Evaluation of Hemostatic Effects of Ankaferd as an Alternative Medicine

Yavuz Beyazit, MD; Mevlut Kurt, MD; Murat Kekilli, MD; Hakan Goker, MD; Ibrahim Celalettin Haznedaroglu, MD

Abstract

Ankaferd Blood Stopper (ABS), a unique traditional herbal mixture, has been used topically to stop bleeding for centuries in Anatolia. ABS is a standardized mixture of the plants *Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum,* and *Urtica dioica*. Through its effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics, and cell mediators, ABS is now becoming an official alternative hemostatic medicine for intractable bleedings that are resistant to conventional anti-hemorrhagic measures in Turkey. Furthermore, ABS seems to have a considerable therapeutic benefit, because of its anti-infective, antineoplastic, and wound healing properties, to restore and maintain tissue homeostasis in a variety of diseases. (*Altern Med Rev* 2010;15(4):329-336)

Yavuz Beyazit, MD – Specialist, Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, Ankara, Turkey. Correspondence address: Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, TR-06100, Ankara, Turkey
E-mail: yavuzbeyaz@yahoo.com

Mevlut Kurt, MD – Specialist, Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, Ankara, Turkey.

Murat Kekilli, MD – Specialist, Department of Gastroenterology, Turkiye Yuksek Ihtisas Teaching and Research Hospital, Ankara, Turkey.

Hakan Goker, MD – Professor doctor, Hacettepe University, Faculty of Medicine, Department of Hematology, Ankara, Turkey.

Ibrahim Celalettin Haznedaroglu, MD – Professor doctor, Hacettepe University, Faculty of Medicine, Department of Hematology, Ankara, Turkey.

Introduction

Ankaferd Blood Stopper (ABS) is a traditional medicine that has been used for centuries in Anatolia as a hemostatic agent. The name Ankaferd originates from the union of two words: "Anka" and "Ferd." Anka, which is known as Phoenix in Western tradition, is a mythological bird that bares the mark of every animal and has multi-colored feathers and a face resembling that of a human. The bird, male and unique, that represents eternity of soul and rebirth in many cultures, burns itself and comes back to life again from its ashes. Ferd, meaning peerless, emphasizes the uniqueness of Anka. The word Ankaferd, which can be translated as the single power of the Phoenix, is now creating its own history as a modern drug.

ABS-induced formation of the protein network with vital erythroid aggregation involves the entire physiological hemostatic process.[1-3] There are distinctly important components of the ABS-induced hemostatic network. The spectrin and ankyrin receptors on the surface of red blood cells (RBC) are essential for RBC aggregation. Those proteins and the required ATP bioenergy are part of the molecular make-up of ABS and can be detected by proteomic analysis. ABS also upregulates the GATA/FOG transcription system affecting erythroid functions. Urotensin II is also affected by ABS and represents the link between injured vascular endothelium, adhesive proteins, and active erythroid cells.[3-5] These concepts have been developed by MALDI-TOF proteomic molecular analyses, cytometric arrays, transcription analysis, and SEM ultrastructural examinations as well as numerous *in vitro* and *in vivo* investigations.[4-6] Three ABS phase III studies, performed in vascular port insertion bleeds, anterior epistaxis, and post-tonsillectomy hemorrhages, provide support for its approval as a hemostatic agent in Turkey.[7-9] Hence, ABS could be effectively used both in individuals with normal hemostatic parameters and in patients with deficient primary and/or secondary hemostasis. *In vitro* data on the antibacterial and wound healing profile of Ankaferd and bleeding control in gastrointestinal disorders[10-16] and mediastinal bleeding[17,18] provide further support for its use. Further investigations are being performed to elucidate the ABS hemostatic effects on distinct tissues in various tissue injury models.

Mechanism of Action

ABS is a standardized mixture of the plants *Thymus vulgaris* (dried leaf), *Glycyrrhiza glabra* (dried leaf), *Vitis vinifera* (dried leaf), *Alpinia officinarum* (dried leaf), and *Urtica dioica* (dried root), each of which has some effects on the endothelium, blood cells, angiogenesis, cellular

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proliferation, vascular dynamics, and/or cell mediators.[3,19,20] The amount of each herb in each pharmaceutical form is summarized in Tables 1 and 2.

