Original Article

Hemostatic Efficacy of a Traditional Medicinal Plant Extract (Ankaferd Blood Stopper) in Bleeding Control

Clinical and Applied Thrombosis/Hemostasis
2015, Vol. 21(4) 348-353

DOI: 10.1177/1076029613504129
cat.sagepub.com

Ozgur Sogut, MD[1], Mehmet Ozgur Erdogan, MD[2], Rustu Kose, MD[3], Mehmet Emin Boleken, MD[4], Halil Kaya, MD[5], Mehmet Tahir Gokdemir, MD[5], Abdullah Ozgonul, MD[6], Ismail Iynen, MD[7], Levent Albayrak, MD[5], and Mehmet Akif Dokuzoglu, MD[5]

Abstract

The aim of this study is to assess the in vivo hemostatic effect of Ankaferd Blood Stopper (ABS) on rats using a tail bleeding model. Wistar rats were randomized into 4 groups of 9 each: group 1, control, no pretreatment, irrigated with saline; group 2, no pretreatment, irrigated with ABS; group 3, control, heparin pretreatment, irrigated with saline; and group 4, heparin pretreatment, irrigated with ABS. To control bleeding, compressive dressings were placed after instilling 1 mL of either ABS or saline to the bleeding area. Without heparin pretreatment, ABS shortened hemostasis time by 1.57 minutes and reduced the amount of bleeding by 0.85 g. With heparin pretreatment, ABS shortened hemostasis time by 3.29 minutes and reduced the amount of bleeding by 1.32 g. The ABS was more effective than saline irrigation for treating tail tip bleeding in rats, with or without heparin pretreatment, while also using a compressive dressing.

Keywords

tail bleeding, Ankaferd Blood Stopper, hemostasis, heparin sodium, experimental

Introduction

The management of patients with trauma has improved significantly over the years. However, uncontrolled posttraumatic bleeding remains a major problem, accounting for approximately 40% of trauma-related deaths, and uncontrollable bleeding is the leading cause of potentially preventable death in patients with major trauma.[1-6] In trauma, most hemorrhagic deaths occur within the first 6 hours. Hence, effective and rapid control of bleeding may decrease mortality.[7]

Life-threatening bleeding in patients with trauma is usually caused by a combination of vascular injury and coagulopathy.[5,8] About one-third of all patients with trauma having bleeding present with coagulopathy upon hospital admission.[8,9] This subset of patients has a significantly increased incidence of multiple organ failure and death compared to patients with similar injury patterns in the absence of coagulopathy.[8] The management of traumatic coagulopathy includes the transfusion of fresh-frozen plasma, platelets, fibrinogen, and cryoprecipitate, if available.[5] However, in certain patients with trauma, such as when coagulopathy is concurrent with hypothermia or acidosis, or in patients receiving anticoagulant or antiaggregant treatment (ie, patients with clotting disorders), there is a limit to the level of hemostasis that adequate replacement can provide in the control of life-threatening bleeding.[5,6,9]

Alternative and potentially life-saving treatments include the use of local hemostatic agents that reduce red blood cell

[1] Faculty of Medicine, Department of Emergency Medicine, Bezmialem Vakif University, Istanbul, Turkey
[2] Department of Emergency Medicine, Haydarpasa Numune Research and Training Hospital, Istanbul, Turkey
[3] Faculty of Medicine, Department of Plastic and Reconstructive Surgery, Recep Tayyip Erdogan University, Rize, Turkey
[4] Faculty of Medicine, Department of Paediatric Surgery, Harran University, Sanliurfa, Turkey
[5] Faculty of Medicine, Department of Emergency Medicine, Harran University, Sanliurfa, Turkey
[6] Faculty of Medicine, Department of General Surgery, Harran University, Sanliurfa, Turkey
[7] Faculty of Medicine, Department of Otolaryngology-Head and Neck Surgery, Harran University, Sanliurfa, Turkey

Corresponding Author:
Ozgur Sogut, Faculty of Medicine, Department of Emergency Medicine, Bezmialem Vakif University, Vatan Str, Fatih, 34093 Istanbul, Turkey.
Email: osogut@bezmialem.edu.tr

Table 1. Outline of the Study Design.

