemostatic materials. Several biopolymer-based products, such as Chitoflex®, HemCon®, and Celox®, have become available and demonstrated strong hemostatic efficacy. Many studies have been conducted by global researchers to create and produce more sophisticated biopolymer-based hemostatic materials with varied molecular structures and shapes, based on the unique benefits. The molecular structure of hemostatic materials, including components and chemical changes, can have a significant impact on the hemostasis effect. Notably, biopolymers have demonstrated valuable intrinsic bioactivities as pro-coagulation, pro-healing, and anti-infection [9]. Despite their connection by glycosidic bonds, the physical and chemical properties of the polysaccharides, such as molecular weight, solubility, functional groups, and so on, vary, which can provide them with a variety of hemostatic properties, as explained in the following sections. Polypeptides, which are abundant in tissue and blood, also play an important role in coagulation and can be used as a starting point for hemostatic material design. Furthermore, several functional groups have recently been added into biopolymers to affect their physical and physiological characteristics, resulting in multifunctional biopolymers. Given the growing importance of biopolymer functionalization, we examined the modification of polymers based on their functional designs, such as bio-adhesion, charge stimulation, and the inclusion of procoagulant functional groups and ions. Even with the same component, hemostatic materials can be made in a variety of forms, such as powder, sponge, gauze, and hydrogel, each of which has its own hemostatic mechanism [51]. Such materials have demonstrated special benefits for hemostasis under various conditions (bleeding location, depth, environment, and so on). For example, bleeding induced by a gunshot wound is distinguished by piercing, deep, and uneven wounds, for which standard gauze-type materials may be insufficient. Incompressible bleeding wounds caused by brain, heart, and other organ traumas frequently necessitate the material's capacity to bio-adhere. In terms of moving locations, bio-adhesion and stretchability of hemostatic materials must be considered to minimize subsequent bleeding induced by material movement and degradation. As a result, the materials' appropriate form design is critical for achieving their hemostatic effect.

Aim: The aim of this work is to make an overview of perspective technologies for creation of the gel for stopping massive hemorrhage.

Tasks:

Describe what is massive bleeding and standard methods to control it.

Perform a literature review of existing bleeding stopping gel.

Examine perspectives technologies for creating of the gel for stop massive bleeding.

Hemostatic mechanism. It is vital to understand the hemostatic effect of the materials, specifically how cells, proteins,

and other blood constituents are impacted. The physiology of coagulation is originally investigated in depth in order to optimize the composition of hemostatic materials. Furthermore, the designable point—the process that the material can control - is underlined. Based on previous research, they were classified hemostatic processes into physical and physiological hemostasis based on their role in the body's coagulation process.

The physiological process of hemostasis. Under normal circumstances, bleeding from a small blood vessel will stop spontaneously within a few minutes owning to physiological hemostasis at the injury site, which mainly involves primary hemostasis (vascular contraction and platelet thrombosis) and secondary hemostasis (blood coagulation) (Fig 1) [39].

