Mini-Review

DOI: 10.5582/ddt.2022.01037

Potential applications of Chinese herbal medicines with hemostatic properties

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SUMMARY Various herbal medicines with hemostatic properties have been applied for centuries to accelerate hemostasis and control bleeding. However, the mechanisms of action and active constituents remain unknown. This report provides an overview of current clinical hemostatic agents and their disadvantages, then focuses on the clinical value of Chinese herbal medicines with unique hemostatic features that modern medicines lack. A comprehensive review of hemostatic agents derived from Chinese herbal medicines and their potential medical applications is also presented.

Keywords blood coagulation, hemorrhage, Pollen Typhae, mechanism

1. Introduction

Seepage from ruptured blood vessels results in the loss of valuable blood from the circulatory system. When blood flows out of damaged vessels, local blood vessels contract to suppress bleeding and platelets simultaneously aggregate to form thrombus that blocks damaged sites. Fibrin generated through the activation of a series of blood coagulation factors, strengthens platelet aggregation to form stable thrombus at wounds to stop bleeding (hemostasis) (Figure 1) (*1,2*). Bleeding is not only caused by injury, but also by abnormalities among clotting factors or platelets (*3*). An excessive loss of blood by bleeding can lead to death. Thus, hemostasis is critical to maintain healthy biological activities, prevent blood loss, and function as a physiological self-defense mechanism that impedes bacterial and viral invasion (*4*). This review provides an overview of current clinical hemostatic agents and their disadvantages, then summarizes the features of Chinese herbal hemostatic agents and their potential applications to contemporary and future medicine.

2. Hemostatic system and hemostasis

Hemostasis is achieved when procoagulants and anticoagulants are balanced (*2,3*). The human hemostatic system comprises platelets, coagulation and fibrinolytic factors, vessels, and endothelial cells that line the insides of vessels (*4*). Local blood vessels constrict to contain bleeding from damaged vessels and activated platelets rapidly aggregate to form soft plugs at sites of damage. This process is primary hemostasis, which starts immediately after platelets adhere to the subendothelial matrix (*5*). After primary hemostasis, coagulation factors on the surface of the phospholipid bilayer membranes of activated platelets convert fibrinogen through a proteolytic coagulation cascade into insoluble cross-linked fibrin, which forms a mesh that is incorporated into and around a soft aggregate plug. The mesh strengthens and stabilizes blood clots during the process of secondary hemostasis (*5*). Fibrinolysis also plays a significant role in hemostasis by dissolving blood clots formed during wound healing after hemostasis (*6*).

3. Characteristics of clinical hemostatic agents and issues

Table 1 shows the classification of clinical hemostatic agents. Carbazochrome and adrenochrome are hemostatic capillary stabilizers that treat hemorrhage by improving capillary fragility (*7-10*). These agents might be applicable to stopping extravascular blood leakage. Carbazochrome is clinically administered orally and by intravenous injection. Although details of the mechanism(s) remain obscure, this agent exerts hemostatic effects regardless of the impact on the coagulation and fibrinolytic systems and platelet activity. Administering these agents orally can control purpura, as well as bleeds from the skin and mucous membranes (*9,10*). However, the effects are not potent, and this agent is not applicable to bleeds due to tissue wounds.

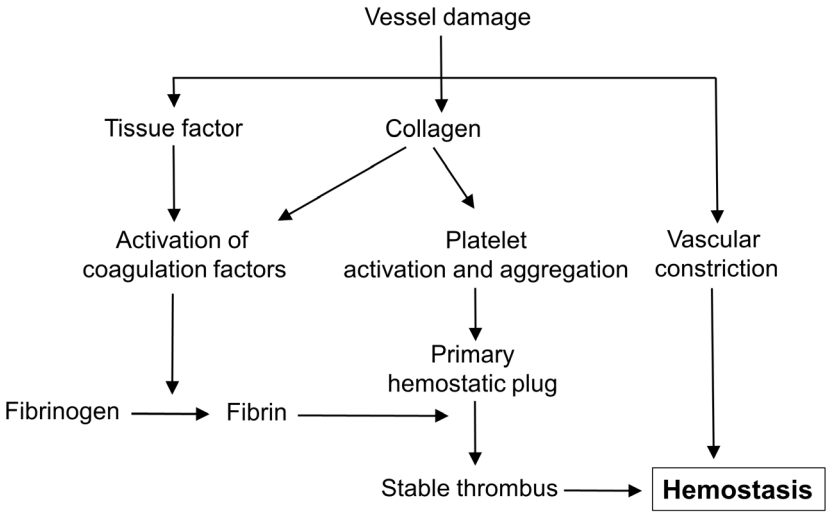

Figure 1. Overview of hemostasis and its components.

