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In Vivo Hemostatic Effect of the Medicinal Plant Extract Ankaferd Blood Stopper in Rats Pretreated With Warfarin

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Aim: Ankaferd comprises a mixture of *Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum* and *Urtica dioica*. Ankaferd Blood Stopper (ABS) has been approved in the management of bleedings. This study aimed to evaluate in *vivo* hemostatic effect of ABS in rats pretreated with warfarin. *Materials and methods:* Wistar rats (210-270 g) were treated either with warfarin (2 mg/kg) or vehicle (0.9% NaCl) orally before bilateral hind leg amputation. ABS was administered topically to one of the amputed legs. The duration of bleeding and the amount of bleeding were measured to evaluate the hemostatic effect of ABS. *Results:* Topical ABS administration to amputed leg shortened the duration of bleeding markedly in both untreated and warfarin-treated rats by 31.9% [1.42 min (95% CI: 0.35-2.49)] and 43.5% [5.12 min (95% CI: 2.16-8.07)] respectively. The amount of bleeding in ABS-administered amputed leg showed a decrease by 53.8% in warfarin-treated group. *Conclusions:* ABS has in *vivo* hemostatic actions that may provide a therapeutic potential for the management of patients with deficient primary hemostasis in clinical medicine.

Keywords: Ankaferd; warfarin; bleeding; hemostasis; in vivo; rats

Introduction

Ankaferd is a medicinal plant extract, which has previously been used in Turkish traditional medicine as hemostatic agent.[1] Ankaferd comprises a standardized mixture of plants *Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum*, and *Urtica dioica*. Ankaferd Blood Stopper (ABS) as a medicinal product has been approved in the management of external hemorrhage and dental surgery bleedings in Turkey (www.ankaferd.com). The safety and efficacy reports on the product have indicated its sterility and nontoxicity.

A very recent in vitro study by Goker et al[1] has shown that exposure of ABS resulted in a very rapid formation of network within the plasma and serum. Routine hemostasis and biochemical tests revealed that the network formation due to ABS depended upon the interactions of the substance with the blood proteins, mainly fibrinogen, and indicated that ABS could affect both fibrinogen and other proteins possibly via agglutination of these molecules. The network of ABS might cover the entire physiological hemostatic process without affecting any individual clotting factor.[1] Thus, this unique mechanism of action provides ABS with the advantage over other hemostatically active plant extracts and might,

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Table 1. Description of Study Groups

Group	Medication	Daily dose (mg/kg)	Route of Administration	Duration (Days)	Solution Applied to Bleeding Area
Warfarin-treated group	Warfarin	2	PO	4	ABS for 1 limb and 0.9% NaCl for the other
Untreated group	Saline	—	—	4	ABS for 1 limb and 0.9% NaCl for the other

NOTES: ABS = Ankaferd Blood Stopper; PO = by mouth.

therefore, be effective both in subjects with normal hemostatic parameters and in those with primary and/or secondary hemostatic disorders.

In the light of the above-mentioned data, this study aimed to investigate the in vivo hemostatic effect of ABS in rats. Additionally, the hemostatic effect of ABS was also evaluated in rats, which were pretreated with warfarin.

Materials and Methods

Animals

A total of 14 Wistar albino rats (average weight 240 ± 30 g) of both sexes were used in this study. The animals were kept in a room at a constant temperature of 22 ± 1°C with a 12-hours light and 12-hours darkness cycle and fed standard pellet chow and water that were available ad libitum. All experiments were carried out in accordance with the European Community Council Directive of November 24, 1986 (86/609/EEC) and were approved by the Fatih University Medical School Ethics Committee.

Experimental Design

The rats were pretreated with either warfarin dissolved in saline (2 mg/kg) or vehicle (0.9% NaCl) orally by a feeding catheter custom-made of silver for 4 consecutive days before bilateral hind leg amputation (see Table 1). International normalized ratio (INR) values of the rats were checked to make sure that overt warfarin effect is clearly significant in the studied animals and found to have INR of >20 in all of them. Each group (warfarin pretreated group and control group) consisted of 7 animals.