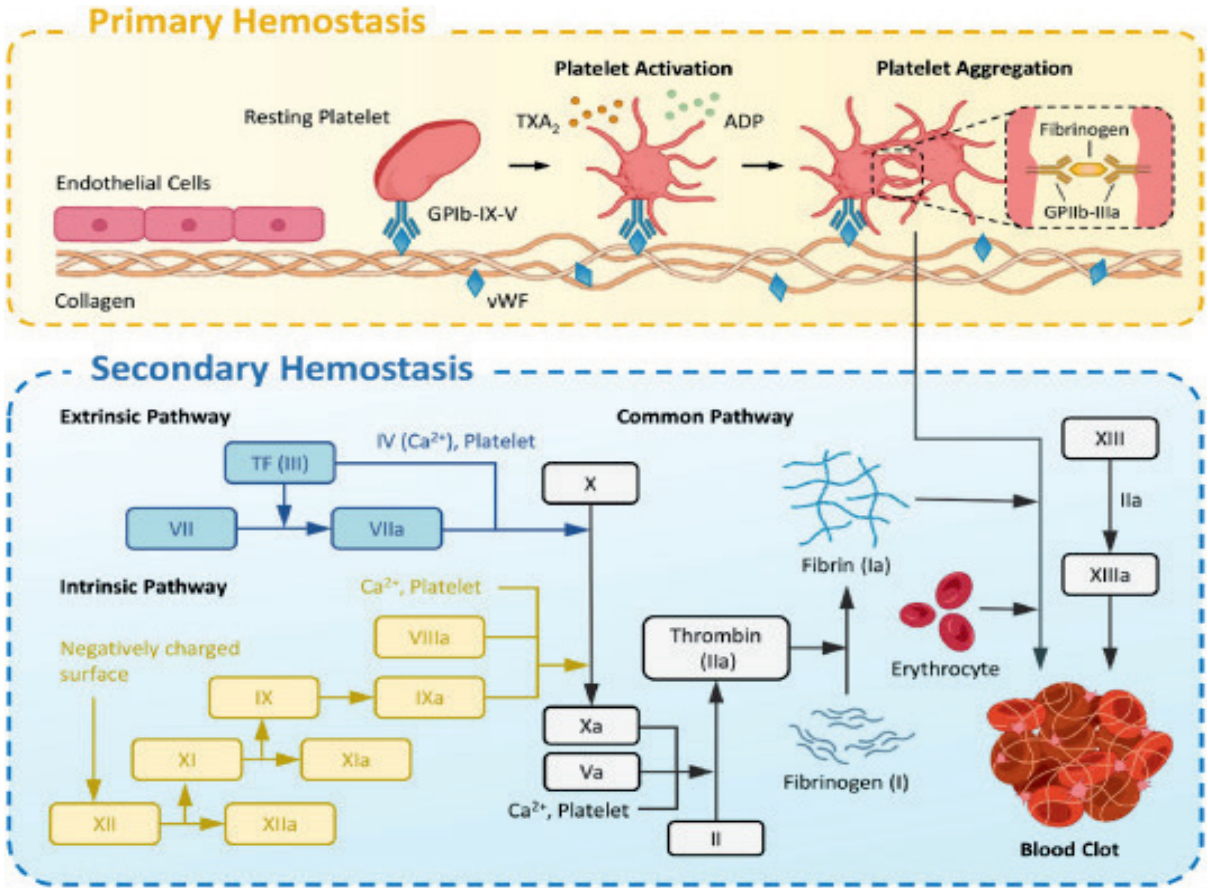

Figure 2. *Schematic illustration of the physiologic hemostasis process: primary and secondary hemostasis [39].*

When there is bleeding, the injured blood artery constricts to halt and restrict blood flow. Platelets will attach to exposed subcutaneous tissue (mostly type I, III, and IV collagen) via glycoprotein Ib-IX-V in the presence of von Willebrand factor (vWF) (GPIb-IX-V). The intracellular signaling pathways are stimulated, resulting in the production of endogenous adenosine diphosphate (ADP) and thromboxane A2 (TXA2), both of which can promote platelet aggregation [53]. Following platelet activation, the most prevalent glycoprotein on the platelet membrane, GPIIb-IIIa, will change conformation, enhancing its affinity for fibrinogen. Platelet thrombus might develop, bridged by fibrinogen and Ca2+, to plug the wound and accomplish primary hemostasis. Platelet adhesion, release, aggregation, and contraction during primary hemostasis are all referred to as the platelet activation process [56]. Secondary hemostasis occurs when the coagulation factors are activated in succession to create thrombin, and fibrinogen (solvable) converts to (insolvable), resulting in blood coagulation. Coagulation may be broken down into three phases:

- formation of the prothrombinase complex;
- activation of the thrombin;
- and generation of the fibrin.

There are intrinsic and extrinsic mechanisms for the production of prothrombinase complexes. All coagulation factors are produced from blood in the intrinsic route, which is generally activated by interaction of the blood with negatively charged foreign substances such as collagen. Factors XII, XI, IX, and IV (Ca2+) are the most often involved coagulation factors. The extrinsic route is a coagulation process that begins with the exposure of tissue factor (TF), a transmembrane glycoprotein found outside of the circulation, and the coagulation components involved mostly include TF, Ca2+, and factor VII [18]. The two paths will ultimately merge to form a single process. Factor Xa (a is short for activated) and factor Va create a factor Xa-factor Va-Ca2+-phospholipid complex on the surface of the phospholipid membrane, which is known as the prothrombinase complex, with the aid of Ca2+. Prothrombin is converted into thrombin, which then converts fibrinogen into fibrin monomer and promotes its aggregation [46]. The synergy

of fibrin, factor XIIIa, and blood cells will then complete blood coagulation. It's worth noting that, while the coagulation process has two steps, they overlap and may work together.

Common mechanisms of hemostasis. Hemostasis is a complicated process that involves several cells, proteins, ions, and external influences. Overall, the materials' hemostatic action may be examined from both physical and physiological perspectives (Fig. 3). The physical mechanisms of hemostasis are described by the concentration effect, adhesion sealing, and charge stimulation. Platelets, erythrocytes, fibrin, thrombin, and Ca2+ ions have been the focus of physiological interest as major participants in hemostasis. It is worth noting that modern materials frequently use a range of hemostatic processes in a synergistic manner to produce hemostasis.

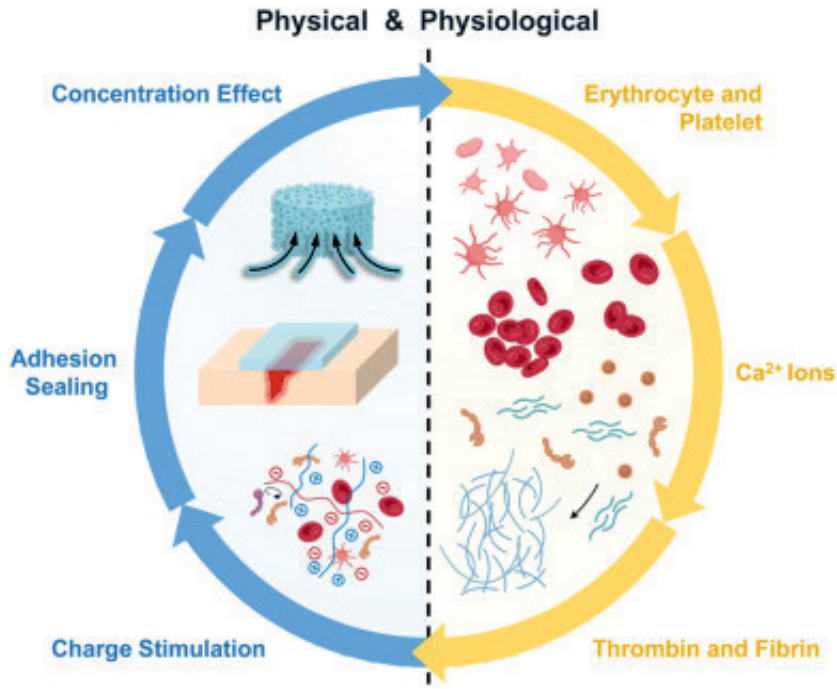

Figure 3. *Schematic illustration of common hemostatic mechanisms from the physical and physiological aspects [70].*

