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Review

Emerging haemostatic sprays: From material design to clinical translation

Akriti Nepal [a], Huyen Tran [c], Nam-Trung Nguyen [b], Hang Thu Ta [a,b,*]

[a] School of Environment and Science, Griffith University, Nathan, Queensland, 4121, Australia
[b] Queensland Quantum and Advanced Technologies Research Institute, Griffith University, Nathan, Queensland, 4121, Australia
[c] Thrombosis and Haemostasis Unit, The Alfred Hospital, Melbourne, Victoria, 3004, Australia

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ABSTRACT

Haemostatic sprays have emerged as a transformative class of topical agents for the rapid control of bleeding in surgery, trauma, and endoscopy, particularly in settings where conventional approaches such as suturing, cauterisation, or mechanical compression are impractical. Delivered in a non-contact and conformal manner, these systems enable efficient coverage of irregular, deep, and non-compressible bleeding sites. Their haemostatic action arises from synergistic biochemical and physical mechanisms, including activation of the coagulation cascade, plasma absorption driven concentration of clotting factors, and formation of adhesive or barrier-type matrices at the wound surface. Commercial and non-commercial products such as Hemospray®, PuraStat®, Raplixa™, Ankaferd Blood-Stopper®, EndoClot®, OOZFIX™, and CMCS-COHA have demonstrated clinically meaningful reductions in bleeding, improved procedural visibility, and favourable patient outcomes across gastrointestinal, surgical, and trauma indications. Alongside these, a rapidly expanding portfolio of pre-clinical sprayable biomaterials spanning mineral, polysaccharide, protein, peptide, hydrogel, and nano-engineered platforms offers new opportunities to address unmet needs in non-compressible and complex haemorrhage.

This review provides a comprehensive and integrated analysis of haemostatic sprays, covering material classes, mechanisms of action, clinical applications, and translational performance. Key challenges, including tissue irritation, thromboembolic risk, impaired visualisation, and limitations in adhesion or durability, are critically examined, together with emerging strategies to improve biocompatibility, targeting accuracy, and suitability for pre-hospital or low-resource settings. By synthesizing current clinical evidence with advances in biomaterial design and spray-delivery technologies, this review defines the present capabilities of haemostatic sprays and outlines a roadmap for their next-generation development. These innovations are poised to further enhance the safety, speed, and effectiveness of bleeding control in modern surgical and emergency care.

1. Introduction

In recent years, the frequency of surgical operations has significantly risen due to advancements in medical technology and procedural convenience [1]. Simple surgical procedures typically result in local wounds where bleeding is adequately controlled by the body's natural haemostasis process. Blood loss becomes a concern when it exceeds 10% of the total blood volume, which is approximately 6–7% of an average adult's body weight [2]. To prevent excessive blood loss, haemostatic agents can be applied early in medical treatment to the wound sites [3–8].

Among various types of wounds and bleeding, gastrointestinal bleeding (GIB) represents a considerable health burden. In the United States alone, it accounts for approximately 20,000 fatalities annually, with an associated mortality rate of around 10% for acute upper gastrointestinal haemorrhage [9–12]. The mortality rate has remained relatively stable since the 1950s, partly due to the aging population. Notably, 25% of patients with acute upper gastrointestinal haemorrhage are over the age of 80, contributing to the challenge of managing peptic ulcer bleeding as individuals age [10,13]. Older individuals are more likely to have comorbidities such as cardiovascular disease, chronic kidney disease, and the use of anticoagulant or antiplatelet medications, all of which increase the risk and severity of gastrointestinal haemorrhage while complicating its management [14,15]. Additionally, aging is associated with physiological changes, including reduced gastric mucosal defense, delayed healing, and impaired coagulation, making elderly patients more vulnerable to severe bleeding and poorer clinical outcomes [16]. As the proportion of older adults continues to rise, the burden of managing GIB in this population remains a significant

* Corresponding author at: School of Environment and Science, Griffith University, Nathan, Queensland, 4121, Australia.
E-mail address: h.ta@griffith.edu.au (H.T. Ta).

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challenge despite advancements in haemostatic interventions.

Endoscopic haemostasis techniques are widely employed in gastrointestinal practice, including injection therapy (e.g., epinephrine, thrombin, fibrin glue), thermal coagulation, and mechanical devices such as clips or ligation. More broadly, conventional haemostatic approaches encompass mechanical compression, electrocautery, and suturing. Although effective in many scenarios, these methods present limitations, particularly in anatomically complex or difficult-to-access bleeding sites. They may prolong operative time, induce collateral thermal damage, and require precise positioning for efficacy [8,17]. Traditional materials such as gauze or non-absorbable dressings may lead to adhesion formation, infection risk, or require removal [18].

To address these shortcomings, contact-based biomaterial systems have been developed. Absorbent packings such as gelatin sponges, collagen matrices, and bioabsorbable foams enhance blood absorption and promote coagulation. Products including Gelfoam®, Floseal®, Avitene®, and related materials improve local clot formation but remain limited in narrow or irregular surgical fields. Their performance depends largely on direct contact and sufficient surface coverage, which may be inadequate in deep or branching haemorrhagic sites.[8,17,18].

Injectable and volume-expanding haemostatic sponges were introduced to manage internal or non-compressible bleeding [19]. These materials can be compressed for delivery and expand upon contact with blood, forming a mechanical barrier while concentrating coagulation components [20–24]. Although effective for puncture wounds, their reliance on volumetric expansion may limit performance in complex cavities where uniform distribution cannot be achieved. Excessive expansion may also generate undesirable pressure on surrounding tissues. In parallel, positively charged polymer-based systems have been explored to accelerate coagulation through electrostatic interactions with negatively charged blood components such as platelets and erythrocytes [18,25–27]. While these strategies enhance clot formation kinetics, they remain fundamentally dependent on direct material–tissue contact.

Despite these advances, contact-dependent and volume-filling haemostatic systems remain limited in achieving rapid, uniform, and minimally invasive coverage across irregular, deep, or diffuse bleeding surfaces. This unmet clinical need has driven the development of spray-based haemostatic technologies.

Unlike traditional haemostatic approaches that rely on direct contact or precise positioning, haemostatic spray technologies enable non-contact and conformal delivery. Administered via endoscopic catheters or aerosolised applicators, sprays allow rapid and uniform deposition over complex anatomical surfaces without extensive tissue manipulation. This mode of application may reduce procedural time, minimise collateral thermal injury, and improve haemostatic control in actively haemorrhaging or anatomically challenging environments [8,28–31].

Haemostatic sprays have emerged as indispensable tools in both surgical and emergency settings. Their efficacy lies in a dual mechanism: biochemical activation of the coagulation cascade (e.g., thrombin or fibrin-based systems) and physical absorption that concentrates blood components and forms a protective barrier [4,32–35]. Delivered through endoscopic catheters, gas-assisted applicators, or direct spray

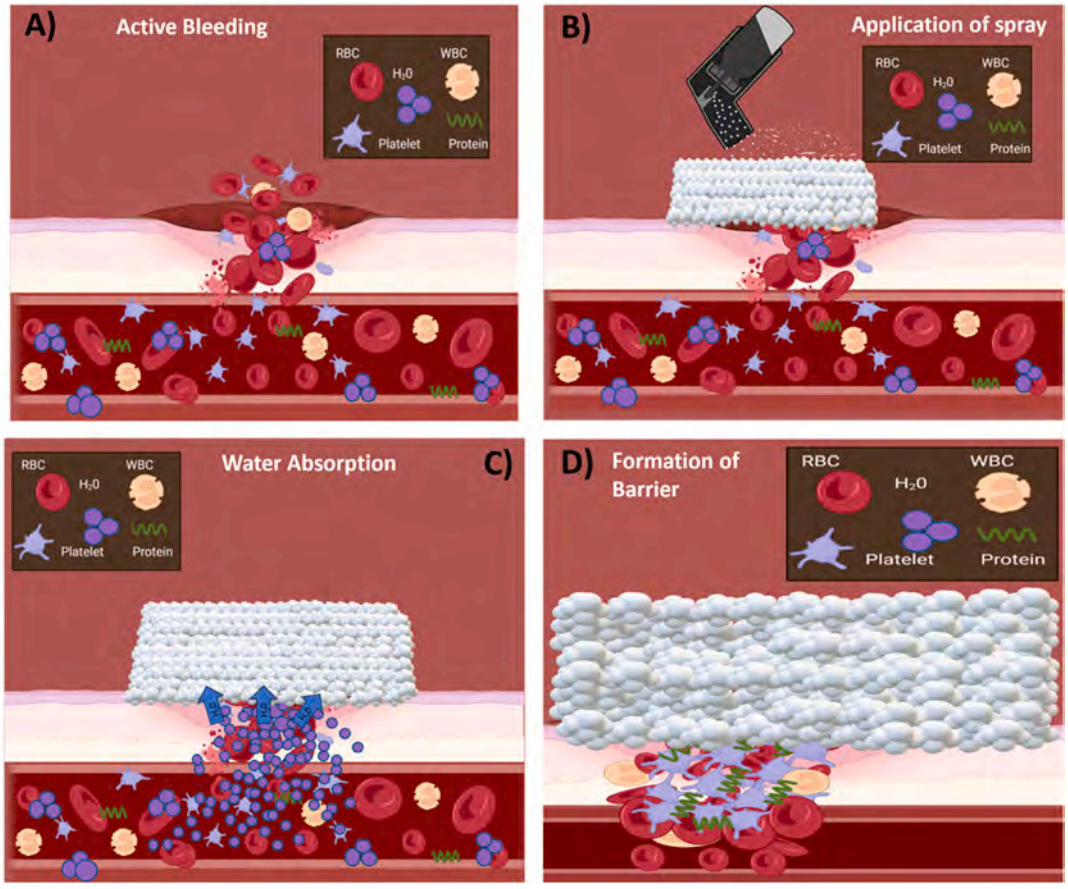

Fig. 1. Mechanism of action of Haemostatic Sprays (A) Endoscopic visualisation of an actively bleeding intraluminal site showing extravasation of blood components, including plasma, coagulation factors, platelets, white blood cells (WBCs), and red blood cells (RBCs).
(BC) Application of haemostatic spray to the bleeding site, followed by rapid absorption of plasma water, leading to concentration of blood cells and coagulation factors and formation of a physical barrier that limits further blood loss.(D) Formation of a cohesive mechanical barrier that stabilizes the clot and promotes rapid haemostasis.

devices, these systems are particularly effective on irregular and hard to reach surfaces.

