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REVIEW ARTICLE

Gelatin-based hemostatic agents for medical and dental application at a glance: A narrative literature review

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Abstract Uncontrolled bleeding is linked to higher treatment costs, risk of post-surgical infection and increased disease and death. Hemostatic agents are used to treat excessive bleeding. A good hemostatic agent controls bleeding effectively, reduces the need for blood transfusion, removes the need for systemic drugs to control bleeding, results in shorter surgery time, and reduces the cost and length of hospital stay of the patient. Gelatin-based hemostatic agents have been widely used in medical and dental procedures, owing to their biodegradability and biocompatibility, as well as availability and low cost of raw materials. In this narrative literature review, we discuss the background and different types of gelatin-based hemostatic agents in medical and dental procedures, the comparison of gelatin-based and non-gelatin-based hemostatic agents, and the usage and development of enhanced or novel gelatin-based hemostatic agents. Gelatin-based hemostatic agents are effective and important part of bleeding control, as evidenced by its wide application in medicine

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and dentistry. The development of novel combination gelatin-based hemostatic agents has much potential for effective control of excessive bleeding.

Contents

1. Introduction

The ability to control bleeding is critical to the success of any surgical procedure. Conventional methods to reduce bleeding during surgery include ligation, compression to the bleeding site, electrical cauterization, and clipping. Hemostatic agents are routinely used in sinus surgery (Woodworth et al., 2009), vascular surgery (Vyas and Saha, 2013), cardiovascular surgery (Tackett et al., 2014) and ophthalmic surgery (Wolkow et al., 2018). Additionally, some dental procedures such as exodontia, tissue biopsies, endosseous implantation, and periodontal surgery gain benefits from the use of hemostatic agents.

An ideal hemostatic agent is light, stable, and can be easily applied to a bleeding site. The agent must be sufficiently flexible to adapt to the wound to ensure that they reach and apply pressure to areas of injury that are inaccessible. Ideally, the agent must not cause degradation of the contact tissue, not disintegrate into particles that can enter the bloodstream, be stable enough to withstand high pressures from bleeding in the vessels, and be easily removed when bleeding has stopped (Mani et al., 2014) (Fig. 1).

Increased disease and death, increased hospital expenditures, and unwanted postsurgical repair/infections are unwanted outcomes that are associated with uncontrolled surgical bleeding. Additionally, blood transfusion may be required, which has been linked to a higher incidence of postoperative complications and safety concerns. Topical hemostatic agents can be used to treat excessive bleeding in areas that are difficult to reach using conventional methods. Various hemostatic agents, including gelatin-based hemostatic agents,

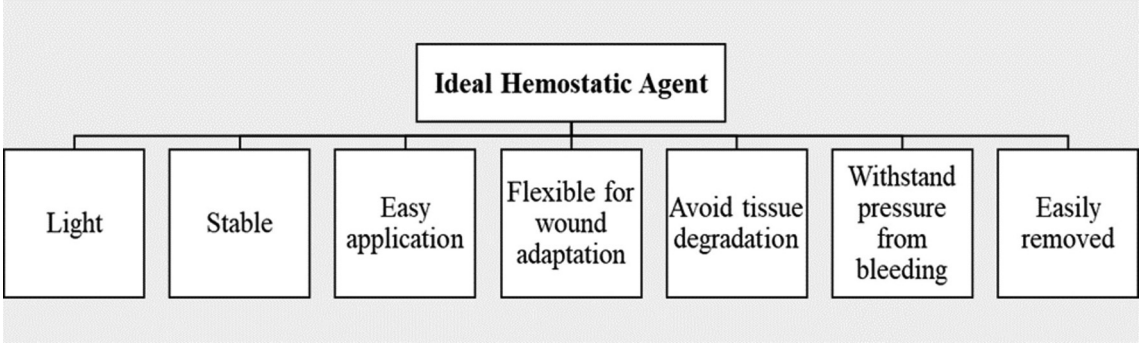

Fig. 1 Ideal hemostatic agents properties.

are currently available on the market. Gelatin is an excellent component of hemostats because of its biodegradability and biocompatibility, high availability of raw material, low cost, widespread use, good foaming capabilities (Song et al., 2018) and low immunogenicity (Gorgieva and Kokol, 2011). Gelatin is a denatured protein synthesized from the partial hydrolysis of structural animal collagen proteins. It is widely used in pharmaceuticals, cosmetics, and food products owing to its unique properties (Sahoo et al., 2015).

