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Inorganic hemostats: The state-of-the-art and recent advances

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ABSTRACT

Hemorrhage is the most common cause of death both in hospitals and on the battlefield. The need for an effective hemostatic agent remains, since all injuries are not amenable to tourniquet use. There are many topical hemostatic agents and dressings available to control severe bleeding. This article reviews the most commonly used inorganic hemostats, subcategorized as zeolite and clay-based hemostats. Their hemostatic functions as well as their structural properties that are believed to induce hemostasis are discussed. The most important findings from *in vitro* and *in vivo* experiments are also covered.

Contents

1. Introduction

Irrepressible bleeding can result in mortality but can also debilitate the process of wound healing and increase the possibility of infection

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[1,2]. In the recent conflicts in Iraq and Afghanistan, exsanguinating hemorrhage accounted for almost 50% of the combat fatalities before evacuation [3]. Uncontrollable hemorrhage is the second leading cause of death in civilians and the most common cause of mortality during orthopedic, cardiovascular, hepatic and spinal surgeries [4,5]. Blood clotting disorders such as hemophilia can complicate hemostasis [6–8]. An ideal hemostatic agent should not only stop the flow of bleeding within minutes but should be bacteriostatic and/or bactericidal [9]. Furthermore, safety, efficacy, usability, cost-effectiveness, approvability, ease of manufacturing, absorbability and minimal tissue reactivity are other parameters which should be considered when selecting an appropriate hemostatic agent [10,11]. Although a large variety of hemostatic products have been developed and marketed in the last few decades, many of the materials fail to meet all of these requirements, and so the search for the ideal hemostatic agent continues. Over the past decade, the Committee on Tactical Combat Casualty Care (CoTCCC) has added hemostats based on inorganic species to the official guidelines since the products were found to be superior to other hemostatic agents. The CoTCCC now considers some of these dressings as the hemostatic agents of choice to control life-threatening hemorrhages which are not amenable to tourniquet application [12].

Notably, a variety of inorganic materials have been developed that can accelerate the coagulation of the blood, including zeolites and clays. Hemostats based on these materials have high utility because the materials are free of animal or human derived proteins which can lead to allergic reactions. In this review, after discussing the basic principles of hemostasis, inorganic coagulation accelerators such as zeolites and clays will be considered. A critical overview of their mechanisms of action is discussed as well as the structural features that are believed to stimulate hemostasis. This review also collates the findings on the most effective inorganic hemostatic agents in both human and animal trials.

2. An overview of hemostasis

The clotting process, or hemostasis, is a physiological process that prevents blood loss through the formation of a stable hemostatic clot at the site of bleeding [13]. It is a complex mechanism that involves the coordinated activation of various plasma proteins, platelets, cells and coagulation factors which are generated from the liver and enter the blood circulatory process in an inactive state [13,14]. These factors can activate each other when the coagulation cascade is started and according to their function, can initiate and complete each step of the coagulation process [15]. Overall, hemostasis takes place via the synchronized action of three mechanisms: (1) vasoconstriction; (2) formation of a platelet plug; and (3) blood clotting. When injury to a blood vessel occurs, a reflex local contraction of vascular smooth muscle is triggered that leads to vasoconstriction. This action compresses the blood vessels, retarding blood flow and limiting blood loss. At the same time, when the blood is exposed to collagen fibers in the basement membrane of the vessel, platelets stick to the collagen and become activated, releasing various chemicals such as adenosine diphosphate, thromboxane and serotonin, which enhance further vasoconstriction as well as platelet aggregation over the injured surface [16]. This phase of hemostasis is short-term, and ultimately results in primary hemostatic plug formation [17]. In the next stage, secondary hemostasis, the soft platelet plugs cross-link to form a stable and permanent plug. This occurs throughout the coagulation cascade and involves a series of plasma proteins, coagulation factors, calcium ions (Ca^{2+}) and platelets that lead to the conversion of fibrinogen into fibrin. The coagulation cascade is divided into two basic pathways; intrinsic pathway (contact activation), and extrinsic pathway (tissue factor). The details of the coagulation cascade are indicated schematically in Fig. 1.

The extrinsic pathway or tissue factor pathway is initiated by a tissue factor (tissue thromboplastin, factor III), a protein that is not present in the blood, but is released from the vessel walls and the surrounding tissue upon vascular insult [18]. In contrast, the intrinsic pathway or contact activation pathway is triggered by factor XII, an enzyme that is activated by contact of the blood with a foreign surface. Ultimately, these two pathways assemble into a common pathway and lead to the activation of factor X, an enzyme that cleaves prothrombin to thrombin in the presence of Ca^{2+} and factor Va,a cofactor that in the presence of Ca^{2+} forms the prothrombinase complex, a complex responsible for the rapid conversion of prothrombin to thrombin [15,19]. Thrombin not only transforms the soluble plasma protein fibrinogen into the insoluble protein fibrin but also activates factor XIII in the form of XIIIa, an enzyme that facilitates the adherence and cross-linking of the fibrin proteins together, subsequently forming a reinforced plug. As will be shown in the following sections, inorganic hemostats perform their actions through enhancing one or more of the above processes. Specifically, they work through three mechanisms (Table 1):

1. Absorbing water from the blood and concentrating the blood components at the hemorrhagic site: materials with this ability are called factor concentrators.
2. Activating the blood coagulation cascade: materials with this ability are called procoagulants.
3. Providing a physical barrier to blood flow by cross-linking cellular blood components: materials with this ability are called mucoadhesives.

Table 1 summarizes which of these phenomena contributed to the hemostatic action of zeolite and clay-based hemostats, as described in the following section.

3. Zeolite

Zeolites, microporous crystalline aluminosilicate minerals, are found in nature and are considered “molecular sieves” of a family of porous solids [20]. The structural framework of a zeolite is based on tetrahedral units of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ that are co-ordinated via shared oxygen atoms (Fig. 2).

Zeolites possess cage-like cavities that can accommodate both water molecules and a variety of positively charged ions such as Ca^{2+} and sodium (Na^{+}). The cations are relatively loosely held, so that they can exchange with other cations in contact with physiological solutions [21]. Zeolites are chemically similar to clay minerals (both are aluminosilicates) but they are structurally different. Clay minerals with a layered crystalline structure can shrink and swell as water is eliminated and absorbed, respectively, between the layers. By contrast, zeolites contain interconnected channels in a rigid, 3-dimensional crystalline structure which facilitates the movement of water molecules in and out of their pores while remaining rigid [22]. Zeolites offer long-term physical and chemical stability, an ability to exchange ions with the surrounding solutions; they have no biological toxicity and are capable of absorbing high amounts of water. These features make the materials valuable candidate for hemostatic applications [23–28]. The accelerated coagulation response induced by zeolites is dependent on multiple factors [29].

Zeolites can entrap large volumes of water within their pores due to the electrostatic interaction between water and the Ca^{2+} that reside in open porous internal space. As a result, they concentrate coagulation factors and platelets in the hemorrhaging blood (Fig. 3) [27,30].

Zeolites can also function with the body's own coagulation cascade and speed up the intrinsic pathway of blood coagulation through releasing Ca^{2+} [27]. Ca^{2+} (known as clotting factor IV) play key roles in the immobilization and orientation of clotting enzymes on cellular surfaces, since they serve as the ionic bridge between two negatively charged residues (e.g. cellular surface and clotting factors) [31]. The ions are consumed within thrombosis and fibrinolysis when fibrin and negatively charged glycosylated residues are cross-linked by factor XIII [32]. Hence, the presence of these ions can stimulate the activation of the intrinsic pathway and accelerate the generation of required thrombin for fibrin production [32,33].

Zeolite is marketed as QuikClot granular powder (QC, Z-Medica Corporation, Wallingford, CT), Advanced Clotting Sponge (ACS, Z-Medica,

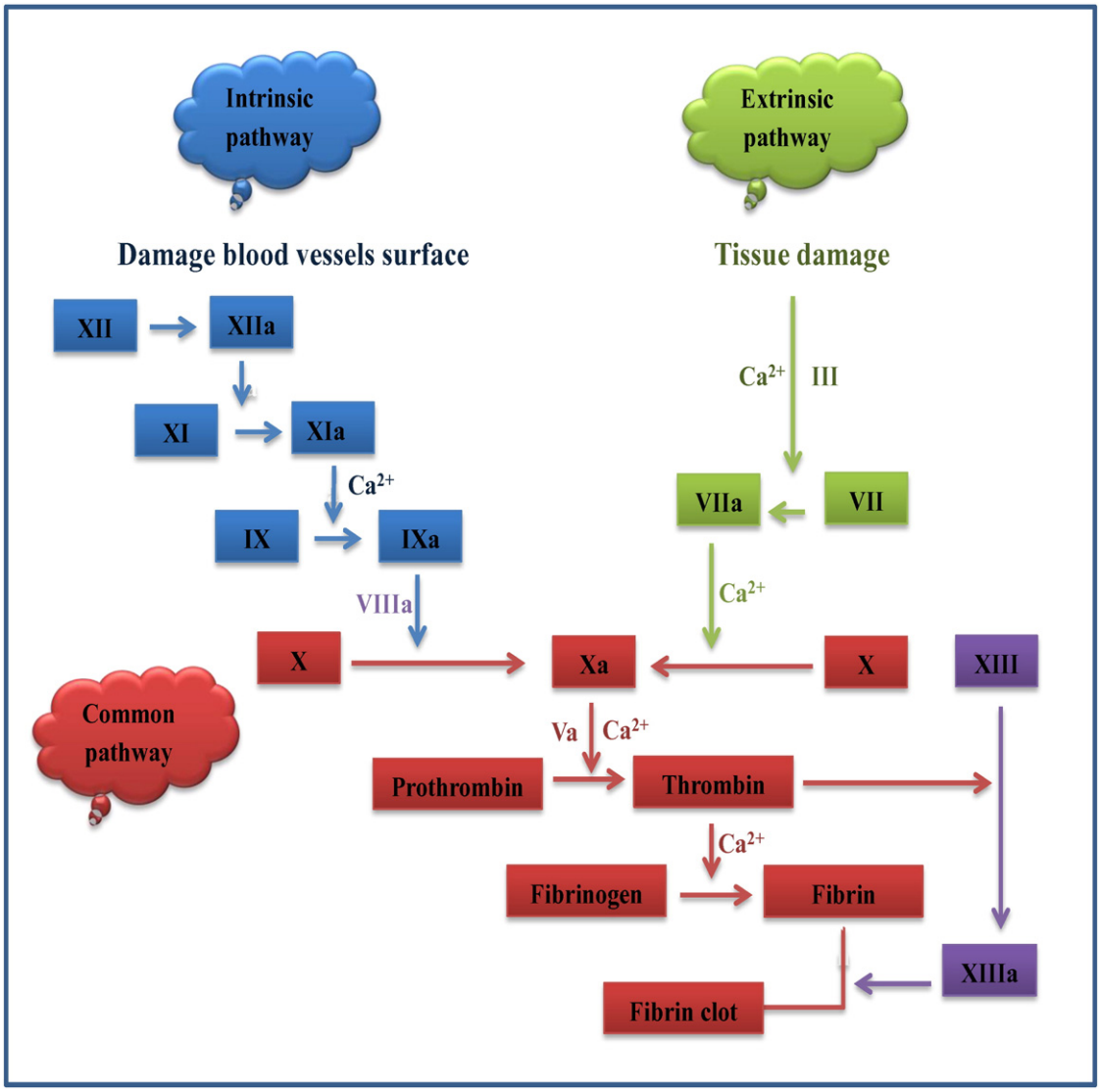

Fig. 1. Schematic of the coagulation cascade. Activation of both intrinsic and extrinsic pathways leads to the fibrin clot formation in the common pathway.

