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Pleiotropic cellular, hemostatic, and biological actions of Ankaferd hemostat

Berat Z. Haznedaroglu [a], Yavuz Beyazit [b,*], Sharon L. Walker [c], Ibrahim C. Haznedaroglu [d]

[a] *Department of Chemical and Environmental Engineering, Yale University, New Haven 06511, CT, United States*
[b] *Department of Gastroenterology, Türkiye Yüksek İhtisas Hospital, Sihhiye 06100, Ankara, Turkey*
[c] *Department of Chemical and Environmental Engineering, University of California, Riverside 92521, CA, United States*
[d] *Department of Hematology, Hacettepe University Faculty of Medicine, Sihhiye 06100, Ankara, Turkey*

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Abstract

Sustaining hemostasis in clinical hemorrhages is a challenging task and requires extensive effort to stabilize medically hard-to-treat traumatic injuries. Several hemostatic agents are preferred to control external and internal bleedings, yet commercially available products are not sufficiently effective or fast-acting to achieve hemostasis in extreme cases. Ankaferd Blood Stopper (ABS) is a herbal extract traditionally used as a hemostatic agent. Recent studies have shown that ABS could be utilized successfully as a hemostatic agent for the

* Corresponding author. Tel.: +90 312 306 1320; fax: +90 312 306 1344.
E-mail address: yavuzbeyaz@yahoo.com (Y. Beyazit).

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management of clinical hemorrhages when conventional methods were ineffective. This review serves as a basis to provide recent findings on several applications of ABS, specifically preclinical, biological, and clinical studies both *in vitro* and *in vivo*. Another section focuses on the ultrastructural morphology and protein network formation of ABS in an effort to understand the hemostatic mechanisms of this unique agent at tissue level.

Keywords: Ankaferd Blood Stopper; Hemostasis; Hemostatic agent; Hemorrhagic diathesis; Antineoplastic

1. Introduction

Ankaferd Blood Stopper (ABS) is a folkloric herbal extract that has been traditionally used in Anatolia as a hemostatic agent [1]. ABS comprises a standardized mixture of the plants *Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioica*; each has known effects on the endothelium, blood cells, angiogenesis, cell proliferation, vascular dynamics, and/or cell mediators [1–4]. The concentrations of the effective substances in each pharmaceutical form are summarized in Table 1. Recently, ABS has been established as a novel topical hemostatic agent for the management of clinical hemorrhages when the conventional methods to control bleeding by ligature or other hemostatic measures have proved ineffective [5–9]. The agent is effective in both bleeding individuals with normal hemostatic parameters and in patients with deficient primary and/or secondary hemostasis [10–13]. ABS also modulates the cellular apoptotic responses to hemorrhagic stress, as well as hemostatic hemodynamic activity [14], and has considerable influence on the proteins present in tissue and blood. Furthermore, dose-dependent reversible down-regulation of proteinase-activated receptor 1 (PAR-1) is mediated by ABS in the presence of lipopolysaccharides (LPS). In addition to its anti-hemorrhagic properties, ABS has been shown to act as a topical biological response modifier [13].

2. Molecular basis of Ankaferd

ABS induces the formation of an encapsulated complex protein web with vital erythroid aggregation covering the entire physiological hemostatic process, as depicted in Fig. 1. This ABS-induced protein network formation depends primarily on the interactions between ABS and blood proteins, particularly with fibrinogen-gamma. The overall hemostatic effects of ABS depend on the protein agglutination and polymerization modulating the erythroid aggregation and vascular endothelium. The formation of the proteinaceous structure can be visualized microscopically in samples with pre- and post-application of ABS [1,2,7]. Representative examples of human plasma, serum, and whole blood are shown in Fig. 2.

There are several crucial components to the ABS-induced protein network. In the presence of ABS, vital erythroid aggregation takes place in conjunction with the spectrin and ankyrin receptors on red blood cell membranes. Essential erythroid proteins (spectrin-alpha, actin depolymerization factor, NADH dehydrogenase [ubiquinone] 1-alpha subcomplex, mitochondrial $NADP^{[+]}$ dependent malic enzyme) and the required adenosine triphosphate (ATP) bioenergy source are included in the protein library of ABS [1]. ABS also up-regulates the GATA/FOG transcription system affecting erythroid functions and urotensin-II [3]. Urotensin-II is also an essential component of ABS and acts as a link between injured vascular endothelium, adhesive proteins, and active erythroid cells. These concepts have been proven via matrix-assisted laser desorption/ionization-time of flight mass spectrometer (MALDI-TOF) proteomic molecular analyses, cytometric arrays, transcription analysis, and scanning electron microscopy (SEM) ultrastructural examinations as well as numerous investigations interacting with *in vitro* and *in vivo* research settings [1,13,15]. Additionally, ABS affects the levels of various critical proteins and factors, including protein-2 (AP2), androgen receptor (AR), cyclic AMP response element or activating transcription factor-1 (CRE-ATF1), cyclic AMP response element binding protein (CREB), E2F1-5,

Table 1
Ingredients of spray, ampoule and pad forms of Ankaferd Blood Stopper®.

Form of the active substance	Amount of the active substance				
	Spray (mg/mL)	Ampoule (mg)	Pad (mg)		
Size of vehicle		2 mL	2.5 × 7 cm 3 mL	5 × 7.5 cm 10 mL	20 × 20 cm 100 mL
Urtica dioica[a]	0.06	0.12	0.18	0.6	6
Vitis vinifera[b]	0.08	0.16	0.24	0.8	8
Glycyrrhiza glabra[b]	0.09	0.18	0.27	0.9	9
Alpinia officinarum[b]	0.14	0.14	0.21	0.7	7
Thymus vulgaris[c]	0.10	0.10	0.15	0.5	5

[a] Dried root extract.
[b] Dried leaf extract.
[c] Dried grass extract.