Pharmacobiological management of hemostasis within clinical backgrounds via Ankaferd hemostat (Ankaferd blood stopper)

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Abstract
Ankaferd hemostat (Ankaferd blood stopper [ABS], Istanbul, Turkey) is a hemostatic agent affecting red blood cell-fibrinogen interactions. ABS has been traditionally used in Anatolia as a hemostatic agent for centuries. ABS contains a standardized combination of the plants namely Glycyrrhiza glabra, Thymus vulgaris, Alpinia officinarum, Vitis vinifera, and Urtica dioica. The hemostatic effect of ABS depends upon the quick promotion of a protein network, particularly fibrinogen gamma, in relation to the erythrocyte aggregation. The aim of this review is to indicate pharmacobiological basis and clinical backgrounds of ABS. Current perspective for using ABS is to provide hemostasis and accelerating wound healing particularly in cases which are difficult to manage. Future controlled trials are needed to elucidate the actions of ABS with in hemostasis, antithrombotic, anti-inflammatory, anti-infective, antifungal, and anti-oxidative effects.

Keywords
Ankaferd hemostat, clinical hemorrhages, infections, wound healing, cancer

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Introduction
Ankaferd hemostat (Ankaferd blood stopper (ABS), Istanbul, Turkey) is a hemostatic agent affecting red blood cell–fibrinogen interactions. ABS had been traditionally used in Anatolia as a hemostatic agent for centuries. ABS shows the hemostatic effect via affecting the physiology of the red blood cells. ABS contains a standardized combination of the plants namely Glycyrrhiza glabra, Thymus vulgaris, Alpinia officinarum, Vitis vinifera, and Urtica dioica. Recently, ABS has been established as a novel topical hemostatic agent for the management of clinical hemorrhages if the conventional methods were ineffective to control bleeding. ABS is as effective in the management of the patients with primary or secondary hemostatic deficiencies as in the bleeding individuals with normal hemostatic parameters. ABS has an expanding spectrum of clinical indications. Current state of ABS development as a drug is depicted in Table 1. The aim of this article is to indicate pharmacobiological basis and clinical background of ABS.

Basic Ankaferd hemostat (ABS) effects on hemostasis
The hemostatic efficacy of ABS depends upon the quick promotion of a protein network, particularly fibrinogen gamma, in relation to the vital erythrocyte aggregation. ABS induces the constitution of a complex protein network with vital erythrocyte aggregation covering the whole physiological hemostatic process. The essential effects of ABS are ascribed to the formation of protein network and polymerization modulating the...
Several metabolic pathways. Coagulation proteins (Factors V, VIII, IX, X, XI, and XIII) are involved in the process of hemostasis. Those regulatory molecules affect cellular biology.  

Ankaferd hemostat (ABS) is an effective and safe drug that has been demonstrated to have hemostatic, anti-inflammatory, and antineoplastic properties. Table 1 summarizes the clinical actions of Ankaferd hemostat and the state of drug development regarding Ankaferd hemostat.  

Table 1. Ankaferd blood stopper (ABS) as a drug (current state of drug development in distinct pathobiological states).

| Clinical actions of Ankaferd hemostat | The state of drug development regarding Ankaferd hemostat |
|--------------------------------------|----------------------------------------------------------|
|                                     | In vitro experiments | Pre-clinical development | In vivo animal studies | Case reports | Case series | Controlled clinical trials | Randomized clinical trials |
| Topical pro-hemostatic effects       | +                   | +                        | +                     | +           | +          | +                            |                          |
| Anti-hemorrhagic effects             | +                   | +                        | +                     | +           | +          | +                            |                          |
| Topical wound-healing effects        | +                   | +                        | +                     | +           | –          | –                            | –                         |
| Topical anti-infective effects       | +                   | +                        | +                     | +           | –          | –                            | –                         |
| Topical anti-neoplastic effects      | +                   | +                        | +                     | +           | –          | –                            | –                         |