Group	Heparin Sodium Dose, IU/kg	Duration, Days	Solution Administered for Tail Tip Bleeding
1	-	-	Saline
2	-	-	ABS
3	640 tid ip	3	Saline
4	640 tid ip	3	ABS

Abbreviations: ABS, Ankaferd Blood Stopper; ip, intraperitoneally; tid, three times a day.

transfusion requirements and may also decrease postinjury complications, such as multiple organ failure and infection. An ideal topical hemostatic agent should be effective across a wide range of hemostatic dysfunctions, simple to store and use, and show rapid action.[5] A variety of topical agents are currently available for use as adjuncts to traditional surgical techniques in patients with coagulapathy.[8,10] Many previous trials have evaluated different agents as adjunctive measures, including collagen-, gelatin-, or cellulose-based products, fibrin sealants, and synthetic glues.[10,11]

Ankaferd Blood Stopper (ABS) is a traditional folk medicine that has been used for centuries as a hemostatic agent in Anatolia.[12] It contains hemostatically active plant extracts with no inorganic or synthetic additives, and it is recommended as a topical hemostatic agent in postoperative and posttraumatic bleeding.[13,14] Several animal studies have demonstrated the efficacy of ABS for the management of clinical hemorrhages when conventional methods to control bleeding have proven ineffective.[13-16] Mechanistically, ABS facilitates the very rapid formation of an encapsulated protein network by interacting with blood proteins, mainly fibrinogen.[12] This ABS-induced protein network provides focal points for erythrocyte aggregation, both in vivo and in vitro. This unique mechanism of action involves the entire physiological hemostatic process rather than acting on individual components of the coagulation cascade.[12,14] As such, ABS can be used to control bleeding in individuals with normal hemostatic parameters as well as in those with deficient primary or secondary hemostasis.[14]

This study used a rat tail bleeding assay to compare the efficacy of saline versus ABS irrigation in conjunction with a compressive dressing for achieving hemostasis. In addition, the hemostatic effect of ABS was evaluated in rats that were pretreated with standard heparin (heparin sodium).

Materials and Methods

Animals

Male Wistar rats (200-250 g) were used in this study ($n = 36$). The animals were purchased locally from the Research Institute of Physiology (Gaziantep, Turkey). They were kept in the Department of Physiology animal housing facility under specific pathogen-free conditions at room temperature with free access to water; they were fed standard rat pellets throughout the study. All experimental procedures were approved by a local animal ethics committee and were in accordance with the guidelines established by the European Community Council Directive of November 24, 1986 (86/609/EEC).

Ankaferd Blood Stopper

Ankaferd Blood Stopper (Trend Teknoloji Ilac AS, Istanbul, Turkey) is a licensed pharmaceutical plant extract that is directly applied to injured skin and mucosa as a liquid (solution or spray) or in a treated dressing. This usage has been approved by the Turkish Ministry of Health and produces active hemostasis for the management of dental, postsurgical, and posttraumatic hemorrhage. Each 100 mL of ABS liquid product contains a standardized mixture of 5 mg *Thymus vulgaris* (thyme) herbal extract, 9 mg *Glycyrrhiza glabra* (licorice) leaf extract, 8 mg *Vitis vinifera* (grape) leaf extract, 7 mg *Alpinia officinarum* (lesser galangal) leaf extract, and 6 mg *Urtica dioica* (stinging nettle) extract.[14] The plant proteins identified in ABS via 2-dimensional gel electrophoresis and mass spectrometer analysis with matrix-assisted laser desorption ionization-time of flight are nicotinamide adenine dinucleotide phosphate-dependent malic enzyme, ribulose bisphosphate-carboxylase large chain, maturase K, ATP synthase β subunit, ATP synthase α subunit, chalcone flavanone isomerase 1, chalcone flavanone isomerase 2, and actin-depolymerization factor. In addition, various human protein-like proteins (eg, spectrin ankyrin, actin; essential erythroid proteins) that are considerably important for vital erythroid aggregation (hemostasis) are included in the functional proteomics of ABS.[17]

This study used a liquid form of ABS supplied in 2-mL ampoules to achieve hemostasis in a rat tail bleeding model.