Gelatin has been certified as generally recognised as safe (GRAS) by the United States Food and Drug Administration (FDA), and is compliant with the US, European, and Japanese pharmacopoeia. The main drawbacks of gelatin are its low mechanical strength and poor resistance to hydrolysis, which can be overcome by crosslinking gelatin using physical, chemical, or enzymatic methods (Masutani et al., 2014; Yang et al., 2016). While gelatin-based hemostats help achieve hemostasis without the use of sutures, ligatures, or cautery, their use is not without risk. Gelatin is produced from the skin, horns, and/or hoofs of bovine or porcine sources (Wolkow et al., 2018), and may include biological derivatives that may induce immunologic reactions in some individuals.

The aim of this narrative literature review is to discuss the background and different types of gelatin-based hemostatic agents in medical and dental procedures, the comparison of gelatin-based and non-gelatin-based hemostatic agents, and the usage and development of enhanced or novel gelatin-based hemostatic agents.

1.1. Types of available gelatin-based hemostatic agents

Although gelatin-based hemostatic agents are often produced using similar ingredients, their formulation and packaging is varied according to their different applications. Porcine skin is used to produce Gelfoam®, Surgifoam/Spongostan, and Surgiflo, while bovine skin is used in Floseal (Pfizer, 2012; Baxter, 2014). Gelatin sponges, first developed as Gelfoam® (Pfizer, USA) in 1945, eliminated the requirement for blood from human supplies; moreover, they were more durable than fibrin but still provided outstanding clot formation (Pfizer, 2012). They can be used either alone or presoaked with thrombin-like fibrin sponges. Surgifoam/Spongostan (Ethicon, U.S.A.), Surgiflo (Ethicon, U.S.A.), and Floseal (Baxter, U.S.A.) were produced for surgery use in the following decades (Yao et al., 2012).

Reports of adverse allergic reactions such as anaphylaxis during surgery are rare with the use of gelatin-based hemostatic agents in patients. Hence, gelatin-based hemostatic agents are regarded as relatively safe (Zhou et al., 2021). Gelatin-based hemostatic agents form a mesh-like framework that holds clotting molecules in the body to allow the formation of a clot. The gelatin matrix also expands as it continues to absorb blood, leading to the formation of a physical structure that prevents further bleeding (Sae-Jung and Apiwatanakul, 2018).

1.1.1. Passive hemostatic agents

Passive hemostatic agents were introduced in the 1940 s as first-generation hemostatic agents for commercial use (Sundaram and Keenan, 2010). These agents form a barrier that enhances clotting, and effectively halts a small amount of bleeding. Hence, they are also known as mechanical hemostatic agents. These agents are usually inexpensive, easy to prepare, and stable in storage, and are prone to swelling when large amounts of bleeding are present, limiting their use to larger blood vessels with lower blood flow and less bleeding. Passive hemostatic agents are activated only in the presence of blood and have no effect on the clotting cascade (Sundaram and Keenan, 2010).

Various passive hemostatic agents are available on the market that come in a variety of forms: 'fleeces' and sponges, or gauze-like sheets are the most common. Passive topical hemostats function by creating a physical framework to allow platelet aggregation and eventually clot formation. They not only operate as a physical barrier to stop the flow of blood by creating a matrix for platelet adhesion; they also accelerate the development of the platelet plug that forms the foundation of the fibrin clot (Sundaram and Keenan, 2010).

Considering mechanical hemostats rely on the formation of fibrin for hemostasis to be achieved, their use is limited to individuals with a functioning coagulation cascade. This form of hemostatic treatment would not be useful for patients bleeding due to a substantial coagulopathy, for example. Mechanical agents help to speed up the coagulation cascade, allowing for faster hemostasis. Despite the fact that most mechanical hemostats have a similar underlying mechanism of action, their effectiveness differ (Khoshmohabat et al., 2016). Mechanical hemostats such as cellulose, collagen sponges, and polysaccharide spheres usually contain a sponge, foam, pad, or other absorbent substance combined with a topical hemostatic agent (porcine/bovine collagen or gelatin) to create a mesh framework at the bleeding location, which triggers the coagulation pathway leading to clotting (Burks and Spotnitz, 2014). The most effective products are typically bovine collagen and polysaccharide spheres; porcine gelatins have been shown to have greater potency when paired with topical thrombin. Due to their vast availability and minimal related costs, mechanical hemostats are often used as first-line agents. Mechanical hemostats are most beneficial when only minor bleeding is present (Burks and Spotnitz, 2014). Some commercially available mechanical hemostatic agents include Gelfoam®, Gelfoam® Plus, Avitene®, Surgicel Nu-Knit®, Surgifoam®, Surgicel®, UltrafoamTM and Arista®.