Although all these plants affect the hemostatic system in different ways, the exact mechanism of ABS is still unknown. Findings from one study suggest the hemostatic actions of ABS might be explained by its rapid (<1 sec) induction of a protein network in human plasma and serum samples.[5] Electron microscopy reveals that blood cells, particularly erythrocytes and activated leukocytes, aggregate rapidly in the presence of ABS, thereby participating in the network formation (Figure 1). All these findings are evident in light (Figures 2 and 3) and electron microscopic analyses.

In vitro tests demonstrated that coagulation Factors II, V, VII, VIII, IX, X, XI, and XIII were not affected by the addition of ABS to fresh normal plasma or serum, whereas plasma fibrinogen activity decreased from 302 to <10 mg/dL, and fibrinogen antigen decreased from 299 mg/dL to <30 mg/dL in parallel with thrombin time prolongation. Total protein, albumin, and globulin levels decreased after the addition of ABS to fresh serum.[3,5]

These studies indicate that the ABS-induced network formation depends upon interactions between ABS and blood proteins, such as fibrinogen, and that ABS might affect fibrinogen and other proteins via agglutination of these molecules. Macroscopic appearance of protein network formation before and after adding ABS to human plasma, serum, and blood can be seen in Figure 4. The basic mechanism of action for ABS appears to be the formation of an encapsulated protein network that provides focal points for erythrocyte aggregation. Rather than affecting an individual clotting factor, this protein mesh affects the entire physiological hemostatic process that controls bleeding.[3]

Animal Studies

Several animal studies demonstrate the efficacy of ABS.[1,21,22] In Wistar rats, topical administration of ABS to amputated legs statistically significantly ($p<0.001$) shortened the duration of bleeding in both untreated and warfarin-pretreated rats by 31.9 percent (1.42 min [95% CI: 0.35-2.49]) and 43.5 percent (5.12 min [95% CI: 2.16-8.07]), respectively,[23] thus, demonstrating its

Table 1. Ingredients of Ampoule and Pad Forms of ABS

Name of Active Ingredient	Amount of Active Ingredient (mg)			
	Ampoule	Pad		
Size of vehicle	2 mL	2.5 x 7 cm 3 mL	5 x 7.5 cm 10 mL	20 x 20 cm 100 mL
Urtica dioica[1]	0.12	0.18	0.6	6.0
Vitis vinifera[2]	0.16	0.24	0.8	8.0
Glycyrrhiza glabra[2]	0.18	0.27	0.9	9.0
Alpinia officinarum[2]	0.14	0.21	0.7	7.0
Thymus vulgaris[2]	0.10	0.15	0.5	5.0