Beforehand all operations, a list of randomization was developed by using RAND() function of Microsoft Excel. RAND() function generates random real numbers between 0 and 1. A table of 7 rows including 7 cells, each representing an individual rat, was filled with RAND() function. For the rats, of which numbers generated were lower than 0.50, ABS was planned to be applied to right leg and saline to left leg. However, if the number generated was equal or higher than 0.50, then ABS would be applied to left leg and saline to right leg for those rats.

On the fifth day, the animals were anesthetized with ketamine (80 mg/kg). Both hind legs of the animals were prewarmed for 5 minutes in 10 mL of saline at 37°C in a water bath. Then, both legs were lifted from the saline and 5-mm leg segments amputed above the knees.

For each animal, one of the amputed legs was treated with topical ABS (a total of 4 mL [1 mL/puff × 4]; Ankaferd Drug Inc, Istanbul, Turkey). The other leg was treated with the same volume (4 mL) of vehicle (0.9% NaCl) topically and served as the control.

Both ABS and saline were prepared in similar-looking dark-colored spray bottles before by a staff who worked in neither the surgical operations nor the evaluation of bleeding. The researchers and their assistants who had applied the study medication to the cut limbs and who followed and evaluated the bleeding were not aware of the contents of the medication they applied, that is they work blinded to the medication they used.

Bleeding Assay

Study parameters were duration of bleeding and amount of bleeding. Duration of bleeding was defined as the time passed after the start of bleeding (ie, amputation or tail-cut) to cessation of bleeding. Bleeding start and stop times were measured using a chronometer.

The amount of bleeding was measured by means of a blotting paper. The blood was collected on blotting paper, which was weighed before and after the procedure on a 0.1-g accurate scale. The difference in the weight of the blotting paper before and after the procedure indicated the amount of bleeding.

Sample Size Calculation

Group sample sizes of 14 in each study arms, will achieve 80% power to detect 50% change in the duration of bleeding in Ankaferd group when compared to control group, with estimated standard deviations are 60% of the average durations of bleeding with a 2-sided significance level (α) of .05. When the average duration of bleeding in control group is set at 100 units, with the above assumptions, average duration of bleeding in Ankaferd group will be 50 units and standard deviations of duration of bleeding will be 50 and 30 units in control and Ankaferd groups, respectively. This, in turn, translates into effect size of 1.05, which is quite large (see below). Effect size greater than 0.80 is usually accepted as "large effect size."

$$\text{Effect size} = \frac{\text{mean}_1 - \text{mean}_2}{\sqrt{\text{SD}_1^2 + \text{SD}_2^2/2}}$$

$$\text{Effect size} = \frac{100 - 50}{\sqrt{60^2 + 30^2/2}} = 1.05.$$

In as much as this sample size of 14 in 2 study arms would be enough to detect the above-defined difference, a design with dependent samples of totally 14 subjects (rats) with 2 units (legs) on each to study would be even better.

Statistical Analysis

The data were presented as mean and 95% confidence limits. Median and interquartile ranges (IQR) were also given. Besides measured values of the duration of bleeding and the amount of bleeding, absolute differences and percentage differences between right and left legs were calculated for each rat separately. These figures correspond to absolute and percentage shortening of duration and lessening of amount of bleeding with ABS as compared to saline.

Because ABS and control groups were paired (limbs of same animals), statistical analyses appropriate for dependent samples were used. In the initial analysis, the data in each group were analyzed separately with Wilcoxon test and also with paired Student *t* test, to test the robustness of data with regards to parametric assumptions. Since 2 comparisons ([1] ABS vs control in warfarin-treated group and [2] ABS vs control in untreated group) were performed instead of a single comparison for testing the primary hypothesis of the study "whether the effect of ABS is significantly better than saline (whatever the subjects are pretreated with)", the type I error level was adjusted downward to 0.025 (0.05 divided by 2) for the results of Wilcoxon tests and paired Student *t* tests. Therefore, *P* values less than .025 should be regarded as significant for these tests.

In addition to the univariate tests defined above, a repeated measures analysis of variance (RM-ANOVA) model was built. In the model, which was fully saturated, the between-subjects factor was the type of pretreatment (warfarin vs saline) and the within-subjects factor was the type of solution applied to the bleeding limb (ABS vs saline). The dependent variables were the duration of bleeding and the amount of bleeding for the first and second models, respectively. The overall effects of ABS and warfarin and their interaction were analyzed by RM-ANOVA with Greenhouse-Geisser test. Overall effect of ABS correspond to effect of ABS independent of the type of pretreatment (whether warfarin-treated or not) and overall effect of warfarin correspond to effect of warfarin (whether treated with ABS or not). If ABS-warfarin interaction term is significant ($P < .05$), it means that the effect of ABS is not similar between warfarin-treated and untreated groups. *P* values less than .05 were regarded as significant for RM-ANOVA. All analyses were done using SPSS version 9 statistical analysis package.