Physical mechanisms. Concentration Effect. External ways of increasing the concentration of procoagulant components in the blood, such as platelets, erythrocytes, coagulation factors, and so on, is an efficient and widely used hemostasis approach [70]. As a result, the concentration effect is most commonly employed in inorganic hemostatic compounds. The early investigations began using zeolite because of its benefits such as low cost, stability, plentiful supply, and no possible danger of disease transmission. Because of its peculiar porosity structure, it may rapidly absorb water and concentrate erythrocytes, platelets, and coagulation components to stop bleeding. The FDA authorized zeolite-based Quick Clot TM in 2002, and the Committee on Tactical Combat Casualty Care (CoTCCC) recommended it for use in bleeding situations [45]. However, due to a significant exothermic reaction, its clinical usage has been limited. Another commercially available hemostatic porous material is gelatin sponge, which can provide the hemostatic effect by increasing the concentration of platelets and coagulation components [34]. According to some, traditional cotton gauze might cause needless blood loss owing to water absorption [58].

As a result, the link between hydrophilicity and hydrophobicity must be considered when designing hemostatic materials, as discussed more in the following sections.

Adhesion and Sealing. Tissue adhesives can strongly attach the wound, conform to odd shapes, and are simple to use, making them ideal for battlefield and first aid applications. These qualities also provide them a wide range of applications in hemostasis [4]. Many hemostatic sealants have been produced, and they are primarily classified into two types. One category is biological materials, such as fibrin glue and other first generation tissue adhesives. It might promote the production of an insoluble fibrin coat at the bleeding site and seal the vessel by containing thrombin and virus-inactivated fibrinogen. However, because to its low tissue binding strength, fibrin glue is ineffective for applications needing resistance to strong mechanical stresses and blood pressure. Furthermore, such biological products may be immunogenic [27]. Chemosynthetic adhesive is the other kind. A notable example is cyanoacrylate-based glue, which has demonstrated strong tissue adherence due to its isocyanate composition. Unfortunately, heat damage during polymerization, as well as the harmful effects of breakdown products such as formaldehyde and alkyl cyanoacetate, should be cause for worry [54]. The materials are meant to accomplish moist adherence in the face of difficult conditions such as wetness and even gushing blood. Furthermore, specific hemostatic adhesives for different tissues should be developed in accordance with the various physiological

parameters. In response to such demands, innovative and intelligent hemostatic tissue adhesive development is currently in full swing [34].

Charge Stimulation. Blood proteins and cells are known to have negatively charged surfaces [14]. Electrostatic interactions between the materials and the procoagulant components can trap and activate them, accelerating the clotting process. When a positively charged hemostatic substance is given to the wound, a large number of blood cells congregate on it [19]. Some studies have demonstrated that the hemostatic activity of positively charged nanoparticles may outperform negatively charged nanoparticles by targeting wounded regions via opsonization with fibrinogen [12]. Nonetheless, several investigations have suggested that negatively charged materials may potentially increase coagulation. After coming into touch with negatively charged molecules, factor XII is activated to factor XIIa. Negatively charged compounds, such as alginate, can activate factor XII, so speeding up hemostasis [5]. As a result, both positive and negative charges can enhance clotting via various hemostatic processes, and the hemostatic impact will vary depending on the material and bleeding event.

Physiology-related mechanisms. Platelet. Platelet activation and aggregation are inextricably linked to the two phases of physiological hemostasis and play a critical role in the process [49]. The 5-hydroxytryptamine and TXA2 produced by active platelets can improve blood vessel contraction during primary hemostasis. The release of coagulation factors (fibrinogen and factor V) from activated platelet -granules can speed up the clotting process. The pseudopodia of platelets within blood clots will connect to fibrin via activated GPIIb-IIIa [13]. As a result, numerous methodologies based on platelets have been used to generate hemostatic materials. A nanoplateletsome was created utilizing the platelet membrane, which could target damaged blood arteries and regulate catastrophic bleeding [13]. Synthetic platelet replacements can efficiently control bleeding and have the added benefit of being mass-produced. For example, vWF-binding peptides (CBP and VBP) and fibrinogen mimicking peptides (FMP) have been employed to adorn the surface of liposomes in order to imitate platelet adhesion and aggregation, resulting in an improved hemostatic effect. Furthermore, platelets are engaged in the host's immune system and have a high importance for tissue regeneration [32].

Erythrocyte. The specific influence of erythrocytes on hemostasis has been gradually identified, as evidenced by platelet activation, thrombin production, and clot contraction. By releasing ADP and TXA2, erythrocytes can improve platelet adhesion and aggregation. The interaction of erythrocytes with fibrinogen can have an impact on the structure, mechanical characteristics, and lytic resistance of blood clots [62]. During the coagulation process, erythrocytes undergo a series of time-dependent shape changes, according to research. Those in the wound thrombus will lose their natural biconcave-disk shape and become densely polyhedral, which will help to form a tight contact between the materials and the bleeding tissue. This is consistent with Litvinov et alwork .'s on pulmonary emboli, in which the erythrocytes altered from biconcave to compressed polyhedral, generating polyhedron-erythrocytes [23].