1.1.2. Active hemostatic agent

Active hemostats contain a built-in biological activity that triggers initiation of the coagulation process, causing a clot to form at the location of wound. The protein thrombin is usually incorporated, which catalyzes the final phase of the blood clotting cascade, i.e., fibrinogen transformation into fibrin. This enzyme bypasses the general coagulation cascade, and instead goes straight into fibrin production, which is significant when the coagulation cascade is disrupted. Many standard sealant formulations include thrombin. Bovine thrombin was initially approved by the US FDA for use in surgical bleeding in the late 1970 s (Vyas and Saha, 2013). However, the use of bovine thrombin was hindered due to antibody development which reacted with coagulation factors in the human blood. Thrombin sourced from humans therefore became the next alternative; however, it was scarce, and carried a significant risk for blood-borne infection transmission. Examples of thrombin from human origin are Evithrom and Gelfoam® Plus. The FDA authorized recombinant human thrombin (rhThrombin)

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for surgical use in humans in 2008 as a material that would be accessible, but without the risks associated with use of natural human thrombin, such as adverse immune reactions or blood infections. It was created to supply thrombin without the dangers of antibody formation or transmission of blood-borne infections. An example of commonly used agent containing rhThrombin is Recothrom (Vyas and Saha, 2013).

1.1.3. Flowable hemostatic agent

Flowable hemostatic agents are made from gelatin matrices and flow like a viscous liquid. An example of flowable hemostatic agent is topical thrombin solution, which is effective at reaching deeply located wounds, and can be used in a wet field. Besides ophthalmic surgery, these agents are useful in various surgeries. Examples of these agents include Surgiflo (Johnson & Johnson) and Floseal (Baxter), which consist of a gelatin matrix and a thrombin component. Floseal consists of a gelatin-glutaraldehyde crosslink that is ground into nanometer-size particles and a reconstituted thrombin solution (1000 U/ml). To use, both gelatin and thrombin are combined using a special applicator syringe and introduced to the bleeding site. The gelatin particles absorb the blood and swell, then form a tamponade with the surrounding tissue to halt bleeding. Floseal has been demonstrated to be beneficial in a variety of procedures, including cardiovascular (Tackett et al., 2014), hepatic (Izzo et al., 2008), and endoscopic sinus surgery (Echave et al., 2014). The classification of different types of hemostatic agents, their mechanisms of action and brand names are shown in Table 1.

1.2. Hemostatic properties of gelatin

Platelets produce initial hemostasis when a vessel is injured during surgery, followed by the clotting pathway, which includes transformation of prothrombin into thrombin to produce an insoluble fibrin meshwork for hemostasis (Gale, 2011). Hemostatic agents containing gelatin are saturated with pure thrombin and are available in a variety of forms, including sponge and liquid (Sundaram and Keenan, 2010). When thrombin is administered to a wound site, it takes part in coagulation and creates a fibrin clot; meanwhile gelatin in the formulation expands to generate a tamponade that halts bleeding mechanically, while activating platelets and inducing aggregation (Chiara et al., 2018).

An effective hemostatic agent controls bleeding, lessens the need for blood transfusions, frees the patient from drug use to control systemic bleeding, leads to shorter surgery time, and reduces hospital stay length and cost (David et al., 2015).

Table 1 Hemostatic agents used in medical and dental applications.