Newington, CT, USA) and Advanced Clotting Sponge plus (ACS+, Z-Medica, Newington, CT, USA).

3.1. QuikClot granular powder (QC)

QC was approved by the FDA for external application in 2002 [34]. This product consists of granular zeolite powder with 1% residual moisture. QC is a factor concentrator that works via rapid absorption of the water content of the blood, concentrating platelets, blood cells, and clotting factors at the site of injury, thereby promoting coagulation [1,29,35]. QC is biologically inert and sterile and so the possibility of allergic reactions or viral infection transmission is minimal [36]. QC can be applied as a first aid kit to arrest bleeding from injuries within both combat and noncombat field operations, where other conventional treatments have failed [2,37].

Table 1
Mechanism of action of inorganic hemostats according to the literature.

	Factor concentrator	Procoagulant	Mucoadhesive
QuikClot granular (QC)	✓		
Advanced Clotting Sponge (ACS)	✓		
Advanced Clotting Sponge plus (ACS+)	✓		
QuikClot Combat Gauze (QCG)		✓	
QuikClot Combat Gauze XL (QCX)		✓	
QuikClot Combat Gauze Trauma Pad (QCTP)		✓	
QuikClot Interventional (QCI)		✓	
WoundStat (WS)		✓	✓

3.1.1. QC in vivo animal tests

Alam et al. assessed the hemostatic performance of QC in a groin injury porcine model against other hemostats, Rapid Deployment Hemostat bandage (RDH, polysaccharide, Marine Polymer Technologies, Cambridge, MA), TraumaDEX (TDEX, polysaccharide, Medafor Inc., Minneapolis, Minnesota) and a control (no dressing) [38]. QC had superior efficacy compared to the other dressings; it was the only agent that resulted in 0% mortality [38]. QC was also tested in a liver injury swine model and produced the lowest blood loss compared with gauze (1397 ml versus 5338 ml respectively) [39]. Seven out of eight QC-treated animals survived, whereas the number of survived subjects in the gauze group was one out of eight. Margulis et al. employed QC in a laparoscopic partial nephrectomy porcine model [36]. In this study, QC conferred an immediate and continuous hemostasis [36]. A comparative study performed by Kozen et al. to evaluate the efficiency of QC in a fatal

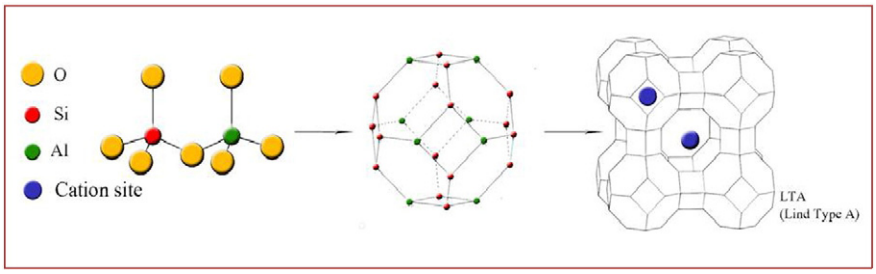

Fig. 2. The zeolite structure.

hemorrhagic groin injury [40] found that QC was more effective in cases of moderate bleeding than HemCon (HC, chitosan wafer dressing, HemCon Inc., Portland OR) and standard dressing (SD, control) [40]. QC improved survival significantly compared with these dressings. The failure of HC was attributed to its adhesion to the soft tissue surrounding the vessels so that it was not capable of sealing the actual vascular injury. However, Acheson et al. tested three different hemostatic products, QC, HC and fibrin sealant dressing (FSD, Fort Detrick, MD) as compared with Army Field Bandage (AFB, control) in a porcine arterial hemorrhage model and identified FSD as the superior hemostatic agent. QC was ineffective in controlling hemorrhage because it was washed away from the wounded area resulting in unopposed bleeding (hemostasis rate was 0%) [41].

3.1.2. QC in humans

Wright et al. have described the hemostatic ability of QC in a multiple gunshot victim who suffered from hypothermia, acidosis, and coagulopathy which were not amenable to conventional treatment [42]. QC achieved hemostasis with no evidence of hypothermic injury. One case study considering treatment of an uncontrollable pelvic bleeding with QC was reported by Shanmugam and Robinson [43]. Here, QC resulted in complete hemostasis where other measures such as packing, drawing pins, stenting and embolization failed to control bleeding. A comprehensive analysis on the effectiveness and suitability of QC was also reported by Rhee et al. in 103 patients sourced from US military and civilian personnel [44]. QC was used in both external (head, neck, buttock, groin) and intracorporeal (chest, abdomen, pelvis) locations (Fig. 4).

QC controlled bleeding in 92% of cases and had 100% efficacy when applied by first responders. However, eight failures were observed and thought to be due to both the inability to apply the product to the wound site alongside the coagulopathy state of the patients [44]. A serious adverse effect of QC is burning of the surrounding tissue at the bleeding site [41,44–47] believed to be related to QC trapping water molecules into its pores via an exothermic reaction which increased local tissue surface temperatures by as much as 90 °C [48,49]. Wright et al. demonstrated that QC in a swine injury model led to increased temperature at both the tissue surface and internal to the tissue, at about 95 °C and 50 °C, respectively, which caused thermal injury and necrosis to the surrounding tissues alongside impairment to the wound healing process [48]. McManus also reported thermal injuries resulting in the application of QC to four patients; the partial thickness of burning was 1–2% total body surface area [50]. According to the evidence gathered in Iraq, another adverse effect associated with the use of QC is related to its granular nature that makes it unsuitable for high pressure bleeding as it can be flushed out or blown away from the wound site through heavy blood flow [46]. The difficulty of removing QC at the site of bleeding because of its granular nature is an additional concern that may result in inflammatory granuloma formation [51]. QC was removed from military inventory in 2008, but a

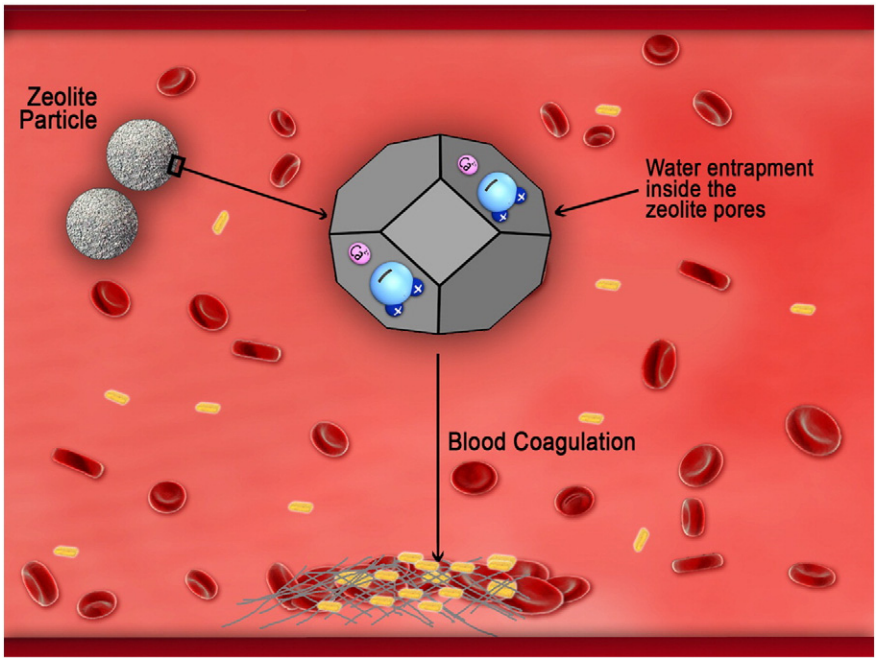

Fig. 3. Summary of the potential hemostatic effects of zeolite. This schematic captures the effects of zeolite on the blood coagulation through absorption of water molecules into its pores resulting from the interaction with Ca^{2+} residing into zeolite pores. The interaction leads to concentrating the blood cells and clotting factors and promoting hemostasis.

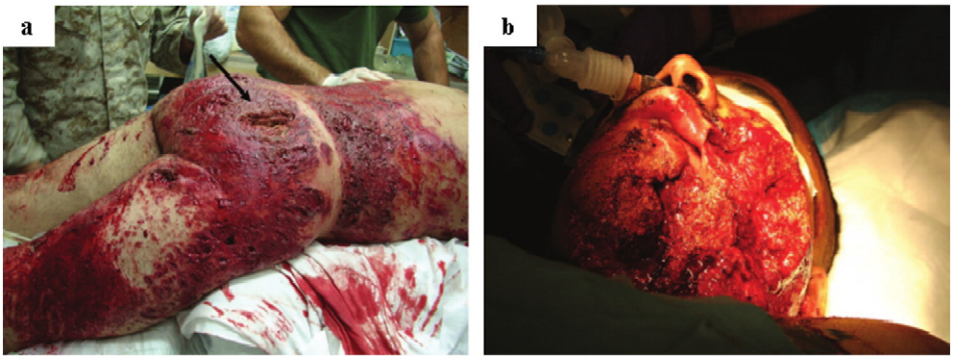

Fig. 4. QC showed high hemostatic performance (a) in a soldier who suffers from a severe gluteal wound caused by improvised explosive devices in the military and also (b) in a sailor who experienced extreme lacerations on his face via a rotor blade from a helicopter [44].

newer generation of zeolite hemostats such as the ACS and ACS+ has been commercialized and these are compositionally similar to QC.

3.2. Advanced Clotting Sponge (ACS)

ACS received FDA approval in 2005 for external use [51]. ACS is similar to QC but consists of larger beads of the zeolite which are packaged in a gauze [52]. ACS is a factor concentrator and shares a similar mechanism of action to QC [29]. It is reported to be more effective than QC, especially when it comes to irregular cavities and perfuses hemorrhage and it achieves effective hemostasis without being freely distributed into the wound. The product is also easier to remove than QC [37].

3.2.1. ACS in animal models

ACS was as effective as QC in prompting hemostasis and prolonging survival time [35,38,53,54]. ACS controlled blood loss and improved survival in a groin injury swine model. Both agents outperformed SD with a 75% survival rate [53]. However, a dramatic increase in wound temperature was noted in QC and ACS-treated animals (58.1 °C and 58.2 °C respectively) compared with SD-treated animals (38.8 °C) which caused some localized edema. To overcome this, the literature suggests that altering the chemical composition of zeolite may be useful [55,56]. Ahuja et al. prepared sodium-exchanged QC (Na-QC), barium-exchanged QC (Ba-QC) and silver-exchanged QC (Ag-QC) through immersion of QC in aqueous solutions of sodium chloride (NaCl), barium nitrate ($Ba(NO_3)_2$) and silver nitrate ($AgNO_3$) respectively. The modified QC compositions were packaged in airtight mylar foil packages and their hemostatic properties were compared to ACS, HC, SD and non-dressing (ND) groups in a severe groin injury swine model [56]. Based on the results, the modified QCs were found to be more effective in inducing hemostasis and improving survival as compared with ND and SD groups. The modified materials dramatically declined the temperature peak by 5–10 °C at the wound site in comparison with ACS and no evidence of tissue necrosis was observed [56]. Nevertheless, the peak temperatures in these groups were still significantly higher compared with the ND, SD, and HC groups. However, Alam et al. claimed that, when the zeolite beads are packaged into a loose mesh bag, as with ACS, efficacy may be decreased since the bag acts as a barrier against achieving hemostasis [35]. Although ACS was superior to QC in controlling hemorrhages, there was still heat generation at the bleeding site which led to tissue damage [38,53]. This problem was addressed by pre-hydrating the zeolite so that it could absorb water less exothermically. The modified formulation was commercialized as ACS+.