Table 1. Classification of hemostatic agents

Mode of action	Hemostatic agent(s)
Capillary stabilizers	Carbazochrome and adrenochrome
Coagulation accelerator	Hemocoagulase
Anti-fibrinolytic	Tranexamic acid
Topical	Thrombin, collagen, oxidized regenerated cellulose, liquid fibrin glue, adrenaline and water-insoluble sponge prepared from gelatin
Vasoconstrictor	Epinephrine (adrenaline)

The enzyme hemocoagulase (reptilase) is a blood coagulation accelerator purified from snake venom that has been recognized for ~18 centuries (*11*). Its activity is associated with batroxobin, a defibrinogenating hemostatic agent derived from *Bothrops atrox moojeni* (pit viper) venom (*12*). Hemocoagulase works by causing the cleavage of fibrinogen into fibrin monomers which eventually leads to the formation of fibrin polymers (*13*). The characteristics and nature of batroxobin differ from those of thrombin. Batroxobin remains systemically active as well as at local sites of application in the absence of important clotting factors. Snake venom has evolved to contain several enzymes, including proteases, several of which specifically act on the blood coagulation system (*14,15*). Although much effort has been directed towards using these enzymes to regulate the blood coagulation system, hemocoagulase seems to remain the sole clinically applied venom-derived agent. Hemocoagulase is used to control pulmonary hemorrhage, hemorrhage in alcoholic cirrhotic liver disease, oral, genital, dental bleeds, and bleeds from wounds and is administered intramuscularly or intravenously to control renal hemorrhage (*16-18*). Biopharmaceutial hemocoagulase is used many bleeding situations, but it cannot be orally administered due to high risk of anaphylaxis-like symptoms.

Tranexamic and ε-aminocaproic acids are anti-fibrinolytic agents that inhibit plasmin, a protease that dissolves fibrin clots and has antithrombotic activity. These agents to the lysine-binding site of plasminogen, thus inhibiting its binding to fibrin. They also inhibit plasminogen activator action on fibrin, thus preventing fibrin degradation and exerting hemostatic effects (*19*). Tranexamic acid is a prevalent hemostatic agent that is clinically administered as an internal medicine and by injection (*20,21*). It is applied when bleeding tendencies might be associated with systemic hyperfibrinolysis (due to leukemia, aplastic anemia, purpura for example, and abnormal peri- and post-operative bleeding), and abnormal bleeding possibly associated with focal hyperfibrinolysis (epistaxis pulmonary, genital, and renal bleeds, as well as abnormal peri- and post-operative bleeds) (*22*). Tranexamic acid can be delivered orally, but its therapeutic value is limited for bleeding tendencies associated with systemic hyperfibrinolysis and abnormal bleeds that might be associated with hyperfibrinolysis,.

Topical hemostatic agents applied to the skin can stop bleeding from small blood vessels and capillaries. Thrombin, collagen microfibers, oxidized regenerated cellulose, liquid fibrin glue, adrenaline and water-insoluble sponges prepared from gelatin are all functional topical agents (*23-26*). Thrombin purified from human or bovine blood dissolved in physiological saline or powdered, can be sprayed onto bleeding

Table 2. Hemostatic herbal medicine and active components (Kosuge *et al*.)

Crude drug	Origin	Active compounds	*Ref.*
地楡 (Chiyu)	*Sanguisorba officinalis* L.; roots	3,3',4-Tri-O-methylellagic acid	*42*
田七 (Denshichi)	*Panax pseudo-ginseng Wall.* var. Notoginseng (BURKILL) HOO and TSENG; radix	Dencitine (β-N-oxalo-L-α-b-diaminopropionic acid)	*41*
蒲黄 (Hoou)	*Typha lactifolia* L.; pollen	Isorhamnetin 3-rutinoside-7-rhamnoside, unknown,	*40*
槐花 (Kaika)	*Sophora japonica* L.; ground buds	Quercetin	*37*
蓮房 (Rembo)	*Nelumbo nucifera* GAERT.; ground toruses	Quercetin	*39*
小連翔 (Shorengyo)	*Hypericum erectum* Thunb.; ground herb	Wedelolactone, Demethylwedelolactone	*43*
側柏葉 (Sokuhakuyo)	*Biota orientalis* (L.) ENDL.; leaves and branches	Quercitrin	*44*
大薊 (Taikei)	*Cirsium japonicum* DC.; ground herb	Pectolinarin	*38*