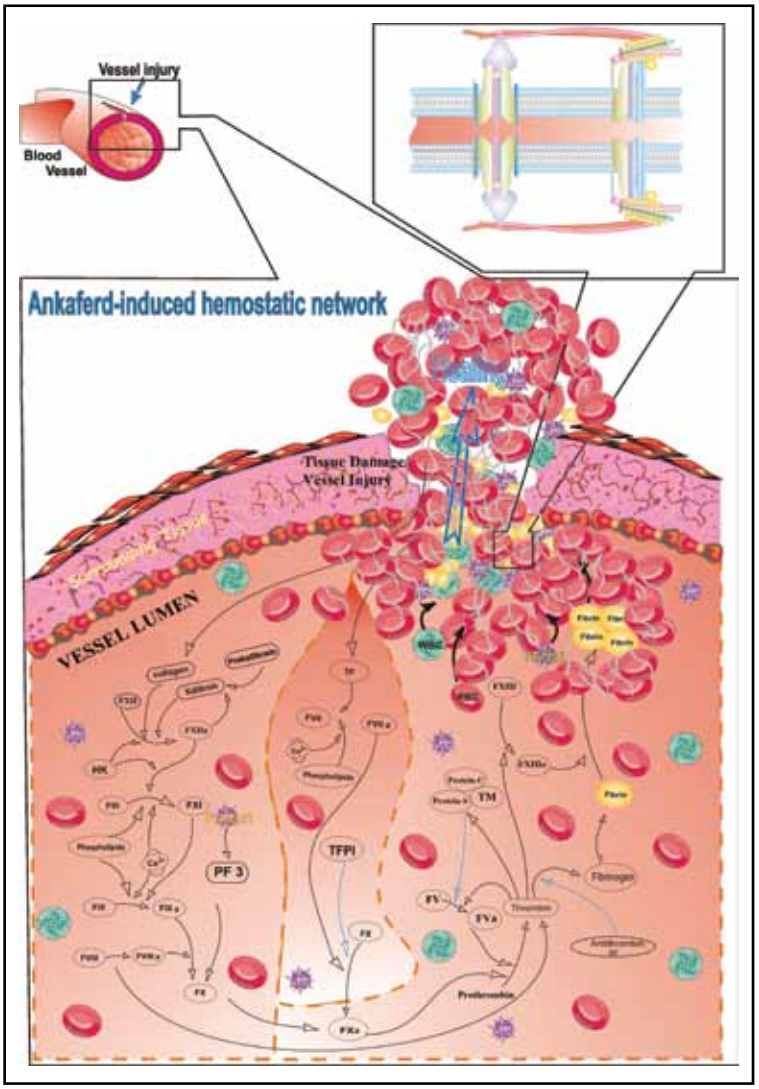
dried root extract,[1] dried leaf extract [2]

Table 2. Ingredients of Spray Form of ABS

Name of Active Ingredient	Amount of Active Ingredient (mg/mL)
Urtica dioica[1]	0.06
Vitis vinifera[2]	0.08
Glycyrrhiza glabra[2]	0.09
Alpinia officinarum[2]	0.14
Thymus vulgaris[2]	0.10

dried root extract,[1] dried leaf extract [2]

Figure 1. Encapsulated Protein Network: The Basic Mechanism of Action of ABS



This protein network provides focal points for erythrocyte aggregation and covers the entire physiological hemostatic process. RBC elements (e.g., spectrin and ankrin surface receptors, and internal ferrochelatase enzyme), related transcription factors (e.g., GATA-1), and RBC-related proteins (e.g., urotensin II) are the main targets of ABS.

Figure 2. ABS-induced Erythrocyte Aggregation (< 1 sec): Red Blood Cells under the Light Microscope (a) Before and (b) Immediately after Ankaferd Application

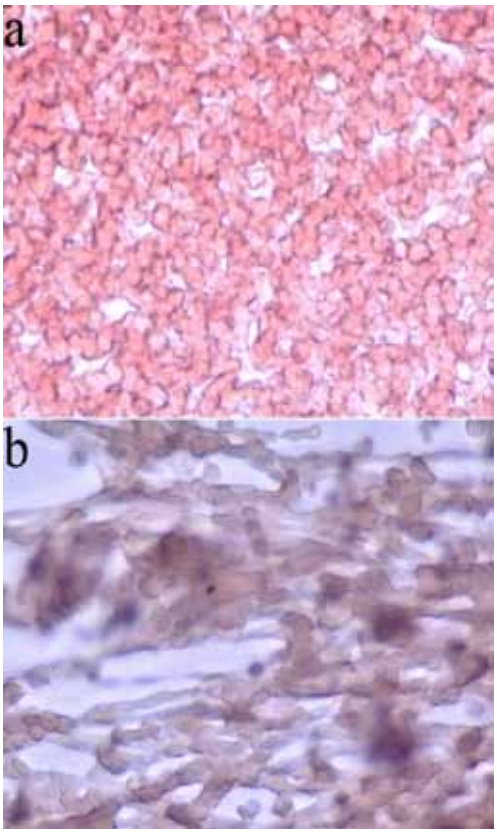
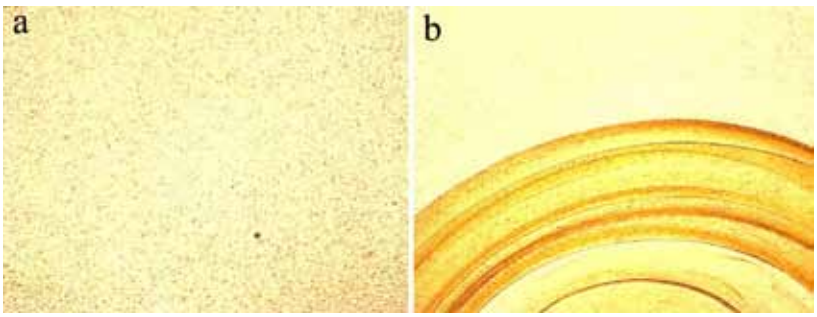