Groups and Experimental Design

Wistar rats were randomized into 4 groups of 9 animals each, as follows: group 1, control, no pretreatment, irrigated with saline; group 2, no pretreatment, irrigated with ABS; group 3, control, heparin pretreatment, irrigated with saline; and group 4, heparin pretreatment, irrigated with ABS. As shown in Table 1, all groups were given an equal volume (0.25 mL) of either standard heparin sodium solution (640 IU/kg) or saline (0.9% NaCl) intraperitoneally (ip) 3 times a day for 3 consecutive days.

Bleeding Assay

On day 3, the rats were anesthetized ip with a mixture of ketamine hydrochloride (Ketalar; Eczacibasi, Istanbul, Turkey), xylazine (Rompun, 2% solution; Bayer, Germany), and atropine at doses of 30, 5, and 1.2 mg/kg, respectively. The bleeding assay was performed via tail tip amputation. The rats were placed in the prone position, and a distal 10-mm segment of the tail was amputated transversely using a scalpel. After vascular bleeding was established, the wounds were irrigated with an equal volume (1 mL) of either saline (groups 1 and 3) or ABS

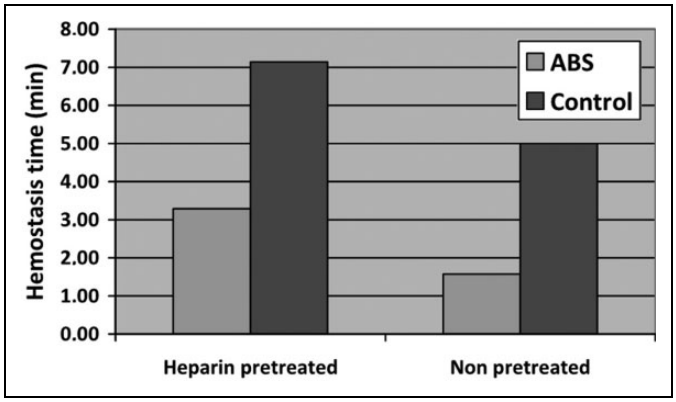

Figure 1. Hemostatic effect of Ankaferd Blood Stopper (ABS, 1 mL) on the duration of tail bleeding (hemostasis time) in rats pretreated with standard heparin sodium (640 IU/kg intraperitoneally [ip] for 3 days) and untreated rats.

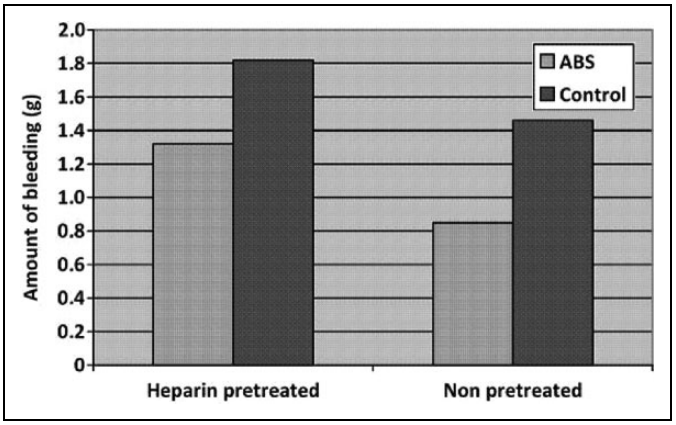

Figure 2. Hemostatic effect of Ankaferd Blood Stopper (ABS, 1 mL) on the amount of tail bleeding in rats pretreated with standard heparin sodium (640 IU/kg intraperitoneally [ip] for 3 days) and untreated rats.