Thrombin and Fibrin. Many coagulation factors are involved in secondary hemostasis, which eventually motivates thrombin production. This, in turn, will increase the transition of fibrinogen into fibrin, resulting in blood coagulation. Thrombin was added to the materials as a medication and demonstrated excellent hemostatic efficacy [37]. Currently, fibrin and thrombin are commercially accessible as coagulation components and are widely employed in clinical settings. Immunogenicity and the potential of virus contamination are long-standing downsides, as such substances are taken from animals (cattle, pigs) or human blood [41]. Furthermore, the time-consuming procedure of lyophilized powder dissolving and mixing limits their pre-hospital utilization, such as in battlefield and emergency treatments. As a result, one design element may be how to stimulate the coagulation cascade and induce more thrombin and fibrin synthesis [19]. On the other hand, suppression of fibrinolytic system activation has received a lot of interest. Many antifibrinolytic medicines have been tested in humans. This is exemplified by tranexamic acid (TXA), a proven life-saving medicine that may competitively limit the activation of plasminogen to plasmin, preventing fibrin clot breakdown [48; 50]. **Ca2+ ions** are ubiquitously engaged in the coagulation process and play a crucial role at all stages as the sole non-protein clotting agent [37]. Platelet surface activated GPIIb-IIIa cannot bind to fibrinogen and assemble in the absence of Ca2+ ions. Intracellular Ca2+ ions can expose phosphatidylserine on the surface of platelets, providing additional sites for coagulation complex aggregation and considerably promoting thrombin production. Furthermore, prothrombinase complex, an essential activator for thrombin production, must be generated by the action of Ca2+ ions. Calcium-containing biomaterials have been shown to efficiently achieve hemostasis. Calcium-modified oxidized microporous starch has been shown to activate the coagulation cascade and produce platelet adhesion in rabbit liver and femoral artery injuries, successfully controlling bleeding. Chen et al. also created mesoporous silica nanoparticles modified with tannic acid, silver nanoparticles, and calcium ions. When exposed to blood, Ca2+ ions were released from the materials, promoting the activation and circulation of the coagulation cascade [6]. Inorganic compounds containing Ca2+ ions, such as whitlockite, can release Ca2+ ions, so initiating the coagulation cascade [43].

Polyme - based component design. Polysaccharide-derived hemostatic material:

Chitosan-derived Material. Chitosan is the only known natural cationic polymer, derived from partial deacetylation of chitin [30]. Chitosan and its derivatives, such as carboxymethyl chitosan (CMCS), hydroxypropyl chitosan, and quaternary ammonium chitosan, have been widely used in regeneration medicine, drug delivery, hemostasis, and other fields due to their credible biocompatibility, biodegradability, and inherent hemostatic and antibacterial capacity [24] HemCon®, a commercially available chitosan-based hemostatic substance (licensed by the FDA in 2002), stands out for its superior hemostatic action on the battlefield. HemCon® is a lyophilized film that has been dissolved in acetic acid. According to research, the high acidity of HemCon® can cause a significant inflammatory reaction after

implantation. Celox®, a chitosan powder licensed in 2007, has been demonstrated to be beneficial in three models for mixed arterio-venous hemorrhages [21]. These studies have confirmed chitosan's hemostatic action. Chitosan pro-coagulation is also not dependent on the traditional coagulation pathway, according to research. Positively charged chitosan has been shown to have a hemostatic impact on erythrocyte aggregation and platelet adhesion [30; 33]. The Xu group created an in-situ imine crosslinked CMCS-based liquid bandage (LBA). When exposed to UV radiation, the compounds may crosslink with amino groups on the tissue. Furthermore, because of the CMCS's hemostatic action, the LBA can increase blood cell adhesion and aggregation, allowing for successful hemostasis. The combination of blood clot formation and wound closure may have contributed to the LBA's remarkable hemostatic ability [33; 35]. Furthermore, research on chitosan modification is rapidly expanding. Song et al. created a hemostatic hydrogel by grafting a catechol group onto chitosan. The mouse model for liver incision, tail amputation, and foot trauma had an outstanding hemostatic effect. This has been linked to the catechol group and amino group in chitosan, which have synergistically increased the adhesion capacity of erythrocytes and platelets. Furthermore, the hemostatic efficacy was synergistically improved by combining chitosan and caffeic acid with mesoporous silicon. The mesoporous silicon in the composite material was designed to be capable of tissue adhesion, coagulation cascade activation, and erythrocyte and platelet aggregation [37; 38]. Some have argued that the positive charge of chitosan may delay thrombin production and blood coagulation due to its suppression of contact activation and inability to significantly stimulate the activation of non-adherent platelets during the early stage of coagulation [26]. Nonetheless, chitosan-based hemostatic material design has clearly become a hotspot through altering the shape and combination with other materials, as well as chemical modification.

