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Review Paper

Green Blood Stoppers: Evaluating Herbal Coagulants as Sustainable Alternative to Chemical Agents

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ABSTRACT

The physiological process of haemostasis, which includes blood coagulation is essential for stopping uncontrollable bleeding after vascular damage. Both intrinsic and extrinsic routes, as well as common pathways regulate the intricate interactions between platelets, clotting factors and reactions of the vascular wall components. Despite the routine clinical use of traditional haemostatic drugs such as etamsylate, carbazochrome sodium, fibrin glue and tranexamic acid. The demand for a safe alternative are increasing due to their high cost, side effects and limited availability. Medicinal herbs rich in bioactive compounds such as terpenoids, alkaloids, flavonoids and tannins have been known for their chief role in wound coagulation and healing since time immemorial. Platelet activation, aggregation, vasoconstriction and clot formation are the mechanisms involved in hemostasis which are played by plants like *Blumea balsamifera* and *Moringa oleifera*. History, classification, mechanism of action and therapeutic applications of conventional and herbal blood coagulants are well elaborated in this article. It highlights their advantages, limitations, synergistic potentials and challenges for clinical translation and standardization. This review emphasizes the need for combining traditional knowledge with modern pharmacology in order to develop reliable, effective and accessible haemostatic agents from herbs by comparison of plants and synthetic drugs.

INTRODUCTION

The process by which blood transforms from a liquid to a gel and forms a blood clot is called coagulation or clotting. Haemostasis or the

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stopping of blood loss from a damaged vessel is the outcome and repair follows. Platelet activation, adhesion and aggregation as well as fibrin deposition and maturation are all components of the coagulation process.^[1] Co-ordination of different blood components, including coagulation factors, cells, etc., is a complex system involved in the physiological process of blood coagulation.^[2]

The term “Haemostasis”, which means “To halt bleeding”, is derived from the Greek words “Haeme” which means “Blood” and “Stasis” which means “To stop”.^[3] The haemostatic system is activated in pathological circumstances that call

for surgery, anaesthesia or any other intrusive procedure. Infectious agents, cytokines and trauma can also upset this equilibrium. As a result, there is a significant chance of both prothrombic and hemorrhagic anomalies during the perioperative phase. The condition may also be made worse by metabolic acidosis, hypoxia, hypothermia and extracorporeal circulation.^[4] The cells called haemocytes are responsible for haemostasis. Haemocytes generate the blood clotting factors C and G which cause coagulation by interacting with hemolymph proteins in a calcium dependent way.^[5]

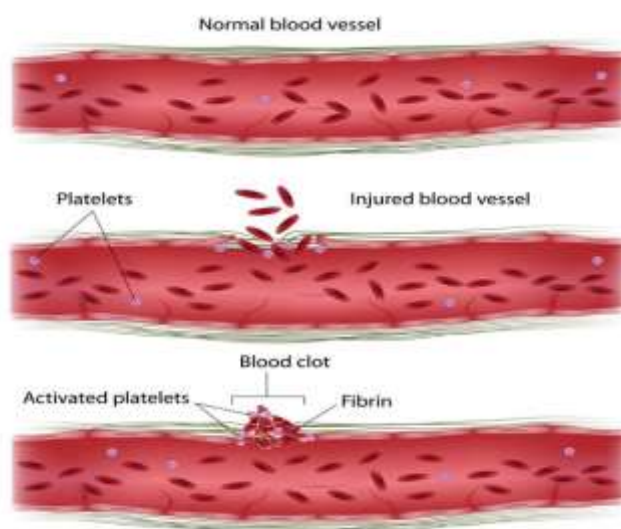


Figure1: Process of blood coagulation

Almost immediately following damage to the endothelium of a blood artery, coagulation starts. Two processes are triggered when blood is exposed to the subendothelial space: platelet alterations and the exposure of subendothelial platelet tissue factor to coagulation factor VII, which eventually results in the creation of cross-linked fibrin. Primary haemostasis is the process by which platelets instantly create a plug at the site of damage. Simultaneous secondary haemostasis takes place when coagulation factors other than factor VII react in a cascade to create fibrin strands

that fortify the platelet block.^[6] Coagulation is a fascinating process that’s surprisingly consistent across all forms of life. In mammals, it relies on a combination of protein based elements, known as coagulation or clotting factors and cellular components like platelets.^[7]

The pathway that has been studied the most and is best understood is the one found in humans. Haemorrhage, bruising or thrombosis can be caused by coagulation disorders.^[8]

HISTORY:

Galen, Celsius, Aristotle, and Hippocrates all understood that freshly drawn blood usually clots within just a few minutes. They offered detailed insights into various tendencies of both superficial and internal bleeding. It was often observed that blood would start to solidify as it cooled down. There was a common belief that when a wound was exposed to air, it caused the blood to cool, which in turn stopped the bleeding.^[9]