Table 2. The Effect of Topical ABS (1 mL) on Hemostasis Time and Amount of Tail Bleeding in Rats Pretreated With Heparin Sodium Standard (640 IU/kg ip for 3 Days) and Untreated Rats.[a]

Characteristic	ABS	Control	ABS vs Control, %	Statistical Significance, P[b]
Hemostasis time, min				
Heparin	3.29 (2.41-4.17)	7.14 (4.73-9.56)	53.9	.004
No heparin	1.57 (0.84-2.30)	5.00 (4.24-5.76)	68.6	.001
Amount of bleeding, g				
Heparin	1.32 (1.06-1.58)	1.82 (1.45-2.19)	27.5	.018
No heparin	0.85 (0.68-1.03)	1.46 (1.06-1.85)	41.8	.006

Abbreviations: ABS, Ankaferd Blood Stopper; ip, intraperitoneal.
[a]Data are expressed as the mean (95% confidence interval) or percentage.
[b]Mann-Whitney *U* test.

(groups 2 and 4), followed by gentle compression with a sterile gauze pad for 1 minute.

The parameters examined were hemostasis time and amount of bleeding. Hemostasis time was defined as the interval (minute) between the start of bleeding (ie, cutting off the tail tip) and the achievement of hemostasis and was measured using a stopwatch. To determine the amount of bleeding, each sterile gauze pad was weighed before and after the procedure using a precision laboratory balance, and the difference in weight (g) was used as a measure of the amount of bleeding. The measurements were carried out by an investigator blinded to the treatment. Each animal was monitored for 20 minutes even if bleeding ceased, to detect any rebleeding; no instances of rebleeding were observed. At the end of the experiment, the rats were euthanized using an overdose of anesthesia.

Statistics

Statistical analyses were carried out using the SPSS statistical package, ver 15.0 (SPSS, Chicago, Illinois) for Windows. Hemostasis time (minute) and the amount (g) of blood lost from the tail wound were recorded and compared among non-pretreatment and pretreatment groups (eg, no pretreatment, irrigated with saline; group 1 vs no pretreatment, irrigated with ABS; group 2, and heparin pretreatment, irrigated with saline; group 3 vs heparin pretreatment, irrigated with ABS; group 4, respectively) with and without ABS using the Mann-Whitney *U* test. Results are presented as the mean and 95% confidence intervals (CIs). The mean and standard deviation (SD) were also given for each group. A 2-tailed P value of less than .05 was considered statistically significant.

Results

A statistically significant difference was observed between groups 1 (control, no pretreatment) and 3 (control, heparin pretreatment; $P = .006$) with respect to mean hemostasis times. The mean hemostasis times were higher in group 3, compared with group 1, animals (7.14 ± 2.61 and 5.00 ± 0.81 minutes, respectively).

The amount of bleeding was also significantly different between groups 1 and 3 ($P = .035$). The mean amount of bleedings was higher in group 3, compared with group 1, animals (1.81 ± 0.39 and 1.45 ± 0.42 g, respectively).

Without heparin pretreatment (groups 1 and 2), the duration of hemostasis time following tail amputation was shortened by 68.6% with ABS administration (group 2) from 5.00 ± 0.81 minutes (95% CI] 4.24-5.76) in the saline-administered control

Figure 3. View of bleeding secondary to transverse amputation of the tail tip in a rat pretreated with standard heparin sodium (640 IU/kg for 3 days intraperitoneally [ip]).

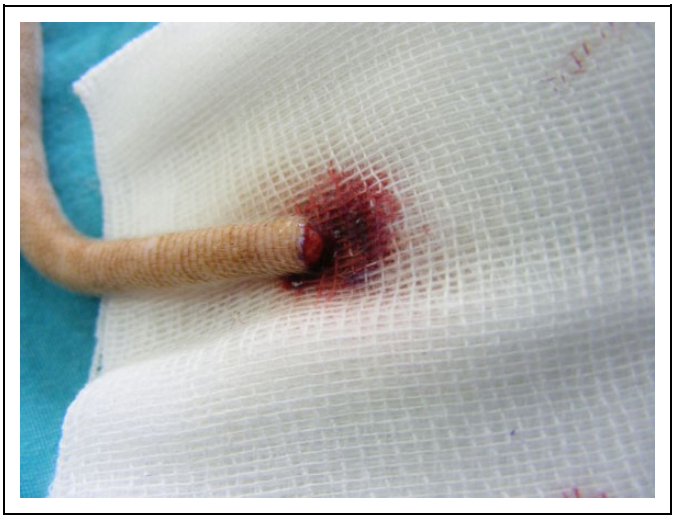

Figure 4. Effective hemostasis is achieved rapidly after topical administration of Ankaferd Blood Stopper (ABS, 1 mL).