Figure 3. ABS-induced Protein Network Formation (< 1 sec): Plasma under the Light Microscope (a) Before and (b) Immediately after Ankaferd Application



effectiveness as a topical agent either alone or in the presence of warfarin. In a similar study, ABS was able to decrease the duration and amount of bleeding in rats pretreated with acetylsalicylic acid or low-molecular weight heparin. Duration of bleeding following tail-cut was shortened by 22.97 min (95% CI: 17.29-28.64) in the acetylsalicylic group and 19.43 min (95% CI: 12.35-26.51) in the low-molecular weight heparin group. Duration of bleeding was also shortened in control animals by 23.81 min (95% CI: 15.52-32.09). ABS also significantly decreased the amount of bleeding, as measured by means of blotting paper in untreated-, acetylsalicylic-, and low-molecular weight heparin groups.[21]

Application of ABS in spray, solution, and tampon forms to superficial and deep abdominal lacerations has been shown to successfully control bleeding in a swine model.[1] After application of an ABS tampon with gentle pressure for 40 seconds to a superficial skin laceration, rebleeding did not occur during the ensuing 25 minutes. After confirming continuous bleeding from a deep skin laceration, application of 2-3 mL of an ABS solution resulted in instant hemostasis. Rebleeding was not observed in a second incision treated with a tampon of ABS. After an upper midline laparotomy incision was made through the skin and underlying subcutaneous and muscle tissue to expose the transverse fascia, ABS spray was successful in controlling the bleeding from that incision. ABS spray also managed to control the bleeding due to liver injury (grade II lesion according to the American Association for the Surgery of Trauma [AAST]).[1]