3.3. Advanced Clotting Sponge plus (ACS+)

ACS+ gained FDA approval for external usage in 2006. It consists of synthetic zeolite beads packaged into loose mesh bags similar to that of ACS, the difference being that the zeolite is preloaded with some water (hydration) [57]. Similar to ACS and QC, ACS+ has no intrinsic hemostatic property and works as factor concentrator [35,58]. ACS+ does not have the damaging thermal profile of QC and ACS, and is easier to handle and remove [38,53]. However, it is no more effective than QC and ACS in the management of arterial hemorrhage [59].

3.3.1. ACS+ in animal models

Arnaud et al. compared the temperature change and the hemostatic efficacy of ACS+ with ACS and SD in a swine model of lethal groin injury and concluded that ACS+ is superior to ACS as it was less exothermic at the site of injury. Compared with SD, it exhibited comparable efficacy in arresting hemorrhage [52]. ACS+ outperformed SD in a femoral arterial injury model in terms of controlling bleeding and improving survival (60% versus 13%) [60]. Although, ACS+ is only FDA approved for external use, it has shown promise in a Grade IV liver injury swine model where it resulted in significantly mean lower total blood loss than using gauze control (4.6 ml/kg compared to 8.3 ml/kg) [58]. Histopathological findings also did not reveal any significant difference in the amount of necrosis between the groups [58]. Eryilmaz et al. demonstrated the beneficial effect of ACS+ in an extremity arterial injury swine model in providing hemostasis in comparison with the SD (control group) [61]. However, Kheirabadi et al. examined ACS+ in an extremity arterial hemorrhage swine model and found that although the application of ACS+ resulted in no thermal injury at the bleeding site, it was found to be ineffective for hemostasis [59]. Rhee et al. in their studies concerning 103 documented military and civilian cases reported that ACS+ failed to control hemorrhage in a patient who suffered a fracture at the femoral neck resulting from a high-velocity bullet [44]. The ineffectiveness of ACS+ was attributed to the nature of the wound which makes the product unable to reach the source of hemorrhage [44].

3.4. Other zeolite-based hemostats

Other commercial zeolite-based hemostats include QuikClot 1st Response™, QuikClot Sport™ and QuikClot Sport Silver™, which reportedly have less side-effect than QC. Their active ingredients are placed inside a porous mesh bag resulting in cleaner application and the ability to apply direct manual pressure to the dressing and wound. QuikClot Sport Silver™ offers antibacterial activity for external applications and does not cause burning to the wound site [62]. As stated previously, when zeolite-based hemostats come into contact with the blood, positively charged Ca^{2+} in the powder are released immediately in the blood stream and the electrostatic attraction between water molecules in the blood and the Ca^{2+} which reside in open porous internal space result in heat generation [56]. Replacing some of the Ca^{2+} with some ions such as silver not only decreases heat generation at the wound area but offers anti-bacterial activity. Studies relating to zeolite-based agents are shown in Table 2.

Table 2
Studies relating to zeolite-based hemostatic agents.

References	Model	Hemostatic agents	Treatment groups	Survival	Blood loss	Wound temperature (°C)	Remarks
[63]	Massive splenic injury in 40 rats	QC	QC	237.5 min	14.1%	38.7	QC application resulted in desirable hemostasis and improved survival. Combination of RL and QC reduced blood loss and improved survival than RL alone. However, increased body temperature was observed in the QC-treated groups.
			RL	92.2	61.8%	–	
			QC + RL	233.3	27.4%	39	
			ND	153.9	33.69%	–	
[38]	A complex groin injury in 30 Yorkshire swine	QC	QC	100%	4.4 ml/kg	42–44	Among the hemostatic agents tested, QC was found to be the most effective agent in this model.
		RDH	RDH	33.4%	~15	–	
		TDEX	TDEX	66.6%	~13	–	
			SD	66.6%	~12	–	
			ND	17%	~22	–	
[40]	A complex groin injury in 48 swine	QC	QC	92%	8%	61.0	QC achieved hemostasis with greater efficacy in comparison with HC and SD. However, thermal injury resulting from QC use was observed.
		CX	CX	100%	0%	37.6	
		HC	HC	67%	33%	38.2	
			SD	50%	83%	38.8	
[41]	Femoral artery injury in swine	QC	QC	0%	59.7 ml/kg	70.8	No hemostatic advantage was seen for QC than AFB. In addition, the exothermic reaction of QC with the blood produced high temperatures at the bleeding site causing localized tissue damages
		HC	HC	0%	86.8	37.1	
		FSD	FSD	66.6%	40.8	36.8	
			AFB	0%	64.2	36.9	
[53]	A groin injury in 32 swine	ACS	ACS	75%	10.3%	37.8	ACS was equally efficacious as QC in hemostatic properties. It offers easier application and removal compared with QC.
		QC	QC	75%	7.4%	58.2	
			SD	12.5%	22.3%	58.1	
			ND	0%	31.5%	37.5	
[56]	A complex groin injury in 60 swine	ACS	ACS	90%	10.3 ml/kg	55.3	The modifications in the chemical composition of zeolite decreased the exothermic reaction and attenuated heat induced tissue damage.
		CD	HC	75%	~12	~37	
		Na-QC	Na-QC	57%	~16	~52	
		Ba-QC	Ba-QC	75%	~10	~50	
		Ag-QC	Ag-QC	75%	~13	49	
		SD	SD	50%	~17	~37	
			ND	0%	~19	~37	
[52]	A groin injury in 33 Yorkshire pigs, including transection of both femoral artery and vein	ACS ACS+	Evacuated wound:				The authors conducted 2 studies: 1 in evacuated wound (blood removed from the wound) and non-evacuated wound (blood in the wound). The lower heat release was associated with ACS+. Wound temperature in evacuated wound was significantly lower with ACS+ treatment with respect to ACS treatment.
			ACS	63.6% 134 min	18.8%	61.4	
			ACS+	100% 180 min	18.2%	40.3	
			SD	12.5% 97 min	22.3%	38.0	
			Non-evacuated wound:				
			ACS	67% 131 min	8.7%	50.8	
			SD	25% 105 min	21.85	–	
[58]	A grade IV liver injury in 33 swine	ACS+ CX			Blood loss at 2 min:		Application of ACS+ achieved 100% survival and no significant difference was seen between groups in the extent of necrosis. However, the body core temperature declined further from 35.0 °C at the time of injury to 34.2 °C on closure.
			ACS+	100%	4.0	34.2	
			CX	81.8%	3.5	–	
			GC	72.7%	4.0	–	
					Blood loss at 10 min:		
			ACS+		4.6 ml/kg		
			CX		3.7		
			GC		8.3		
[61]	Arterial injury in 16 swine	ACS+					ACS+ was found to be more effective in reducing blood loss. However, peak heat production was observed immediately after 5 min. In the following, the heat production significantly decreased at 15 min.
						After 5 min:	
			ACS+	100%	1100 ml	~80	
			SD	100%	2800	~29	
						After 15 min:	
			ACS+			~30	
			SD			~28	

Agents defined: QuikClot (QC); lactated Ringer's solution (RL); Rapid Deployment Hemostat bandage (RDH); TraumaDEX (TDEX); standard dressing (SD); non-dressing (ND); Celox (CX); HemCon (HC); fibrin sealant dressing (FSD); Army Field Bandage (AFB); Advanced Clotting Sponge (ACS); gauze control (GC); Advanced Clotting Sponge plus (ACS+).

Zeolite-based hemostats, while offering improved hemostatic capability in lethal hemorrhage animal models and in some clinical studies, failed to meet all of the qualifications of the ideal hemostatic agent. The major concerns with the original QC were the difficulty in removing it and the exothermic reaction produced which led to tissue damage at the application site. Although the safety concerns were addressed by the introduction of the newer product (ACS+), which produced minimum exothermic reaction and was easy to use and remove, the product has not been found to be effective against arterial bleeding. Thus, this generation of hemostats was replaced by second-generation dressings such as clay materials which are reportedly more efficient in controlling hemorrhage.

4. Clay-based hemostatic agents

Clay minerals are hydrous aluminum silicates consisting of tetrahedral silicate sheets and octahedral aluminate sheets [64]. Based on the ratio of tetrahedral to octahedral sheets, these clays can be classified into two groups, 1:1 clay and 2:1 clay [65,66]. Clay 1:1 is comprised of one silica tetrahedral layer to one aluminum octahedral layer such as kaolin while 2:1 clay consists of an octahedral sheet sandwiched between two tetrahedral sheets such as smectite (Fig. 5).

Clays have high thermal stability, large specific surface area, small particle size, unique crystal structures and significant surface charge as well as ion exchange capability. The materials are also expandable, due to water entrapment between the silicate sheets [66]. Clays can induce blood clotting and staunch blood flow when applied to a hemorrhaging wound [67].

4.1. Kaolin group

Kaolin is clay consisting of the mineral kaolinite and is a 1:1 clay [64]. The characteristics of kaolin include relatively low surface area, low cation exchange capacity and a minimal charge on the layer [68]. The absorption property and surface charge of kaolin are low which can be associated with low surface area and substitution of other elements (e.g. ferric iron and titanium) for Al and Si [68,69]. The efficacy of kaolin in the acceleration of the body's natural clotting ability was first recognized by Margolis [70]. Kaolin in contact with plasma can lead to the activation of the intrinsic blood coagulation cascade. There are several factors which cumulatively contribute to this ability of kaolin. It has been proven that the polar aluminosilicate framework of the kaolin provides an ideal surface for the contact activation of the intrinsic pathway of the blood clotting cascade, referred to as the "glass effect" (where blood coagulates quickly upon contact with polar glass-like surfaces compared with non-polar surfaces) [71]. The net negative surface charge of kaolin is also involved in triggering the intrinsic pathway of blood coagulation cascade by the autocatalytic activation of coagulation factors XII and XI along with prekallikrein and cofactor HWK–kininogen (Fig. 6) [72–75].

The principle behind such phenomena is that factor XII binds to a negatively-charged surface via positively charged amino acids in its heavy chain [76]. The binding supposedly leads to subtle conformational changes in FXII resulting in the formation of active FXIIa through auto-activation. This activated factor has been shown to directly contribute to fibrin formation [77,78]. Hence, the presence of the negative charge on the surfaces of kaolin is considered as a key contributor to the activation of clotting factor XII and subsequently the initiation of the intrinsic pathway of blood coagulation.

Kaolin has been marketed under various names including QuikClot Combat Gauze™ (QCG, Z-Media, Wallingford, CT), QuikClot Combat Gauze XL (QCX, Z-Medica, Wallingford, CT), QuikClot Combat Gauze TraumaPad (QCTP, Z-Medica Corporation, Wallingford, CT) and QuikClot® Interventional™ (QCI, Z-Medica Corporation, Wallingford, CT). The materials reportedly expedite hemostasis without the complications related to the previous product line. These products will be discussed in the following sections.