(group 1) to 1.57 ± 0.78 minutes (95% CI 0.84-2.30 minutes; $P = .001$). With heparin pretreatment (groups 3 and 4), the duration of hemostasis time following tail amputation was shortened by 53.9% with ABS administration (group 4) from 7.14 ± 2.61 minutes (95% CI 4.73-9.56) in the saline-administered control (group 3) to 3.29 ± 0.95 minutes (95% CI 2.41-4.17 minutes; $P = .004$; Table 2; Figure 1).

Without heparin pretreatment (groups 1 and 2), ABS administration decreased the amount of bleeding by 0.85 ± 0.18 g or 41.8% (95% CI 0.68-1.03 g) compared to the saline-treated group (mean ± SD 1.46 ± 0.42 g; 95% CI 1.06-1.85; $P = .006$). With heparin pretreatment (groups 3 and 4), ABS decreased the amount of bleeding by 1.32 ± 0.28 g or 27.5% (95% CI 1.06-1.58) compared to the saline-treated group (mean ± SD 1.82 ± 0.39 g; 95% CI 1.45-2.19; $P = .018$; Table 2; Figure 2).

Discussion

This study evaluated the hemostatic effects of ABS as a novel topical hemostatic agent in vivo in a rat tail bleeding model alone or in the presence of standard heparin sodium. Several hemostatic measures including tourniquets, nonadherent pads soaked with saline–adrenaline solution, or subcutaneous insufflation with epinephrine solution are preferred to control external and internal bleeding.[18-20] In addition, local hemostatic agents such as collagen-, gelatin-, or cellulose-based products, fibrin, and synthetic glues or adhesives can be used for venous or moderate arterial bleeding associated with parenchymal injuries.[8,18] The effect of cellulose-based hemostatic agents on bleeding has been less well studied, and only case reports that support their use are available. These topical agents can be particularly useful when there is easy access to the bleeding area.[8]

Sustaining hemostasis in acute life-threatening hemorrhage among patients with trauma is a challenging task and requires extensive effort; commercially available hemostatic products are generally insufficient or too slow to achieve hemostasis in extreme cases.[18] The ABS, which has long been used as a traditional medicine in Anatolia, represents an alternative treatment modality for several kinds of bleeding, such as external and dental surgical bleeding.[12,13] Its significant effect on hemostasis has been shown in several animal and human studies involving vascular, skin, and visceral surgery.[15,16,21]

One previous in vitro study clearly showed that the addition of ABS to human umbilical vein endothelial cells (HUVECs) established a rapid formation of a complex protein web between the HUVECs and increased the level of activity of the transcription factors.[22] These transcription factors regulate numerous intracellular biological pathways, including hemostasis, infection, cellular proliferation, and inflammation.[22,23] The cellular effects of ABS as depicted in HUVECs depend on the dose and concentration.[23]

The external application of ABS as a spray, solution, and or on a treated dressing has been shown to be effective in halting bleeding in superficial and deep abdominal skin in a swine bleeding model. In 1 study, it was reported that a 40-second application of an ABS-treated dressing was sufficient to obtain hemorrhage control in skin lacerations, whereas 1.5 and 3.5 minutes applications were effective for controlling hemorrhage from the saphenous vein and artery, respectively.[16] Gungor et al[21] demonstrated that the topical use of ABS, applied endoscopically, was effective for controlling active nonvariceal upper gastrointestinal bleeding, particularly in young patients with no coagulopathy. Ulus et al[24] showed that topical application of ABS in an experimental major arterial vessel injury model reduced bleeding time and blood loss under normal and elevated intra-arterial blood pressure. They suggested that ABS-induced erythroid aggregation had an important impact on the vascular tissue level.