2. Cellulose-based Material. Cellulose is the most prevalent polysaccharide in nature, accounting for more than 50% of plant carbon content. It has traditionally been utilized for hemostasis, as with cotton [15]. However, cellulose's hydrogen network and extremely crystalline structure give it a very low solubility, which severely limits its applicability. Oxidation may improve its solubility and biodegradability. Oxidation can convert partial hydroxyl groups in cellulose into carboxyl groups, resulting in oxidized cellulose. Interestingly, oxidized cellulose has been shown to have antibacterial characteristics because the carboxylic groups generate a bactericidal environment by lowering the pH value [3]. Oxidized cellulose has become a popular hemostasis derivative. Surgicel®, for example, with oxidized regenerated cellulose as its major component, has been one of the most therapeutically used hemostatic products [9]. Its hemostatic mechanism may be divided into two parts. First, when it comes into touch with the wound, it absorbs the excess water from the blood, and then it gelatinizes to close the wound. Second, cellulose can stimulate platelet activation and aggregation, as well as combine with Fe3+ ions, which are produced from acidic hemoglobin and speed up thrombus formation [68; 60]. By varying the concentration of oxidized microsatellite cellulose (OMCC) in a collagen solution, Li et al. created a range of composite cellulose/collagen composites. Multiple hemostatic mechanisms have been demonstrated by the composite hemostat. The hydrophilic carboxyl group in hemoglobin can interact with the Fe3+ ions to generate a brownish gel that can seal the wound. In addition, the interaction between the oxidized cellulose and the platelets was explored preliminary. Cheng et al. successfully carboxyl functionalized cellulose nanocrystals using 2, 2, 6, 6-tetramethylpiperidine-1oxyl (TEMPO). Carboxylated cellulose nanocrystals not only offered Ca2+ ion cross-linking sites, but also aided in platelet recruitment and activation [11]. For the treatment of unmanageable large bleeding, a carboxymethyl cellulose (CMC) fiber-reinforced composite was created. The addition of CMC improved the mechanical characteristics of the composites, including toughness, mechanical strength, and fatigue resistance. More crucially, the scattered CMC fibers might activate platelets by increasing the release and expression of CD61 (GPIIIa) and P-selectin [60]. To exploit the hemostatic mechanism and make it versatile through logical design has become the key to developing novel cellulose-based hemostats.

3. Based on alginate and hyaluronic acid material. Alginate is a biopolymer made up of unbranched linear chains of -l-guluronate (G block) and -d-mannuronate (M block) residues that are randomly ordered. Hyaluronic acid (HA) is an extracellular matrix (ECM) macromolecule composed of repeating disaccharide units, particularly -d-glucuronic acid and N-acetyl-d-glucosamine. Because of the abundance of carboxyl groups in their backbones, alginate and HA are both anionic polysaccharides [20; 17]. The anionic polysaccharide, like collagen, glass, and kaolin, can interact with positively charged amino acids on factor XII via the negative charge supplied by the carboxyl groups, activating the intrinsic route and initiating the coagulation cascade [5; 55]. Wang et al. created a hybrid HA-polyurethane cryogel for wound hemostasis and healing. The scientists discovered that the hydrogel could considerably reduce APPT but had no effect on PT using coagulation four indices testing, suggesting that the hydrogel might activate the intrinsic route due to the negative charge of HA. Alginate may also form a "egg-box" shape with Ca2+ ions. Calcium ions in calcium alginate are released in exchange for Na + ions after interaction with blood. The released Ca2+ ions may enhance a prothrombin activation cascade, resulting in fast hemostasis [18]. Wu et al. created a calcium alginate-coated chitosan microsphere using the ion-exchange process.

The released Ca2+ ions might activate platelets and coagulation factors, increasing the intrinsic and extrinsic pathways for the production of thrombin. However, as the authors point out, negatively charged alginate reduces erythrocyte adherence [63]. Overall, alginate and HA have a modest hemostatic impact on their own. As a result, several chemical modification and hybridization techniques have been developed. To replicate the clotting action of platelets, serotonin, a platelet activator, has been conjugated onto the HA [2]. Chemical alteration, in addition to electrostatic interaction, can endow additional hemostatic processes, such as tissue attachment. Yan and colleagues added the catechol

and aldehyde groups to alginate. The dual-functionalized alginate may combine with hydrazide-modified poly(l-glutamic acid) to generate a robust bio-adhesive hydrogel with better hemostatic properties [65]. Other biological characteristics of alginate and HA are also noteworthy. Their moisturizing characteristics, for example, are frequently employed in the cosmetics and pharmaceutical sectors. Granulation tissue regeneration and fibroblast proliferation may also be used for wound repair following hemostasis [18; 66].

Polypeptides-derived hemostatic material:

4. Collagen-based material. Collagen is the most abundant protein in mammalian tissues, and it is primarily responsible for structural stability. In the meanwhile, collagen plays an important function in physiological hemostasis. Subendothelial collagen has the ability to bind to platelet receptors, enhancing platelet adhesion and aggregation and activating clotting pathways. Negatively charged collagen can activate the intrinsic pathway as a precondition for secondary hemostasis. Collagen is the only ECM protein known to yet to stimulate platelet activation [40; 59]. However, the variability and immunogenicity of animal collagens have steadily been a source of worry. A solution is to use bioengineering technology to create synthetic collagen using a bottom-up design. A recombinant hemostatic collagen sponge with improved procoagulant action has been developed, which may induce blood cell adhesion more effectively than native collagen sponge [28]. Furthermore, Hartgerink's group has created a nanofiber made of collagen mimetic peptide that can generate large-scale nanofibrous hydrogels. Similar to animal collagen, it exhibits procoagulant action manifested as platelet adhesion and activation (increased P-selectin secretion) [35]. Hydrolysis is another method for addressing collagen's biosafety. Gelatin is a collagen hydrolysate with great economic value and proven biocompatibility, biodegradability, and non-immunogenicity. The gelatin's arginine-glycine-asparagine (RGD) sequence can promote cell adhesion and migration, making the gelatin useful in tissue regeneration [25]. Notably, gelatin has been found to have hemostatic properties through aggregating and activating platelets. The cationic groups of gelatin can aid in the trapping of negatively charged erythrocytes inside the blood clot, resulting in the formation of a thick fibrin mesh [1; 36]. There are several gelatin-based products available, including Gelfoam® and Surgifoam®, which have a high application value [4; 16]. Many chemical modifications and material composite strategies have been used to enhance gelatin's hemostatic function. For example, methacrylic anhydride (MA) has been changed in gelatin to improve bio-adhesion, which can aid in wound closure and hemostasis [10]. To inhibit bleeding and resist water, alginate and genipin are mixed with gelatin. Furthermore, the sponge is appropriate for postoperative fast hemostasis and tumor recurrence prevention [8]. It should also be noted that collagen is the primary component of ECM. When compared to refined collagen, ECM retains the physical and chemical signals as well as the biological features of the tissues. The ECM has an influence on angiogenesis, immunomodulation, stem cell recruitment, and other features to promote tissue regeneration in a bioactive microenvironment [69]. However, its use in hemostatic materials is limited.