4.1.1. QuikClot Combat Gauze™ (QCG)

QCG is composed of rayon/polyester gauze impregnated with kaolin [79]. The dressing was approved by FDA for external application in 2013 [80]. QCG acts as a procoagulant; when it contacts the blood, kaolin immediately dissociates from the gauze and activates the intrinsic clotting cascade [70,75]. In comparison to granular agents, the application and removal of QCG are easily accomplished and require no additional procedures. As an effective, non-absorbable hemostatic dressing in the treatment of external wounds, QCG remains at the wound site for up to 24 h until further medical care can be provided [1,80]. Nonetheless, QCG, unlike other hemostatic dressings, does not provide immediate hemostasis and results in greater blood loss than many other agents [81,82]. The CoTCCC chose QCG for all military personal in 2008. It is also recommended as the first-line hemostatic agent

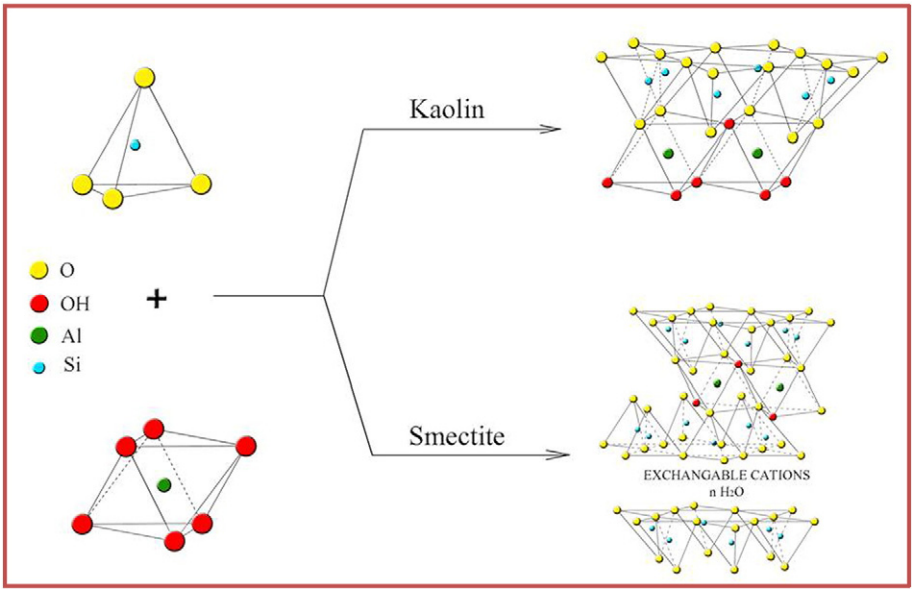

Fig. 5. The structure of kaolin and smectite.

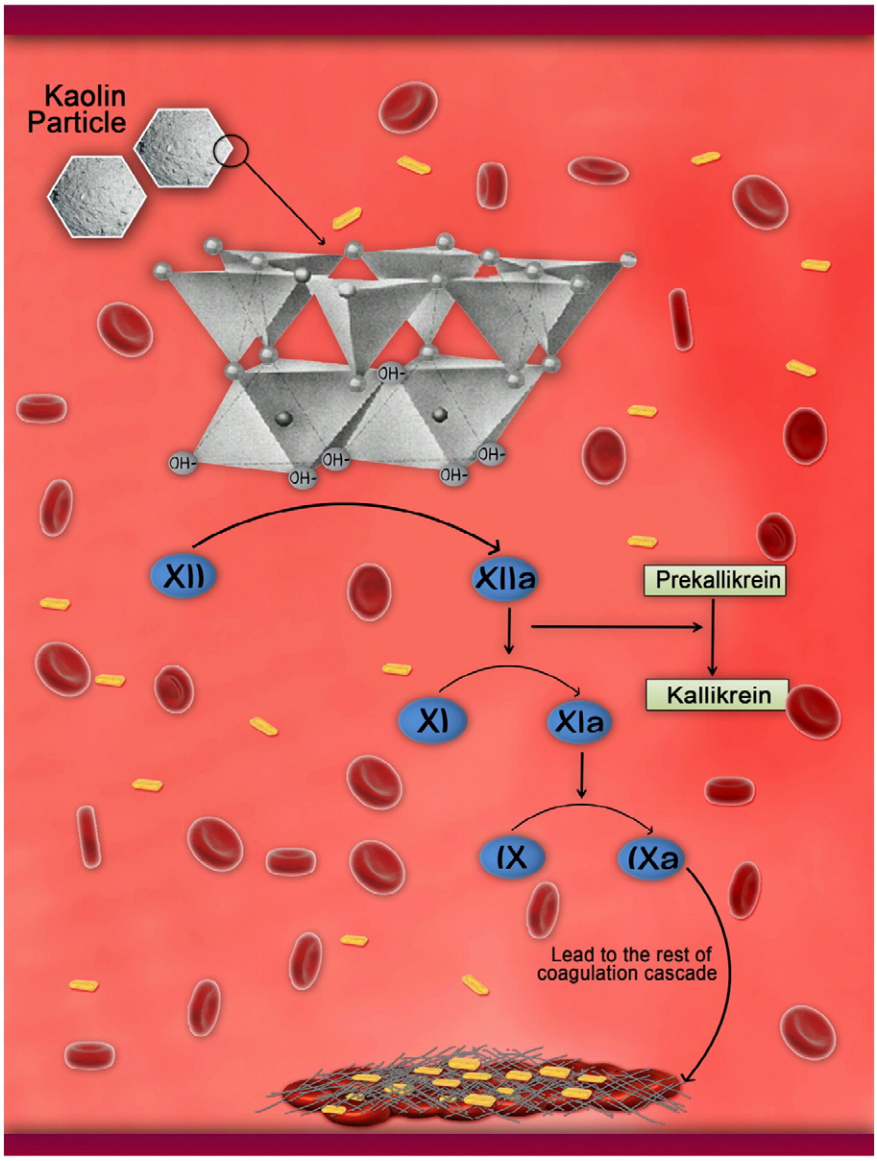

Fig. 6. Thrombogenic potential of kaolin and its impact on the blood coagulation cascade. This schematic represents the possible effects of kaolin on the activation of intrinsic coagulation pathway through its negative surface charge leading to activation of the coagulation cascade.

for life-threatening bleeding that is not controllable by tourniquet placement [83].

4.1.1.1. Animal studies of QCG. The superiority of QCG over the hemostatic dressings HC, TraumaStat (TS, OreMedix, Lebanon, OR, silica and chitosan-based dressing), Celox-D (CX, SAM Medical, Portland, OR, chitosan) and placebo QuikClot gauze (PG, without kaolin) was reported by Kheirabadi et al. using an arterial bleeding swine model [84]. QCG increased in vitro clotting rate and clot strength and reduced blood loss and demonstrated the highest survival rate (80%) compared to the competitors. The authors ascribed the QCG hemostatic ability to Kaolin's high surface area and flexibility as well as the type of gauze it was impregnated into [84]. Johnson et al. assessed the efficacy of QCG in femoral artery and vein injury swine models and compared it to a control group which received a standard wound packing with a layer of petroleum gauze and the roller bandage (Kerlix, Covidien, Mansfield, MA) [79]. QCG application not only markedly decreased the proportion of bleeding than control (50 ml compared to 351 ml) but also provided more latitude in the administration of fluid resuscitation. The results also demonstrated that the clots formed in the QCG group were more robust than the clots formed in the control group so that it increased the number of animal movement (3–40 versus 0–9 respectively) with less risk of re-bleeding [79]. As a result, QCG was considered an efficient hemostatic dressing.

As QCG is a procoagulant agent and its hemostatic function depends on the presence of inherent coagulation factors and the host clotting pathway, there remains some concern about the efficacy of the product in coagulopathic conditions [85]. In this regard, some animal studies have been performed to examine the effectiveness of QCG in both coagulopathy-induced animals (characterized as those that have huge hemorrhage and clotting factor depletion) and non-coagulopathy animal models. In a severe grade V liver injury swine model in which a hypothermic dilutional coagulopathy was induced, use of QCG decreased blood loss from 58 ml/kg in the standard packing group to 25 ml/kg. Based on histological examination, liver sections exposed to QCG were more likely to contain surface clots compared to those exposed to PG. There was no evidence of inflammatory response, tissue necrosis or residual material on the surface of the liver [80]. In a model of severe acidosis and coagulopathy, Causey's group also proved the utility of QCG, with a successful hemostasis rate of 93% and 100% on the first and second

applications, respectively. The efficacy of QCG compared to standard gauze (SG) was also confirmed by a thrombelastograph analyzer (TEG); a medical instrument that records viscoelastic changes in the blood during thrombosis and fibrinolysis. The clotting time declined in QCG-treated animals in comparison to the SG group (19.5 versus 52.33 s) [86]. However, efficacy of QCG was contradicted by Floyd et al. who reported 50% animal survival in a hemodilution coagulopathic swine model. This was confirmed on histopathological examination since clotting was only seen in two of the ten QCG-treated wounds [87]. The authors suggested that QCG may not be a reliable candidate for external application in coagulopathic combat casualties. However, differences in severity and mechanism of causing coagulopathy in the animals are likely to contribute to these contradictory findings [88].

4.1.1.2. Human studies of QCG. Ran et al. evaluated QCG during 'Operation Cast Lead' in the Gaza Strip in 2009 [89]. The dressing was used in 14 soldiers of the Israeli Defense Force (out of a total of 56 hemostatic interventions in 35 cases) who experienced injuries in their head, neck, axilla, buttocks, abdomen, back, and pelvis [89]. QCG achieved hemostasis with 79% efficiency (11 out of 14) and a survival rate of 93%. However, it failed to achieve hemostasis in three injuries (neck, buttock, and thigh) and this was associated with the severity of injuries in the soft tissue and vascular system as well as an inability for QCG to be delivered to the bleeding site [89]. Fedor also reported the influence of QCG in a patient with leech bites [90], where it was found to be an efficient adjunct for the treatment of bleeding. There was no evidence of re-bleeding and infection at the site of bleeding [90]. Another beneficial application of QCG was reported by Chávez-Delgado et al. [91] in a study of 230 patients undergoing tonsillectomy. QCG was seen to be more efficient than standard surgical cotton gauze (CG) in controlling surgical bleeding after tonsillectomy. At 5 min, QCG provided rapid and complete hemostasis in 84.8% of patients compared with 34.8% in the CG group [91]. Additionally, complete removal of the tonsils along with less blood loss and faster postoperative recovery was observed in QCG-treated patients compared to CG-treated patients (34.4 ml versus 54.6 ml respectively).

4.1.2. QuikClot Combat Gauze XL (QCX)

Similarly to QCG, QCX consists of hydrophilic gauze impregnated with kaolin. The only difference is that QCX offers a new large size gauze option (a two-ply gauze compared with single-ply gauze in QCG) with a higher kaolin content (approximately 2.7 times more kaolin than the original product) [92]. QCX causes hemostasis through the activation of the intrinsic clotting pathway and the production of hemostatic clots at the bleeding site [12]. The product is pliable, conforms to any wound shape and size, is easy to remove and is hypoallergenic. QCX is produced in large sample sizes as injuries have sometimes required two packs of QCG to treat a wound [93].

4.1.2.1. QCX in animal model. QCX has been successfully used in a swine arterial bleeding model, where it was compared with QCG and three chitosan-based gauzes namely CeloxGauze (CEL, MedTrade Products Ltd., Crew, UK), Celox Trauma Gauze (CTG, MedTrade Products Ltd., Crew, UK) and ChitoGauze (HCG, HemCon Medical Technologies Inc., Portland, OR) [92]. QCX and CTG outperformed QCG since they achieved immediate hemostasis in 80% and 70% of applications respectively compared to 30% with QCG [92]. QCX also resulted in a higher survival rate of 70% than the 60% found with QCG. The differences observed in hemostatic performance of QCG and QCX may be associated with the total mass of gauze or quantity of clotting agent [92]. Of particular note, however, is that both QCG and QCX did not create any significant tissue damage. The dressing demonstrated some endothelial cell loss near the injury site as well as minor necrosis of the muscle. There were no signs of lesion in any of the nerve tissue examined.

4.1.3. QuikClot Combat Gauze TraumaPad (QCTP)

QCTP consists of kaolin-impregnated gauze packaged into an easy-tear pouch and vacuum sealed. The presence of kaolin in the product strongly facilitates the coagulation process by the activation of the intrinsic pathway and decreasing the initial time of blood clot formation [86]. Thus, this clot activating function of kaolin establishes QCTP as an effective hemostatic agent.