Types of hemostats	Mechanism of action	Class	Band	Manufacturer	Common usage	References
Passive (Mechanical)	Physical matrix for initiation of the clot	Porcine gelatine	Gelfoam® sponge and powder	Pfizer	Spinal surgery	(Prabhu and Prabhu, 2019)
			Surgifoam sponge and powder	Ethicon/ Johnson & Johnson	Vascular surgery	(Vyas and Saha, 2013)
			Spongostan	Ethicon/ Johnson & Johnson	Oral surgery	
		Bovine collagen	Ultrafoam	Integra	Oral surgery	
			Avitene sheet, flour	Becton and Dickinson (BD)	Oral surgery	
		Oxidized regenerated cellulose	Surgicel	Ethicon/ Johnson & Johnson	Oral surgery	
			Nu-Knit	Ethicon/ Johnson & Johnson		
		Polysaccharide spheres	Hemostase - MPH	Cryolife	Cardiothoracic surgery	
			Arista AH	Medafor		
Active	Converts fibrinogen into fibrin to form clot. Promotes activation of coagulation factors	Bovine thrombin	Thrombin JMI	Pfizer	Vascular surgery	(Iannitti et al., 2021)
		Human-pooled plasma thrombin	Evithrom	Ethicon/ Johnson & Johnson	Neurosurgery	
		rhThrombin	Gelfoam® Plus Recothrom	Pfizer Zymogenetics / BMS		
Flowable	Combination of effects of gelatin and thrombin	Porcine gelatin +thrombin	Surgiflo	Ethicon/ Johnson & Johnson	Spinal fusion surgery	(David et al., 2015)
		Bovine gelatin and human-pooled plasma thrombin	Floseal	Baxter	Cardiovascular surgery	(Tackett et al., 2014)

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Hence, a flowable hemostatic material with better hemostatic qualities was developed and tested using animal and human studies (Nasso et al., 2009; Schreiber and Neveleff, 2011). The tremendous absorbent capability of gelatin sponge is characterised by its ability to absorb liquids 40 times its own weight and increase its volume by 200 percent, allowing local platelets to concentrate on the bleeding surface (Sae-Jung and Apiwatanakul, 2018). During blood absorption, the platelets enter the sponge's empty spaces, allowing additional coagulation factors to be released, including prothrombin kinase, which is essential to the hemostasis cascade and the stop of bleeding (Schreiber and Neveleff, 2011).

1.3. Gelatin-based hemostatic agents in dental applications

Hemostatic agents function to stop bleeding and encourage hemostasis. They are also known as antihemorrhagic agents. In dentistry, the use of gelatin-based hemostatic agents such as Gelfoam® has been reported, with good results in managing post-operative bleeding after dental extraction and periodontal surgeries. Gelfoam® liquefies in the oral cavity in a week and absorbs completely in 4–6 weeks with very minimal tissue response (Mani et al., 2018). Moreover, a blood clot can develop on a scaffold made of Gelfoam®. For large extraction sites, Gelfoam® has been utilised to help in primary closure; it is placed into the socket and secured with a suture (Mani et al., 2018).

Another gelatin-based hemostatic agent used in dentistry is Floseal®, a patented gelatin-based granule that forms a thrombin-gelatin matrix and enters and expands in small cavities. The expansion exerts mechanical pressure and compression onto the bleeding area. Following that, thrombin assists with creation of a stable fibrin clot, which results in haemostasis. Ali et al., 2022 conducted a prospective study to determine the effectiveness of Floseal® to stop bleeding after dental extraction in patients with genetic bleeding disorders. The study found that for individuals with extremely rare factor deficits, pre-existing clotting factor inhibitors, and those who have allergies to clotting concentrates, Floseal® use is cost-effective, avoids the possibility of *peri*-procedural FVIII inhibitor formation, and offers a haemostatic option (Ali et al., 2022).

The use of Surgiflo® in medical and dental surgery has also been reported. Surgiflo® is a dry, porcine gelatin-thrombin haemostatic matrix that can be absorbed by the body. The safety of Surgiflo® is supported by a retrospective study of postoperative haemorrhagic complications and allergic reactions to Surgiflo® in patients with removal of submandibular glands. The study showed that Surgiflo® successfully creates a sound hemostasis and stops bleeding following submandibular gland removal. There are no known side effects or adverse reactions reported with Surgiflo® use, making it safe (Bannister and Ah-See, 2014).

2. Comparison between gelatin-based and other hemostatic agents

2.1. Oxidized regenerated cellulose (ORC)

Both gelatin- and cellulose-based topical hemostatic agents have their advantages and disadvantages owing to their different origins/sources. Gelatin-based hemostatic agents originate from animal skin gelatin and are usually produced in sponge form where they can halt bleeding in small vessels. The material is easily metabolized in the body in 4–6 weeks. However, gelatin is prone to swelling into large volumes, which may compress the nerve, thus limiting its application in tighter areas. Meanwhile, oxidized regenerative cellulose (ORC) is an easy-to-handle material that does not stick to instruments, and has antimicrobial properties due to its low pH. However, this acidic property can induce inflammation in the tissue site (Achneck et al., 2010).