The present in vivo study using a rat tail bleeding model showed that ABS has a hemostatic effect in rats with or without heparin pretreatment, when applied with a compressive dressing. In normal rats, it was possible to achieve hemostasis in a mean time of 1.57 minutes with topical administration of ABS; even after exacerbation of bleeding with heparin pretreatment, topical ABS treatment facilitated hemostasis within a mean time of 3.29 minutes.

Although previous animal studies have shown that ABS effectively induces hemostasis in patients with coagulopathy due to defective platelets or coagulation factors, clinical reports regarding its efficacy under such conditions are contradictory.[6,25] Some studies have indicated that ABS treatment is effective in patients with normal hemostatic parameters as well as those with primary or secondary coagulation defects[18,26,27]; however, another study found insufficient hemostasis.[21] Aktop et al[28] used Celox and ABS as a new hemostatic agents to evaluate the efficacy of these new generation hemostatic agents on early-stage soft tissue healing of warfarin-treated rats by measuring the tissue factor (TF) activities. They showed that both the hemostatic agents positively affected the hemostasis. In the Celox-treated group, dermal tissues had higher TF activity when compared to ABS-treated group. Moreover, the ABS affected the early-stage healing positively in clinical aspect, whereas Celox was more effective on hemostasis by means of increasing TF activities.

In a rat tail bleeding model, Kosar et al[13] reported that topical ABS administration reduced both the duration and the amount of bleeding in animals treated with acetylsalicylic acid or enoxaparin. Similarly, Cipil et al[25] found that topical ABS administration markedly shortened the duration of bleeding after leg amputation, with or without previous warfarin treatment. In the present study, the effectiveness of ABS was found to be statistically significant when compared to either untreated or heparin-treated controls, both in terms of decreasing hemostasis time as well as bleeding volume. After vascular bleeding was induced through tail tip amputation in the heparin-treated group, the application of ABS solution resulted in instant hemostasis (Figures 3 and 4, respectively). These results are unique in that they are the only data in which the hemostatic effect of ABS is compared between normal (untreated) and heparin-treated rats using a tail bleeding model.

Conclusion

Our preliminary study demonstrated that ABS applied with a compressive dressing markedly improves hemostasis after tail tip amputation in a rat tail bleeding model, in both heparinized and nonheparinized animals. As such, this safe, effective, and rapid-acting topical should be considered a potential adjunct therapy for the management of uncontrolled bleeding following major trauma. Randomized controlled clinical trials are needed to compare ABS application alone and in combination with other local hemostatic procedures (eg, pressure point control, tourniquets, or pharmacological agents).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World J Surg*. 2007;31(7):1507-1511.
2. Holcomb JB. Methods for improved hemorrhage control. *Crit Care*. 2004;8(suppl 2):S57-S60.
3. Hoyt DB. A clinical review of bleeding dilemmas in trauma. *Semin Hematol*. 2004;41(1 suppl 1):40-43.
4. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995;38(2):185-193.
5. Spahn DR, Rossaint R. Coagulopathy and blood component transfusion in trauma. *Br J Anaesth*. 2005;95(2):130-139.
6. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German trauma registry on 8724 patients. *Injury*. 2007;38(3):298-304.
7. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. *Am J Surg*. 2009;197(5):565-570; discussion 570.
8. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care*. 2013;17(2):R76.
9. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54(6):1127-1130.
10. Netscher DT, Carlyle T, Thornby J, Bowen D, Harris S, Clamon J. Hemostasis at skin graft donor sites: evaluation of topical agents. *Ann Plast Surg*. 1996;36(1):7-10.
11. Drake DB, Wong LG. Hemostatic effect of Vivostat patient-derived fibrin sealant on split-thickness skin graft donor sites. *Ann Plast Surg*. 2003;50(4):367-372.
12. Beyazit Y, Kurt M, Kekilli M, Goker H, Haznedaroglu IC. Evaluation of hemostatic effects of Ankaferd as an alternative medicine. *Altern Med Rev*. 2010;15(4):329-336.
13. Kosar A, Cipil HS, Kaya A, et al. The efficacy of Ankaferd blood stopper in antithrombotic drug-induced primary and secondary hemostatic abnormalities of a rat-bleeding model. *Blood Coagul Fibrinolysis*. 2009;20(3):185-190.
14. Goker H, Haznedaroglu IC, Ercetin S, et al. Haemostatic actions of the folkloric medicinal plant extract Ankaferd blood stopper. *J Int Med Res*. 2008;36(1):163-170.
15. Karakaya K, Ucan HB, Tascilar O, et al. Evaluation of a new hemostatic agent Ankaferd blood stopper in experimental liver laceration. *J Invest Surg*. 2009;22(3):201-206.
16. Bilgili H, Kosar A, Kurt M, et al. Hemostatic efficacy of Ankaferd blood stopper in a swine bleeding model. *Med Princ Pract*. 2009; 18(3):165-169.