Two millennia later, in the early 1720s, French surgeon Jean-Louis Petit made a revolutionary discovery: He saw that clots that formed in blood vessels were essential for halting bleeding following limb amputations. This was the first time that the relationship between blood clotting and haemostasis had been linked. Friedrich Hoff, a Swiss physician, expanded on this understanding in 1828.^[9] The Origins of blood clotting ideas can be found in ancient Greece, when the words “Hema”(blood) and “Thrombus” (clump) first appeared. Novel theories of Coagulation that deviated from the accepted “Traditional Galen Medicine” were met with scepticism and contentious discussions in the seventeenth century. But it was Dr. Marcelo Malpighi who promoted these ground-breaking theories with a single-lens microscope. He discovered that blood is made up of red blood cells and a network of fibrous material that we now refer to as fibres.^[10] After seeing patients recover from limb amputation, French surgeon Jean-Louis Petit was the first to associate coagulation and haemostasis in the early 1970s. A young British surgeon named Dr. William Hewson then noticed that blood coagulum developed from the liquid portion of the blood, which is now known as plasma. Additionally, he found that the plasma contains globulin, albumin and the precursor of fibrin among other things.^[11,12] Fourcroy Coined the

name “fibrin” in 1801 and showed that the plasma contains its precursor. In 1847, forty years later, Virchow discovered the predecessor of fibrin and called it “fibrinogen”. Alexander Schmidt named the enzyme “thrombin” in 1872 after his research shown that fibrinogen is converted into fibrin by an enzymatic mechanism. Schmidt hypothesised the existence of a precursor prothrombin, after realising that thrombin cannot exist in blood in its active state.

Paul Morawitz’s traditional hypothesis of coagulation, which was developed in 1905 and included four components – prothrombin, thrombin, fibrinogen and fibrin- in the presence of calcium, was based on these findings.^[13] Until 1947, when Paul Owren presented new information on the biochemical mechanisms of coagulation, this traditional view of coagulation remained in use.^[14] The cascade model, put forth by Macfarlane in 1964, describes the sequence in which the clotting factors are activated. Each clotting factor is a proenzyme (Zymogen) that awaits predecessor-mediated proteolytic cleavage to commence its function, limiting indiscriminate activation or destruction. This concept was followed by David and Ratnoff’s waterfall model.^[15] Henrik Dam found that vitamin K played a significant role in coagulation in 1935. A novel model known as the “cell-based model” was created as a result of recent coagulation research, according to which exposure to cells with TF expressed on their surface triggers blood coagulation in vivo.^[16]

TIMELINE EVALUATION:

The Ancient Era, which predates the year 1000 CE, is where we should begin. Herbal medicines were popular at the time. Herbs including Blumea, Tulsi, Neem and Terminalia arjuna were used extensively in ayurveda and traditional Chinese medicine (TCM), particularly to treat bleeding



diseases. Not to be overlooked is yunnan baiyao, a herbal TCM powder used to treat wound today.^[17] Things became slightly more technical from the mediaeval to renaissance Era (1000-1600 CE). Aluminium potassium sulphate or alum, gained popularity as a wound cleanser and clotting agent. In order to aid in healing, people also employed coagulants produced from animal, such as spider webs or compounds from crustaceans that resembled chitosan.

Following this, medicine advanced significantly in the 18th and 19th centuries. In 1856, Alexander Schmidt made a significant discovery that helped to clarify the blood clotting process by describing how fibrinogen changes into fibrin. Improvements in ligation and sutures also led to improvements in surgical techniques. Emerging coagulant materials such as tannic acid, cotton gauze and gelatin sponges were particularly useful in military medicine.^[18]

Early 20th century (1900-1950):

- The concept of fibrin glue was first introduced.
- Plasma transfusions were utilized during world war I and world War II.
- The discovery of vitamin K in 1935 contributed to the treatment of bleeding caused by prothrombin deficiency.
- The initial synthetic coagulants were developed.^[19]

Mid to late 20th century (1950-2000):

Recombinant coagulation factors :-

- Factor VIII and IX for the treatment of hemophilia A and B.

Topical hemostats:-

- Products based on thrombin, oxidized cellulose and gel form.
- The creation of antifibrinolytics: such as epsilon-aminocaproic acid (EACA) and tranexamic acid.
- Synthetic Polymers: Bioadhesive sealants are introduced.^[20]

Modern Era (2000-present):

- Development in biology include fibrin sealants and recombinant thrombin.
- Haemophilia gene therapy trials.
- Coagulation testing at the point of care (e.g., ROTEM, TEG).
- Plant-based inventions (rekindled interest in herbal coagulants): Procoagulant effect of Tulsi, Neem, and Blumea is being researched.
- Hydrogel patches and nanotechnology for wound treatment.
- Haemostatic scaffolds that are 3D printed and agents that are spray-based (like Arista AH).

Current Examples:

Dressings based on chitosan: - such as Hemcon and Celox

Gauze infused with kaolin: - for example, Quikclot.^[21]

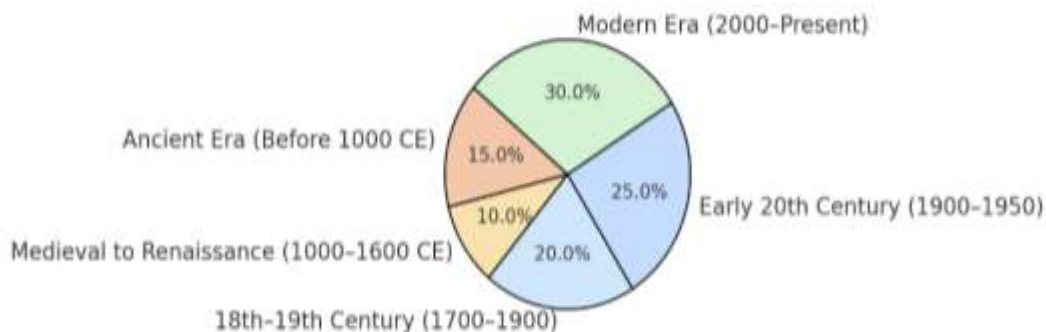


Figure 2: Proportional influence of Historical Eras on Coagulation Therapy Development