A study by Slezak et al., in 2019 reported that recombinant thrombin (RECOTHROMVR [rT]) plus gelatin sponge carrier was more effective compared to ORC when tested in heparinized and non-heparinized hemostat (Slezak et al., 2019). However, cellulose-based hemostatic agents suggest minimal morbidity compared to gelatin when used in wound healing. An in vivo study reported how limited inflammatory reactions with cellulose compared to gelatin when used over 28 days (Kang et al., 2012).

2.2. Fibrin glue

A study comparing the effectiveness of gelatin sponge (GS) and polyglycolic acid sheets with fibrin glue dressing (PGA-FG) for wound healing showed that GS promoted better bone remodelling compared to PGA-FG. Increased osteoblast lining on the defect bone surface was observed when the bone was histologically evaluated (Koshinuma et al., 2016).

A systematic review reported that most local hemostatic agents were more effective than suturing alone in controlling post-operative bleeding following dental extraction. In addition, no statistically significant difference was observed in local hemostatic agents in controlling post-operative bleeding (Koshinuma et al., 2016).

2.3. HemCon

HemCon is a recently introduced local hemostatic material that was shown effective to stop bleeding after dental extraction in patients taking oral antiplatelet medications. Hemostasis is achieved sooner and less postoperative pain is caused compared to the conventional method of pressure application to the wound using sterile gauze (Kale et al., 2012).

Compared to an absorbable gelatin sponge (GS), HemCon is more effective at stopping bleeding after dental extraction. GS can stop bleeding in most cases, but sometimes additional gauze pressure or suture is needed to control bleeding. Meanwhile, HemCon is able to stop bleeding without the need for additional hemostatic measures (ElShiha, 2012). The summary of differences is shown in Table 2 and Fig. 2.

3. Novel/enhanced gelatin hemostatic agents

3.1. Gelatin enriched with chitosan

Chitosan-based hemostatic dressings have been widely used now in many forms such as bandage (Hemcon Chitosan Bandage) and sheets (Clo-Sur PAD). However, some of the dressings have been reported to emit a strong acidulous odour when acetic acids are used as solvent for their manufacture. More-

Table 2 Comparison between hemostatic agents and gelatine-based hemostatic agent.

Type of hemostatic agent	Comparison	Common usage	References
Oxidized regenerated cellulose	Gelatin sponge was more effective hemostat compared to ORC.	Neurosurgical	(Slezak et al., 2019)
	ORC suggest minimal morbidity for wound healing compared to gelatin-sponge.	Oral surgery	(Kang et al., 2012)
Fibrin glue	Gelatin sponge promotes better bone remodelling compared to PGA-FG.	Gastrointestinal, cardiovascular, vascular surgery	(Koshinuma et al., 2016)
Hemcon	Hemcon able to stop bleeding without the need for additional measures compared to gelatin sponge	Oral surgery	(ElShiha, 2012)