5. Silk Fibroin-based Material. Silk fibroin (SF) is a natural protein produced from silkworm cocoons that consists of two chains joined by disulfide and is mostly utilized in fashion fabrics and surgical sutures. The SF has piqued the interest of numerous biological sectors due to its guaranteed biocompatibility, biodegradability, and changeable mechanical characteristics. Under specific external circumstances, the SF can undergo gelation transition, and the process is as follows: The secondary structure of the SF will shift from random coil to physically crosslinked -sheet structure in the presence of hydrophobic and hydrogen bond interaction [64]. The quick gelation is advantageous for wound closure. Yan and colleagues created a supramolecular hemostat (CS/TA/SF hydrogel) comprising SF, chitosan, and tannic acid that crosslinks with the others via electrostatic contact and hydrogen bonding. The CS/TA/SF hydrogels demonstrated wet adhesion qualities, and the SF and tannic acid may promote thrombus formation by direct contact with platelets and coagulation factor, demonstrating efficient hemostatic performance for both arterial and visceral bleeding [47]. Aside from hydrogels, SF has been created in a variety of ways to prevent bleeding. For example, due to the increased cell-attachment capabilities of the SF and the rougher surface morphology of the microspheres, a microsphere containing the SF and alginate was created for fast hemostasis [31]. Using the different intrinsic biodegradability and biocompatibility, the SF and chitosan-based cryogel with exudate absorption capabilities and compressive elasticity, which is conducive to the concentration effect, was created [67]. The SF's hemostatic mechanism has been investigated as a typical hemostatic substance. Wei et al. examined the mechanism of SF and discovered that it may considerably stimulate platelets, inducing platelet aggregation and adhesion as well as enhanced platelet-fibrinogen binding. Although several studies have indicated the hemostatic action of the SF, it was usually coupled with additional components, making it impossible to determine the efficiency of the SF alone. As a result, the SF's whole hemostatic mechanism remains to be thoroughly investigated [51; 61].

6. Keratin-based Material. Keratin is a natural substance that may be found in skin, hair, nails, and other body components. Its high concentration of cysteine residues promotes the production of disulfide bonds, giving keratin tissues strength and elasticity. Notably, keratin has a good hemostatic effect and has been widely used in the development of hemostatic materials. A radical polymerized expandable keratin-based sponge demonstrated a hemostatic effect for penetrating hepatic hemorrhage in rats and femoral artery transection hemorrhage in a pig model [57]. To achieve bio-adhesion and improve mechanical characteristics, an approach of catechin crosslinking and cellulose combination was used to create a nanocomposite hydrogel for speeding blood coagulation [52]. As a new hemostat, a powder-type keratin was developed for easy storage and mobility. The nanosizing has increased the surface area of the keratin particles, giving them enhanced water absorption and film forming characteristics. Research into the mechanism of keratin hemostasis is also progressing. Burnett et al. investigated the hemostatic mechanism of KeraStatTM

(KeraNetics), a keratin-based hydrogel, at the preliminary stage. Platelet adhesion tests revealed that 1 integrin-mediated platelet adhesion was implicated in the hemostatic process. Furthermore, as biogenic polypeptides, keratins are challenging to manage in terms of amino acid composition, batch-to-batch variation, and complicated keratin-related proteins. These have stymied the investigation of its usage in hemostasis. The synthesis of recombinant keratin by bioengineering technologies may eventually alleviate the aforementioned difficulties. Guo's group employed Escherichia coli to express two forms of human hair keratin for hemostasis. The findings of the APTT and PT tests revealed that human hair keratin might engage in both the intrinsic and extrinsic routes, particularly the former, which increased blood clotting via fibrin coagulation [22].

The data on the table 1, 2 below, represents summarized information about hemostatic mechanisms and limitations of polysaccharides and polypeptides biopolymer – based hemostatic materials.

Table 1. *Component design for biopolymer-based (polysaccharide) hemostatic materials.*

Materials	**Chitosan and its derivates**	**Cellulose and its derivates**	**Alginate and Hyaluronic acid**
Hemostatic mechanisms	▪ Positively charged amino; ▪ Erythrocyte aggregation; ▪ Platelet adhesion.	▪ Concentration effect; ▪ Negatively charged carboxyl; ▪ Complexation with Fe3+; ▪ Platelet activation and aggregation.	▪ Concentration effect; ▪ Negatively charged carboxyl; ▪ Activating intrinsic pathway.
Limitation	▪ Poor solubility.	▪ Weak pro-healing bioactivity; ▪ Potential acidosis risk	▪ Low hemostatic ability; ▪ Insufficient chemical stability

Table 2. *Component design for biopolymer-based (polypeptide) hemostatic materials.*