4.1.3.1. QCTP in animal model. Although kaolin-based hemostats appeared to be ineffective for controlling hemorrhage in some coagulopathic animals, Kheirabadi et al. reported the successful use of QCTP to stop lethal coagulopathic bleeding in large soft tissue wounds when the agent was combined with negative-pressure wound therapy (NP) [94]. The results showed that the addition of NP to QCTP (QCTP + NP) reduced mortality to 10%, from 90% with QCTP (when it was used alone). This combination also produced a significant reduction in blood loss compared to QCTP alone (19 versus 97 ml/kg).

4.1.3.2. QCTP in human model. In a case analysis performed by Abbott et al. on 117 patients who experienced spinal deformity surgery [95], 52 patients underwent intraoperative packing with QCTP during the surgery and the rest received standard operative care with gauze packing (control group). The amount of blood loss and transfusion requirements decreased in the QCTP group (40% and 42% respectively) with respect to the control group. It was concluded that QCTP is a cost-effective and efficient agent to achieve hemostasis in patients undergoing spinal deformity surgery [95].

4.1.4. QuikClot® Interventional™ (QCI)

QCI comprises a kaolin-impregnated polyester gauze pad packaged in a foil pouch for aseptic removal. QCI is FDA approved as an adjunct to manual compression and is indicated for local management and for controlling bleeding at the vascular access site [96]. Since kaolin is a potent coagulation initiator, one would expect this material to have a hemostatic mode of action similar to that of other kaolin-based hemostats.

4.1.4.1. QCI in human models. A trial involving 120 patients undergoing coronary angiography or angioplasty found a hemostatic technique based on QCI utilization combined with short-time compression to be more effective than conventional compression techniques; short compression (group 1) and prolonged compression (group 2) both without QCI utilization for radial access closure [97]. The QCI achieved hemostasis and significantly reduced the risk of occurrence of radial artery occlusion (RAO) after percutaneous trans-radial coronary procedures. None of the patients in the QCI group developed RAO which occurred in 5% of patients in group 1 and 10% in group 2. Additionally, the rate of active bleeding after compression removal occurred in 20% of QCI-treated patients in comparison with 90% in group 1, and 2% in group 2 [97]. In another trial of forty patients undergoing diagnostic angiography or percutaneous coronary intervention via a femoral artery approach, hemostasis within 4.9 min was achieved in 97.5% of patients using QCI. Only one hemostasis failure occurred requiring extra compression time to achieve hemostasis [98]. The summary of results from studies relating to kaolin-based hemostats are presented in Table 3.

In summary, with respect to the outcomes from animal models and sparse clinical trial data, kaolin-based hemostatic agents deliver superior hemostatic power when compared to zeolite-based hemostats. The materials can promote hemostasis without complications as gauze rolls are highly efficacious hemostatic dressings for temporary treatment of external wounds [29]. Accordingly, the first kaolin-based hemostat; QCG was fielded from 2008 for all U.S. military personnel and NATO militaries as a primary hemostatic dressing. Though the hemostatic abilities of these inorganic materials are more pronounced than those of other hemostats, the main disadvantage of these dressings is that they may not stop bleeding immediately after the application and often require more than one application [103]. Another disadvantage

Table 3
Studies relating to kaolin-based hemostatic agents.

References	Model	Hemostatic agents	Treatment groups	Survival	Blood loss	Remarks
[84]	Femoral artery injury in 38 swine	QCG	QCG	167.3 min	37.4 ml/kg	QCG was found to be the most efficient dressing tested in this arterial hemorrhage model.
		HC	HC	0	108.2	The application of HC and CX discontinued after six unsuccessful tests. There was no
		CX	CX	0	113.8	remarkable rise in wound temperature after treatment with dressings.
		TMS	TMS	90.0	79.8	
			PG	121	75.5	
[79]	Femoral artery and vein injury in 22 swine	QCG			bleeding in 1 min:	QCG was superior over the standard pressure dressing control group at controlling
			QCG	–	654 ml	hemorrhage and preventing further loss of blood when the limb was vigorously moved.
			SD	–	582	There was no evidence of tissue injury.
					bleeding in 5 min:	
			QCG		50	
			SD		351	
[99]	Femoral artery and vein transection in 12 swine	QCG		Transection model:		Both QCG and TMS were found to be effective in achieving hemostasis. However, QCG had
	and a femoral artery puncture injury in 16 swine	TMS	QCG		0% EBV	the potential to significantly reduce in vitro clotting time compared to TMS.
				100%		
			TMS	180 min	1.3% EBV	
				100%		
				180 min		
			QCG	puncture model:	19% EBV	
				88%		
			TMS	174 min	31% EBV	
				50%		
				153 min		
[100]	Femoral artery punch in 24 swine	QCG	QCG	100%	374 ml	There was no significant difference in hemostasis between groups. Both QCG and XG did not
		XG	CXG	100%	204	outperform SD in this setting.
			SD	100%	260	
[101]	Groin injury in swine, including both femoral	QCG				QCG was superior over SD in controlling hemorrhage and provided a more robust clot that
	artery and vein transection in the presence of		QCG	–	36 ml	effectively tolerates hemodilution in comparison with SD groups.
	hemodilution		SD	–	340	
[102]	Grade IV liver injury in 48 swine	QCG		48 h survival:	Blood loss at 15 min:	QCG and CX have been shown to be more effective hemostatic adjuncts than SG for
		CX				providing hemostasis in this model. However, there were four and two deaths observed in
		CXG	QCG	58.3%	5.3 ml/kg	CX and QCG groups respectively due to bowel obstruction.
			CX	83.3%	5.7	
			CXG	41.7%	10.1	
			SG	50.0%	11.1	
				14 days survival:		
			QCG	50.0%		
			CX	58.3%		
			CXG	41.7%		
			SG	41.7%		
[80]	Severe liver injury in hypothermic	QCG	QCG	87%	25 ml/kg	QCG was thought to be safe and effective for the treatment of liver injuries under conditions
	coagulopathic swine		PG	50%	58	of hypothermia and coagulopathy. The resuscitation requirements were reduced in QCG group compared with PG group. However, there was no statistically significant difference in mortality since the study size was relatively small.
[92]	Femoral artery injury in 50 swine	QCX	QCX	70%	32 ml/kg	The outcomes with the QCX were significantly better than with QCG in this model.
		QCG	QCG	60%	62	
		CTG	CTG	50%	65	
		CEL	CEL	90%	29	
		HCG	HCG	70%	40	
[91]	230 patient undergoing tonsillectomy	QCG	QCG	–	34.4 ml	84.8% of QCG-treated patients experienced complete hemostasis at 5 min, while only 34.8% of
			CG	–	54.6 ml	CG-treated patients had partially stopped bleeding. At 10 min, hemostatic success achieved in 91.3% of the QCG group versus 51.1% of CG group.
[94]	Soft tissue injury in 38 hypothermic,	QCTP	QCTP	10	97 ml/kg	Although, QCTP had limited efficacy to control hemorrhage in this model, its combination
	coagulopathic swine		G	0	95.1	with NP increased mean survival time and reduced blood loss.
			(QCTP + N)	90	19	
			(G + NP)	80	33	
[95]	52 patients undergoing spinal deformity surgery	QCTP	QCTP	–	974 ml	Patients in the QCTP group had significantly less blood loss and transfusion volume than
			SG	–	1620	controls.

Agents defined: QuikClot Combat Gauze (QCG), TraumaStat (TMS), plain gauze laparotomy pads (PG), Celox Gauze (CXG), standard gauze (SG), QuikClot Combat Gauze XL (QCX), Celox Trauma Gauze (CTG), Celox Gauze (CEL), Cotton Gauze (CG), HemCon ChitoGauze (HCG), laparotomy gauze (G), QuikClot Combat Gauze TraumaPad (QCTP), Negative pressure (NP).

of the kaolin hemostats is that these dressings may be less effective in coagulopathic patients since their hemostatic function depends solely on the blood-clotting activity of the hosts [103]. Hence, there is still a need to produce a fast-acting hemostatic agent which can address this deficiency.

4.2. Smectite group

Smectite clays are 2:1 phyllosilicates consisting of an octahedral alumina layer sandwiched between two tetrahedral silica layers [66]. Smectite displays several properties including a large surface area, a large cation exchange capacity and high viscosity resulting from their small particle sizes [104]. They can absorb large amounts of water attributed to their structure [104]. In comparison to kaolin, smectite demonstrates higher plasticity, absorption, swelling and viscosity making it an excellent candidate for a wide range of industrial and medical applications [68,69,104]. When smectite is exposed to the blood, its negative surface charge leads to the activation of the intrinsic coagulation pathway [59].

Smectite has been commercialized as WoundStat ™ (WS, TraumaCure, Bethesda, Maryland, USA).

4.2.1. WoundStat ™ (WS)

WS was developed by the Virginia Commonwealth University Medical Center and consists of smectite and a super water absorbent poly-acrylic acid salt [105]. It was approved by the FDA in 2007 for emergency external use. This product is supplied in granular form and was added to the Tactical Combat Casualty Care (TCCC) guidelines in 2008 [29,72]. WS works primarily as a mucoadhesive agent and forms a barrier to bleeding through cross-linking cellular blood components. Upon exposure to the blood, WS absorbs water rapidly and swells into a clay paste with high plasticity and strong adhesiveness. Similarly to QCG, it also possesses potent procoagulant activity since it carries a negative charge and can activate the coagulation cascade [59,106]. The main advantages of WS include its facile use (it can be poured in the wound), conformability for all kinds of wound cavities and durability [1,106]. It is also non-toxic and does not generate heat unlike zeolite-based products. However, WS is non-biodegradable and has to be physically removed from the wound area [107]. Unlike QCG, WS has demonstrated faster hemostasis onset [60].

4.2.1.1. WoundStat ™ in animals. Two studies have assessed the efficacy of WS in an arterial hemorrhage swine model [59,105]. In the first study, 100% survival rate in animals treated with WS was reported compared to 0% using other hemostatic agents including QC, HC, ACS+ and AFB (control group) [105]. In the second study by Kheirabadi et al., WS conferred considerable benefits with respect to decreased blood loss and increased survival time compared to Super Quick Relief (SQR, Biolife, LLC, Gainesville, FL, USA), CX, HC and ACS+. WS had a significantly higher hemostasis success rate than the SQR and CX groups (100% in WS-treated animals versus 70 and 60% in the SQR and CX groups respectively). However, histological examination revealed some residual particles in the arteries treated with WS which may lead to thromboembolic complications [59].

WS has also been reported to offer 100% survival alongside reduced blood loss, compared to HC, CX and ACS+ in a model of mixed arterial and venous femoral injuries [57]. It developed a red clay-like texture that allowed the dressing to conform easily to the shape of the wound. However, the efficacy of WS in stopping bleeding was contradicted by Kheirabadi et al. [108], who reported that WS was ineffective compared to QCG and achieved hemostasis in only 2 out of 15 cases [108]. Based on histologic examination, more damage to the endothelium, smooth muscle, and adventitia was experienced by WS-treated vessels compared with the other groups. WS along with some residues was also found in the lumen of arteries as well as on the adventitia of arteries and veins. Studies relating to WS are presented in Table 4.