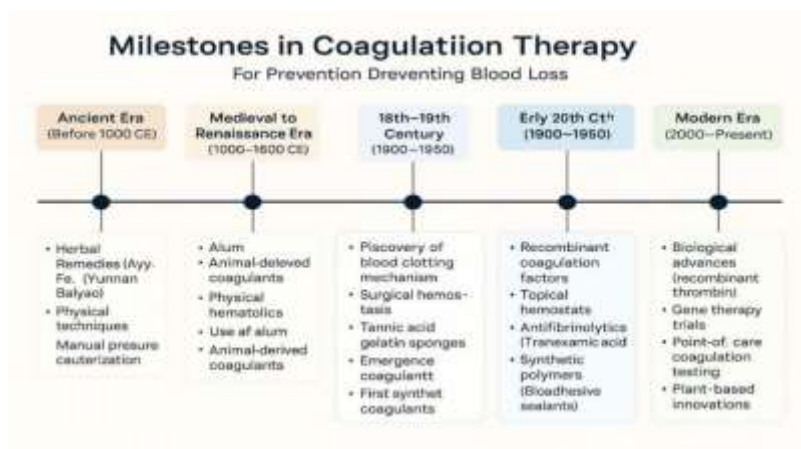


Figure 3: Milestones in coagulation therapy for prevention preventing blood loss

CLASSIFICATION OF BLOOD COAGULANTS:

Classification by mechanism of action:

Categorisation according to the mode of action. Based on how they work, haemostatic materials are divided into three groups: **mucoadhesive agents, procoagulants and factor concentrators**. By drawing water out of the blood, factor concentrators concentrate the blood's constituent parts at the site of injury. Procoagulants work by triggering the blood coagulation cascade and adding coagulation factors. By cross-linking blood components,

mucoadhesive substances create a physical barrier to blood flow.^[22]

Classification of topical hemostatic agents:

External dressings, mechanical hemostats, synthetic/semisynthetic sealants, and active or adhesive agent are the several types of hemostats that are applied topically. Topical active agents, which include thrombin and fibrinogen, function by actively initiating the fibrin clot formation and coagulation cascade.^[23]

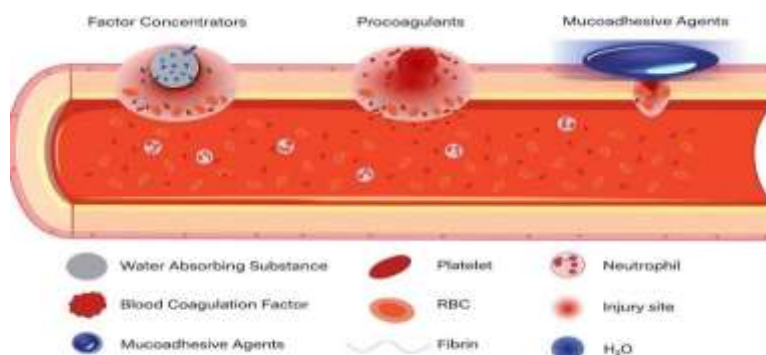


Figure 4: Application and outlook of topical hemostatic agents

Typically, they are offered in liquid form (fibrin glues) or in conjunction with collagen (fibrin patch). Because of their haemostatic and adhesive sealing properties, these substances are also occasionally referred to as adhesive hemostats. Porcine gelatin, bovine collagen-oxidized cellulose and polysaccharide spheres generated from plants are all found in topical mechanical hemostats. By encouraging platelet activation and

aggregation, these topically administered agents create a clotting matrix at the site of bleeding. Passive haemostats are the name given to these hemostasis, these hemostats can improve the functioning coagulation system. Topical synthetic/semisynthetic sealants are often provided as low-viscosity solutions that link tissue surfaces by polymerising into a solid layer.^[24,25]

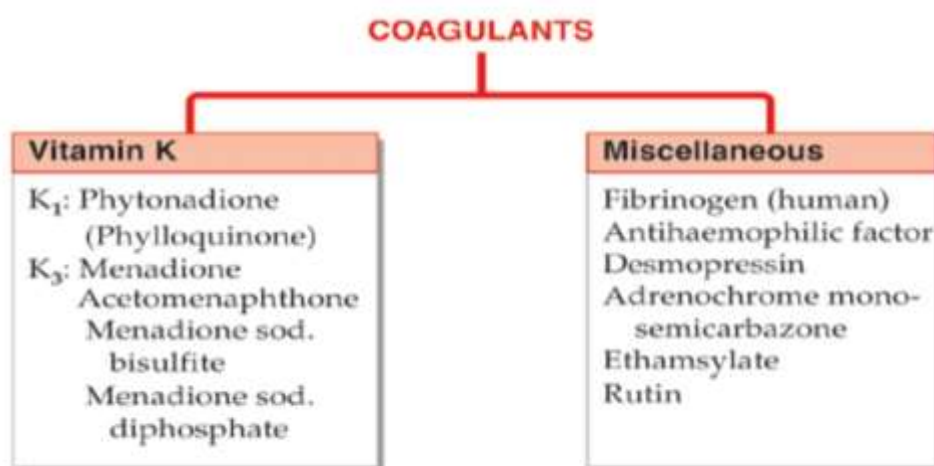


Figure 5: Classification of coagulants^[26]