Powder-based haemostatic sprays such as TC-325 (Hemospray®) have demonstrated strong efficacy in forming protective barriers that facilitate both rapid haemostasis and natural healing [36–42]. Solution-based sprays provide more uniform coverage and improved adaptability to complex wound geometrics. The dual-action mechanism is illustrated in Fig. 1, where haemostatic spray is shown first being applied to an actively bleeding site (A–B), followed by rapid water absorption that concentrates blood components (C), ultimately forming a cohesive mechanical barrier that promotes rapid haemostasis (D).

The evolving landscape of medical procedures and the growing need for effective intraoperative bleeding management highlight the significance of haemostatic sprays. This review aims to comprehensively explore the role, mechanisms, clinical applications, challenges, recent advances, and future directions of haemostatic sprays, with the primary objective of enhancing understanding within the medical community and supporting informed clinical decision-making. Key highlights include: i) a detailed examination of the classification and mechanisms of haemostatic sprays, covering their categorisation by mechanism, ingredients, and applications, along with the biochemical and physical processes underlying their efficacy; ii) an in-depth analysis of clinical applications, including effectiveness across various surgical procedures and emergency settings, particularly trauma and pre-hospital care; iii) an evaluation of current challenges and potential adverse effects, offering a balanced perspective on their limitations; iv) a focused review of recent advances in commercial haemostatic sprays, highlighting emerging technologies and innovative formulations; and v) the identification of research gaps and future directions to guide further exploration and advancement in the field.

By addressing these specific aspects, this review for the first time aims to provide a comprehensive understanding of haemostatic sprays, guiding medical practitioners and researchers in informed decision-making and fostering future innovations in medical practice.

2. Classification of Haemostatic sprays

2.1. Commercially (clinically) available haemostatic sprays

Rapid haemostasis is crucial for controlling haemorrhage during surgical, endoscopic, and emergency interventions. Traditional methods such as epinephrine injection, cyanoacrylate adhesives, thermal coagulation, argon plasma coagulation, and mechanical devices like clips and band ligation are effective yet possess significant limitations, including a 5–10% risk of rebleeding and diminished efficacy in cases of active or diffuse haemorrhage [29]. The constraints have prompted the advancement of haemostatic sprays, which provide non-contact, extensive, and swiftly applicable covering over irregular wound surfaces. Haemostatic sprays have shown efficacy in managing both upper and lower gastrointestinal haemorrhages and are progressively acknowledged in therapeutic guidelines; however, additional trials are required to clarify their functions and long-term effects [29]. For instance, Fig. 2(A) shows Hemospray, a mineral-based spray that absorbs fluid and promotes coagulation without causing biliary obstruction, making it advantageous over traditional methods like cautery. Fig. 2 (B-C) illustrate the Ankaferd BloodStopper, with subfigures showing its application from dental to general bleeding control. Fig. 2 (D) features PuraStat, known for its effectiveness in bleeding ulcers, while Fig. 2(E) displays Topical Haemocoagulase used in digestive endoscopy. Finally, Fig. 2(F) depicts the EndoClot Polysaccharide Haemostatic Spray, a plant starch-based innovation not yet available in the US. Given their expanding clinical relevance, these commercially available sprays are best examined by grouping them into their major material classes, each offering distinct advantages and limitations.

2.1.1. Mineral-based commercial haemostatic spray-hemospray (TC-325)

Hemospray is made of inorganic, non-absorbable, mineral-based bentonite/kaolin-derived powder. It is the most extensively researched spray technology and has obtained FDA approval for non-variceal

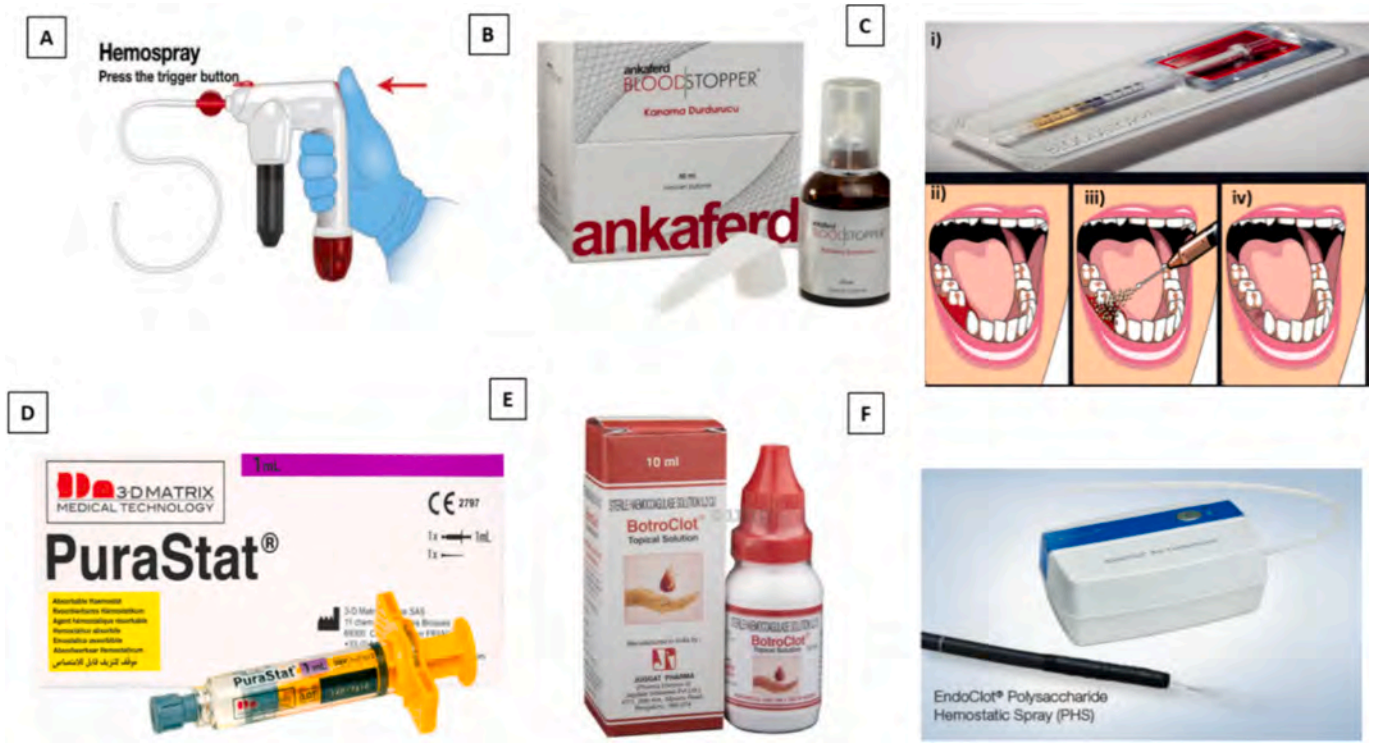

Fig. 2. Commercially available haemostatic spray systems and their material bases. (A) Hemospray (TC-325), a mineral-based powder. (B-C) Ankaferd BloodStopper, derived from plant polyphenolic extracts; (i–iv) application steps in dental bleeding. (D) PuraStat, a synthetic self-assembling peptide hydrogel. (E) Topical Haemocoagulase, an enzymatic protein-based agent. (F) EndoClot Polysaccharide Haemostatic Spray, based on modified plant starch.

gastrointestinal haemorrhage. The mineral particles, upon application, swiftly absorb water, concentrate clotting components, and establish a mechanical barrier that facilitates secondary haemostasis without infiltrating tissue or inducing heat damage [43]. Clinical evidence, comprising pilot randomized controlled trials, case series, and prospective studies, indicates elevated rates of immediate haemostasis with minimal procedure-related problems [29,43,44]. Comparative trials in malignant haemorrhage indicate superior initial haemostasis (90% versus 40% with standard therapy) and decreased rebleeding rates [44]. Its simplicity, non-contact application, and capacity to address extensive or difficult locations render it advantageous, especially for rapid or diffuse haemorrhaging.