The anti-neoplastic effect of ABS was preliminary defined by Goker et al. They investigated the anti-neoplastic effects of ABS on SAOS-2 osteosarcoma cell survival and growth. A dose-dependent inhibition in cell proliferation and a marked decrease were observed in the survival of SAOS-2 cells. In another study, the anti-neoplastic effects of ABS on colon cancer cells were defined. Following the addition of ABS to the culture medium, the inhibition of cellular reproduction and loss in the viabilities of human colon CaCo-2 cells were observed. Akalin et al. showed the anti-proliferative effects of ABS on lymphoid neoplastic cells (B-CLL and RAJI tumor cell lines). With the addition of ABS, first, the inflation of the hematopoietic tumor cells was detected. The inflation and proliferation continued on B-CLL cells at day 3 and produced aggregation islands. Mumcuoglu et al. demonstrated that depending on the concentration and duration of the application, ABS could cause apoptosis via regulating PAR1 and p53-dependent p21 involvement in apoptosis stimulation within leukemia cells. Turk et al. also demonstrated that the most resistant cell type was SK-MEL-10 and the least resistant neoplastic cell type was A2058 since the effect of 0.19% ABS could be seen within just 15 min. The antineoplastic effect of ABS was also apparent on the light microscopic images of untreated M307 primary cells. Another study disclosed that ABS induces DNA damage, apoptosis, and cytotoxic activity via generating reactive oxygen species in melanoma cell lines.

Animal studies in Ankaferd hemostat (ABS)

Many studies have been conducted on preclinical animal models to demonstrate the efficacy and safety of ABS. Bilgili et al. reported that the application of ABS (spray, solution, and tampon forms) to superficial and deep abdominal lacerations could control bleeding successfully. In another animal study, partial nephrectomy was applied to 24 Wistar rats. The effectiveness of ABS was compared to several conventional anti-hemorrhagic methods. Hemostasis was successfully achieved by ABS. Moreover, warm ischemia times decreased by ABS. Kuru et al. reported that rectal application of ABS showed favorable effects on bursting pressures, tissue plasminase and hydroxyproline levels, and the histopathological findings of colonic anastomosis. The rectal administration of ABS had positive effects on the improvement of colorectal anastomosis. As a natural product of plant origin, ABS may be used effectively and safely to obtain better healing results after.
colorectal anastomosis. In another study, the rats underwent femoral vein puncture. One subgroup was treated with ABS tampon or spray, and the other control group was left untreated. After 2 weeks, each group underwent partial tissue excision from the same femoral region as well as from the brain, heart, kidney, and liver. ABS provided hemostasis and was observed to stop bleeding. There were no histopathological changes at the tissue level and no pathological effects in other organ tissues under light microscope.

Ankaferd hemostat (ABS) in clinical medicine

ABS has hemostatic, antithrombotic, anti-infective, anti-neoplastic, and wound-healing effects. The specific molecules which have the potential to contribute within ABS to its action are depicted in Table 2. ABS has also been employed in controlled clinical trials as depicted in Table 3.