sites (*23*). Microfibrillar collagen is a hemostatic agent that maintains the three-dimensional structure of bovine dermal collagen, exerts powerful platelet aggregation activity, and adheres tightly to wounds (*27*). Oxidized cellulose is a common surgical hemostat that seems to work *via* caustic action by decreasing the pH and generating an artificial clot (*28*). Fibrin glue is a mixture of fibrinogen, factor XIII, thrombin, and calcium that mimics the last stages of the clotting cascade and forms fibrin clots (*29*). These topical agents achieve hemostasis by generating adhesive cross-linked fibrin in wounds. Epinephrine (adrenaline), a hormone secreted by the medulla of the adrenal glands, works as a topical hemostatic agent by exerting vasoconstrictor effects that stop bleeding (*30,31*).

4. Chinese herbal medicines

Various herbs have a long history of ethno-medical application to control bleeds and are popular worldwide, so they might be valuable sources of new hemostatic drugs (*32*). Here, we focused on the hemostatic potential of Chinese herbal medicines. Several Chinese herbs with hemostatic action have been applied for many years. Kosuge *et al*. rigorously evaluated the active components in 12 Chinese hemostatic herbal medicines during the 1980s and analyzed their activities using mouse tail bleeding assays *in vivo* (*33,34*). Tail bleeding reflects platelet activity (*35*). Kosuge *et al*. identified hemostatic activities in Denshichi, *Panax pseudo-ginseng* Wall. var. *notoginseng* (Burkill) Hoo & Tseng; Chiyu, *Sanguisorba officinalis* L; Kanrenso, *Eclipta prostrata* L; Seikon, *Rubia cordifolia* L; Sokuhakuyo, *Biota orientalis* (L.) ENDL; Renbo and Gusetsu, *Nelumbo nucifera* Gaertn (*36*). Table 2 shows the hemostatic components in these herbal medicines and their active compounds (*37-44*) (Table 2). Although Kosuge *et al*. isolated and determined the structures of these compounds, they did not elucidate their hemostatic mechanisms and sites of action.

Among these Chinese herbal medicines, Denshichi is renowned for treating hemorrhagic diseases and it might help to stop uncontrollable bleeds. For example, the livers of patients with hepatitis produce less blood coagulation factors (*45*), and patients medicated with antithrombotic agents have decreased hemostatic activity (*46*); hence, bleeding can be difficult to stop after tooth extraction. Denshichi hemostasis has been applied in dental practice in Japan (*47,48*). Denshichi notably also has many other pharmacological activities in addition to hemostatic activity (*49-51*). Sun *et al*. subsequently reported that terpene glycosides in Chiyu exert hemostatic activity by inhibiting α2-plasmin inhibitor, an inhibitor of fibrinolysis (*52*), but other herbal medicines have not yet been reported.

5. Hemostatic activity of Pollen Typhae

Several cattail species in the family Typhaceae, including *Typha angustifolia* L. (narrow leaf cattail, lesser bulrush, or jambu), *T. latifolia* L. (common cattail), and *T. orientalis* Preel (broadleaf cumbungi or raupo) are perennial herbaceous plants that inhabit North and South America, Europe, Asia, and Africa (*53*). Dried pollens of a series of cattails (Pollen Typhae) comprise an established Chinese herbal medicine used to treat internal and external hemorrhagic conditions (*32*). Hematuria, blood discharge from the anus, metrorrhagia and erythrocyturia have been treated with oral Pollen Typhae for centuries. Pollen Typhae has also served as a hemostyptic agent to treat excoriations or cuts on the skin surface (*54*). Pollen Typhae is believed to work against bleeding and has been administered orally and topically for centuries. Although not fully understood, more is known about the mechanism of action and the active substance in Pollen Typhae than any other herbal medicine. The hemostatic activity of Pollen Typhae extract (PTE) has been assessed in mice *in vivo* and in human blood *in vitro* (*55*). The effects of PTE on the extrinsic and intrinsic coagulation pathways have been assessed by measuring prothrombin (PT), activated partial thrombin (APTT) and plasma recalcification times (*55,56*). Pollen Typhae extract significantly and dose-dependently decreases the amount of time required to form clots in PT and APTT tests and in recalcified plasma (*55*). These findings suggested that PTE promotes the coagulation system in human plasma. Indeed, negatively charged polysaccharide in PTE activates factor XII, which is a proenzyme in the intrinsic coagulation pathway that

accelerates coagulation (*2*). Activation of the intrinsic coagulation pathway by acidic polysaccharide in PTE partly contributes to the hemostatic activity of topical Pollen Typhae. The time-dependent activation of factor XII to factor XIIa by acidic polysaccharide from PTE has shown that Pollen Typhae has potential as a rapid hemostyptic (*56*).