MECHANISM OF ACTION:

Extrinsic and intrinsic pathway are commonly utilized to classify the mammalian Coagulation System (Fig. 6). The extrinsic tissue factor (TF) is generated by each of these cascades: The formation of prothrombinase complex (FXa:

FVa) and ultimately thrombin is facilitated by the intrinsic (FIXa:FVIIIa)tenase complex and factor (FVIIa). The independent activation of the intrinsic and extrinsic pathways, which subsequently converge into a unified pathway (FX, FV, FII), is outlined by the conventional cascade coagulation model. The reviews offer a

comprehensive explanation of the coagulation cascade.[27,28]

There are two basic pathways in the coagulation cascade of secondary haemostasis that result in the synthesis of fibrin. These are the tissue factor pipeline, also referred to as the extrinsic pathway and the contact activation pathway, also referred to as the intrinsic pathway, which both result in the same basic processes that generate fibrin. It was

once believed that the two coagulation cascade paths were equally significant, but it is now understood that the tissue factor (extrinsic) pathway is the main mechanism for the start of blood coagulation.[29]

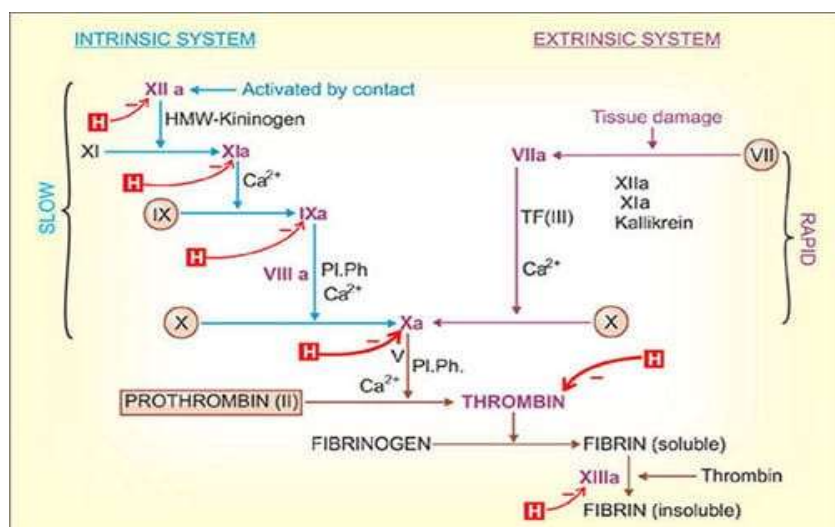


Figure 6: Mechanism of blood coagulation

The extrinsic tissue factor pathway plays a key role in our body's ability to stop bleeding. Its main job is to kick off a "Thrombin burst", which is when thrombin the star player in the coagulation cascade gets released quickly to activate the process further. Interestingly, FVIIa, one of the activated coagulation factors, is found in large amounts compared to others.

Here's how it works:

1. When a blood vessel is damaged, FVII leaves the bloodstream and teams up with tissue factor found on leukocytes and stromal fibroblasts- cells that carry tissue factor- to form an activated complex known as TF-FVIIa.
2. TF-FVIIa activates FX and FIX.
3. FXIa, FXII, FXa, and thrombin all play a role in activating FVII.

4. Tissue factor pathway inhibitors (TFPI) significantly limited the activation of FX (To produce FXa) by TF-FVIIa.
5. The prothrombinase complex, made up of FXa and its co-factor FVa, converts prothrombin into thrombin.
6. FVIII and FV, which create a complex with FIX, are additional components of the coagulation cascade that thrombin later activates. Thrombin also frees FVIII from its bond with VWF.
7. The cycle Continues with FVIIIa, the co-factor of FIXa, and the "tenase" complex they form, which activates FX. (" Tenase" is blend of "ten" and the enzyme suffix-"ase").[29]

Contact activation pathway (intrinsic):

The intrinsic contact activation pathway kicks off with a complex that forms on collagen, involving high molecular weight kininogen (HMWK), prekallikrein and FXII also known as Hageman factor. This process converts FXII into FXIIa and prekallikrein into kallikrein. When FXIIa is around, FXI gets transformed into FXIa. Then, factor XIa steps into activate FX, turning it into FXa, and it also activates FIX, which teams up with its co-factor FVIIIa to create the tenase complex. Interestingly, people with severe deficiencies in FXII, HMWK and prekallikrein don't experience bleeding issues, highlighting just how minor a role the contact activation system has a more significant impact on innate immunity and inflammation.^[29,30] In studies with animal models, blocking factor XII and Pk seems to disrupt innate immunity. This disruption might actually help protect against thrombosis while keeping the risk of bleeding low. Inhibition of factor XI looks even more promising, as it has shown the expected results in early clinical trials.^[29,30]

Final Pathway:

The way we divide coagulation into two pathway is a bit arbitrary, based on lab tests that measured clotting times after using glass (the intrinsic pathway) or thromboplastin, which is a mix of tissue factor and phospholipids (the extrinsic pathway). It's a bit of an over simplification to say

that prothrombin only turns into thrombin when influenced by these pathways. In reality, activated platelets start producing thrombin right at the beginning of the platelet plug, which actually helps to activate even more platelets.^[31] In addition to turning fibrogen into fibrin, thrombin also kicks off the activation of factor VIII and V, along with their inhibitor protein C, but only when thrombomodulin is around. Plus, it's important to note that activating factor XIII creates covalent linkages that crosslink the fibrin polymers formed from those activated monomers.^[29,32] FVIII and FIX continue to activate to produce the tenase complex, which keeps the coagulation cascade in a prothrombotic state until the anticoagulant pathway down-regulate it.^[29] There are two stages to the coagulation process. The first stage is **the initiation phase**, which takes place in cells that express tissue factors. **The propagation phase**, which takes place on activated platelets, comes next. About 5% of thrombin generation is attributed to the beginning phase, which is mediated by tissue factor exposure and continues via the traditional extrinsic pathway. In the propagation phase, the typical intrinsic pathway leads to increased thrombin synthesis; approximately 95% of thrombin is produced during this second phase.^[33]

HERBS USED AS BLOOD COAGULATING AGENTS:

NAME OF HERBS	PLANT NAME	BOTANICAL NAME	FAMILY	CHEMICAL CONSTITUENTS	MECHANISM OF ACTION	THERAPEUTIC USE	TOXICITY	REFERENCE
Blumea	Sambong	Blumea balsa mifera (L.) DC	Compositae	Monoterpenes, sesquiterpenes, diterpenes, flavonoids, organic	It suggested that the effects of blumeatin on the platelet aggregation were dependent upon the concentration used. The injection of B.balsamifera extracts	Platelet aggregation, Wound healing, anti-obesity, disease and insect resistance activities, enhancing	cute toxicity shows some transient effects on body weight and food/water consumption at high doses,	34-35



				acids, esters, alcohols, dihydroflavone, sterols, volatile oils etc.	decreased the blood pressure, expanded the blood vessels and inhibited the sympathetic nervous system in order to address the high pressure and insomnia. The infusion of the plant also had the function of diuresis.	percutaneous penetration, antitumor, hepatoprotective, super oxide radical scavenging, antioxidant, antimicrobial, anti inflammation, antiparasmodial, antityphosinase etc.	appears to be adaptive responses with no significant long term effect. However caution is advised, as high concentrations of its volatile oil may lead to mild liver injury and it is crucial to follow proper guidelines of dosage.	
Moringa seeds	Saragva nising, Drumstick seed	Moringa olifera Lum.	Moringaceae	Flavanoids, Quercetin, Phenolic acids, Tannins etc.	Moringa seeds contains cationic proteins and lectins that act as coagulant agents that work by binding to negatively charged components like fibrinogen or other clotting factors, promoting their aggregation and accelerating the formation of clots of blood and gives its procoagulant effect	Wound healing, anti-inflammatory, antioxidant, antimicrobial, antifertility, anticancer, anti-hepatotoxic, anti ulcer etc.	Same research studies determine that high dose of moringa seed can cause organ damage issues, at very high dose can lead to damage in vital organ like liver and kidney	36
Alum	Phaktari	Potassium Aluminate (Potassium Aluminium Sulphate)	-	XAl(SO ₄) ₂ · 12H ₂ O { Aluminium (Al), Sulphate (SO ₄ -2), Monovalent cation (X), Water (H ₂ O), Double sulphate }, ect.	It is allow to neutralize stomach acid, slow protein degradation and enhance immune response	As Blood clotting agent, Wound healing, skin treatment, oral hygiene etc.	It can cause toxicity if ingested in large amounts especially in individuals with kidney problems or when used in specific medical procedures	37

Turmeric	Haladi	Curcuma longa Linn.	Zingiberaceae	Curcumin, carbohydrates, proteins, alkaloids, glycosides, terpenes, steroids, flavonoids, tannins, saponins	Turmeric may promote hemostasis (stopping bleeding) when applied topically on wound, potentially due to the presence of proteolytic enzymes that could facilitate fibrin clot formation and initiate wound healing process.	Stop bleeding only when applied externally, wound healing, antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anti-ulcer, antifertility etc.	Topically applied turmeric is generally considered safe, with toxicity related to blood coagulation being unlikely when used on the skin	38
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CONVENTIONAL DRUGS:

1. TRANEXAMIC ACID:

Introduction:

In Certain situations, antifibrinolytic medications such as tranexamic acid (TXA), have been demonstrated to lower mortality with little side effect and to effectively prevent bleeding consequences in a range of haemostatic challenges.^[39] A drug called tranexamic acid is used to treat or stop significant blood loss from severe trauma, postpartum haemorrhage, surgery, teeth extractions, and nosebleeds.^[40]



Figure 7: Tablets of Tranexamic Acid
Mechanism of action:

The mechanism of action of tranexamic acid by blocking lysine binding sites on plasminogen

molecules, tranexamic acid, a synthetic lysine derivative, prevents plasminogen from interacting with produced plasmin and fibrin, hence exerting antifibrinolytic actions. Consequently, secondary haemostasis stabilises the created fibrin meshwork by inhibiting plasminogen activation.^[41] The synthetic analogue of the amino acid lysine is called tranexamic acid. It binds plasminogen's four to five lysine receptor sites reversibly, acting as an antifibrinolytic. This stops fibrin from degrading and maintains the matrix integrity of fibrin by reducing the conversion of plasminogen to plasmin.^[42]

Pharmacokinetics:

Dosage forms:[oral and intravenous forms]

When administered to healthy individuals, the half-life of intravenous TXA has been observed to be two hours. The time to maximum concentration, as determined by AUC, is unaffected by food intake.^[41] According to reports, oral and intravenous TXA have a 33%-34% bioavailability. The cumulative excretion of TXA in urine over a 24-hour period is over 90%, indicating exponential elimination of the intravenous version of the medication. The primary excretion mechanism is renal clearance.