Ankaferd hemostat (ABS) in gastrointestinal bleeding

Gastrointestinal (GI) bleeding is a significant life-threatening condition and a common cause of hospitalization. Although endoscopic management reduces the rates of re-bleeding, need for surgery, and mortality in active bleeding, early recurrence still occurs in around 20% of cases despite the effective initial hemostasis. Therefore, there is an ongoing intensive research for novel techniques or treatment modalities that are efficient and safe for the managing of GI bleedings. During the research for a supplementary hemostatic agent for the treatment of GI hemorrhages, collected findings suggested that ABS could be efficient for the “difficult-to-manage” subtypes of GI hemorrhage. In an observational study by Ozaslan et al., five adult patients with bleeding peptic ulcer disease, in which ABS was used as a primary hemostatic agent, were reported to have achieved success in controlling of the bleeding within minutes. Similarly, Purnak et al. reported a successful hemostasis control in a patient with a bleeding peptic ulcer complicated with defective hemostasis. In this reported case, at the time of bleeding, the patient was under-treated with a cytotoxic chemotherapeutic agent leading to thrombocytopenia. There are case reports showing that ABS was used safely in GI bleeding in infants and children. The first pediatric experience with ABS in an infant with bleeding peptic ulcer was recently demonstrated by Yarali et al. They applied 1-mL ABS which was spurt over the ulcer surface, and in a very short period white-gray adherent clot was developed on the ulcer and bleeding ceased.
Ergeneoglu et al. showed that applying ABS was a useful different technique for the control of sternal bleeding during cardiac surgery. Atalay et al. showed that the local use of 10-mL ABS decreases bleeding significantly during the operation. Therefore, transfusion requirements of erythrocyte suspension and platelets decreased in patients who received clopidogrel and acetylsalicylic acid undergoing emergent operations.56

### Table 3. Clinical trials that used Ankaferd hemostat.

| Study summary                                                                 | Patient population                      | References |
|-----------------------------------------------------------------------------|----------------------------------------|------------|
| With normal hemostasis by using ABS it is possible to completely prevent    | 630 patients undergoing coronary        | Gorgulu et al.27 |
| radial artery occlusion, and the study showed that ABS is effective in      | angiography                             |            |
| preventing bleeding complications.                                          |                                        |            |
| ABS was compared with formocresol for 3, 6, and 12 months for pain,         | 6- to 9-year-old 30 patients with      | Yaman et al.28 |
| swelling, mobility, resorption, furcation, and periapical bone destruction. | dental problems                        |            |
| ABS was as effective as formocresol for a pulp dressing of primary molar.   |                                        |            |
| Clinical effect of ABS on hemostasis on peri-adenoidectomy period was       | 90 patients who needed adenoidectomy    | lynen et al.29 |
| evaluated. ABS decreases the duration and quantity of blood loss post-      |                                        |            |
| adenoidecomy and increases postoperative quality of life.                   |                                        |            |
| ABS compared on hemostasis by phentylephrine. ABS is effective, safe,       | 49 patients with anterior epistaxis     | Teker et al.30 |
| rapid, and simple alternative to the phentylephrine in patients with cancer. |                                        |            |
| The study reported that ABS reduces intra-operative hemorrhage and          | 47 patients with chronic tonsillitis,   | Teker et al.31 |
| operation time for patients with chronic tonsillitis, tonsillar hypertrophy,| tonsilar hypertrophy, and              |            |
| and obstructive sleep apnea syndrome                                       | obstructive sleep apnea syndrome        |            |
| ABS and HCT groups were compared in terms of operation time,                | 61 patients who underwent total         | Guler et al.32 |
| postoperative drainage, duration of postoperative hospitalization, and      | thyroidectomy                          |            |
| complications. ABS is more effective than HCT to control hemorrhage         |                                        |            |
| following total thyroidecomy                                               |                                        |            |
| ABS improves soft-tissue healing during periodontal defect filling by the   | 15 patients with chronic periodontitis   | Pamuk et al.33 |
| ACB by stimulating angiogenesis and vascular endothelial cell function.     |                                        |            |
| Forty-five of the patients underwent tubeless PCNL with the use of ABS as   | 90 patients who underwent PCNL          | Istanbulluoğlu et al.34 |
| a hemostatic agent, whereas the remaining ones underwent tubeless PCNL      | because of renal and/or upper           |            |
| without ABS. ABS is a potent and safety hemostatic agent in tubeless PCNL.  | ureter stones                           |            |
| Patients were selected so that 80 patients have INR values of ≤2, whereas   | 205 patients with a single tooth to     | Amer et al.35 |
| the remaining patients have the INR values ranging from 2 to 3 and the       | be extracted that can be removed with   |            |
| procedures were applied. ABS is an effective hemostatic agent comparable    | forceps                                 |            |
| to tranexamic acid in controlling post-extraction bleeding in OAT patients   |                                        |            |
| of INR values ≤3.                                                           |                                        |            |
| Twenty-five CABG patients received a high-dose clopidogrel (600 mg), and    | 50 CABG patients who medicated with     | Atalay et al.36 |
| 300-mg ASA have been included into the study (ABS group). Twenty-five       | clopidogrel and ASA prior to CABG surgery |            |
| patients have also been included as control group. Local use of ABS reduces | 60 child patients who underwent         | Yasar and Ozkul37 |
| bleeding from the mediastinum after CABG.                                  | adenoidectomy                           |            |
| A statistically significantly shorter duration of bleeding and a lower number| 50 patients who were scheduled for      | Akpinar et al.38 |
| of packs are needed to obtain ABS tamponade-induced hemostasis during       | urgent or acute CABG                    |            |
| adenoidectomy as compared to saline-soaked gauze sponge application.        |                                        |            |
| Twenty-five CABG patients who were premedicated with clopidogrel and ASA    | 40 pregnant women with a term in a      | Eyi et al.39 |
| were included, and 25 patients who were premedicated with the same          | vertex position who required a mediolateral episiotomy |            |
| antiplatelet agents were as a control group. The use of local ABS decreases | 20 patients with grade 3–4 oral mucositis| Atay et al.40 |
| bleeding and transfusion requirements in patients premedicated with         |                                        |            |
| clopidogrel and ASA undergoing emergent CABG.                               |                                        |            |
| The patients were randomly assigned to two approaches on ABS and SS.        |                                        |            |
| Application of 4 mL of ABS compared to SS-lesshened bleeding.               |                                        |            |
| After developing oral mucositis patients with malignancy used only ABS.     |                                        |            |
| The healing duration of oral mucositis was shorter with the topical ABS     |                                        |            |
| application. Additionally, hemorrhages from oral mucositis lesions were     |                                        |            |
| healed within 2 days with ABS.                                              |                                        |            |