2.1.2. Plant-extract haemostatic spray - Ankaferd blood stopper (Ankaferd)

Ankaferd is a standardised mixture of plant extracts (e.g., *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, *Urtica dioica*). It generates a protein network that clusters erythrocytes to establish a physical barrier independent of the traditional coagulation cascade. It is extensively utilized in Turkey for gastrointestinal, surgical, and dental haemorrhaging, although it lacks substantial worldwide clinical research or global regulatory endorsement. Systematic reviews indicate encouraging haemostatic efficacy and acceptable safety profiles; still, additional mechanistic and rigorously controlled clinical investigations are necessary prior to broad implementation [28,31]. Recent clinical studies and practice-based reports focusing on Ankaferd have reinforced its efficacy as a practical adjunct or salvage therapy, particularly in cases of non-variceal gastrointestinal bleeding and in situations requiring rapid, non-contact haemostasis, including applications by less experienced endoscopists. Retrospective cohort studies and clinical experience have shown high rates of immediate haemostasis with low rates of rebleeding. However, the evidence is mostly regional and observational, which shows that we still need well-designed multicenter randomized controlled trials and more in-depth mechanistic studies before we can recommend wider use [45–47].

2.1.3. Polysaccharide-based haemostatic spray - EndoClot® polysaccharide haemostatic system (EndoClot)

EndoClot is made up of polysaccharide particles (modified starch) that come from plants and can be absorbed. It works by quickly drying blood at the site of bleeding, which concentrates platelets and coagulation factors to speed up clot formation. It is very useful for controlling diffuse exudation and severe mucosal haemorrhage during endoscopic operations because it doesn't require contact and works quickly. Prior reviews indicated its primary application in Europe and Asia, emphasizing constraints regarding degradation behaviour and long-term outcome data [31]. However, EndoClot (notably the EndoClot PHS System) obtained U.S. Food and Drug Administration approval in 2021 and is now extensively utilized in the United States for the management of gastrointestinal bleeding [48]. Recent prospective clinical investigations have shown that non-variceal upper gastrointestinal bleeding has high rates of rapid haemostasis and good safety profiles, which supports its regular usage in clinical settings. Furthermore, contemporary guideline-based evaluations, including the European Society of Gastrointestinal Endoscopy (ESGE) Technical and Technology Review, acknowledge EndoClot and other topical Haemostatic powders as effective adjunctive or rescue therapies, particularly in complex bleeding situations such as arterial bleeding linked to lumen-apposing metal stent placement. Nonetheless, despite extensive implementation and significant short-term effectiveness, inconsistencies in rebleeding outcomes and a paucity of long-term comparative data persist as recognized limitations, highlighting the necessity for additional multicenter randomized trials and prolonged follow-up studies [28,49–51].

2.1.4. Synthetic peptide–based haemostatic spray - PuraStat® (self-assembling peptide hydrogel) (PuraStat)

PuraStat is made of synthetic RADA16-I peptide forming a nanofiber hydrogel on contact with fluids. It converts into a transparent, self-assembling hydrogel upon contact with blood, creating a mechanical barrier that occludes mucosal haemorrhage. It is very efficacious for post-endoscopic interventions, haemorrhaging ulcers, and mucosal lesions. Its transparency preserves endoscopic visibility, providing a benefit over opaque powders.

2.1.5. Protein-based (fibrin sealant) sprays - Raplixa™ and other fibrin-based sprays

These sprays are made of human-derived fibrinogen and thrombin in lyophilised powder form. Fibrin sealants mimic the concluding stages of the coagulation cascade by producing fibrin at the application site in the FINISH-3 trial [52]. Fibrin powders and sprays are extensively utilized in cardiac, vascular, neurosurgery, and trauma operations for their capacity to enhance clot stability, even in coagulopathic conditions [30].

2.1.6. Cyanoacrylate and synthetic polymer–based spray - cyanoacrylate adhesive sprays (e.g., Glubran®2)

Glubran is made of N-butyl-2-cyanoacrylate/synthetic copolymer adhesives. Cyanoacrylate-based sprays polymerise on contact with moisture, forming a strong adhesive barrier. They are used particularly for preventing bleeding after endoscopic mucosal resection (EMR) and other mucosal defects. Studies report reduced post-procedural bleeding when Glubran®2 is applied prophylactically [53].

2.1.7. Clinical and guidelines-based performance standards for haemostatic sprays

Regulatory and guideline-based parameters pertinent to gastrointestinal and surgical bleeding were used to interpret the clinical performance of haemostatic sprays. These include international endoscopy guidelines, specifically the American College of Gastroenterology (ACG) guidelines and the European Society of Gastrointestinal Endoscopy (ESGE) Technical Review, which specify the indications, efficacy, and safety requirements for topical haemostatic powders, gels, and sprays, as well as U.S. FDA approvals for endoscopic haemostats [14,61]. Furthermore, ESGE recommendations for the management of non-variceal gastrointestinal haemorrhage expressly advocate haemostatic sprays as first-line or rescue therapy in cases of diffuse or refractory bleeding [61].

Commercial haemostatic sprays are also subject to FDA 510(k) clearance, which establishes minimum safety, biocompatibility, and clinical effectiveness standards for endoscopic haemostatic devices, including polysaccharide- and polymer-based haemostatic sprays [62]. In Europe, devices may be CE-marked under the European Medical Device Regulation (EU MDR), while in certain Asian countries, national regulatory authorities govern product approval and clinical use. As a result, Table 2 compares commercial haemostatic sprays based not only on haemostasis time and tissue adhesion, but also on their adherence to internationally accepted clinical guidelines and regulatory approvals, providing a clinically relevant and translationally meaningful comparison.

3. Overall clinical perspective

According to Table 1 (commercial haemostatic sprays) and Table 2 (performance comparison), Hemospray (TC-325) is one of the most extensively studied and clinically established haemostatic sprays currently available. Its rapid action, typically achieving haemostasis within approximately 1 min, combined with broad applicability across variceal and non-variceal gastrointestinal bleeding and demonstrated efficacy in malignant haemorrhage, supports its frequent use as a first-line or rescue therapy in emergent and complex clinical scenarios. Its mineral-based formulation enables efficient fluid absorption and Factor

Table 1
Formulation and working mechanism of various commercial haemostatic sprays.

Product name	Formulation	Active ingredient	Mechanism	Indications	References
Haemostatic Powder Spray (TC-325): Hemospray	Mineral based powder	Kaolin	Kaolin activates factor XII, accelerating the transformation of prothrombin to thrombin, speeding up fibrin clot formation.	Used in endoscopic haemostasis during management of non-variceal upper gastrointestinal bleeding (NVUGIB), oesophageal variceal bleeding, acute variceal bleeding (AVB) management as adjunct to standard therapy, and gastrointestinal haemorrhage management. Particularly useful for cases where traditional haemostatic treatments are ineffective or less efficient.	([54]; [43]; [29]; [44]; [34]; [55]; [56]; [31]; [57]; [58]; [59])
Ankaferd Blood Stopper	Herbal extract blend	Tannic acid, Gallic acid, other phenolics	Forms a protein network that facilitates rapid erythrocyte aggregation and creates a mechanical barrier to stop bleeding.	Used for controlling bleeding in various settings, including gastrointestinal bleeding. Data primarily from Turkey shows promising results in managing gastrointestinal bleeding.	([28]; [31])
Endo Clot Polysaccharide Haemostatic System (PHS)	Polysaccharide based powder spray	Absorbable Modified Polymer (AMP): a plant derived, starch-based polysaccharide, biocompatible, absorbable and biodegradable	Absorbs water, concentrating blood cells and coagulation factors to enhance rapid clot formation and stabilization.	Used for managing gastrointestinal bleeding in settings where traditional methods fail. Available in United States, EMEA (Europe, Middle East, Africa),	([28]; [31]; [57])
Purastat	Highly absorptive mineral powder	Inorganic substances (not specified)	Functions through the rapid absorption of blood and concentration of coagulation factors, facilitating quick clot formation.	Used for treating bleeding ulcers and reducing delayed bleeding following GI endoscopic submucosal resection in the colon.	[57]
Raplixa	Fibrin sealant powder	Human fibrinogen, Thrombin	Delivers fibrinogen and thrombin directly to the wound, where thrombin converts fibrinogen into fibrin to form a clot.	Approved for adults to control bleeding in surgical procedures such as spinal, vascular, hepatic, or soft-tissue surgeries, where conventional methods are insufficient.	[52]
Modified Cyanoacrylate Glue (Glubran 2®)	Cyanoacrylate-based adhesive	Cyanoacrylate	Rapidly polymerizes in the presence of moisture, forming a strong bond that seals tissue and stops bleeding.	Indicated for preventing early or delayed post-endoscopic mucosal resection (EMR) bleeding, particularly in cases of large non-pedunculated polyps. Used as an adjunct to prophylactic clipping to enhance haemostasis and reduce re-intervention needs.	[53]
Topical Hemocoagulase Spray	Enzyme-based solution	Hemocoagulase	Converts fibrinogen to fibrin, forming a stable clot and simultaneously inhibiting the fibrinolysis process.	Applied intraoperatively to achieve haemostasis during digestive endoscopy procedures, especially when traditional methods like norepinephrine spray are ineffective.	[60]

XII activation, facilitating rapid clot formation without deep tissue penetration. Nevertheless, its comparatively high cost may limit routine use in resource-constrained settings.