17. Demiralp DO, Haznederoglu IC, Akar N. Functional proteomic analysis of Ankaferd® blood stopper. *Turk J Hematol*. 2010;27(2):70-77.
18. Haznedaroglu BZ, Beyazit Y, Walker SL, Haznedaroglu IC. Pleiotropic cellular, hemostatic, and biological actions of Ankaferd hemostat. *Crit Rev Oncol Hematol*. 2012;83(1):21-34.
19. Mitchell RT, Funk D, Spiwak R, Logsetty S. Phenylephrine tumescence in split-thickness skin graft donor sites in surgery for burn injury—a concentration finding study. *J Burn Care Res*. 2011;32(1):129-134.
20. Kahalley L, Dimick AR, Gillespie RW. Methods to diminish intraoperative blood loss. *J Burn Care Rehabil*. 1991;12(2):160-161.
21. Gungor G, Goktepe MH, Biyik M, et al. Efficacy of Ankaferd blood stopper application on non-variceal upper gastrointestinal bleeding. *World J Gastrointest Endosc*. 2012;4(12):556-560.
22. Yılmaz E, Gülec S, Torun D, Haznederoglu IC, Akar N. The effects of Ankaferd® blood stopper on transcription factors in HUVEC and the erythrocyte protein profile. *Turk J Hematol*. 2011;28(4):276-285.
23. Karabıyık A, Yılmaz E, Gülec S, Haznederoglu IC, Akar N. The dual diverse dynamic reversible effects of Ankaferd blood stopper on EPCR and PAI-1 inside vascular endothelial cells with and without LPS challenge. *Turk J Hematol*. 2012;29(4):361-366.
24. Ulus AT, Turan NN, Ozyalcin S, et al. Surgical and histopathological effects of topical Ankaferd® hemostat on major arterial vessel injury related to elevated intra-arterial blood pressure. *Turk J Hematol*. 2011;28(3):206-212.
25. Cipil HS, Kosar A, Kaya A, et al. In vivo hemostatic effect of the medicinal plant extract Ankaferd blood stopper in rats pretreated with warfarin. *Clin Appl Thromb Hemost*. 2009;15(3):270-276.
26. Kurt M, Oztas E, Kuran S, Onal IK, Kekilli M, Haznedaroglu IC. Tandem oral, rectal, and nasal administrations of Ankaferd blood stopper to control profuse bleeding leading to hemodynamic instability. *Am J Emerg Med*. 2009;27(5):631.e1-e2.
27. Kurt M, Disibeyaz S, Akdogan M, Sasmaz N, Aksu S, Haznedaroglu IC. Endoscopic application of Ankaferd blood stopper as a novel experimental treatment modality for upper gastrointestinal bleeding: a case report. *Am J Gastroenterol*. 2008;103(8):2156-2158.
28. Aktop S, Emekli-Alturfan E, Ozer C, et al. Effects of Ankaferd blood stopper and celox on the tissue factor activities of warfarin-treated rats [published online May 23, 2013]. *Clin Appl Thromb Hemost*. 2013. doi:10.1177/1076029613490254.