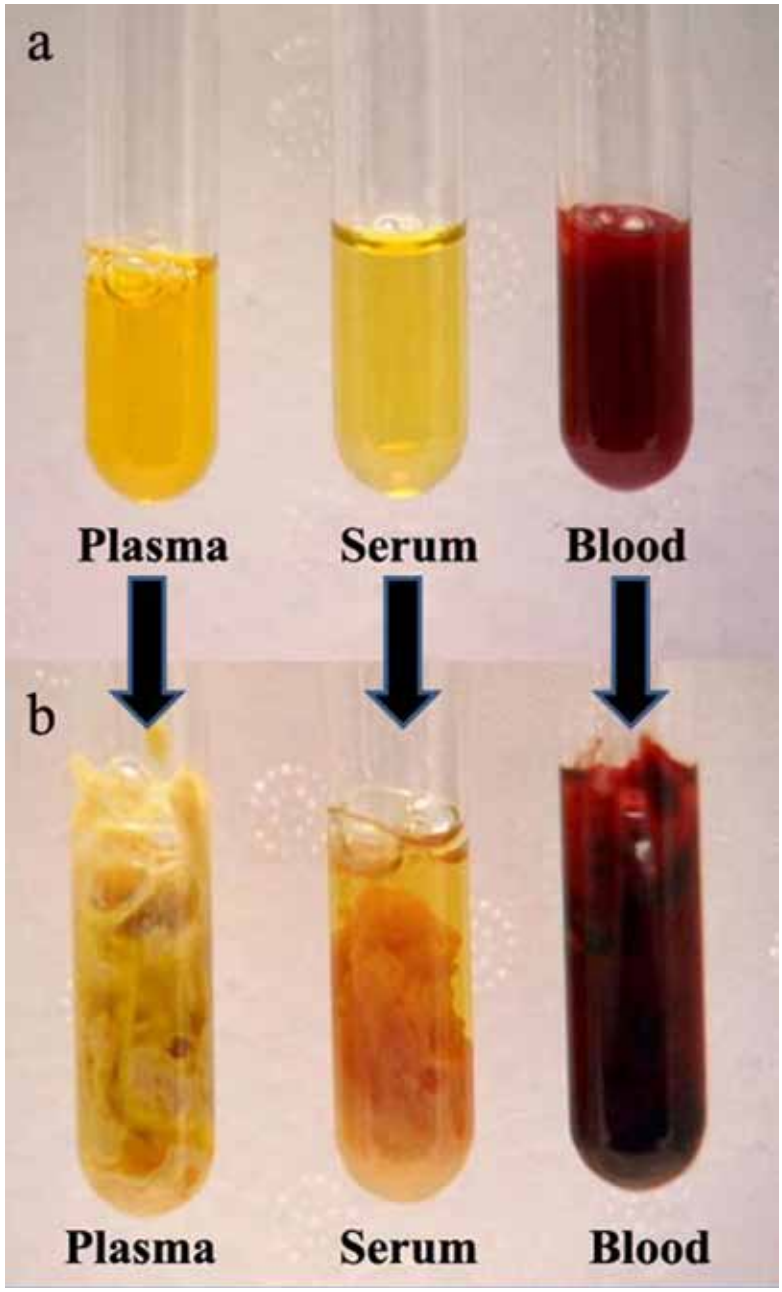
In a study demonstrating the hemostatic effects of ABS in an experimental rat model, ABS, as Surgicel, was effective in achieving hemostasis following liver excision.[8] An ABS tampon efficiently stopped bleeding from saphenous vein (grade II) and artery (grade IV) injuries. ABS provided hemostasis in a rat partial nephrectomy model.[24]

In cases of trauma involving major arteries and veins of internal organs, it is crucial to control the hemorrhage in a timely manner. Several hemostatic products are being developed for use in pre-hospital settings following combat trauma or civilian casualty.[25] An ABS tampon may be a candidate for use in this setting pending its ability to reduce blood loss and increase survival in more complicated trauma models involving coagulopathy and more complex injuries.

Human Studies

Hemostatic failure, a serious problem encountered in dentistry, can cause excessive postoperative bleeding, delayed wound healing, and increased risk of infection. Currently used agents

Figure 4. Macroscopic View of the ABS-induced Protein Network Formation in Plasma, Serum, and Whole Blood (<1 sec): Plasma, Serum, and Whole Blood (a) Before and (b) Immediately After Ankaferd Application



for hemostasis, like fibrinogen and plasma-derived blood coagulation factors, may carry the risk of transmission of viral infection and formation of clotting factor inhibitors. ABS may offer a convenient alternative during dental procedures. ABS might also be effective for patients with hemophilia and/or other hemostasis defects during dental procedures as indicated in case reports later in this article.

In a study by Ercetin et al,[26] 25 patients with dental problems received ABS as a topical solution during dental extractions and periodontal surgery. For most patients 1 to 2 mL of ABS was enough for adequate control of bleeding. Only five patients needed a second application of ABS. Eighteen patients reported a metallic taste in the mouth lasting 3-5 minutes, and one patient experienced oral numbness and a sensation of the mouth being stretched, which reversed within 10 minutes. One patient passed watery stool 24 hours after the administration of ABS. In this patient, an oral metallic taste and burning sensation in the throat continued for 24 hours. Laboratory parameters, including complete blood count, basic renal function tests, hepatic enzymes, and cystatin-C did not change after ABS application.[26]

Safety was also demonstrated in a randomized, placebo-controlled, crossover phase I clinical study in healthy volunteers. Topical ABS pad application for 120 minutes was no different from placebo in regard to both local skin effects and systemic laboratory tests.[27]