PuraStat, a self-assembling peptide hydrogel, is a very good tissue adhesive and promotes epithelial healing and is therefore highly appropriate for application in post-endoscopic resection bleeding and mucosal healing. Its moderate price range (USD 500–700 per syringe) and growing clinical use additionally enhance its feasibility, although cold storage temperatures (2–8 °C) may limit usability in some environments as shown in Table 3.

Raplixa, although slower to initiate clotting as a solo agent compared with TC-325, is very versatile in the operating field, including cardiovascular, hepatic, and soft tissue surgery. Its fibrinogen–thrombin matrix simulates the natural coagulation cascade and is of tremendous value in coagulopathic patients. The cost, however, is significant (USD 1500–2500 per vial), therefore widespread application will be restricted beyond high-resource surgical centers. Significantly, when combined with a gelatin sponge, Raplixa facilitates haemostasis, with clots developing in 1–2 min. Conversely, less expensive agents such as Ankaferd Blood Stopper (~USD 100–150) and Topical Hemocoagulase (~USD 20–50) offer regionally available alternatives but with less extensive clinical evidence and international regulatory approval compared to Hemospray, PuraStat, or Raplixa.

In summary, Hemospray (Fig. 3) represents a well-validated option for endoscopic haemostasis in large-volume gastrointestinal bleeding, supported by the breadth of clinical evidence and regulatory approval. However, alternative sprays such as PuraStat and Raplixa demonstrate distinct advantages in specific contexts, including mucosal healing and surgical haemostasis, underscoring that product selection should be guided by bleeding type, clinical setting, and practical considerations rather than a single universally superior agent.

3.1. Non-commercial (pre-clinical) haemostatic sprays

Uncontrolled visceral haemorrhage continues to be a clinical challenge, especially in trauma and surgical practices where speedy and successful haemostasis is vital for survival. Both in civilian and military contexts, conventional haemostatic methods like electrocoagulation or local injection haemostasis can be ineffective in cases of incompressible or internal bleeding [67,68]. To address these limitations, pre-clinical haemostatic sprays have been developed as promising substitutes. These sprays facilitate the body's innate haemostatic process using quick physical and biochemical action [69,70].

Mechanistically, non-commercial haemostatic sprays are intentionally designed to utilize certain physical, chemical, and biological routes to attain fast haemostasis in intricate wound environments. Some of these mechanisms are concentrating coagulation factors through plasma absorption, activating the intrinsic coagulation cascade through charged

Table 2
Performance comparison of commercially available haemostatic sprays with guideline and regulatory benchmarking.

Material type	Key strength	Weakness	In vivo haemostatic time	Tissue adhesion	Clinical context	Guideline/Regulatory status (national standards)	References
Hemospray (TC-325)	Mineral-based (kaolin); strong fluid absorption; Factor XII activation; rapid coagulation	Temporary visualisation impairment; rebleeding risk in severe cases	Often achieves haemostasis immediately around ~1 min (initial haemostasis rate: 98–99%)	Moderate	First-line and rescue therapy for nonvariceal & variceal GI bleeding, malignant bleeding	FDA-approved endoscopic haemostat; recommended as rescue/adjunct in ACG and ESGE guidelines	([43]; [44]; [61]; [34]; [14])
Purastat	Self-assembling peptide hydrogel; strong adhesion; promotes healing	Cost; limited long-term data	~ 1 min	High	Post-endoscopic resection bleeding, bleeding ulcers	Included in ESGE Technical Review for topical haemostatic agents	([61]; [63]; [57]; [64])
Raplixa	Fibrin sealant (fibrinogen + thrombin); mimics physiological coagulation	Cost; limited GI-specific data	N/A		General surgical bleeding: applied via spray directly to bleeding sites.	FDA-approved fibrin sealant for surgical haemostasis	
Raplixa+gelatin	Rapid clot formation: enhanced haemostatic efficacy when combined with gelatin	Higher cost: human plasma derived (infection risk minimal but present	1–2 min	High	Surgical bleeding (vascular, hepatic, soft tissue, cardiac)	FDA-approved fibrin sealant system	([65]; [52]; [35]; [66])
Ankaferd Blood Stopper®	Forms protein network and aggregates RBCs rapidly; effective mechanical barrier.	Limited global regulatory approval.	Rapid, typically within seconds to ~1 min	Moderate	GI bleeding, dental bleeding, postoperative bleeding; widely used in Turkey	Included in ESGE Technical Review as topical haemostat (limited evidence)	[28,31,61]
EndoClot® Polysaccharide Haemostatic System	Strong water absorption; concentrates clotting factors; fully absorbable and biodegradable.	Limited availability in some regions.	Rapid (<1 min)	Low–Moderate	Diffuse mucosal bleeding; post-procedural bleeding where standard tools fail	FDA 510(k) cleared (2021); included in ESGE Technical Review	([28]; [61]; [31]; [57])
Glubran® 2 (Cyanoacrylate-Based Adhesive)	Rapid polymerisation on tissue; creates strong adhesive seal; prevents delayed bleeding	Requires careful application; risk of tissue sticking	Immediate	Very High	Preventing early and delayed bleeding after EMR; large non-pedunculated polyps; adjunct to prophylactic clipping	CE-marked Class III medical device under the European Medical Device Regulation (EU MDR) for surgical and endoscopic tissue adhesive applications; not specifically FDA-cleared as a dedicated endoscopic haemostatic spray in the United States	[53]
Topical Hemocoagulase Spray	Converts fibrinogen → fibrin; inhibits fibrinolysis; rapid clot stabilization	Limited evidence beyond digestive endoscopy; potential enzyme degradation	Rapid	Moderate	Haemostasis in digestive endoscopy when norepinephrine or standard sprays insufficient	Approved for clinical use in China and reported in clinical practice in parts of India and Southeast Asia; not FDA-approved in the United States and not specifically recommended in major ACG or ESGE endoscopic guidelines.	[60]

or porous surfaces, forming hydrogels in situ through dynamic covalent or ionic crosslinking, and strong tissue adhesion through covalent and non-covalent interactions. Commercially available sprays typically have relatively fixed compositions, whereas preclinical systems allow systematic tuning of material chemistry, microstructure, and bioactivity to optimise performance in terms of speed, stability, tissue compatibility, and multifunctional capability. The subsequent sections highlight the mechanistic differences among material categories and relate these mechanisms to their demonstrated in vivo haemostatic efficacy and clinical relevance.

As described in Table 4, various composite materials have been explored for the development of pre-clinical haemostatic sprays, each exhibiting distinct mechanisms of action and target clinical uses. These materials are evaluated by key performance indicators, including coagulation time (CT), total blood loss, tissue adhesion, and ease of use. Functional efficacy of short-listed formulations is visually depicted in Fig. 4, representing their performance under a series of pre-clinical models such as gastric perforation, post-surgical bleeding, and internal haemorrhage. In addition, a comparative review of these materials based on their strengths, limitations, and functional performance is summarised in Table 5.

3.1.1. *Clay-based sprays*

Clay-based sprays primarily achieve haemostasis through plasma absorption mediated concentration of clotting factors and activation of the intrinsic coagulation pathway via negatively charged surfaces [71,72]. Early formulations, such as zeolite powders (e.g.,-first-generation QuikClot), produced exothermic reactions upon contact with blood,

Table 3
Storage condition and cost of some commercial haemostatic sprays.

Product	Storage condition	Components needed	Price (currency)	Reference
Hemospray (TC-325)	Room temperature (single-use canister)	Endoscopic catheter and delivery system	Approx. USD 1500–2000 per application	([43]; [44]; [34])
Ankaferd Blood Stopper	Room temperature	Spray vial	~USD 100–150 (per 50 mL) – mostly marketed in Turkey	([28]; [31])
EndoClot Polysaccharide Haemostatic System	Room temperature	Powder cartridge, CO_2 propellant delivery system	~USD 1200–1800 per kit (not FDA-approved, Europe/Asia only)	([28]; [31]; [57])
PuraStat	Refrigerated (2–8 °C)	Pre-filled syringe, endoscopic catheter	~USD 500–700 per syringe	[57,63,64]
Raplixa (fibrin sealant powder)	Room temperature (lyophilized)	Spray applicator, fibrinogen + thrombin powder	~USD 1500–2500 per vial	([65]; [52]; [35]; [66])
Glubran®2 (Cyanoacrylate)	Room temperature	Syringe + delivery catheter	~USD 100–200 per vial (1–2 mL)	[53]
Topical Hemocoagulase	Refrigerated (2–8 °C)	Spray solution vial	~USD 20–50 per vial (varies by region)	[60]