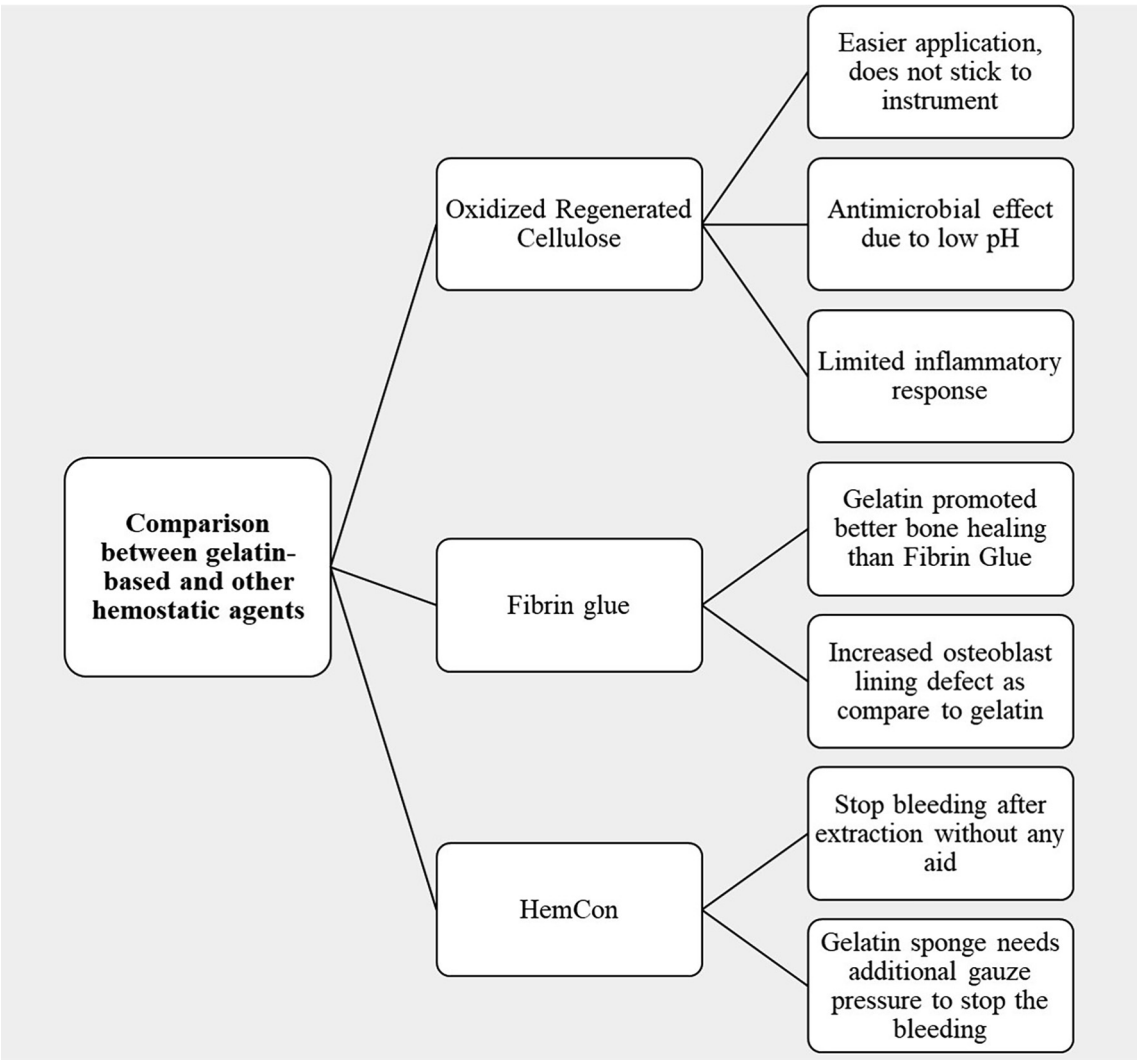

Fig. 2 Comparison between gelatin-based and other hemostatic agents.

over, most of them are produced in the form of sheets or thin sponges, which reduces their ability to flow and provide effective hemostatic action in complex wounds or cavitary bleeding. The sheets also tend to be easily disintegrated during application (Lan et al., 2015).

Gelatin on the other hand, has great hemostatic effect thanks to its natural properties, which include non-immunogenicity, biocompatibility, biodegradability and accessibility. Gelatin is found in formulations for various applications, including continuous drug release and tissue regeneration with skin, cartilage and bone. Furthermore, it can trigger activation of platelets and functions as an absorbent substance for bleeding control. However, gelatin itself is easily dissolved in water, and therefore is frequently cross-linked with other natural and synthetic polymers to improve its mechanical and chemical stability. Meanwhile, chitosan

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has good viscosity and filming characteristics, and has free amino acid groups that can be used for cross- linking. Together, the two materials form a natural, semi- interlinked polymer structure that mimics a porous natural scaffold or dressing (ElShiha, 2012).

To prepare the highly absorbent hemostatic chitosan–gelatin sponge (CG), both materials are mixed via modified gradual-base extraction, which is then followed by a freeze-drying step. The qualitative and quantitative properties of the final material are evaluated for hemostatic effectiveness, mode of action, compatibility with wound tissue, toxicity to cells and antimicrobial ability. Together, CG had better absorbent properties with higher platelet aggregation than their individual parts. Cytotoxicity tests showed high cell proliferation and viability with CG in mouse fibre cell line (L929) and antimicrobial tests showed that CG inhibited *Escherichia coli* and *Staphylococcus aureus* bacteria. The results support the use of CG as a hemostatic agent in surgery for its highly absorbent and low pressure properties (Yang et al., 2010).