This is associated with a higher frequency of TXA consequences involving renal failure.^[43] Depending on serum creatinine levels, a dose decrease should be performed for both oral and intravenous forms. The binding affinity of tranexamic acid to plasminogen and plasmin is six to ten times more than that of related substances, specifically e-aminocaproic acid.^[44]

Side effects:

Side effects are rare. They encompass alteration in color perception, convulsions, thrombosis, and hypersensitivity reaction. Tranexamic acid to be safe for use during pregnancy and breastfeeding.^[45]

Contraindications:

Tranexamic acid allergy seizures' past active thromboembolic illness or a history of venous or arterial thromboembolism severe renal impairment brought on by drug build up; mild to moderate renal impairment necessitates dose modification.^[46]

Dosage:

The dosage for the treatment of dental extraction in individuals with haemophilia, two to three 500 mg tablets should be taken orally every eight hours (based on a dose of 25 mg/kg/day). As the usual treatment for local fibrinolysis, 0.5-1.0g should be injected slowly (at a rate of 1ml/minute) two to three times per day. It is advised to administer 1.0g, or 15 mg/kg, by gradual intravenous infusion every 6-8 hours for general fibrinolysis.

2. FIBRIN GLUE:

Introduction:

Fibrin glue (also called fibrin sealant) is a surgical formulation used to create a fibrin clot for

hemostasis, cartilage repair surgeries or wound healing. It contains separately packaged human fibrinogen and human thrombin.^[47]

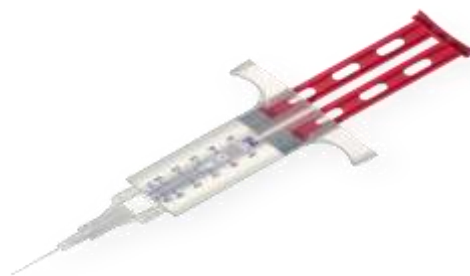


Figure 8: Fibrin glue injection

Mechanism of action:

- The principle is based on wound healing following injury where the inciting inflammation allows formation of thrombus (clot) through a series of event in the coagulation cascade.
- Fibrin glue mimics this coagulation cascade resulting in its adhesive capacity.
- Fibrin glue bypass the initial extrinsic and intrinsic coagulation cascade but replicate the physiological final common pathway of coagulation cascade.
- Thrombin activate fibrinogen to fibrin monomer, factor XIII (present in the fibrinogen component of the glue) cross links and stabilizes the clot's fibrin monomers while aprotinin inhibits fibrinolytic enzyme, consequently resulting in a stable clot.
- There is subsequent proliferation of fibroblasts and formation of granulation tissue within hours of clot polymerization.
- Clot organization is complete two weeks after application.
- The resultant fibrin clot degrades physiologically.^[48]

Side effects:



Possible adverse effects include bleeding disorder and allergic reactions such as flushing, stringing, generalized urticaria, angiodema, bronchospasm and anaphylaxis.

Other adverse effect in studies occurred in roughly equal proportions in treatment and placebo group.^[49]

3. CARBAZOCHROME SODIUM:

Introduction:

Carbazochrome sodium sulfonate (CSS) can stop bleeding because it can increase capillary permeability and cause damaged capillary endings to contract.^[50]

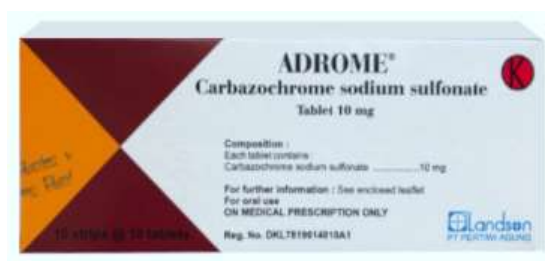


Figure 9: Carbazochrome sodium sulfonate tablets

Mechanism of action:

Even through the exact mechanism of action is still unknown, recent research indicates that it may reverse the rise in endothelial cell permeability brought on by bradykinin, trypsin and thrombin by preventing the formation of intracellular actin stress fibres and restoring tight cellular connectivity.^[51]

Use:

Carbazochrome sodium sulfonate (CSS) is also utilised in urology an otolaryngology.^[52]

Side effects:

Research indicates that CSS can help clients with refractory chronic prostatitis with their discomfort, post –urination symptoms and nasal bleeding symptoms.^[52]

4. ETAMSYLATE:

Introduction:

Etamsylate, also known as ethamsylate, is an antihemorrhagic drug that is thought to function by enhancing platelet adhesion and capillary endothelium resistance.^[53]

Additionally, it prevents the production and function of prostaglandins that lead to vasodilation, platelet disintegration and increased capillary permeability.^[54]



Figure 10: Etamsylate injection

Mechanism of action:

Action mechanism, Etamsylate is a haemostatic drug that also has proaggregant and angio-protective properties. It promotes the release of thrombopoiesis from the bone marrow. Haemostatic effect is brought on by the activation of thromboplastin creation on tiny blood vessel injury sites and the reduction of Pgl2 (prostacyclin) synthesis. It also promotes platelet adhesion and aggregation, which ultimately results in the reduction and cessation of haemorrhage. The exact way that etamsylate works is uncertain. It has been demonstrated to shorten the duration of wound bleeding and blood loss.^[55]

Use:

Regardless of the source or site of the bleeding, use to stop and treat small vessel bleeding. Additionally, it lessens or stops bleeding before, during, after delicate procedures.