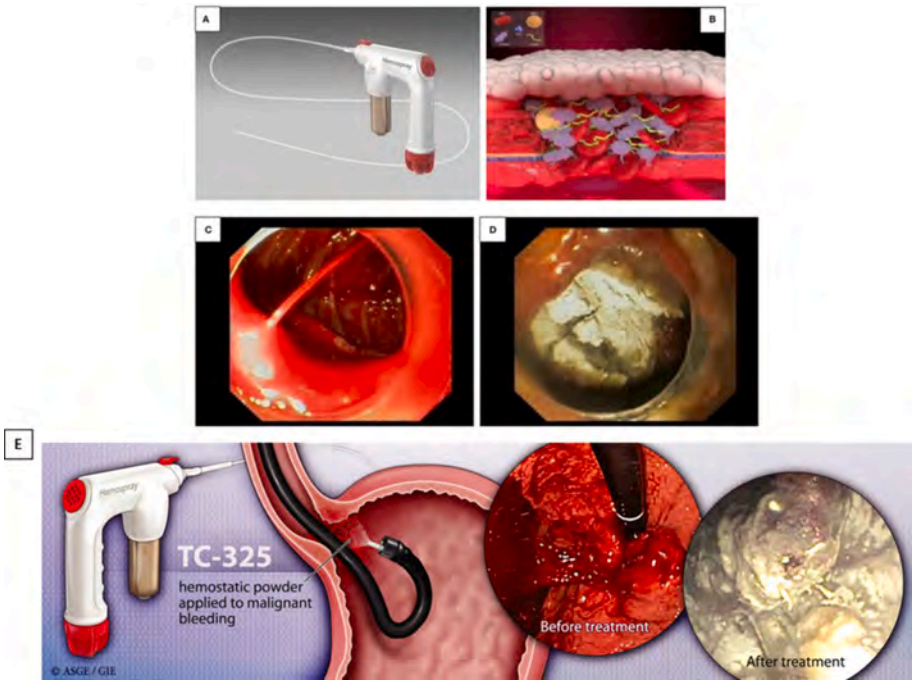

Fig. 3. The figure illustrates the mechanism of action of Hemospray®, depicting its role in forming a mechanical tamponade, initiating the coagulation cascade, and facilitating immediate clot formation to stop bleeding effectively [44]. (A) Hemospray® device. (B) Activation of the coagulation cascade by Hemospray® results in immediate coagulation. (C) Significant GI bleeding before and (D) after Hemospray® procedure. (E) Hemospray applied to the malignant bleeding [57].

posing a significant risk of thermal injury [71]. Kaolin-based dressings (e.g. Combat Gauze) largely replaced zeolite due to their ability to activate coagulation without heat generation and improved safety profile [72].

This mechanism is further supported by quantitative analyses demonstrating that clay-based haemostatic systems markedly accelerate clot formation and reduce blood loss in vivo. Formulations incorporating kaolin or zeolite have been reported to shorten clotting times by approximately 40–70% compared with standard gauze, with haemostasis achieved within 10–30 s in clinically relevant arterial bleeding models. In large-animal swine femoral and groin injury models, clay-based dressings reduced total blood loss by more than 50% relative to conventional compression and achieved near-complete haemorrhage control, with reported survival rates approaching 100% [23,73,74]. In some studies, time to haemostasis was reduced from several minutes with gauze to under 1 min using kaolin- or zeolite-based materials. These quantitative improvements correlate directly with the physicochemical characteristics of clay materials, including high specific surface area, interconnected porosity, and negatively charged surfaces, which enhance platelet adhesion, promote Factor XII-mediated intrinsic pathway activation, and facilitate rapid plasma absorption [71,72].

In in vivo applications, mesoporous zeolite bonded to cotton fibres are applied directly as sprayable powders or aerosolized onto the wound surface, forming a cohesive clot-promoting layer. Electrospun clay membranes are delivered as flexible sheets that can be gently pressed or layered over irregular anatomical wound sites to create a physical barrier, absorb exudates, and initiate clotting through surface activation. Their spray-compatible nanoporous structure allows them to rapidly bind with blood and adhere to moist tissue upon contact [74,75]. Quantitatively, clay-based haemostatic systems have demonstrated significant reductions in clotting time (approximately 40–70% compared with standard gauze), with haemostasis achieved within 10–30 s in arterial injury models. Total blood loss has been reported to decrease by more than 50% relative to untreated controls in large-animal femoral artery injury studies [73–75].

Moreover, advanced composites combining kaolin and zeolite leverage their complementary mechanisms to accelerate coagulation without the thermal drawbacks of pure zeolite formulations, and their efficacy has been validated in vivo. For instance, in a lethal swine groin/femoral artery injury model, zeolite-based dressings achieved 100% survival, rapid haemostasis within seconds to under 1 min and effective haemorrhage control without causing excessive tissue damage

Table 4
Composite materials for the preparation of preclinical haemostatic spray.

Materials used	Preparation	Mechanisms	Indications	References
OOZFIXTM: Carboxymethyl starch, calcium chloride, ethanol	Carboxymethyl starch and calcium chloride dissolved in ethanol, then filtered, dried, finely ground, and sieved into a sprayable powder	Calcium ions crosslink with starch to form a porous ionic network that rapidly absorbs blood, concentrates coagulation factors, and accelerates clotting; stable clot maintained by reduced desorption	Surgical haemostasis, especially in narrow/complex sites; rapid haemostasis with biodegradation	[81]
Thrombin sealants: Bovine or Recombinant Human Thrombin	Derived from bovine plasma or produced recombinantly; supplied as solution or powder.	Thrombin converts fibrinogen into fibrin and activates factor XIII, which crosslinks the fibrin to stabilize the clot and accelerate the natural coagulation process at bleeding sites.	- General surgical procedures - Cardiovascular surgery, including major vascular procedures like aortic dissections and aortic aneurysms.	[35]
Fibrin Sealants: Freeze-dried fibrinogen, factor XIII, fibronectin; human or bovine thrombin	Fibrin sealants are prepared in two parts: one containing thrombin and the other fibrinogen reconstituted at point of care	When delivered in fibrin sealants, this mechanism closely mimics physiological coagulation, producing a stable fibrin network.	- Various types of interventions in cardiovascular surgery - Redo cardiac procedures - Major aortic procedures - Treatment or prevention of diffuse bleeding	
Vivostat: Autologous fibrinogen and thrombin (from patient's blood)	Patient's blood processed into fibrinogen and thrombin, delivered via specialized spray device application and rapid activation of the sealant.	In autologous systems such as Vivostat, sprayed fibrinogen and thrombin rapidly form a fibrin clot with high biocompatibility and minimal risk of immune genicity.	- Cardiothoracic surgery - Paediatric cardiac surgery, particularly in cases with proven coagulopathy	
Thermosensitive nasal spray: Chitosan, Tranexamic Acid (TXA), β-Glycerophosphate	Formulated as a thermosensitive in situ gel. At low temperature, it remains liquid for easy spray delivery. At nasal cavity temperature, it transitions to a gel.	Transitions to gel on nasal delivery, adheres to mucosa, prolongs TXA contact, stabilizes clot	Epistaxis management, post-surgical nasal wound care; enhanced mucosal retention and drug delivery (nosebleeds).	[86]
Chitosan and sodium alginate micro/nanofibrids: Chitosan, sodium alginate	These haemostatic agents are formulated using chitosan and alginate fibrids. The fibrids are created using a wet process with a flow reactor, producing micro- and nanofibrids. The formulation process involves freeze-drying or spray-drying the fibrid suspension to convert it into a powder form suitable for application as a topical agent. This method ensures controlled release and efficient delivery of the active ingredients to the wound site.	On blood contact, fibrids swell and activate intrinsic coagulation pathway; form physical barrier.	Emergency and surgical haemostasis; rapid bleeding control in trauma and operative settings	[90]
Carboxymethyl Chitosan - Aldehyde-modified hyaluronic acid grafted with catechol groups haemostatic spray (CMCS-COHA): Hyaluronic acid, chitosan, Dopamine hydrochloride, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.	Bi-component powder of carboxymethyl chitosan (CMCS) and aldehyde-modified hyaluronic acid grafted with catechol groups (COHA).	Upon contact with blood, CMCS and COHA rapidly absorb plasma and self-crosslink within ~10s via Schiff-base linkages, electrostatic interaction, and cation–π association: hydrogel traps blood cells/platelets and adheres tightly to tissue, forming a pressure-resistant barrier.	External and internal non-compressible bleeding; rapid barrier formation with strong adhesion.	[84]
Carboxymethyl chitosan/poly-γ-glutamic acid/oxidized dextran (CPO) powder spray: Carboxymethyl chitosan, poly-γ-glutamic acid, oxidized dextran, 1-(3-Dimethylaminopropyl)-3-ethylcarbapenem (EDC), N-Hydroxybutanediimide (NHS)	CMCS, γ-PGA, and OD are physically mixed and processed to create the CPO powder.	On blood contact, powder absorbs water and forms hydrogel within ~15 s via amide and Schiff-base bonds; aldehyde groups of OD react with tissue amines, improving adhesion and sealing.	Gastric perforation haemostasis; antibacterial wound healing in infected mouse models.	[82]
Chitosan-based hydrogel: Chitosan	Injectable chitosan hydrogel was prepared, which converted from sol to gel form under physiological conditions.	Hydrogel absorbs plasma, concentrates coagulation factors, and forms stable clot; biodegradable with effective biodistribution.	Liver injury bleeding and degradation evaluation	[77]
Chitosan based multifunctional flexible haemostatic bio-hydrogel:3-(3,4-dihydroxyphenyl) propionic acid-modified chitosan (DCS) and PEG-modified crosslinkers (PEGSH)	The hydrogel is synthesized via a green approach by cross-linking PEGSH with 3-(3,4-dihydroxyphenyl) propionic acid-modified chitosan in a stretchy, self-sealing, and adhesive matrix.	Rapidly absorbs blood, activates coagulation by surface interaction, and strongly adheres even in humidity; forms protective barrier suppressing blood loss.	Effective for irregular wound surfaces and moderate to severe bleeding control	[83]
Natural derived polysaccharide/protein hydrogels: Chitosan, alginate and natural proteins	Hydrogels were fabricated using naturally derived proteins and polysaccharides.	Enhance clot formation, support tissue integration; provide controlled degradation and biocompatibility.	Surgical bleeding control and wound healing	([77]; [78])
Sprayable macroporous alginate/chitosan stacked hydrogels: Alginate and chitosan	Developed through a layer-by-layer stacking method, these hydrogels possess interconnected macropores to enhance fluid uptake.	Macropores enhance fluid uptake; conform to wound geometry, enabling rapid haemostasis and tissue regeneration.	Wound healing and bleeding control in surgical and trauma applications	([91]; [85]; [83]; [78])
SSAD Haemostatic powders: Skin secretion of *Andrias davidianus* (SSAD), hyaluronic acid,	Mucus is collected from *Andrias davidianus*, purified, lyophilized, and	Particle porosity/topography promotes blood absorption and	Rapid Haemostasis: Effective in liver and	[42]