The oral effects of PTE have also been assessed in mouse tail-bleeding models. Oral PTE significantly decreases the duration of tail bleeding compared with control mice (*55*).Pollen Typhae extract with and without an acidic polysaccharide that might contribute to oral hemostatic activity was administered to mice. Hemostatic activity persisted in PTE without acidic polysaccharide (*55*), indicating that compounds other than acidic polysaccharides are responsible for the hemostatic properties of orally administered Pollen Typhae. Isorhamnetin, a flavonoid extracted from Pollen Typhae, shortens the duration of tail bleeds in mice when injected intraperitoneally (*i.p.*) (*46*). Therefore, the compound in oral Pollen Typhae responsible for the reduced tail bleeding duration is likely to be isorhamnetin or a derivative (*55*). Topical PTE also has hemostatic effects in the mouse tail bleeding model. Blood loss measured in the tips of mouse tails immersed in PTE revealed significantly reduced blood loss (*55*).

Although the detailed mechanisms and components involved in the hemostatic action require validation, the hemostatic action of topical and oral Pollen Typhae have been confirmed *in vivo* and *in vitro*. The hemostatic activity of Pollen Typhae applied to wounds is due to activation of the intrinsic coagulation pathway, whereas the oral effects are due to platelet activation and/or vasoconstriction.

Biocompatible carbon dots (CDs) are quasi-spherical charcoal nanoparticles with high stability and low toxicity, the efficacy and safety of which are under evaluation. Fusing traditional Chinese medicine (TCM)-based CDs have attracted considerable interest to treat common diseases (*57*) and they have hemostatic properties (*58,59*). Hemorrhagic states have been treated with charcoal-processed products of Pollen Typhae for many years in China. The hemostatic bioactivity of CDs derived from Pollen Typhae Carbonisata have been identified and their pharmacodynamics have been investigated (*60*). This provides new insights into potential biomedical applications of Pollen Typhae to hemostasis for future drug discovery.

6. Discoveries of novel hemostatic agents from Chinese herbal medicines

Many plants and plant-derived agents have hemostatic activity and perhaps even more novel hemostatic substances in Chinese medical herbs await discovery. We screened extracts derived from 114 plant species in a library of common herbal crude extracts and identified potential hemostatic agents by measuring blood coagulation activities (*61*). Seventeen herbal extracts induced extrinsic blood coagulation. Among them, Goboushi and Gaiyou activated coagulation factor XII, which is the key enzyme in the intrinsic blood coagulation pathway and promoted blood coagulation. Because we found the activities of these plants using the procoagulant effect *in vitro* as an index, an actual hemostatic effect *in vivo* was not apparent. Nonetheless, these crude extracts remain novel hemostatic candidates from known medicinal plants.

Ebrahimi *et al*. comprehensively reviewed the ethno-pharmaceutical applications of medicinal plants or their isolates that stimulate the hemostatic process (62). Although that report included non-Chinese herbal medicine, the authors found *via* a literature search that several plants could be considered as sources of new herbal hemostatic medicines.

7. Conclusions

Many hemostatic agents are clinically applied depending on the situation, but they do not always meet medical needs. Some herbal medicines with hemostatic properties have characteristics that complement modern medicines. Pollen Typhae is of interest because it can be applied internally and externally. The mechanisms of the effects of orally-administered Pollen Typhae obviously differ from those of clinical oral hemostatic agents such as capillary stabilizers and anti-fibrinolytic agents, but its hemostatic effects are clearly comparable.

Although the mechanisms of action and active constituents of plant-derived hemostatic compounds await further investigation, many plants contain natural compounds that have been applied for centuries to control bleeding. New hemostatic sources in Chinese herbal medicines that might be discovered in the future should become clinically valuable under various conditions after their mechanisms of action and active principles are elucidated.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

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Received May 14, 2022; Revised June 10, 2022; Accepted June 19, 2022.

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Released online in J-STAGE as advance publication June 26, 2022.