The major concern with WS is the possibility of thrombosis in distal organs such as the brain and lungs [66]. The application of WS can also cause local inflammatory response and damage to an inner layer of the blood vessels and can be accompanied by excessive clotting, traveling of the clot and its entering to the circulatory system, causing thrombosis in distal organs [1,110]. Kheirabadi et al. compared the safety of WS with QCG and Kerlix (KX, Covidien, Mansfield, MA, regular gauze) in an animal model with both arterial and venous injuries [110]. Computed tomography angiography revealed that the majority of WS-treated vessels were occluded by the formation of a thrombus layer inside the vessel; whereas no blood clot or thrombus was seen in QCG or KX-treated vessels. WS residues and thrombus were also found in the lungs of two subjects. As can be seen from Fig. 7, direct observation also confirmed the occlusion WS-treated vessels by huge thrombi. Histological evidence emphasized the presence of considerable endothelial and transmural damages in subjects treated with WS. Hence, WS is

Table 4
Studies relating to smectite-based hemostatic agent.

References	Model	Hemostatic agents	Treatment groups	Survival	Blood loss	Remarks
[105]	Femoral artery vascular injury in 25 swine	WS	WS	100%	1.9 ml/kg	WS was superior to all the other hemostatic agents tested in this study.
		QC	QC	0%	54	
		ACS+	ACS+	0%	62.7	
		HC	HC	20%	76.8	
			AFB	0%	59.7	
[59]	Femoral artery injury in 46 swine	WS	WS	180 min	9.5 ml/kg	WS was more efficient in treating arterial hemorrhage followed by SQR and CX powders. The application of ACS+ was stopped after 6 animals. A dramatic increase in temperature and axonal necrosis was observed in SQR group. The least and moderate tissue damages were observed with HC and with WS respectively.
		CX	CX	138	40	
		HC	HC	83.3	85.6	
		ACS+	ACS+	0	86.8	
		SQR	SQR	164	34.5	
[57]	Femoral artery and vein injury in 30 swine	WS	WS	100%	4.6 ml/kg	Although, WS appeared more effective than other agents in providing hemostasis, it was more difficult to remove and copious irrigation was required for complete removal.
		CX	CX	83%	12.9	
		HC	HC	67%	10.0	
		ACS+	ACS+	50%	15.8	
			AFD	0%	27	
[109]	Femoral artery injury in 21 swine	WS	WS	100%	–	Although, WS was an effective hemostatic agent, it revealed severe diffuse fibrogranulomatous inflammation and moderate myocyte necrosis
			PG	100%	–	
[108]	Femoral artery injury in 55 hypothermic, coagulopathic swine	WS	WS	75 min	–	WS was ineffective under coagulopathic conditions. FAST dressing demonstrated the highest efficacy since it delivers fibrinogen and thrombin to the wound.
		QCG	QCG	119	–	
		FAST	FAST	145	18.2 ml/kg	
			GZ	74	63.3	

Agents defined: WoundStat (WS), standard army field dressing (AFD), gauze (GZ), fibrinogen-based dressing (FAST), Super Quick Relief (SQR).

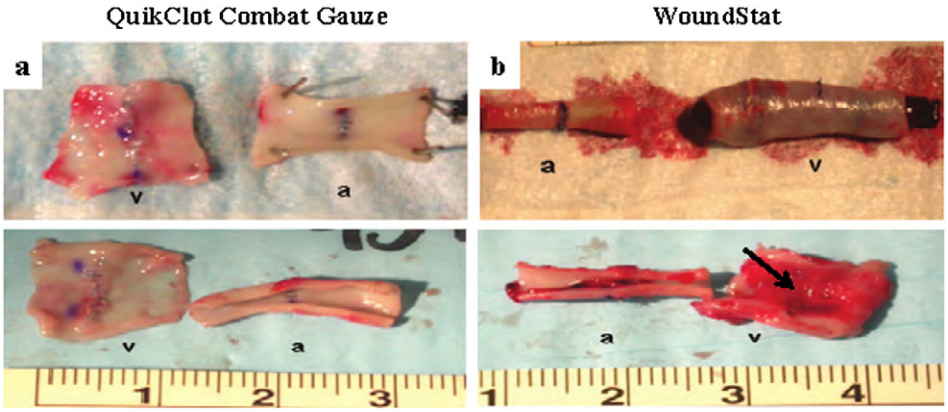

Fig. 7. QCG or WS-treated arteries (represented by a) and veins (represented by v) from the pigs which were taken instantly after recovery [110]. Direct observation of (a) the QCG-treated vessels when the wounds were reopened indicated that there is no significant thrombus or blood clot in the vessels after recovery. In contrast, direct observation of (b) both veins and arteries treated with WS represented large red clots with no blood flow via the vessels. As the arrow shows, a red thrombus layer covered the entire inner wall in the vein.

considered inferior to QCG since its use can result in thromboembolic risk [110].

There are additional safety concerns related to the cellular toxicity of WS. In a study by Bowman et al. the in vitro cellular toxicity of WS in different cell types was assessed in comparison with other minerals such as bentonite, kaolin (the principal ingredient of QCG), and zeolite (the main component of ACS+) [111]. Results showed that both WS and the bentonite presented higher cytotoxicity on endothelial and macrophage-like cells (are present in wounds) compared with other minerals. The authors claimed that direct contact of WS and bentonite with these cells is the principal cause of cytotoxicity. It was found that the hemostats containing kaolin and zeolite such as QCG and ACS+ result in lower toxicity. Indeed, since kaolin is coated on gauze (QCG) and zeolite is packaged in small porous bags, their contact with tissues is limited which may, in part, explain the lower toxicity.

Although WS has been reported to be an effective hemostatic offering improved survival over SD [93], it can cause significant inflammatory response, neurovascular changes, necrosis and extensive bleeding [93]. Removal of WS also requires extensive and meticulous debridement [110]. Although it was temporarily considered as a backup agent to a gauze-type hemostatic for combat medical personnel [110], based on subsequent animal safety studies, the use of WS was halted by the U.S. Army in 2009 with the FDA recommending that it should be removed from the United States market [110].

5. Challenges and perspective

In spite of improvements in surgical techniques and the development of various hemostatic agents, hemorrhage still remains the leading cause of morbidity and mortality. The objective of this review was to consider the state-of-art in the use of inorganic materials for hemostatic applications. Inorganic materials have shown to be effective in arresting hemorrhage. The net negative surface charge of inorganic hemostats serves as an ideal platform for activating proteins as well as activation of the contact pathway of coagulation. Also, their structural properties allow the materials to rapidly absorb high amounts of water from the blood, and to concentrate the cells, platelets and clotting factors at the bleeding site thus promoting hemostasis. However, from this review which has assessed the in vivo, in vitro and clinical responses to applying zeolite, kaolin and smectite-based hemostats for controlling hemorrhage, it is clear that none of the agents have proven to be suitable for all trauma scenarios in normal and coagulopathic casualties. Although zeolite-based hemostatic agents were efficacious for achieving hemostasis, the materials caused thermal injury to tissue through exothermic reaction. Kaolin-based hemostats have appeared to be more efficient than zeolite hemostats, but several studies revealed that the kaolin hemostats may be ineffective to stop bleeding in patients with coagulopathy since their efficacy depends on the individual coagulation function of the host. With regard to smectite-based hemostats, although applying and covering the wound with this agent achieve hemostasis with high survival rates, endothelial injury has been reported to occur, leading to occlusive thrombus and the absence of blood flow in the vessels.

Future research in this space could focus on the design of inorganic hemostats that attenuate tissue burning that has been reported with other hemostatic agents without adversely affecting efficacy. There is also a growing need to improve the antibacterial properties of these hemostats to prevent infection at the wound area. Additionally, since some patient and combat casualties requiring blood transfusion are coagulopathic, production of inorganic hemostats that can control hemorrhage independently of host coagulation status is needed. A promising approach could be the utilization of ion-exchanging process of Ca^{2+} with some cations of a reduced hydration enthalpy such as silver and zinc. Those ions not only work in minimizing heat generation at the wound site but also impart antibacterial properties to the materials. Furthermore, fabrication of inorganic/polymer composite materials can offer a unique opportunity to improve the hemostatic efficacy of inorganic materials, which are not capable to stop bleeding of coagulopathic patients. Indeed, the combination of inorganic materials with hemostatic polymers which have inherent hemostatic properties could bridge the advantages of both types of materials in order to effectively induce rapid hemorrhage at the injury site.

Acknowledgments

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References

[1] M.A. Schreiber, D.J. Neveleff, Achieving hemostasis with topical hemostats: making clinically and economically appropriate decisions in the surgical and trauma settings, AORN J. 94 (2011) S1–S20.
[2] H.B. Alam, D. Burris, J.A. DaCorta, P. Rhee, Hemorrhage control in the battlefield: role of new hemostatic agents, Mil. Med. 170 (2005) 63–69.
[3] H.R. Champion, R.F. Bellamy, C.P. Roberts, A. Leppaniemi, A profile of combat injury, J. Trauma Inj. Infect. Crit. Care 54 (2003) S13–S19.
[4] J.A. Evans, K.J. van Wessem, D. McDougall, K.A. Lee, T. Lyons, Z.J. Balogh, Epidemiology of traumatic deaths: comprehensive population-based assessment, World J. Surg. 34 (2010) 158–163.
[5] P.M. Mannucci, M. Levi, Prevention and treatment of major blood loss, N. Engl. J. Med. 356 (2007) 2301–2311.