A recent study on cytotoxic and anti-inflammatory effects of chitosan and hemostatic gelatin in oral cell culture has been reported. The study's objective was to determine if chitosan

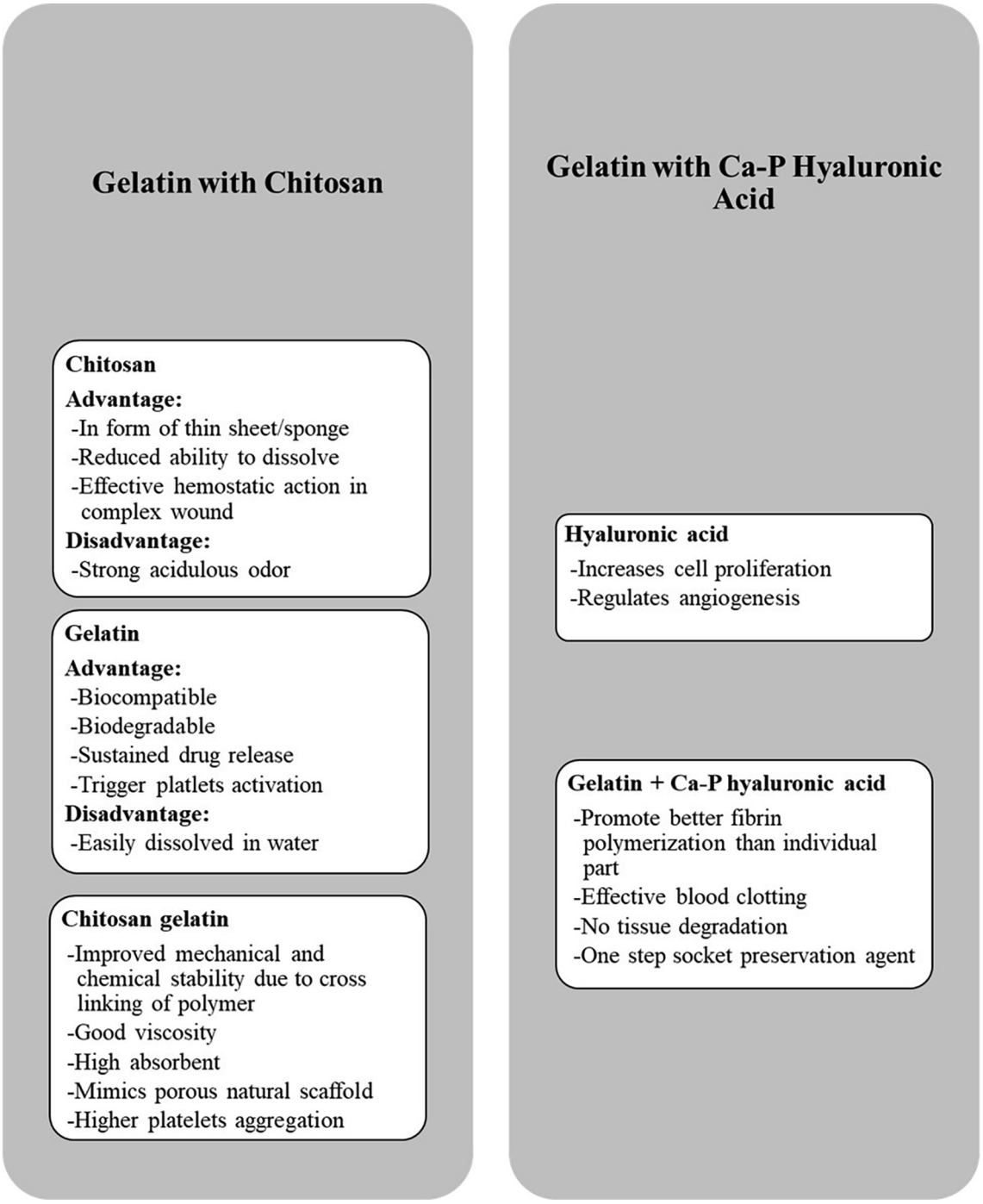

Fig. 3 Novel/enhanced gelatin.