Results

Duration of Bleeding

In untreated group, the duration of bleeding following amputation of hind legs was shortened by 1.42 minutes (95% CI: 0.35-2.49) with ABS administration from 4.21 minutes (95% CI: 3.56-4.86) in the saline-administered control subgroup to 2.79 minutes (95% CI: 1.97-3.61;$P = .028$). Ankaferd Blood Stopper shortened the duration of bleeding by 31.9% (95% CI: 7.9-55.8) in untreated group (Table 2, Figures 1 and 2).

In warfarin-treated group, duration of bleeding following amputation of hind legs was shortened by 5.12 minutes (95% CI: 2.16-8.07) with ABS administration from 12.05 minutes (95% CI: 10.44-13.67) in the saline-administered control subgroup to 6.94 minutes (95% CI: 3.33-10.54;$P = .018$). Ankaferd Blood Stopper shortened the duration of bleeding

Table 2. The Effect of Topically ABS (4 mL) on the Duration of Bleeding of Amputed Legs of Rats Pretreated With Warfarin (2 mg/kg Orally) or Vehicle (0.9% NaCl Orally) for 4 Days[a]

	ABS	Control	ABS vs Control	ABS vs Control (%)	Statistics[b]	
Duration of bleeding (min)						
Warfarin treated	6.94 (3.33-10.54); Median: 7.55, IQR: 7.00	12.05 (10.44-13.67); Median: 12.10, IQR: 3.10	5.12 (2.16-8.07); Median: 4.30, IQR: 6.00	43.5 (17.1-69.9); Median: 30.1, IQR: 53.9	$Z = 2.366$; $P = .018$[c]	$t = 4.241$; $P = .005$[d]
Untreated	2.79 (1.97-3.61); Median: 2.30, IQR: 1.51	4.21 (3.56-4.86); Median: 4.20, IQR: 0.75	1.42 (0.35-2.49); Median: 1.90, IQR: 1.60	31.9 (7.9-55.8); Median: 47.0, IQR: 41.5	$Z = 2.197$; $P = .028$[c]	$t = 3.250$; $P = .017$[d]
Amount of bleeding (mL)						
Warfarin treated	1.64 (0.74-2.53); Median: 1.90, IQR: 1.75	3.60 (2.35-4.85); Median: 3.50, IQR: 1.50	1.96 (0.63-3.29); Median: 1.80, IQR: 2.00	53.8 (26.0-81.6); Median: 45.3, IQR: 50.7	$Z = 2.366$; $P = .018$[c]	$t = 3.613$; $P = .011$[d]
Untreated	2.55 (1.62-3.48); Median: 22.0, IQR: 1.71	3.24 (2.41-4.06); Median: 3.40, IQR: 1.60	0.68 (<0.00-1.74); Median: 0.10, IQR: 2.40	17.2 (<0.0-45.2); Median: 2.4, IQR: 58.9	$Z = 1.153$; $P = .25$[c]	$t = 1.574$; $P = .17$[d]

NOTES: ABS = Ankaferd Blood Stopper; IQR = interquartile range.
[a] Data are given as mean (95% confidence interval) and median with IQR.
[b] Statistical significance is set as *P* values <.025, due to multiple pairwise comparisons (see Statistical Analysis in Materials and Methods).
[c] Wilcoxon test.
[d] Student paired *t* test.

by 43.5% (95% CI: 17.1-69.9) in warfarin-treated group (Table 2, Figures 1 and 2).

Analysis of variance revealed that the difference between ABS and saline subgroups (ABS effect) as well as the difference between warfarin-treated and untreated groups (warfarin effect) were both significant (ABS effect: $F = 25.957$, $P < .001$; warfarin effect: $F = 36.433$, $P < .001$). Moreover, it was established that the effect of ABS was not similar in the warfarin-treated and untreated groups (ABS-warfarin interaction: $F = 8.295$, $P = .014$). Ankaferd Blood Stopper is significantly more effective in shortening duration of bleeding as compared to control, and its efficacy gets more pronounced in the warfarin-treated group than untreated group (Table 3).