[6] R. Kumar, M. Carcao, Inherited abnormalities of coagulation: hemophilia, von Willebrand disease, and beyond, Pediatr. Clin. N. Am. 60 (2013) 1419–1441.
[7] K.P. Ponder, Gene therapy for hemophilia, Curr. Opin. Hematol. 13 (2006) 301–307.
[8] P. Mishra, R. Naithani, T. Dolai, R. Bhargava, M. Mahapatra, A. Dixit, T. Seth, R. Kumar, R. Saxena, Intracranial haemorrhage in patients with congenital haemostatic defects, Haemophilia 14 (2008) 952–955.
[9] Ç. Çinar, M.E. Odabaş, G. Akca, B. Işik, Antibacterial effect of a new haemostatic agent on oral microorganisms, J. Clin. Exp. Dent. 4 (2012), e151.
[10] Y. Li, H. Li, L. Xiao, L. Zhou, J. Shentu, X. Zhang, J. Fan, Hemostatic efficiency and wound healing properties of natural zeolite granules in a lethal rabbit model of complex groin injury, Materials 5 (2012) 2586–2596.
[11] J.B. Glick, R.R. Kaur, D. Siegel, Achieving hemostasis in dermatology—part II: topical hemostatic agents, Indian Dermatol. Online J. 4 (2013) 172.
[12] B.L. Bennett, L. Littlejohn, Review of new topical hemostatic dressings for combat casualty care, Mil. Med. 179 (2014) 497–514.
[13] S. Butenas, K. Mann, Blood coagulation, Biochem. Mosc. 67 (2002) 3–12.
[14] C.T. Esmon, Cell mediated events that control blood coagulation and vascular injury, Annu. Rev. Cell Biol. 9 (1993) 1–26.
[15] S. Samudrala, Topical hemostatic agents in surgery: a surgeon's perspective, AORN J. 88 (2008) S2–S11.
[16] K. Broos, H.B. Feys, S.F. De Meyer, K. Vanhoorelbeke, H. Deckmyn, Platelets at work in primary hemostasis, Blood Rev. 25 (2011) 155–167.
[17] V.J. Marder, W.C. Aird, J.S. Bennett, S. Schulman, G.C. White, Hemostasis and Thrombosis: Basic Principles and Clinical Practice, Lippincott Williams & Wilkins, 2012.
[18] J.H. Morrissey, Tissue factor: an enzyme cofactor and a true receptor, Thromb. Haemost. 86 (2001) 66–74.
[19] M.B. Gorbet, M.V. Sefton, Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes, Biomaterials 25 (2004) 5681–5703.
[20] T. Maesen, The zeolite scene—an overview, Introduction to zeolites science and practice, Stud. Surf. Sci. Catal 168 (2007) 1–12.
[21] S. Mortazavi, A. Atefi, P. Roshan-Shomal, N. Raadpey, G. Mortazavi, Development of a novel mineral based haemostatic agent consisting of a combination of bentonite and zeolite minerals, J. Ayub Med. Coll. Abbottabad 21 (2009) 3–7.
[22] J. Setliff, C.W. Pike, Cementitious Composition, Google Patents, 2014.
[23] K. Pavelić, M. Hadžija, L. Bedrica, J. Pavelić, I. Đikić, M. Katić, M. Kralj, M.H. Bosnar, S. Kapitanović, M. Poljak-Blaži, Natural zeolite clinoptilolite: new adjuvant in anticancer therapy, J. Mol. Med. 78 (2001) 708–720.
[24] M. Katic, B. Bosnjak, K. Gall-Troselj, I. Dikic, K. Pavelic, A clinoptilolite effect on cell media and the consequent effects on tumor cells in vitro, Front. Biosci. 11 (2006) 1722–1732.
[25] G. Rodriguez-Fuentes, M. Barrios, A. Iraizoz, I. Perdomo, B. Cedre, Enterex: anti-diarrheic drug based on purified natural clinoptilolite, Zeolites 19 (1997) 441–448.
[26] F.A. Mumpton, La Roca magica: uses of natural zeolites in agriculture and industry, Proc. Natl. Acad. Sci. 96 (1999) 3463–3470.
[27] J. Li, W. Cao, X.-x. Lv, L. Jiang, Y.-j. Li, W.-z. Li, S.-z. Chen, X.-y. Li, Zeolite-based hemostat QuikClot releases calcium into blood and promotes blood coagulation in vitro, Acta Pharmacol. Sin. 34 (2013) 367–372.
[28] M.G. Rimoli, M.R. Rabaioli, D. Melisi, A. Curcio, S. Mondello, R. Mirabelli, E. Abignente, Synthetic zeolites as a new tool for drug delivery, J. Biomed. Mater. Res. A 87 (2008) 156–164.
[29] J. Granville-Chapman, N. Jacobs, M. Midwinter, Pre-hospital haemostatic dressings: a systematic review, Injury 42 (2011) 447–459.
[30] S. Mortazavi, A. Tavasoli, M. Atefi, N. Tanide, N. Radpey, P. Roshan-shomal, H. Moradi, S. Taeb, CoolClot, a novel hemostatic agent for controlling life-threatening arterial bleeding, World 4 (2013) 123–127.
[31] G.D. Stucky, T.A. Ostomel, Q. Shi, P.K. Stoimenov, P.A. Holden, Inorganic Materials for Hemostatic Modulation and Therapeutic Wound Healing, Google Patents, 2010.
[32] M. Mikaelsson, The Role of Calcium in Coagulation and Anticoagulation, Coagulation and Blood Transfusion, Springer 1991, pp. 29–37.
[33] J. Lovelock, B. Porterfield, Blood clotting: the function of electrolytes and of calcium, Biochem. J. 50 (1952) 415.
[34] M.D. Palm, J.S. Altman, Topical hemostatic agents: a review, Dermatol. Surg. 34 (2008) 431–445.
[35] H.B. Alam, Z. Chen, A. Jaskille, R.I.L.C. Querol, E. Koustova, R. Inocencio, R. Conran, A. Seufert, N. Ariaban, K. Toruno, Application of a zeolite hemostatic agent achieves 100% survival in a lethal model of complex groin injury in swine, J. Trauma Inj. Infect. Crit. Care 56 (2004) 974–983.
[36] V. Margulis, E.D. Matsumoto, R. Svatek, W. Kabbani, J.A. Cadeddu, Y. Lotan, Application of novel hemostatic agent during laparoscopic partial nephrectomy, J. Urol. 174 (2005) 761–764.
[37] H.E. Achneck, B. Sileshi, R.M. Jamiolkowski, D.M. Albala, M.L. Shapiro, J.H. Lawson, A comprehensive review of topical hemostatic agents: efficacy and recommendations for use, Ann. Surg. 251 (2010) 217–228.
[38] H.B. Alam, G.B. Uy, D. Miller, E. Koustova, T. Hancock, R. Inocencio, D. Anderson, O. Llorente, P. Rhee, Comparative analysis of hemostatic agents in a swine model of lethal groin injury, J. Trauma Inj. Infect. Crit. Care 54 (2003) 1077–1082.
[39] A.E. Pusateri, A.V. Delgado, E.J. Dick, R.S. Martinez, J.B. Holcomb, K.L. Ryan, Application of a granular mineral-based hemostatic agent (QuikClot) to reduce blood loss after grade V liver injury in swine, J. Trauma 57 (2004) 555–562.
[40] B.G. Kozen, S.J. Kircher, J. Henao, F.S. Godinez, A.S. Johnson, An alternative hemostatic dressing: comparison of CELOX, HemCon, and QuikClot, Acad. Emerg. Med. 15 (2008) 74–81.
[41] E.M. Acheson, B.S. Kheirabadi, R. Deguzman, E.J. Dick Jr., J.B. Holcomb, Comparison of hemorrhage control agents applied to lethal extremity arterial hemorrhages in swine, J. Trauma Inj. Infect. Crit. Care 59 (2005) 865–875.
[42] F.L. Wright, H.T. Hua, G. Velmahos, D. Thoman, D. Demitriades, P.M. Rhee, Intracorporeal use of the hemostatic agent QuickClot in a coagulopathic patient with combined thoracoabdominal penetrating trauma, J. Trauma Inj. Infect. Crit. Care 56 (2004) 205–208.
[43] V. Shanmugam, M. Robinson, Case report of uncontrollable pelvic bleeding—managed by a previously unreported method (QuikClot®), Color. Dis. 11 (2009) 221–222.
[44] P. Rhee, C. Brown, M. Martin, A. Salim, D. Plurad, D. Green, L. Chambers, D. Demetriades, G. Velmahos, H. Alam, QuikClot use in trauma for hemorrhage control: case series of 103 documented uses, J. Trauma Inj. Infect. Crit. Care 64 (2008) 1093–1099.
[45] K. Robinson, Controlling bleeding in the field: hemostatic powders and dressings debut in the prehospital setting, J. Emerg. Nurs. 30 (2004) 160–161.
[46] M.C. Neuffer, J. McDivitt, D. Rose, K. King, C.C. Cloonan, J.S. Vayer, Hemostatic dressings for the first responder: a review, Mil. Med. 169 (2004) 716–720.
[47] A.E. Pusateri, A.V. Delgado, E.J. Dick Jr., R.S. Martinez, J.B. Holcomb, K.L. Ryan, Application of a granular mineral-based hemostatic agent (QuikClot) to reduce blood loss after grade V liver injury in swine, J. Trauma Inj. Infect. Crit. Care 57 (2004) 555–562.
[48] J.K. Wright, J. Kalns, E.A. Wolf, F. Traweek, S. Schwarz, C.K. Loeffler, W. Snyder, L.D. Yantis Jr., J. Eggers, Thermal injury resulting from application of a granular mineral hemostatic agent, J. Trauma Inj. Infect. Crit. Care 57 (2004) 224–230.
[49] D. Plurad, S. Chandrasoma, C. Best, P. Rhee, A complication of intracorporeal use of QuikClot for pelvic hemorrhage, J. Trauma Inj. Infect. Crit. Care 66 (2009) 1482–1484.
[50] J. McManus, T. Hurtado, A. Pusateri, K.J. Knoop, A case series describing thermal injury resulting from zeolite use for hemorrhage control in combat operations, Prehosp. Emerg. Care 11 (2007) 67–71.
[51] R. Buderi, Naval Innovation for the 21st Century: The Office of Naval Research Since the End of the Cold War, Naval Institute Press, 2013.
[52] F. Arnaud, T. Tomori, W. Carr, A. McKeague, K. Teranishi, K. Prusaczyk, R. McCarron, Exothermic reaction in zeolite hemostatic dressings: QuikClot ACS and ACS+®, Ann. Biomed. Eng. 36 (2008) 1708–1713.
[53] F. Arnaud, T. Tomori, R. Saito, A. McKeague, W.K. Prusaczyk, R.M. McCarron, Comparative efficacy of granular and bagged formulations of the hemostatic agent QuikClot, J. Trauma Inj. Infect. Crit. Care 63 (2007) 775–782.
[54] A.E. Pusateri, J.B. Holcomb, B.S. Kheirabadi, H.B. Alam, C.E. Wade, K.L. Ryan, Making sense of the preclinical literature on advanced hemostatic products, J. Trauma Inj. Infect. Crit. Care 60 (2006) 674–682.
[55] T.A. Ostomel, P.K. Stoimenov, P.A. Holden, H.B. Alam, G.D. Stucky, Host–guest composites for induced hemostasis and therapeutic healing in traumatic injuries, J. Thromb. Thrombolysis 22 (2006) 55–67.
[56] N. Ahuja, T.A. Ostomel, P. Rhee, G.D. Stucky, R. Conran, Z. Chen, G.A. Al-Mubarak, G. Velmahos, H.B. Alam, Testing of modified zeolite hemostatic dressings in a large animal model of lethal groin injury, J. Trauma Inj. Infect. Crit. Care 61 (2006) 1312–1320.
[57] J.G. Clay, J.K. Grayson, D. Zierold, Comparative testing of new hemostatic agents in a swine model of extremity arterial and venous hemorrhage, Mil. Med. 175 (2010) 280–284.
[58] K. Inaba, P. Rhee, P.G. Teixeira, G. Barmparas, B. Putty, B.C. Branco, S. Cohn, D. Demetriades, Intracorporeal use of advanced local hemostatics in a damage control swine model of grade IV liver injury, J. Trauma Acute Care 71 (2011) 1312–1318.
[59] B.S. Kheirabadi, J.W. Edens, I.B. Terrazas, J.S. Estep, H.G. Klemcke, M.A. Dubick, J.B. Holcomb, Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine, J. Trauma Inj. Infect. Crit. Care 66 (2009) 316–328.
[60] F. Arnaud, K. Teranishi, T. Tomori, W. Carr, R. McCarron, Comparison of 10 hemostatic dressings in a groin puncture model in swine, J. Vasc. Surg. 50 (2009) 632–639 (e631).
[61] M. Eryilmaz, T. Ozer, O. Mentes, N. Torer, M. Durusu, A. Gunal, A.İ. Uzar, Is the zeolite hemostatic agent beneficial in reducing blood loss during arterial injury? Turk. J. Trauma Emerg. Surg. 15 (2009) 7–11.
[62] W.H. Suh, K.S. Suslick, G.D. Stucky, Y.-H. Suh, Nanotechnology, nanotoxicology, and neuroscience, Prog. Neurobiol. 87 (2009) 133–170.
[63] A. Mahajna, M. Hirsh, M.M. Krausz, Use of the hemostatic agent QuikClot® for the treatment of massive splenic injury in a rat model, Eur. Surg. Res. 39 (2007) 251–257.
[64] A.J. Ayadi, J. Soro, A. Kamoun, S. Baklouti, Study of clay's mineralogy effect on rheological behavior of ceramic suspensions using an experimental design, Int. J. Res. Rev. Applied Sci. 14 (2013) 374–384.
[65] C. Rosales-Landeros, C.E. Barrera-Díaz, B. Bilyeu, V.V. Guerrero, F.U. Núñez, A review on Cr (VI) adsorption using inorganic materials, Am. J. Anal. Chem. 4 (2013) 8.
[66] L.B. Williams, S.E. Haydel, Evaluation of the medicinal use of clay minerals as antibacterial agents, Int. Geol. Rev. 52 (2010) 745–770.
[67] G.L. Bowlin, M.E. Carr, R.F. Diegelmann, K.R. Ward, Mineral Technologies (MT) for Acute Hemostasis and for the Treatment of Acute Wounds and Chronic Ulcers, Google Patents, 2012.
[68] H.H. Murray, Applied clay mineralogy today and tomorrow, Clay Miner. 34 (1999) 39–49.
[69] H.H. Murray, Traditional and new applications for kaolin, smectite, and palygorskite: a general overview, Appl. Clay Sci. 17 (2000) 207–221.
[70] J. Margolis, The kaolin clotting time: a rapid one-stage method for diagnosis of coagulation defects, J. Clin. Pathol. 11 (1958) 406.
[71] T.A. Ostomel, Q. Shi, P.K. Stoimenov, G.D. Stucky, Metal oxide surface charge mediated hemostasis, Langmuir 23 (2007) 11233–11238.
[72] S.D. Gordy, P. Rhee, M.A. Schreiber, Military applications of novel hemostatic devices, Expert Rev. Med. Devices 8 (2011) 41–47.