alone or in combination with hemostatic gelatin (Spongostand®) had cytotoxic and anti-inflammatory effects on cultures of human pulp cells (HPC), human gingival fibroblasts (HGF), and mice pre-osteoblasts (MC3T3-E1, ATCC). Hemostatic gelatin impregnated with chitosan (0.19 %) were placed immediately in the vicinity of cells and incubated for 24 h after being injected at various concentrations (ranging from 0.0 to 0.5 %). Based on the results, the cytotoxicity of chitosan-impregnated gelatin reduced HGF and HPC cell viability by 11 % and 5 %, respectively. In the gingivitis model, the pro-inflammatory effect was significantly reduced. The assays used to determine the pro-inflammatory effects using prostaglandin E2 (PGE2) showed the following results: cells inflamed with IL-1 expressed more PGE2 on their own and in physiological solution, whereas PGE2 expression was significantly reduced in contact with Chitosan 0.19 % and 1 %. By offering a safe, affordable alternative for any condition and assisting in improving healing in circumstances like oral surgery, periodontics, implantology, or any other requiring ideal, safe grafts, chitosan alone or in combination with gelatin could significantly advance tissue engineering and regenerative medicine (Narvaez-Flores et al., 2021).

3.2. Gelatin + Ca P-Hyaluronic acid

Post-dental surgery, the socket undergoes a series of phases to achieve wound healing, which starts with hemostasis, followed by inflammation, migration, proliferation, remodelling and finally maturation. The final two phases (remodelling and maturation) are crucial to the structural integrity and dimension of the healed tissue. Unwanted changes in the tissue can be prevented by introduction of natural or synthetic bone grafting materials to preserve the socket integrity. However, the clinical use of these materials has been limited due to the requirement for parallel procedures, which include use of hemostatic agents and/or application of a guide membrane post-grafting that increase procedure time and complexity (Kang et al., 2020).

To overcome these problems, a hyaluronic acid-gelatin-biphasic calcium phosphate (HyA-Gel /BCP) scaffold with excellent structural and biological function was fabricated for application in bone regeneration and as a hemostatic agent. The hyaluronic acid (HyA) component increases cell proliferation and regulates angiogenesis to trigger tissue regeneration and wound healing. Meanwhile, the gelatin (GeL) component provides excellent biocompatibility and metabolism in the body. HyA-GeL (HG) cross-linked scaffolds showed excellent bleeding control in a rat model for bleeding of liver. Other than HyA and gelatin, research into calcium phosphate ceramics for tissue regeneration is ongoing due to its biocompatibility, bio-resorption, as well as bone regeneration (Kang et al., 2020).

Furthermore, their application as a hemostat is useful in expediting fibrinogen-fibrin conversion during coagulation, as well as promotion of fibrin polymerization. The HG/TCP/BCP scaffold plug showed that biocompatibility and differentiation markers such as COL1, Runx2, ALP, and OPN expressions were confirmed in Ca/P-based HG scaffolds in a pre-osteoblast cell line. In rabbit-ear-artery bleeding experiments, Ca/P-based HG scaffolds showed exceptional effectiveness for blood clotting. The HG/TCP/BCP scaffold plug resulted in outstanding osteocyte-based bone formation with no degradation of tissue, evidenced through histological analysis of the rabbit-femur defect 3 months post-implantation. Scaffold plugs that used hyaluronic acid-gelatin hydrogel (HG), beta tri-calcium phosphate (TCP), and sponge biphasic calcium phosphate (BCP) showed great hemostatic effects and can also act as a one-step socket preservation agent (Nguyen and Lee, 2014). The summary of Novel/Enhanced Gelatin is depicted in Fig. 3.

4. Conclusion

Gelatin-based hemostatic agents are widely used in medical and dental procedures due to their ability to achieve hemostasis. Every gelatin-based hemostatic agent has its own advantage; as gelatin is generally safe to use and is easily available. The addition of gelatin to other biopolymers has been reported to have promising beneficial effects in controlling blood loss. Therefore, the development of novel or enhanced gelatin-based hemostatic agent must be taken seriously.

Conflict of Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Nining Irfanita Irfan: Methodology, Writing – original draft, Writing – review & editing. **Amir Zulhakim Mohd Zubir:** Methodology, Writing – original draft. **Asrul Suwandi:** Methodology, Writing – original draft. **Muhammad Salahuddin Haris:** Writing – review & editing. **Irwandi Jaswir:** Conceptualization. **Widya Lestari:** Conceptualization, Methodology, Supervision, Writing – review & editing.

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Ethical statement

The authors have no ethical issue to declare.

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