(*continued on next page*)

Table 4 (*continued*)

Materials used	Preparation	Mechanisms	Indications	References
chitosan, dopamine hydrochloride, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, n-hydroxy succinimide.	milled into particles sized between 200 and 800 μm. The powder is then packaged into a spray dispenser for easy application.	intrinsic coagulation activation; even spray distribution enhances clotting efficiency	femoral artery injuries; oral/dental surgeries applications; wound healing.	
Zeolite-based haemostat spray consisting of: Ag-doped β zeolite (Ag-*β*Z), fibrinogen/thrombin (F/T)	Ag-βZ is synthesized by doping β-zeolite with silver using a silver nitrate solution and UV light exposure. Fibrinogen and thrombin are prepared in separate buffered saline solutions. The two are mixed to form the composite haemostat spray.	Thrombin converts fibrinogen to fibrin, forming gel with Ag-βZ; gel enhances clotting, reduces heat, releases antibacterial silver ions.	Post-surgical wound sealing; infection prevention and enhanced tissue integration.	[88]
Zeolite-based haemostatic agent: Zeolite	Zeolite-based granules were prepared and applied topically to bleeding wounds.	Porous structure rapidly absorbs plasma, concentrates coagulation factors, and activates intrinsic coagulation cascade	Lethal complex groin injury; trauma haemostasis	[73]
Sprayable ciprofloxacin-loaded poloxamer hydrogels: Poloxamer 407 (also known as Pluronic® F127, molecular weight ~ 12,600 g/mol), Poloxamer 188 PRO (also known as Pluronic® F68), Ciprofloxacin Hydrochloride (CH).	Pluronic F127 and F68 are dissolved in cold acetate buffer, creating a thermosensitive solution. CH is then added to create a sprayable formulation. The formulation is low viscosity at low temperatures, allowing it to be sprayed onto wounds.	Low viscosity at low temperature for spraying: gels at skin temperature forming hydrogel that adheres and slowly releases ciprofloxacin.	Burn and chronic wound infection treatment; provides antibacterial protection and moist healing.	[87]
Heparin-Encapsulated Metered-Dose Topical "Nano-Spray Gel": Heparin, Ibuprofen, Liposomes	Heparin-loaded liposomes are prepared using a thin-film hydration method followed by extrusion through polycarbonate membranes. Ibuprofen and other gel components are then integrated to form the nano-spray gel.	Creates topical barrier, controlled release of heparin/ibuprofen; reduces inflammation, modulates cytokines, supports tissue repair.	Frostbite treatment; reduces inflammation, improves capillary blood flow, and aids tissue repair.	[92]
Organoid-Based Spray: Human Epidermal Organoids, Hyaluronic Acid, Collagen I, Basement Membrane Extract (BME)	Organoids derived from human skin tissues are cultured in conditions allowing multiple passages and expansion. They are delivered using an auto micro atomization device (AMAD) designed for precise, uniform spray onto wound sites.	Maintains cell viability via optimized atomization; promotes engraftment, epithelial regeneration, angiogenesis.	Severe skin wounds; supports epithelial regeneration, angiogenesis, and enhanced healing.	[89]

[23,72–74].

3.1.2. Protein-based and fibrin-based sprays

Protein and fibrin-based sprays function by directly mimicking the terminal steps of the coagulation cascade, resulting in rapid fibrin clot formation and strong tissue adhesion [35]. These formulations offer high efficacy and strong tissue adhesion, but when manufactured from bovine thrombin or pooled human plasma, they carry risks of immune reaction, anaphylaxis and potential blood-borne pathogen transmission [76]. Autologous fibrin sealants, e.g., Vivostat®, minimise risks and have higher biocompatibility, while retaining fast clot formation and excellent biocompatibility [35].

New advancements have broadened the use of protein-based hydrogels from conventional fibrin-based preparations. Experiments have shown that chitosan-based hydrogels, particularly those containing protein-based elements, show efficient haemostasis in rat models of liver injury with suitable biodegradability and biodistribution [77]. A broader review by Xia et al. [78] also highlights the multifunctional characteristics of natural protein-polysaccharide hydrogels in the achievement of haemostasis as well as wound healing, highlighting their clinical transmissibility to surgery and trauma [78].

3.1.3. Plant polysaccharide-based bio adhesive and thermosensitive haemostatic sprays

Plant polysaccharide-based haemostatic sprays rely on dynamic hydrogel formation and multi-modal tissue adhesion mediated by hydrogen bonding, ionic interactions, and covalent crosslinking [79,80]. Despite their advantages, they exhibit low mechanical strength and can dissolve prematurely reducing barrier stability in heavy bleeding. Newer haemostatic agents like OOZFIX™ and CPO powders have taken care of such drawbacks. OOZFIX™ is a bioabsorbable carboxymethyl starch–calcium ionic assembly with the capacity to absorb blood at a fast rate and establish a stable hydrogel network at the wound site [81].CPO powders, comprising carboxymethyl chitosan/poly-γ-glutamic acid/oxidized dextran, also crosslink rapidly and form in situ hydrogels with robust tissue adhesion [82]. They offer good adhesive capability due to their three-dimensional polymeric framework and presence of bio-adhesive functional groups (such as hydroxyl, amine, and carboxyl). These powders are administered as μm-sized sprayable particles that self-crosslink upon contact with warm blood or wound fluid to form in situ hydrogels that adhere tightly and build physical sealing layers. Their adaptability to wet and irregular wound surfaces make them ideal for the control of non-compressible haemorrhage and surgical bleeding. The functional groups present in it promote tissue adhesion by more than one mechanism. Hydroxyl groups are involved in hydrogen bonding with polar side chains of amino acids present in tissue proteins, enhancing interfacial interaction. Amine groups interact electrostatically with negatively charged extracellular matrix components and get involved in Schiff base reactions with aldehyde groups formed during tissue injury, resulting in covalent linkages. Carboxyl groups, being negatively charged at physiological pH, establish ionic interactions with positively charged residues such as lysine and arginine in proteins, further strengthening adhesion. All of these bonds together cause strong and conformal adhesion to irregular and moist wound surfaces, thereby supporting effective wound healing, accelerated clot formation, reduced blood loss, and enhanced tissue regeneration.

Recent developments, such as chitosan-derived multifunctional flexible haemostatic bio-hydrogel, have demonstrated enhanced