Materials	**Collagen**	**Silk fibroin**	**Keratin**
Hemostatic mechanisms	▪ Platelet activation; ▪ Activating intrinsic pathway	▪ Platelet aggregation and adhesion; ▪ Enhanced binding of platelets and fibrinogen	▪ Platelet adhesion; ▪ Activating intrinsic and extrinsic pathways; ▪ Promoting fibrin clotting
Limitation	▪ Heterogeneity; ▪ Immunogenicity risk	▪ Insufficient chemical stability	▪ Heterogeneity; ▪ Complex keratin-related proteins

Design of hemostasis materials. Researchers must evaluate the effect of diverse shapes on hemostasis while designing hemostatic materials from a macroscopic standpoint. By changing the shapes, physical characteristics of hemostatic materials such as porosity, absorption, surface contact, and so on may be altered. Based on their shape, hemostatic materials may be divided into four categories: powder, sponge, gauze, and hydrogel. In recent years, many types of hemostatic materials have been produced. In addition to the four kinds listed above, various innovative forms of hemostatic materials have evolved as a result of the advancement and integration of medicine, material science, bioengineering, and other fields [29]. Nonetheless, there has been no unified critique of which shape is the greatest, and this should not be the case. There is no such thing as the best, simply the most appropriate. Both the powder and the sponge have a wide surface area and a high capacity for water absorption, allowing them to concentrate blood cells and clotting components. Powder is appropriate for irregular and deep wounds, but due to weak tissue adherence and integrity, it is easily washed away by blood flow. Partially dissolved powders may enter the bloodstream, raising the risk of embolism. As a porous blocking substance, sponge may absorb blood and expand, putting pressure on surrounding tissues. However, for wounds with complicated morphology, hemostasis will require the use of external force, which may cause discomfort in the patients. Furthermore, both hydrogel and gauze-type materials are capable of achieving hemostasis via bio-adhesion and sealing. Because of their distinctive ECM-like architectures, the hydrogels are particularly appropriate for post-hemostasis management, however wet adhesion performance still has to be enhanced [43; 44]. Gauze-type hemostatic materials are convenient to transport and use, although they are limited by wet stickiness. In general, materials tend to fuse with the blood clot during the hemostasis process, and if it needs to be removed, it is simple to induce subsequent bleeding. As a result, various kinds might be blended to improve hemostatic properties.

Conclusion:

The likelihood of bleeding will increase in situations like war, many diseases, and surgical procedures due to underlying causes. Such bleeding is like a "time bomb" with uncertainty and risk, so it's important to stop or lessen the tendency to bleed. A possible strategy is to use micro/nanomaterials to intervene at particular sites that may show early signs of bleeding in order to prevent further exacerbation.

The fusion of material science and biomedicine has led to the development of a wide range of procoagulant - active materials. The design of hemostasis materials should take into account how they contribute to and control the physiological hemostasis process. Additionally, materials that mimic the physiological elements of hemostasis, such

as synthetic platelet-like particles and platelet-mimicking procoagulant nanoparticles, have also been developed. The aforementioned descriptions of the advantages and disadvantages of various hemostatic materials. First, hybrid materials with combined inorganic and polymer components, such as particles and gauzes, have demonstrated impressive synergistic effects. Second, the reversible hemostatic materials are striking. Examples include liquid-to-hydrogel materials that can adapt to irregular shapes and firmly adhere to the wound, while powder-to-hydrogel materials that can simultaneously absorb the water in blood and promote wound healing.

The creation of hemostatic materials is now more intelligent and increasingly concentrated on post-hemostasis management, including drug delivery, tissue regeneration, and detection. For example, after hemostasis, the material should enable in situ tissue regeneration, providing surgeons and patients with a great deal of convenience. Additionally, the material can track important physiological parameters like pH level, blood pressure, blood flow rate, etc. through logical design and interdisciplinarity.

Although numerous studies have demonstrated the excellent hemostatic effect, it is still necessary to further investigate how different kind of the materials affect the hemostatic process.

The hemostatic materials' clinical transformation lags behind their basic research. In general, materials with few, basic components are better for transformation, but this has increased the need for careful planning in their design.

Finally, the molecular structures and forms of hemostatic materials should receive more consideration during design. It is important to thoroughly investigate how the components interact with the coagulation process. It is anticipated that appropriate designs for hemostatic materials will enable rapid development from the lab to the patient bed.

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АУҚЫМДЫ ҚАН КЕТУДІ ТОҚТАТУДЫҢ ӘДІСТЕРІ МЕН ИННОВАЦИЯЛЫҚ ТӘСІЛДЕРІ

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Түйінді

Бақыланбайтын қан кету бес минуттан аз уақыт ішінде өмірге қауіп төндіретін жарақатқа айналуы мүмкін. Бұл жұмыстың мақсаты-жаппай қан кетуді тоқтату үшін гель жасаудың перспективалық технологияларына шолу. Биополимерлер-бұл бірнеше полисахаридтер мен полипептидтерді қамтитын табиғи қосылыстар. Олардың ерекше молекулалық құрылымы мен биологиялық белсенділігінің арқасында олар биомедициналық зерттеушілердің қызығушылығын тудырды және терапевтік өзгерістердің жоғары әлеуетін көрсетті. Биополимерлер синтетикалық полимерлермен және бейорганикалық гемостатикалық материалдармен салыстырғанда гемостазға алғашқы көмек көрсетуде жоғары биологиялық ыдырау қабілетін, сенімді биоүйлесімділігін және экзотермиялық емес реактивтілігін көрсетті. Биополимерлердің функционализациясының өсіп келе жатқан маңыздылығын ескере отырып, біз полимерлердің биоадгезия, зарядты ынталандыру және функционалдық топтар мен прокоагулянт иондарын қосу сияқты функционалдық қасиеттеріне негізделген модификациясын зерттедік. Көптеген зерттеулер тамаша гемостатикалық әсерді көрсетті, дегенмен әртүрлі материалдардың гемостаз процесіне қалай әсер ететінін одан әрі зерттеу қажет. Гемостатикалық материалдардың клиникалық трансформациясы олардың іргелі зерттеулерінен артта қалды. Жалпы алғанда, негізгі компоненттері аз материалдар трансформацияға жақсы жауап береді, бірақ бұл оларды жобалау кезінде мұқият жоспарлау қажеттілігін арттырды. Соңында, жобалау кезінде гемостатикалық материалдардың молекулалық құрылымдары мен формаларына көбірек назар аудару керек. Компоненттердің коагуляция процесінде қалай әрекеттесетінін мұқият зерттеу маңызды. Гемостатикалық материалдардың тиісті конструкциялары зертханалық әзірлемелерден пациенттің төсегіне жылдам өтуге мүмкіндік береді деп күтілуде.