[73] B. Gegel, J. Burgert, J. Gasko, C. Campbell, M. Martens, J. Keck, H. Reynolds, M. Loughren, D. Johnson, The effects of QuikClot Combat Gauze and movement on hemorrhage control in a porcine model, Mil. Med. 177 (2012) 1543–1547.
[74] J.H. Griffin, Role of surface in surface-dependent activation of Hageman factor (blood coagulation factor XII), Proc. Natl. Acad. Sci. 75 (1978) 1998–2002.
[75] P. Walsh, The effects of collagen and kaolin on the intrinsic coagulant activity of platelets. Evidence for an alternative pathway in intrinsic coagulation not requiring factor XII, Br. J. Haematol. 22 (1972) 393–405.
[76] R.W. Colman, A.H. Schmaier, Contact system: a vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes, Blood 90 (1997) 3819–3843.
[77] X. Huang, N.P. Young, H.E. Townley, Characterisation and comparison of mesoporous silica particles for optimised drug delivery, Nanomater. Nanotechnol. 4 (2014) 2.
[78] C. Sperling, M. Fischer, M.F. Maitz, C. Werner, Blood coagulation on biomaterials requires the combination of distinct activation processes, Biomaterials 30 (2009) 4447–4456.
[79] D. Johnson, B. Gegel, J. Burgert, J. Gasko, C. Cromwell, M. Jaskowska, R. Steward, A. Taylor, The effects of QuikClot Combat Gauze, fluid resuscitation, and movement on hemorrhage control in a porcine model, Int. Sch. Res. Not. 2012 (2012).
[80] M.J. Sena, G. Douglas, T. Gerlach, J.K. Grayson, K.O. Pichakron, D. Zierold, A pilot study of the use of kaolin-impregnated gauze (Combat Gauze) for packing high-grade hepatic injuries in a hypothermic coagulopathic swine model, J. Surg. Res. 183 (2013) 704–709.
[81] R.B. Schwartz, B.Z. Reynolds, S.A. Shiver, E.B. Lerner, E.M. Greenfield, R.A. Solis, N.A. Kimpel, P.L. Coule, J.G. McManus, Comparison of two packable hemostatic gauze dressings in a porcine hemorrhage model, Prehosp. Emerg. Care 15 (2011) 477–482.
[82] L.F. Littlejohn, J.J. Devlin, S.S. Kircher, R. Lueken, M.R. Melia, A.S. Johnson, Comparison of Celox-A, ChitoFlex, WoundStat, and Combat Gauze hemostatic agents versus standard gauze dressing in control of hemorrhage in a swine model of penetrating trauma, Acad. Emerg. Med. 18 (2011) 340–350.
[83] D. Johnson, S. Bates, S. Nukalo, A. Staub, A. Hines, T. Leishman, J. Michel, D. Sikes, B. Gegel, J. Burgert, The effects of QuikClot Combat Gauze on hemorrhage control in the presence of hemodilution and hypothermia, Ann. Med. Surg. 3 (2014) 21–25.
[84] B.S. Kheirabadi, M.R. Scherer, J.S. Estep, M.A. Dubick, J.B. Holcomb, Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine, J. Trauma Acute Care 67 (2009) 450–460.
[85] M.J. Martin, Editorial to accompany "a pilot study of the use of kaolin-impregnated gauze (Combat Gauze) for packing high-grade hepatic injuries in a hypothermic coagulopathic swine model", J. Surg. Res. 186 (2014) 116–118.
[86] M.W. Causey, D.P. McVay, S. Miller, A. Beekley, M. Martin, The efficacy of Combat Gauze in extreme physiologic conditions, J. Surg. Res. 177 (2012) 301–305.
[87] C.T. Floyd, S.W. Rothwell, J. Risdahl, R. Martin, C. Olson, N. Rose, Salmon thrombin–fibrinogen dressing allows greater survival and preserves distal blood flow compared to standard kaolin gauze in coagulopathic swine with a standardized lethal femoral artery injury, J. Spec. Oper. Med. 12 (2012) 16–26.
[88] B.D. Ratner, A.S. Hoffman, F.J. Schoen, J.E. Lemons, An introduction to materials in medicine, Biomater. Sci. 484 (1996).
[89] Y. Ran, E. Hadad, S. Daher, O. Ganor, J. Kohn, Y. Yegorov, C. Bartal, N. Ash, G. Hirschhorn, QuikClot Combat Gauze use for hemorrhage control in military trauma: January 2009 Israel Defense Force experience in the Gaza Strip—a preliminary report of 14 cases, Prehosp. Disaster Med. 25 (2010) 584–588.
[90] P.J. Fedor, Novel use of a hemostatic dressing in the management of a bleeding leech bite: a case report and review of the literature, Wilderness Environ. Med. 23 (2012) 44–48.
[91] M.E. Chávez-Delgado, C.V. Kishi-Sutto, X.N.A. de la-Riva, M. Rosales-Cortes, P. Gamboa-Sánchez, Topic usage of kaolin-impregnated gauze as a hemostatic in tonsillectomy, J. Surg. Res. 192 (2014) 678–685.
[92] J.M. Rall, J.M. Cox, A.G. Songer, R.F. Cestero, J.D. Ross, Comparison of novel hemostatic dressings with QuikClot Combat Gauze in a standardized swine model of uncontrolled hemorrhage, J. Trauma Inj. Infect. Crit. Care 75 (2013) S150–S156.
[93] A.H. Smith, C. Laird, K. Porter, M. Bloch, Haemostatic dressings in prehospital care, Emerg. Med. J. 30 (2013) 784–789.
[94] B.S. Kheirabadi, I.B. Terrazas, J.F. Williams, M.A. Hanson, M.A. Dubick, L.H. Blackbourne, Negative-pressure wound therapy: a hemostatic adjunct for control of coagulopathic hemorrhage in large soft tissue wounds, J. Trauma Acute Care 73 (2012) 1188–1194.
[95] E.M. Abbott, S.V. Nandyala, R.M. Schwend, Does a kaolin-impregnated hemostatic dressing reduce intraoperative blood loss and blood transfusions in pediatric spinal deformity surgery? Spine 39 (2014) E1174–E1180.
[96] M. Pahari, R. Moliver, D. Lo, D. Pinkerton, G. Basadonna, QuikClot® Interventional™ Hemostatic Bandage (QCI): A Novel Hemostatic Agent for Vascular Access, Cath Lab Digest Archive, 17, 2010.
[97] L. Politi, A. Aprile, C. Paganelli, A. Amato, G.B. Zoccai, F. Sgura, D. Monopoli, R. Rossi, M.G. Modena, G.M. Sangiorgi, Randomized clinical trial on short-time compression with kaolin-filled pad: a new strategy to avoid early bleeding and subacute radial artery occlusion after percutaneous coronary intervention, J. Interv. Cardiol. 24 (2011) 65–72.
[98] D. Trabattoni, P. Gatto, A.L. Bartorelli, A new kaolin-based hemostatic bandage use after coronary diagnostic and interventional procedures, Int. J. Cardiol. 156 (2012) 53–54.
[99] F. Arnaud, K. Teranishi, T. Okada, D. Parreño-Sacdalan, D. Hupalo, G. McNamee, W. Carr, D. Burris, R. McCarron, Comparison of Combat Gauze and TraumaStat in two severe groin injury models, J. Surg. Res. 169 (2011) 92–98.
[100] J.M. Watters, P.Y. Van, G.J. Hamilton, C. Sambasivan, J.A. Differding, M.A. Schreiber, Advanced hemostatic dressings are not superior to gauze for care under fire scenarios, J. Trauma Acute Care 70 (2011) 1413–1419.
[101] D. Johnson, S. Agee, A. Reed, B. Gegel, J. Burgert, J. Gasko, M. Loughren, The effects of QuikClot Combat Gauze on hemorrhage control in the presence of hemodilution, US Army Med. Dep. J. 2012 (2012) 36–39.
[102] K. Inaba, B.C. Branco, P. Rhee, B. Putty, O. Okoye, G. Barmparas, P. Talving, D. Demetriades, Long-term preclinical evaluation of the intracorporeal use of advanced local hemostatics in a damage-control swine model of grade IV liver injury, J. Trauma Acute Care 74 (2013) 538–545.
[103] B. Kheirabadi, Evaluation of topical hemostatic agents for combat wound treatment, US Army Med. Dep. J. 2 (2011) 25–37.
[104] L.L. Hench, Bioceramics, J. Am. Ceram. Soc. 81 (1998) 1705–1728.
[105] K.R. Ward, M.H. Tiba, W.H. Holbert, C.R. Blocher, G.T. Draucker, E.K. Proffitt, G.L. Bowlin, R.R. Ivatury, R.F. Diegelmann, Comparison of a new hemostatic agent to current combat hemostatic agents in a swine model of lethal extremity arterial hemorrhage, J. Trauma Inj. Infect. Crit. Care 63 (2007) 276–284.
[106] J.W. Carraway, D. Kent, K. Young, A. Cole, R. Friedman, K.R. Ward, Comparison of a new mineral based hemostatic agent to a commercially available granular zeolite agent for hemostasis in a swine model of lethal extremity arterial hemorrhage, Resuscitation 78 (2008) 230–235.
[107] J. Granville-Chapman, N. Jacobs, M. Midwinter, Pre-hospital haemostatic dressings: a systematic review, Inj. Extra 40 (2009) 184–185.
[108] B.S. Kheirabadi, J.E. Mace, I.B. Terrazas, C.G. Fedyk, K.K. Valdez, M.J. MacPhee, D. Beall, J.S. Estep, M.A. Dubick, L.H. Blackbourne, Clot-inducing minerals versus plasma protein dressing for topical treatment of external bleeding in the presence of coagulopathy, J. Trauma Acute Care 69 (2010) 1062–1073.
[109] T. Gerlach, J.K. Grayson, K.O. Pichakron, M.J. Sena, S.D. DeMartini, B.Z. Clark, J.S. Estep, D. Zierold, Preliminary study of the effects of smectite granules (WoundStat) on vascular repair and wound healing in a swine survival model, J. Trauma Acute Care 69 (2010) 1203–1209.
[110] B.S. Kheirabadi, J.E. Mace, I.B. Terrazas, C.G. Fedyk, J.S. Estep, M.A. Dubick, L.H. Blackbourne, Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine, J. Trauma Acute Care 68 (2010) 269–278.
[111] P.D. Bowman, X. Wang, M.A. Meledeo, M.A. Dubick, B.S. Kheirabadi, Toxicity of aluminum silicates used in hemostatic dressings toward human umbilical veins endothelial cells, HeLa cells, and RAW267. 4 mouse macrophages, J. Trauma Acute Care 71 (2011) 727–732.