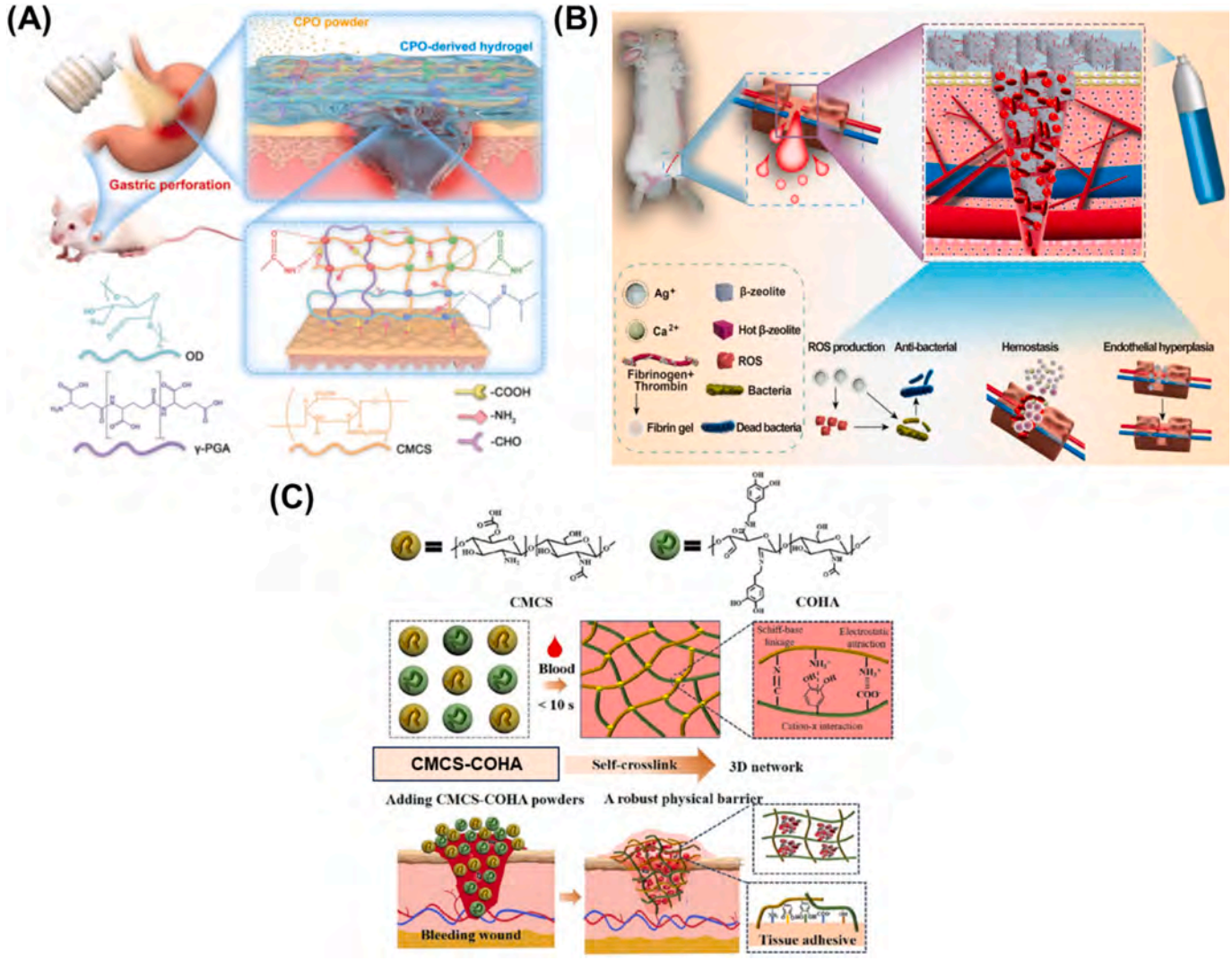

Fig. 4. The figure illustrates the use of composite materials in the preparation of a haemostatic spray, showcasing their role in promoting haemostasis and wound healing. (A) Illustration depicting the gastric perforation model in rats treated with CPO powder [82]. (B) Schematic representation of a composite zeolite-based haemostatic spray, comprising Ag-doped β zeolite (Ag-βZ) and coupled fibrinogen/thrombin (F/T), utilized to seal postsurgical blood bursts, and mitigate bacteria-induced inflammation for enhanced wound healing in rabbits [88]. (C) Schematic depiction of self-crosslinking and wet adhesive properties of CMCS-COHA [84].

coagulation functionality and flexibility, and exhibit efficient response to wound geometries and maintain haemostatic function under dynamic physiological conditions. The hydrogel exhibits rapid blood absorption, activates coagulation through surface contact, and develops a stable adhesive layer, which results in minimal blood loss and improved healing conditions [83].

Tissue adhesion is important for contact between the bleeding site and the haemostatic agent in irregular or wet anatomical areas. The CMCS-COHA hydrogel spray [84] consists of carboxymethyl chitosan (CMCS) which provides amine groups, and aldehyde-modified hyaluronic acid grafted with catechol groups (COHA),which contributes aldehyde and catechol groups. These functional groups interact specifically with tissue proteins, where amine groups from CMCS form Schiff base covalent bonds with aldehyde groups on injured tissue surfaces. On the other hand, catechol groups create hydrogen bonds and cation-π interactions with amino acid residues (e.g. lysine and arginine) in extracellular matrix proteins. Collectively, these covalent and non-covalent interactions result in a stable and conformal hydrogel barrier that adheres strongly to wet and uneven tissue surfaces, thereby enabling rapid haemostasis and promoting a favourable wound healing environment.

Similarly, sprayable macroporous alginate/chitosan stacked hydrogel system has been of great promise in preclinical wound models. Extremely porous and stackable, it promotes blood uptake and accelerates coagulation while preserving structural stiffness and flexibility in tissue cavities. Its macroporous nature promotes efficient blood infiltration and facilitates cellular interaction, favouring haemostasis and tissue regeneration [85].

Additionally, chitosan-based thermosensitive nasal sprays [86] demonstrate extended mucosal retention and enhanced wound contact, with particular application in epistaxis treatment. Including temperature-sensitive polymers like poloxamers (Pluronic F127 [87] enhances drug delivery, adhesion, and spray ability through their thermoreversible gelation properties. These polymers can be in a liquid state at low temperature to enhance spraying and ease of deposition, and then, when exposed to body temperature, undergo a sol-gel transition to form a viscous hydrogel that sticks to the wound surface. This phase change increases tissue retention, decreases material loss, and provides a sustained release platform for therapeutic drugs, improving overall treatment efficacy.

Table 5
Performance comparison of non-commercial sprays.

Material type	Key strength	Weakness	In vivo haemostasis time	Tissue Adhesion	Animal model	References
Clay-Based (e.g. zeolite cotton hybrid, kaolin-zeolite composites)	Rapid water absorption, strong platelet activation, Factor XII activation	Risk of thermal injury in early zeolite formulations	3 min	Moderate	Swine femoral/groin injury	([73]; [75]; [74])
Protein-Based (e.g., fibrin, thrombin sprays/hydrogel)	High efficacy in clot stabilization	Immune /hypersensitivity risk with bovine components; pathogen transmission	~50 s-2 min	High	Liver model in mice and rats;	([77]; [91]; [35]; [76]; [78])
Plant Polysaccharides (Chitosan-alginate hydrogels/sprays)	Biocompatibility and bio absorbability supports coagulation and healing	Moderate mechanical strength	~50 s – 1.2 min	Moderate-High	Rat liver trauma model, Rat femoral artery and tail amputation model	([85]; [80]; [83]; [93])
Adhesive Hydrogels (e.g., CMCS-COHA)	Strong adhesion, pressure resistance	Complex synthesis	< 1 min (instant haemostasis)	Very High	Rat femoral artery injury model and Rat liver model	[84]
OOZFIX™ (Carboxymethyl starch–calcium network)	Rapid clotting via ionic crosslinking; biodegradable.	Less effective in high-pressure arterial bleeding.	~30–60 s	Moderate	Rat gastric perforation model	[81]
CPO Powder (Carboxymethyl chitosan/γ-PGA/OD)	Ultra-fast hydrogel (~15 s); antibacterial & sealing	Moisture-sensitive during storage	<1 min	High	Rat gastric perforation, infected wound	[82]
Chitosan-Based Injectable Hydrogel	Plasma absorption, stable clot, biodegradable.	Moderate strength; slow to gel	~1–2 min	Moderate	Rat liver injury	[77]
Flexible Chitosan Bio-Hydrogel (DCS/PEGSH)	Stretchable, self-sealing, strong adhesion.	Synthesis complexity	<1 min	High	Rat tail and arterial model	[83]
Chitosan–Alginate Micro/Nanofibrids	Strong swelling and coagulation activation	Dissolves after saturation	~1–1.5 min	Moderate–High	Rat femoral artery and liver trauma	[90]
Thermosensitive Nasal Spray (Chitosan–TXA–βGP)	Thermo-gel transition; mucosal retention	Limited to nasal applications	<1 min	Moderate	Sheep epistaxis model	[86]
Natural Polysaccharide/Protein Hydrogels	Healing support and tissue integration	Slower clotting than fibrin	~1–2 min	Moderate	Rat liver model	([77]; [78])
Macroporous Alginate/Chitosan Stacked Hydrogels	High absorbency; conforms to wound shapes	Not easily sprayable	<1 min	Moderate–High	Surgical wound and trauma models	([91]; [85]; [83]; [78])
SSAD Powders (Amphibian secretion-based)	Antimicrobial, regenerative, rapid clotting	Formulation variability	~30 s–1 min	High	Rat/mouse liver and femoral injury	[42]
Zeolite-based containing Ag doped β-zeolite +Fibrinogen/thrombin	Antibacterial and thermally safe	Material cost	Rapid haemostasis (exact time not specified)	High	Rabbit femoral vein injury model	[88]
Ciprofloxacin-loaded Poloxamer Hydrogel	Antibacterial, thermogelation, wound protection	Not primarily haemostatic	Not specified (gels at body temp)	Moderate	Burn and chronic wound models	[87]
Nano-Spray Gel (Heparin/Ibuprofen/Liposomes)	Anti-inflammatory, barrier-forming	Not haemostatic; supportive only	N/A	Moderate	Frostbite wound model	[92]
Organoid-based sprays	Wound healing and epithelial regeneration	Early-stage research	Not reported	High	Skin defect model: murine skin defect models	[89]

3.1.4. *Metal-enhanced and zeolite composite sprays*

Metal-enhanced haemostatic sprays integrate rapid clot formation with antimicrobial activity through metal ion release and nanozyme-mediated catalytic mechanisms. Zeolite composite sprays containing Ag-doped β-zeolite and fibrinogen/thrombin [88] are aerosolized by means of pressurized spray devices, leading to a fine layer that coats the wound surface and rapidly traps plasma, activates platelets, and forms a stable clotting matrix. Sustained release ensures antimicrobial protection around the wound site through the release of Ag^{+} ions. Meanwhile, fibrinogen and thrombin facilitate the quick formation of fibrin clots. This creates a stable biological seal over the wound. Zeolite's porous structure absorbs exudates, moistens the healing environment, and facilitates clot incorporation into the neighbouring tissue. Therefore, these sprays are especially useful in the management of post-surgical wounds.