Amount of Bleeding

In untreated group, the amount of bleeding following amputation of hind legs was not different between ABS and saline groups (2.55 mL [95% CI: 1.62-3.48] and 3.24 mL [2.41-4.06, respectively]; $P = .25$; Table 2, Figures 1 and 2).

In warfarin-treated group, amount of bleeding following amputation of hind legs was decreased by 1.96 mL (95% CI: 0.63-3.29) with ABS administration from 3.60 mL (95% CI: 2.35-4.85) in the saline-administered control subgroup to 1.64 mL (95% CI: 0.74-2.53;$P = .018$). Ankaferd Blood Stopper decreased the amount of bleeding by 53.8% (95% CI: 26.0-81.6) in warfarin-treated group (Table 2, Figures 1 and 2).

Analysis of variance revealed that while the difference between ABS and saline subgroups (ABS effect) was significant (ABS effect: $F = 14.488$, $P = .003$), the difference between warfarin-treated and untreated groups (warfarin effect) was nonsignificant (warfarin effect: $F = 0.369$, $P = .56$). It was seen that the effect of ABS was similar in the warfarin-treated and untreated groups (ABS-warfarin interaction: $F = 3.395$, $P = .09$). In other words, ABS is significantly more effective in decreasing the amount of bleeding as compared to control, and its efficacy is similar in the warfarin-treated and untreated groups (Table 3).

Discussion

This in vivo study on rats demonstrated that topically administered ABS has a hemostatic effect on rats alone or in the presence of warfarin effect. Thus, the present data support the recent in vitro findings, demonstrating the beneficial effect of ABS on hemostatic parameters.[1] Taken together, ABS seems to be a promising therapeutic agent for the management of clinically evident coagulation disorders.

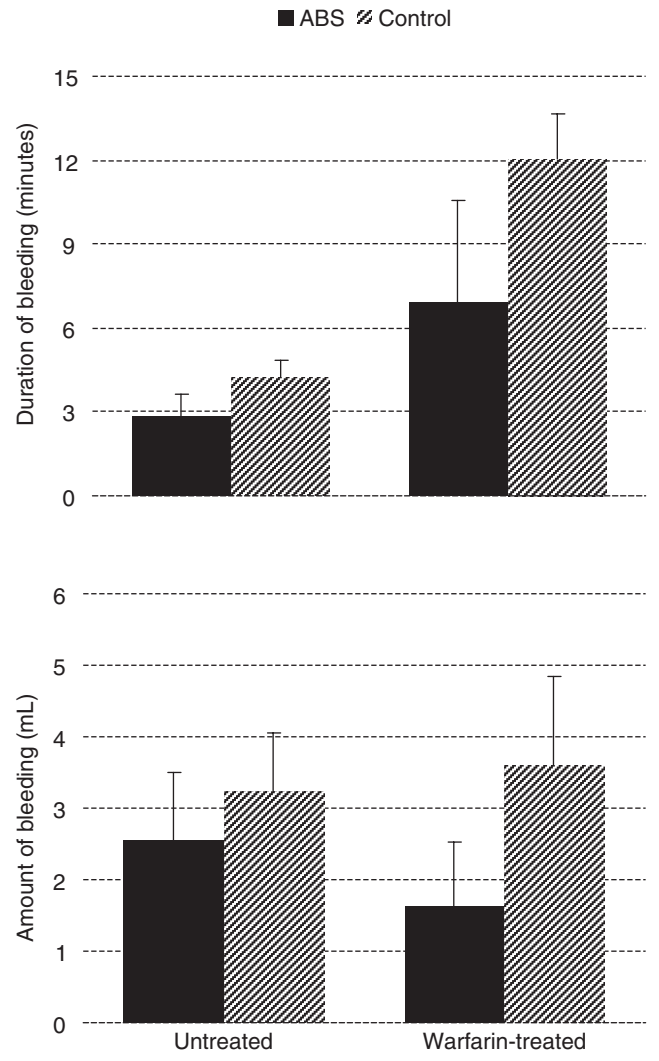

Figure 1. A, The effect of topically administered Ankaferd BloodStopper (ABS; 4 mL) on the duration of bleeding of amputed leg of rats pretreated with warfarin (2 mg/kg orally) or vehicle (0.9% NaCl orally) for 4 days. B, The effect of topically administered Ankaferd BloodStopper (ABS; 4 mL) on the amount of bleeding of amputed leg of rats pretreated with warfarin (2 mg/kg orally) or vehicle (0.9% NaCl orally) for 4 days. Each group consisted of 7 animals. Error bars correspond to 95% CI. *P < .05 vs control.