Common adverse effect:

Skin rash, headache, nausea, vomiting, diarrhoea and injection site reaction (pain, swelling and redness).

ADVANTAGES OF HERBAL HEMOSTATIC AGENTS:

1. Various mechanism of action:

Herbal extracts are rich in a variety of active constituents such as flavonoids, tannins, alkaloids, glycosides and saponins. When combined, all these agents have the capacity to :

- Induce platelet aggregation
- Enhance vascular tone
- Drive the coagulation
- Impair fibrinolysis^[56]

2. Less synthetic additives:

Moreover, They reduce the chance of allergy, disease and immune reactions as they generally do not include animal or donor derived products.

3. Cost-effective and accessible:

In regions where traditional medicine is deeply rooted, finding raw botanical ingredients can be a breeze and often more affordable.

4. Early evidence of efficacy:

Take, for instance, a plant based Turkish extract known as Ankaferd Blood Stopper (ABS), which has shown promising result in curbing gastrointestinal bleeding.^[57] Research conducted

on lab animals indicates that herbal treatments can be just as effective as their synthetic counterparts in reducing bleeding and they tend to have fewer negative effects on tissues, like those seen in rat kidney surgeries.

5. One of the many perks of these products is their porous structure, impressive absorbance capacity, affordability and easy availability, not to mention that they don't carry any risk of bloodborne infections.^[58]

6. You can find them without much hassle, they are user-friendly, durable and won't break the bank.

7. When you add alum as a coagulant aid, the effectiveness of herbal coagulants in filtering out impurities really gets a boost.

8. Plus, since they are biodegradable and leave behind fewer harmful residues, herbal coagulants sourced from natural plants are often viewed as safer options.

9. When you stack herbal coagulants against chemical ones, you'll find that the herbal options come with a bunch of advantages, especially when it comes to being budget-friendly and safe.^[59]

DISADVANTAGES OF HERBAL HEMOSTATIC AGENTS:

1. There is a lack of solid clinical evidence:

Most of the research, We have relies on small scale clinical trials or studies done on animals. Large, randomized and placebo controlled human trials are pretty rare.

2. There is also a lot of uncertainty around standardized dosing and safety profiles:



It is tough to ensure consistency because of variations in plant species, extraction methods and dosage. Taking high doses can pose risks, including potential liver or kidney damage.^[60]

3. Potential side effects and drug interactions:

Overdoses produce nephrotoxic and hepatotoxic effects of some herbal constituents (eg, tannins and phenolics). They could pose additional risks by interacting poorly with anticoagulants or antiplatelet drugs (such as warfarin).^[60]

4. Regulatory and gaps of quality control:

Numerous products have not been approved by the main drug regulators (eg, FDA, EMA) with issues regarding purity, strength and contamination.

5. Unknown processes remained un resolved:

The precise bioactive compounds and molecular mechanisms behind the actions of the majority of herbs remain unclear.

6. They must be taken off after application because they are not bioabsorbable.

Summary Table:

Aspects	Advantages	Disadvantages
Efficacy	Clinically promising for localized bleeding is multi target coagulation	Limited, extensive human trials; frequently small sample or animal based
Safety	Fewer synthetic remnants and less immunogenicity	Drug interactions, potential organ damage and varying quality
Cost/Access	Plant based and usually reasonably priced	None
Mechanisms	Multiple constituents across numerous classes of herbs	In many cases, the mechanistic actions are not fully characterized
Regulation	Traditional use supports heritage	Largely unregulated; there has been little standardization at the international level

COMPARISON:

A. Herbal (Natural) Hemostatic Agent:

1. Chitosan: -

- Chitosan derived from chitin, Shellfish, and fungi.
- This is positively charged polysaccharide helps to induce haemostasis by attracting red blood cells, clumping platelets, and changing the structure of fibrinogen, so avoiding the typical clotting cascade.
- A positively charged polymer made from chitin, shellfish and fungi polysaccharides, chitosan is frequently found in products like Hemcon bandage, Celox, and Traumastat. Even

in cases of coagulopathy , it can do its magic in as little as two minutes.^[61]

- In animal experiments, modified forms (such as chitosan-bio glass composites, foams and hydrogel) exhibit improved haemostatic performance, greatly cutting down on bleeding time.^[62]

2. Ankaferd Blood Stopper (ABS) :-

- Five plants are used to create a basic herbal mixture: Thymu svulgaris, Urti cadioica, vitisviniferaa, Glycyrrhiza glabra and Alpenia officinarum.^[63-65]
- Works by cellular regulation and protein network building rather than particular clotting factor ; It



is effective even in patients with compromised primary or secondary haemostasis.^[66]

- Clinical evidence indicates use in gastro intestinal bleeding, post surgical hemorrhage (Tonsilectomy, postatectomy, etc.) with promising out comes, through safety data is still limited.^[67]