ABS: Ankaferd blood stopper; HCT: hemostasis by conventional technique; ACB: autogenous cortical bone graft; PCNL: percutaneous nephrolithotomy; INR: international normalized ratio; OAT: Oral anticoagulant therapy; CABG: coronary artery bypass grafting; ASA: acetylsalicylic acid; SS: saline solution.

**Ankaferd hemostat (ABS) in cardiovascular surgery**

The amount of cardiac operations increases in all countries and parallel to this situation, the problems of sternotomy healing and hemorrhage lead surgeons to research for new options and use several new techniques and materials. Ergeneoglu et al. showed that applying ABS was a useful...
Ankaferd hemostat (ABS) in ear, nose, and throat bleeding

Active bleeding from the nose is a common ear, nose, and throat emergency. Epistaxis can be serious or even fatal. Local or systemic diseases cause epistaxis. Yasar et al. evaluated the efficacy of ABS tamponade in the control of intra-operative bleeding occurring during adenoidectomy performed in children under the age of 12. The results showed that ABS aids in the control of intra-operative bleeding and reduces the number of packets tamponade required to achieve hemostasis.37

Ankaferd hemostat (ABS) in surgical bleeding

There are numerous studies in the literature indicating that ABS can be used safely in surgical procedures and dental procedures in patients with normal and abnormal hemostasis. Huri et al. presented the first case report demonstrating the efficacy of ABS in a patient with prostate adenocarcinoma undergoing radical retropubic prostatectomy. They provided hemostasis via applying ABS onto tissues with active hemorrhages during radical prostatectomy and reported the clinical efficacy of ABS during radical prostatectomy.48 Another report had also demonstrated similar hemostatic effects of local ABS application to a patient who underwent open partial nephrectomy. ABS was successfully applied to control bleeding without suturing the renal parenchyma. That application on the transected kidney area had provided active hemostasis in the partial nephrectomy case. ABS has a significant effect on active hemostasis during urogenital operations. Major bleeding from renal tissue could be controlled with additional doses of ABS solution which were applied to the bleeding area.49