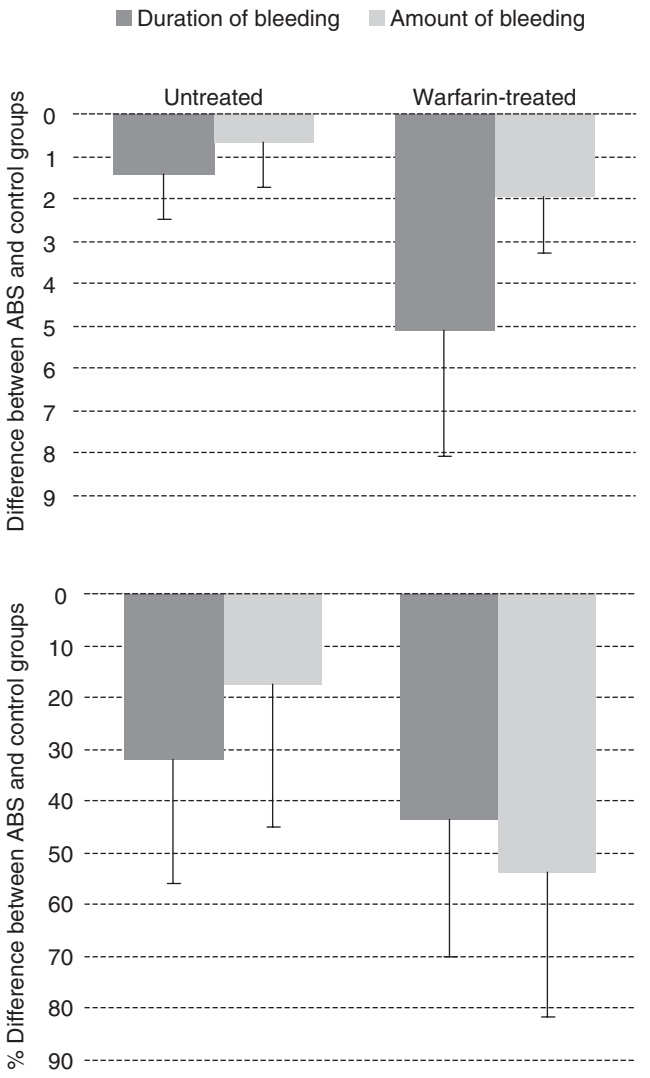

Figure 2. The absolute and percentage differences of the duration of bleeding and the amount of bleeding of amputed leg of rats, between topically administered Ankaferd BloodStopper (ABS; 4 mL) and saline in rats pretreated with warfarin (2 mg/kg orally) or vehicle (0.9% NaCl orally) for 4 days. Each group consisted of 7 animals. Error bars correspond to 95% CI. *P < .05 vs control.

The previous in vitro study clearly demonstrated that addition of ABS to plasma did not affect the individual coagulation factors II, V, VII, VIII, IX, X, XI, and XIII.[1] It decreased plasma fibrinogen activity concomitant with prolongation of the thrombin time.[1] Additionally, total protein, albumin, and globulin levels showed significant decreases after addition of ABS. Thus, these results implied that the basic mechanism of ABS is the formation of an encapsulated protein network that provides focal points for aggregation of red blood cells. Because ABS seems to provide a protein-driven agglutination without affecting the individual coagulation factors, it is advantageous over other plant extracts with hemostatic activity.