In a prospective, controlled clinical trial, Teker et al evaluated the efficacy of ABS as a hemostatic agent compared to hemostasis by means of knot-tie after cold knife dissection tonsillectomy.[8] Reported outcome measures such as blood loss, surgical time, and complications were assessed. A total of 47 consecutive patients were studied; each received an ABS wet tampon application to the right-tonsil hemorrhage and knot-tie technique for left-tonsil hemorrhage. The researchers reported that after tonsil removal the side treated with ABS demonstrated shorter hemostasis time (3.19 ± 0.74 min versus 7.29 ± 2.33 min [mean ± SD], $p<0.01$) and less blood loss (1.57 ± 2.26 mL versus 14.04 ± 7.23 mL [mean ± SD], $p<0.01$) than the knot-tie side.

Case Reports

Gastrointestinal Bleeding

Gastrointestinal bleeding can present serious, sometimes life threatening, problems. A patient with distal cholangiocarcinoma and severe upper gastrointestinal bleeding was treated successfully with ABS when all other methods failed.[28] ABS was effective in treating a solitary rectal ulcer, as well as tumoral and arterial bleeding due to Dieulafoy's lesion of the digestive tract.[10,29] In both cases, a total of 15 mL ABS was applied topically by disposable washing pipe that was passed through the instrument channel of an endoscope. Neither local nor systemic toxicity was observed following the topical application of ABS.[10,28,29]

Topical application of ABS to oral, rectal, and nasal mucosa was effective at controlling profuse bleeding in a patient with hemodynamic instability.[11]

Turhan et al showed that ABS administration to bleeding gastrointestinal carcinomas decreases tumor vascularization.[16] Lower gastrointestinal bleeding due to radiation colitis is a rare but important cause of emergency admissions. Despite novel endoscopic approaches like argon plasma coagulation, it is still a major cause of morbidity and mortality worldwide. ABS has been found to be effective in gastrointestinal bleeding due to radiation colitis in several reports.[15,30]

After Major Surgery

ABS has been shown to help control bleeding after major surgery. Bleeding from the mediastinum is a potential problem following open heart surgery. Coagulant agents, such as fresh frozen plasma and/or platelets, are often used after such surgeries in cases of severe postoperative bleeding. However, they are not effective in all patients. ABS managed to stop bleeding from bypass sutures in 20 patients. In these cases, 4-8 mL ABS solution was sprayed on the bleeding area and the bypass suture line after protamine infusion, building a protein web in the area. The bleeding along the suture line was stopped in all cases, with a mean total mediastinal drainage volume of 550 ± 125 mL. No surgical revision due to mediastinal bleeding was required in any patient, leading the investigators to conclude that ABS is a promising agent for bleeding control in open heart surgeries.[18]

Lung Cancer

Control of massive, potentially fatal lung bleeding during acute respiratory insufficiency secondary to vessel invasion from lung cancer was observed in a 62-year-old male patient. ABS (2 mL) was applied via bronchoscopy and successfully controlled the bleeding.[17]

Hereditary Hemorrhagic Diatheses

ABS Application in Hemophilia A

A 16-year-old male patient with a diagnosis of hemophilia A was brought to the hospital with the complaint of continued bleeding after circumcision two days previously.[31] After the surgery, factor VIII, given at a dose of 50 U/kg per 12 hours, was unsuccessful at stopping the bleeding. Factor VIII treatment was resumed at a dose of 50 U/kg/8 hours, then increased to 100 U/kg/8 hours, since the bleeding did not stop. On the third day after hospital admission, the patient was administered 270 µg/kg NovoSeven® (rVIIa). Despite the addition of cyclophosphamide and prednisolone, the bleeding could not be stopped. However, after the topical application of ABS to the bleeding site, the bleeding completely stopped within minutes.

In another case, a 13-year-old male patient with serious hemophilia A (FVIII level 0.4%), who had been followed since age nine months and admitted to the hospital frequently for extensive hematomas, presented for surgical circumcision, having been delayed by the parents because of fear of prolonged bleeding. Circumcision was performed under general anesthesia and the bleeders tied with 5/0 monocryl. Later, a 2.5 x 7 cm sterile pad was soaked with 3 mL ABS solution and placed around the incision for 1-2 minutes, which successfully helped control the bleeding.[32]

ABS Application in von Willebrand Disease

A 28-year-old female with von Willebrand disease (von Willebrand factor [vWF] 50%) and a history of easy bruising and long bleeding times presented for tooth extraction.[33] After extraction of the first mandibular molar, an ampule of ABS was applied directly, and subsequently by a pad. All bleeding was stopped after 20 minutes.