3. Traditional Chinese Herbal Extract :-

- Extracts from herbs like pollen Tyhae (cattailpollen), Sanguisorba officinalis, Sophorajponica, Nelumbo nucifera Showed significant reduction in coagulation time in vitro, via activation of factors like XII in the intrinsic pathway.^[68]

B. Synthetic Hemostatic agents:

1. Inorganic and mineral substances :-

- **Kaolin** : Such a quickclot, is utilized in trauma dressings because it concentrates clotting components, activates factor XII and absorbs

water from blood; the FDA has approved for emergency bleeding control.^[69]

- **TC 325 (Hemospray)** : An inert bentonite powder used endoscopically to treat gastrointestinal bleeding. It uses mechanical temponade to achieve rapid haemostasis (success in 91-93%).^[70]
- The FDA approved **Stasilon**, a woven fibrin made of fibreglass and bamboo fibre, for topical use in 2007 for specific burn and trauma patients, but only for arterial haemorrhage.^[71]

2. Sealants and synthetic polymers :-

- Regardless of the specific blood components, **Polyethylene glycol (e.g., Coseal)** : Hydrogel adhesives that form a cohesive scaffold attaching to tissue allow instant sealing during cardio vascular surgery.^[72]

Comparison Table:

Feature	Herbal Agents	Synthetic agents
Source	Polysaccharides found naturally or standardized plants.	Lag engineered materials or polymers.
Mechanism	RBC/platelet aggregation; protein networks and factor activation (such as FXII).	Mechanical absorption, triggering of the coagulation cascade, hydrogel sealing.
Speed	Quick (a few minutes), yet subjective.	Extremely fast (seconds to minutes), consistently produced in an industrial setting.
Clinical Use Cases	Traditional medicine, dentistry, minor surgeries and topical bleeding.	Used in trauma kits, endoscopy and surgical sealants.
Benefits	Biodegradable, biocompatible and low antigenicity.	Accurate, repeatable and approved for high risk applications
Safety and Limitations	Potential allergenicity, insufficient large scale testing and variability.	Occasional thermal concerns (Zeolite), limited biodegradability and cost issues.

CHALLENGES IN USE OF HERBAL BLOOD CLOTTING AGENTS:^[73]

1. Lack of scientific validation and standardization: -

- Standardization: The process of evaluating the quality and purity of crude drugs by

means of various parameters like morphological, microscopical, physical, chemical and biological observations.

- Accuracy of plant identification, evaluation and isolation of active ingredients is key challenge.



- Active ingredients in plants are in complex form and needs special precautions, because a single medicinal plant consist of hundreds of constituents.
- Medicinal plant properties are influenced by the time of collection, area of plant origin and environmental conditions.
- Hence scientific validation and technological standardization of herbal medicines is needed for the future advancement of herbal formulation.

2. Lack of Quality and regulatory aspects: -

- Quality control (QC) of herbal formulations is required for its safety and efficacy.
- QC assures quality products that reduce the risks associated with herbal medicine.
- Regulation and legislation of herbal medicines has been enacted in very few countries.
- Most countries do not have any proper regulation of botanicals and quality of herbal products sold is generally not guaranteed.
- European countries- regulated by the European Directive on traditional herbal medicinal products.
- UK- MHRA (Medicines and Healthcare products Regulatory Agency)
- India- AYUSH

3. Limited evidence based studies on efficacy and safety:-

- Evidence based studies on the efficacy and safety of traditional Indian medicines are limited.
- The essential ingredient in most formulations are not precisely defined.
- This is one of the most important challenge to scientists attempting to identify a single bioactive compound.
- In depth studies and more stringent conditions should be followed to make a herbal

formulation so that the role of each and every component is known.

- In order for a drug regulatory agency to meet the high expectations of the public, there is need for well designed, randomized, double-blind and placebo- controlled clinical trials to establish the safety and efficacy of herbal medicines with allopathic drugs.
- Systemic clinical trials will provide new opportunities for basic and applied research in the areas of herbal products and ayurvedic remedies used in India.

4. Lack of pharmacokinetic studies of bioactive molecules: -

- Efficacy of drug depends upon its composition as herbal products have complex composition.
- In vitro assays are cheap and easy, but in herbal preparations sufficient concentration of active constituents at the site of action is difficult.
- Herbal formulations because of which lack data on their disposition and biological fate in humans.
- Pharmacokinetics are vital – drug development process of understanding ADME.
 - To know herbo-drug interaction.
 - Elucidation of metabolic pathways which yields potentially new active compounds and assessment of elimination route and their kinetics.

CONCLUSION:

Adequate haemostasis is essential in clinical as well as in emergent situations and blood coagulation remains an important and vital physiologic defensive system. While conventional drugs such as tranexamic acid, fibrin glue, carbazochrome sodium and etamsylate have been reported as effective, their use had been limited by the disadvantages of side effects, high cost and limited availability in poorly resourced situations.



Medicinal plants compounded with bioactive phytochemicals represent a promising alternative due to their low cost, social acceptability and variety in mechanisms of action. Large haemostatic potential is demonstrated by plants viz., *Blumea balsamifera* and *Moringa oleifera*; however, issues related to standardization, quality control and regulatory validation are the bottlenecks for the clinical utilization. A perfect treatment would be due to combining the rapidity effectiveness of allopathic drugs with the availability and safety of herbal drugs. So to bridge the gap still present between the desk and the patient bed (between traditional believe and clinical application), future studies should focus on better pharmacological understanding, toxicity studies and formulation development.

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