In the present study, we observed that ABS was beneficial as a topical hemostatic agent in bleeding rats. Ankaferd Blood Stopper was found effective in shortening the duration of bleeding and decreasing the bleeding volume in amputed legs. Interestingly, ABS showed its hemostatic action not only in the

Table 3. The Results of Repeated Measures ANOVA With Ankaferd Blood Stopper (ABS) Effect and Warfarin Effect as Independent Factors and Duration of Bleeding and the Amount of Bleeding as Dependent Variables

	Duration of Bleeding		Amount of Bleeding	
Term in ANOVA	F^a	P	F	P
ABS effect (ABS vs control)	25.957	.001	14.488	.003
Warfarin effect (warfarin-treated vs untreated)	36.344	.001	0.369	.56
ABS vs warfarin interaction	8.295	.014	3.395	.09

[a] Repeated measures analysis of variance, Greenhouse-Geisser test.

untreated animals but also in the animals pretreated with warfarin.

Warfarin inhibits coagulation via different mechanisms. It inhibits the vitamin K-dependent synthesis of biologically active forms of calcium-dependent clotting factors II, VII, IX, and X as well as the regulatory factors protein C, protein S, and protein Z.

The data of the present study showed ABS was also effective in modulating hemostasis in rats pretreated with warfarin, implying that application of ABS topically overcomes the actions of warfarin given systemically. The beneficial action of ABS did not seem to be attenuated in animals that pretreated with warfarin, as confirmed by statistical analysis. Although the previous in vitro study showed that ABS did not affect any of the individual clotting factors, we cannot exclude this possibility under in vivo conditions. The duration of bleeding is known as an indicator of the effectiveness of platelet-thrombus formation and therefore, a prolonged duration of bleeding may show the presence of severe thrombocytopenia, platelet dysfunction syndromes, vascular defects, and/or mixed abnormalities such as von Willebrand disease.

In the present study, shortening of the duration of bleeding by topical ABS suggests that the extract shows its hemostatic effect at least partly via modulation of the platelet functions. Other possible mechanisms of its action need further elucidation. Moreover, a very recent clinical case by Kurt et al[2] presented a 52-year-old man who had undergone resection with the diagnosis of distal cholangiocarcinoma. He had signs of recent bleedings upon upper gastrointestinal endoscopic examination. Topical ABS (15 mL) showed effective control of bleeding from the biopsy site. A repeated endoscopy during the follow-up did not reveal any stigmata of bleeding as well.

Ankaferd Blood Stopper comprises a standardized mixture of 5 plants each having some hematological and vascular actions.[3-8] *Glycyrrhiza glabra* has anti-inflammatory, antithrombin, antiplatelet, antioxidant, antiatherosclerotic, and antitumor activities.[6] It inhibits angiogenesis, decreases vascular endothelial growth factor production, and cytokine-induced neovascularization.[6] *Thymus vulgaris* has antioxidative actions, such as prevention of lipid peroxidation.[4] *Vitis vinifera* exerts antitumor and antiatherosclerotic effects.[9,10] *Alpinia officinarum* inhibits nitric oxide production by lipopolysaccharide-activated mouse peritoneal macrophages.[3] *Urtica dioica* causes vasodilation via inducing nitric oxide production by endothelium.[5] Thus, the mechanisms underlying the hemostatic control by ABS require further investigation. The comparative and/or individual effects of Ankaferd on rats anticoagulated with unfractionated heparin or low-molecular-weight heparins or direct thrombin inhibitors would be important topics in upcoming studies based on the results of our present study.

As a conclusion, ABS, a traditional folkloric medicinal plant extract, may provide a therapeutic potential for the management of patients with deficient primary hemostasis in the clinical medicine with its in vivo hemostatic actions. In vitro data on the anti-infectivity of Ankaferd[11] and preliminary successful applications in mediastinal bleedings associated with cardiac surgery[12] represent novel clues for Ankaferd activity. Ankaferd is promoting the very rapid (<1 second) formation of a specific protein network that acts as an anchor for vital erythrocyte aggregation, covering the classical clotting cascade.[1] Phase I studies are completed, and Ankaferd is currently being studied in the treatment of Kirim-Kongo hemorrhagic fever with promising preliminary results, based on its anti-infective and hemostatic efficacy[12-15] even with defective platelets and/or coagulation factors. The effects of Ankaferd protein library on vascular endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics, and cellular mediators are currently being investigated to determine its potential role in many

pathological states, including neoplastic disorders, infectious diseases, inflammation, premature aging, and atherosclerosis.

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