Ankaferd hemostat (ABS) in wound healing

Wound healing, hemostasis, and infection have closed pathological conditions.50 Functional proteomic analyses had defined that antithrombin and pro-hemostatic activities of ABS are related to fibrinogen gamma chain and prothrombin.51 ABS accelerated wound-healing in animal studies and case reports as depicted in Figure 1. Topal et al. investigated the effects of ABS on the deep second-degree burn wound healing and compared its efficiency with silver sulphadiazine (SSD). They showed that the mean percentage of wound contraction in the ABS and SSD groups was significantly higher than in the control group on days 14, 21, and 28 and suggested that ABS could be successfully used for burn wound healing besides (SSD).52 ABS can improve the wound-healing process via providing inhibition of extra cellular matrix-degrading enzymes during wound repair. Moreover, ABS enhanced the stimulated migration of 3T3 fibroblasts to an artificial wounded area.53 ABS may be useful in the treatment of burn lesions. It was observed that the wounds healed rapidly with the topical application of ABS onto the burn lesions.54 The antioxidant components of ABS regulate the cellular proliferation, vascular dynamics, and hemostatic hemodynamic activity.55 Therefore, ABS may be useful by protecting the gastric mucosa from oxidative injury and by accelerating the healing of gastric ulcers.56 One experimental study disclosed that ABS was associated with significantly improved gastric mucosal structure. Therefore, oral administration of ABS could not only be useful in GI hemorrhage but also in infections and wound-related pathologies.57

Ankaferd hemostat (ABS) in infections

ABS has an anti-microbial activity against many microorganisms such as gram-positive and gram-negative bacteria (Figure 2) and several fungal infections. ABS was assessed on 102 clinical isolates from both gram-negative and gram-positive bacteria and four standard strains, including MRSA ATCC 43300, MSSA ATCC 25923, P. aeruginosa ATCC 27853, and E. coli ATCC 35218. Fisgin et al.58 showed that ABS was significantly active against all of the bacteria investigated. Another study disclosed that ABS is highly effective against several gram-negative and gram-positive bacteria including frequent foodborne microorganisms.59 Akkoc et al. assessed the antifungal effect of ABS using an agar well diffusion test. They found that ABS has a high antifungal effect against Zygosaccharomyces bailii, Candida albicans, Aspergillus flavus, and Aspergillus parasiticus. However, Ciftci et al. did not observe any effect of ABS on Candida. They also reported that when ABS was directly applied onto Candida species, it resulted in changes in the growth conditions.60 Another study indicated that ABS could act against Helicobacter pylori. ABS is clinically used for the management of GI bleeding due to benign and malignant lesions. Thus, the possible anti–H. pylori effect of ABS shall expand the therapeutic spectrum of the drug in GI lesions in relation to H. pylori infection such as peptic ulcer disease (PUD) and lymphoid tissue (MALT) lymphomagenesis.61
Future perspectives in Ankaferd hemostat

ABS could be an alternative treatment modality for different types of bleeding that are refractory to treatment with conventional procedures. ABS also provides effective anti-infective, anti-neoplastic, and curative modulator properties. Current perspective for using ABS is to provide hemostasis and accelerating wound healing. Future controlled trials are needed to show the effects of ABS in pleiotropic actions such as anti-neoplastic, antithrombotic, anti-inflammatory, anti-infective, antifungal, and anti-oxidative effects.

Conclusion

ABS serves as a hemostatic agent in a wide variety of clinical hemorrhages. Moreover, ABS also has numerous pleiotropic effects. The expanding spectrum of ABS include anti-infective, anti-neoplastic, and wound-healing properties. Randomized controlled clinical trials of ABS had established its anti-hemorrhagic clinical profile. However, further investigations are needed to elucidate the other pleiotropic activities in clinical backgrounds.

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