ABS Application in Hereditary Thrombocytopenia

Bleeding in a case of a 15-year-old boy with thrombocytopenia with absent radius (TAR syndrome) was described by Calışkan et al.[34] In this report, active bleeding following extraction of two molars was controlled with ABS. ABS was sprayed over the bleeding area, followed by placement of an ABS-soaked tampon. Since slight bleeding was observed when the tampon was withdrawn after eight hours, the same procedures were repeated. The next day, when the tampon was removed, it was observed that the bleeding had stopped completely without any need for thrombocyte suspension.

ABS Application in Glanzmann Thrombasthenia

In a 4-year-old male with Glanzmann thrombasthenia, tooth extraction and circumcision were planned one day apart. Conventional measures were taken to control bleeding, but since slow bleeding persisted an hour after the tooth extraction, a pad with ABS + adrenalin + tranexamic acid was prepared and placed on the bleeding site, successfully controlling the bleeding. The following day, ABS spray was used on the bleeding areas during circumcision and the patient was discharged following a 24-hour observation period. No thrombocyte suspension transfusion was necessary.[35]

More Than a Hemostatic Agent

An unexpected effect of ABS is its antibacterial effect. Because exposure to ABS seems to provide better oxygenation through erythrocyte aggregation, the antibacterial activity of ABS was studied with an agar well diffusion test. Besides demonstrating high inhibitory activity against gram-positive and -negative bacteria, including human pathogens and food spoilage bacteria, ABS was found to be more stable than nisin, the only commercial bacteriocin for food preservation that shows activity against gram-positive and gram-negative organisms. ABS has been shown to be active against multi-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, *Enterococcus* spp, *Escherichia coli*, *Klebsiella* spp, *Acinetobacter* spp, *Pseudomonas* spp, and fungi like *Aspergillus* spp, *Mucor* spp, and *Candida albicans*.[36,37]

Other properties of ABS have been investigated. Demircan et al reported ABS to be an effective modulator of bone healing.[38] In this study of Wistar albino rats, blunt bilateral tibial defects were made and treated with or without ABS on each side; inflammation, necrosis, fibrosis, foreign body reaction, and new bone formation scores were compared. The ABS-treated side was significantly superior to the untreated side in terms of inflammation, necrosis, and new bone formation.

Conclusion

ABS, which has long been used as a traditional medicine, represents an alternative treatment modality for many kinds of bleeding that are resistant to conventional methods. The ability of ABS to induce formation of a protein network not only makes it an effective hemostatic agent, but also confers anti-infective, antineoplastic, and healing modulator properties to the extract. Future controlled studies on these effects are warranted.

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Conflict of Interest

None of the authors has a commercial association or monetary investment in ABS that might pose a conflict of interest. No funding was received for this manuscript.

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(4) requested copies distributed by other mail classes through the USPS:	15 / 15
c. Total paid and/or requested circulation (sum of 15b (1),(2),(3), and (4)):	2611 / 2296
d. Non-requested distribution by mail and outside the mail (samples, complimentary, other free):	
(1) outside-county as stated on Form 3541:	901 / 1158
(2) in-county as stated on Form 3541:	0 / 0
(3) other classes mailed through the USPS as stated on Form 3541:	0 / 0
(4) copies distributed outside the mail as stated on Form 3541:	0 / 0
e. Total non-requested distribution (Sum of 15d (1), (2), and (3)):	901 / 1158
f. Total distribution (sum of 15c and 3e):	3512 / 3454
g. Copies not distributed:	1056 / 676
h. Total (sum of 15f and g):	4568 / 4130
i. Percent paid and/or requested circulation (15c divided by f times 100):	74.3% / 66.47%

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