Кілт сөздер: *қан кету, биополимерлер, қан құйылу, гемостатикалық материал, гемостаз механизмдері, полисахаридтер, полипептидтер.*

МЕТОДЫ И ИННОВАЦИОННЫЕ ПОДХОДЫ ДЛЯ ОСТАНОВКИ ОБШИРНОГО КРОВОТЕЧЕНИЯ

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Аннотация

Неконтролируемое кровотечение может стать опасной для жизни травмой менее чем за пять минут. Целью данной работы является обзор перспективных технологий создания геля для остановки массивного кровотечения. Биополимеры - это природные соединения, которые включают в себя несколько полисахаридов и полипептидов. Благодаря своей особой молекулярной структуре и биологической активности они вызвали любопытство биомедицинских исследователей и продемонстрировали высокий потенциал для терапевтических изменений. Биополимеры продемонстрировали превосходную способность к биологическому разложению, надежную биосовместимость и неэкзотермическую реактивность при оказании первой помощи при гемостазе по сравнению с синтетическими полимерами и неорганическими кровоостанавливающими материалами. Учитывая растущую важность функционализации биополимеров, мы исследовали модификацию полимеров на основе их функциональных свойств, таких как биоадгезия, стимуляция заряда и включение функциональных групп и ионов-прокоагулянтов. Многочисленные исследования продемонстрировали превосходный гемостатический эффект, однако все еще необходимо дальнейшее изучение того, как различные виды материалов влияют на процесс гемостаза. Клиническая трансформация гемостатических материалов отстает от их фундаментальных исследований. В целом, материалы с небольшим количеством базовых компонентов лучше поддаются трансформации, но это увеличило необходимость тщательного планирования при их проектировании. Наконец, при проектировании следует уделять больше внимания молекулярным структурам и формам кровоостанавливающих материалов. Важно тщательно изучить, как компоненты взаимодействуют в процессе коагуляции. Ожидается, что соответствующие конструкции кровоостанавливающих материалов позволят быстро перейти от лабораторных разработок к постели пациента.

Ключевые слова: *кровотечение, биополимеры, кровоизлияние, гемостатический материал, механизмы гемостаза, полисахариды, полипептиды.*

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НОВЫЙ ПРОТИВОТУБЕРКУЛЕЗНЫЙ ПРЕПАРАТ ПРЕТОМАНИД ДЛЯ ЛЕЧЕНИЯ ЛЕКАРСТВЕННО-УСТОЙЧИВОГО ТУБЕРКУЛЕЗА (ОБЗОР)

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Аннотация

В обзоре использовано 61 источников литературы, посвященных новому противотуберкулезному препарату PA-824-претоманиду, который проявляет антимикробную активность против штаммов микобактерии туберкулеза с лекарственной устойчивостью. Согласно изученным данным, комбинации претоманида с другими химиопрепаратами высокоэффективны и перспективны при проведении лечения пациентов с лекарственно-устойчивым туберкулезом.

Ключевые слова: *туберкулез, лекарственно-устойчивый туберкулез, претоманид, противотуберкулезные препараты, химиотерапия.*

Введение. История химиотерапии туберкулеза началась в XX веке с открытия стрептомицина. В 1941 году американским микробиологом Зельманом Ваксманом был выделен актиномицин, обладавший токсическими свойствами. Два года спустя, в 1943 году под руководством Ваксмана Альберт Шац синтезировал стрептомицин — антибиотик, оказавшийся эффективным в отношении возбудителя туберкулёза. С 1946 года антибактериальный препарат стал широко использоваться для борьбы с туберкулёзом. Интересно отметить, что в первые несколько лет применения стрептомицин обладал крайне высокой противотуберкулёзной активностью: даже смыв с флакона, где до этого находился лиофизат препарата, давал клинический эффект [1]. К концу XX века спектр антибактериальных препаратов, применяемых во фтизиатрии, значительно расширился. Было открыто множество противотуберкулезных препаратов (ПТП): ПАСК, изониазид, циклосерин, амикацин, канамицин, рифампицин, этионамид, капреомицин, этамбутол, пиразинамид.

С середины XX века химиотерапия (ХТ), бесспорно, стала занимать ведущее место в лечении туберкулеза. Основная ее задача – добиться не только прекращения бактериовыделения, но и полной ликвидации клинических проявлений болезни, стойкого заживления туберкулезных изменений в пораженном органе, а также максимального восстановления нарушенных функций организма. Терапевтический эффект ХТ обусловлен антибактериальным действием ПТП и направлен на подавление размножения микобактерий туберкулеза