Similarly, *Andrias davidianus*'s skin secretion (SSAD) sprays offer a novel biological route to instant haemostasis and wound healing with minimum immune activation [42]. SSAD has a heterogeneous composition of peptides, proteins, and bioactive molecules possessing procoagulant, anti-inflammatory, and antimicrobial activities. Its composite components induce instant haemostasis through fibrin formation, platelet aggregation, and inhibition of abnormal immune system activation, thereby reducing inflammation and tissue damage. SSAD's bioactive molecules also promote cell proliferation and angiogenesis, enhancing wound healing. This multi-biological mode of action makes SSAD sprays a next-generation solution for haemostatic and regenerative applications.

3.1.5. *Organoid based sprays*

Organoid-based sprays represent a mechanistically distinct class of sprayable biomaterials, delivering micro-atomized human epidermal organoids within a supportive matrix of hyaluronic acid and extracellular proteins. Rather than directly inducing haemostasis through coagulation cascade activation or plasma absorption, these systems primarily function by enhancing post-haemostatic tissue repair through epithelial regeneration, angiogenesis, and cell proliferation [89]. Although organoid-based sprays demonstrate promising regenerative outcomes in keratinocyte cultures and murine skin defect models, their capacity to achieve immediate bleeding control remains at an early stage, and further pre-clinical validation is required to establish their role in acute haemorrhage management.

4. Overall summary

Collectively, these findings highlight that no single haemostatic

spray fulfills all clinical requirements, but certain materials outperform others in specific contexts. Clay-based hybrids, such as kaolin-zeolite composites, are notable for acute trauma management, offering very rapid coagulation (~10–30 s) through plasma absorption and Factor XII activation, with proven efficacy in large-animal arterial injury models [73,74]. Protein- and fibrin-based sprays (e.g., Vivo stat®) demonstrate superior clot stability and adhesion, making them particularly suitable for surgical applications, although their immunogenicity risks and high cost remain limitations [35]. Bio adhesive hydrogels, such as CMCS-COHA, provide instant, pressure-resistant barriers for non-compressible bleeding, offering a strong option for internal applications [84].

In summary, clay-based hybrids are well-suited to field-based trauma because they achieve rapid haemostasis via fluid absorption and contact activation with minimal setup. Protein-based and bio adhesive sprays excel in controlled surgical settings where strong tissue adhesion, durable sealing, and precise application are prioritized.

5. Clinical applications

The clinical performance of haemostatic sprays is fundamentally associated with their material composition and predominant haemostatic processes. As mentioned in the previous sections on material design, differences in physicochemical properties like fluid absorption capacity, surface charge, enzymatic activity, hydrogel formation, and tissue adhesion have a direct effect on haemostatic speed, clot stability, antimicrobial protection, and tissue compatibility. These characteristics dictate the appropriateness of certain spray systems for particular clinical situations, such as diffuse oozing, focal arterial haemorrhage, moist or uneven anatomical surfaces, and high-risk procedural environments. This section looks at the clinical uses of haemostatic sprays by directly linking material design concepts to their use in surgery, endoscopy, trauma, and emergency situations.

Haemostatic sprays have become indispensable in modern surgery and emergency care, offering rapid, effective bleeding control across a range of clinical contexts. Initially developed for combat scenarios, where products like chitosan-, zeolite-, kaolin-, fibrin-, and smectite-based formulations demonstrated life-saving potential, their application has expanded to civilian hospitals for both elective and emergency procedures [94–97].

Commercial products such as Hemospray® (TC-325), EndoClot™, Ankaferd BloodStopper®, PuraStat®, cyanoacrylate glues, topical hemocoagulase, and Raplixa® have shown high initial haemostasis rates and low rebleeding rates, particularly in refractory ulcer bleeding, post-necrosectomy cavity bleeding, and gastrointestinal variceal and non-variceal haemorrhage [28,34,57,98,99] Their application extends across multiple surgical specialties, reducing blood loss, improving visibility in the presence of diffuse oozing, and minimizing complications in complex procedures [59,100].

Besides their role in active bleeding control, haemostatic sprays have also been researched for prophylactic administration for high-risk endoscopic procedures. Their use post-biopsy, post-polypectomy, or (endoscopic mucosal) EMR/ (submucosal resection) ESD has been found to reduce delayed post-procedure haemorrhage, particularly in patients with comorbidities on anticoagulant therapy or background bleeding disorders. Self-assembling peptide gels (such as PuraStat) and polysaccharide-based powders (such as Endo Clot) have been promising in this setting, with cohort and randomized trials indicating lowered rates of secondary bleeding when applied to mucosal injuries. Inherited bleeding disorders are still best managed with systemic prophylaxis (such as factor replacement or DDAVP). However, intra-procedure local adjunct application of topical haemostatic sprays may enhance haemostasis in the intervention site and provide an integrated solution to patient treatment. [28,63,64].

Other than endoscopic use, haemostatic sprays are also integrated into prehospital and military trauma management, where immediate treatment is critical in noncompressible and inaccessible bleeding sites [30,31,35,81,88,101]. Preclinical models, including gastric perforation and postoperative wounds, also indicate the promise of bio-adhesive hydrogel-forming sprays such as OOZFIX™, CPO powders, and CMCS COHA, which possess good adhesion, facilitate tissue regeneration, and maintain haemostasis under challenging conditions [82,84].

6. Challenges, limitations, and future directions

Although broadly applicable, haemostatic sprays also face challenges that limit their widespread use. Side effects such as tissue irritation, allergic response, and, in rare cases, embolization highlight the need for accurate application and safety optimisation. Additionally, physical barriers formed by some sprays may impede routine wound healing or complicate follow-up operations. Issues relating to spray dispersion, impaired visibility of the site of interest during procedures, and unintended coverage of neighbouring tissues also present procedural concerns.

Another important limitation is that most currently available haemostatic sprays are primarily designed to achieve rapid clot formation or mechanical sealing and generally lack intrinsic antibacterial or regenerative functionalities. Given that many surgical and traumatic wounds carry a significant risk of infection, the absence of antimicrobial activity may restrict their performance in contaminated or high-risk settings. Therefore, future spray-based haemostatic systems may benefit from integrating antibacterial and immunomodulatory components while maintaining rapid haemostatic efficacy.

In the future, development needs to be directed toward maximizing the biocompatibility and stability of these preparations to make them safer and more reliable in a wide range of clinical situations. Advanced technologies such as stimuli-responsive nanomaterials (pH-, shear-, or thrombin-activated), platelet-mimetic or magnetic targeting systems, and propellant- or rheology-optimized sprays may deliver more targeted, demand-responsive haemostasis with reduced embolization risk. In addition, recent advances in multifunctional nanozyme- and hydrogel-based biomaterials have demonstrated strong antibacterial activity, oxidative stress regulation, and tissue regenerative capacity in infected wound models [102–104]. Although these systems are not currently formulated as haemostatic sprays, their mechanistic strategies provide valuable design insights for the development of next-generation multifunctional haemostatic spray platforms.

Parallel efforts in manufacturability, cost-effectiveness, and robust comparative clinical trials are required for successful translation. There is also an immense need to devise easy-to-apply sprays that are cost-effective and suitable for use in low-resource or pre-hospital conditions. Lastly, extending functional versatility while ensuring consistent haemostatic performance across a spectrum of trauma and surgical conditions will represent a significant step toward broader clinical adoption.

7. Conclusion

Haemostatic sprays play an increasingly important role in modern surgical, endoscopic, and emergency care by enabling rapid, non-contact control of bleeding in complex and time-critical situations. Their demonstrated utility in both civilian and military settings highlights their effectiveness in managing diffuse or hard-to-access haemorrhage while improving procedural efficiency.

However, limitations including potential tissue reactions, embolization risk, limited durability, and interference with wound healing must be carefully addressed to optimise clinical performance. Variability in spray dispersion and delivery precision further underscores the need for continued refinement.

Future development should prioritise translationally relevant strategies. Systematic structure–function studies are needed to correlate material properties such as porosity, surface charge, crosslinking

chemistry, and adhesive strength with haemostatic speed, clot stability, rebleeding risk, and tissue compatibility in clinically relevant models. In addition, rational design of multifunctional sprays integrating antimicrobial and regenerative features should be pursued without compromising haemostatic efficacy. Standardised pre-clinical evaluation frameworks and alignment with regulatory requirements will be essential to enable meaningful comparison and accelerate clinical translation.

Through material optimisation, harmonised validation, and regulatory readiness, next-generation haemostatic sprays can be developed as safer, more precise, and clinically adaptable technologies, supporting broader use across surgical, emergency, and resource-limited settings.

CRediT authorship contribution statement

Akriti Nepal: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Huyen Tran:** Writing – review & editing. **Nam-Trung Nguyen:** Writing – review & editing, Supervision. **Hang Thu Ta:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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