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Original Article

Biomechanic and biochemical analysis of the effects of local Ankaferd Blood Stopper® application on osseointegration of titanium implants

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Abstract

Aim: Investigations into Ankaferd Blood Stopper® (ABS) on bone healing have revealed positive bone regeneration effects. The exact mechanism of this positive bone tissue metabolism effect is unknown. This study's aim is a biomechanic and biochemical investigation of the effects of local ABS application on the osseointegration of titanium implants.
Methodology: Sprague Dawley rats were divided into four groups of ten rats each. The control group (n=20) received no treatment during the experimental period, while the ABS group (n=20) had ABS applied locally during the surgical application of the titanium implant before insertion into the bone sockets. After 2 (controls n=10 and ABS n=10) and 4 weeks (controls n=10 and ABS n=10) experimental periods, the rats were sacrificed and implants with surrounding bone tissues were removed for reverse torque analysis (Newton), blood sample collection, and biochemical analysis.
Results: The biomechanic bone implant contact ratio detected was higher in week 4 than in week 2 in the ABS group (p<0, 05). Lower phosphor levels were detected in the ABS group than in the 4-week controls (p<0, 05).
Conclusion: According to the biomechanical parameters, ABS is more effective after four weeks than after two weeks when locally applied.

Keywords: Ankaferd Blood Stopper® (ABS), osseintegration, bone implant contact, bone formation, biomechanic

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Introduction

Ankaferd Blood Stopper® (ABS) (Immune Cosmetics Pharmaceutical Co. Ltd., İstanbul, Turkey) is a hemostatic agent present in plant extracts used in the context of Turkish medicine (1). It is a standardized herbal medicine consisting of herbal mixtures, such as Urtica dioica, Thymus vulgaris, Vitis vinifera, Alpinia

officinarum, and Glycyrrhiza glabra (2). ABS affects hemostatic and inflammatory processes, which it produces by intervening in the processes and activities of blood cells, endothelium angiogenesis, cellular proliferation, vascular dynamics, and cellular mediators (1-3).

ABS is generally used to stop or control bleeding that is resistant to traditional anti-hemorrhagic agents (1, 2). However, ABS reportedly has vital effects, such as anti-inflammatory, antioxidant, antimicrobial, and antineoplastic effects, and it positively impacts wound healing. The substances in the herbal mixture extract in ABS have different effects. G. glabra inhibits angiogenesis in bleeding, causes cytokine-induced neovascularization, decreases vascular endothelial growth factor, and has antitumor, anti-inflammatory, antiplatelet, and antioxidant properties (4-12).

T. vulgaris displays different grades of antioxidant activation and helps prevent oxidative damage in vivo, such as atherosclerosis. Vaccination experiments performed on the leaves of V. vinifera showed that it developed resistance against pathogens (13). V. vinifera has strong antitumor and anti-atherosclerotic effects (14, 15). A. officinarum inhibits nitric oxide production in peritoneal macrophages in rats activated with lipopolysaccharide (16). U. dioica reportedly induces hypotensive responses by releasing endothelial nitric oxide, vasorelaxation by opening potassium channels, and negative inotropic action (17, 18).

Dental implants have become a routine treatment option, and significant advances have been made in the use of dental implants in maxillofacial and oral surgery (19). However, dental implant applications may lead to adverse situations, and these are difficult to predict. One of the most important factors determining dental implant success is bone tissue quality (20). The main determinants of this situation are the amount of bone tissue around the implant and its biomechanical features (21, 22). Peri-implant bone tissue stability is the stable state that occurs over time when cellular events cause bone to form in micro-level spaces between the dental implant and the bone tissue. Osseointegration occurs when the implant successfully attaches to the bone surface. This is primarily related to bone quality (23, 24). This study's aim is to examine the effect of ABS when applied to the implant socket on the osseointegration level of titanium implants.

Materials and Methods

Animals and Experimental Design

The study was carried out at the Fırat University Experimental Research Center, having obtained approval from the Fırat University Animal Experiments Local Ethics Committee. The rats required for the study were provided by Fırat University Experimental Research Center. During the study, the instructions and rules in the Helsinki Declaration were observed. The experiment was carried out with 40 Sprague Dawley rats, which were divided into four groups of 10 rats each. The rats used in the experiment were kept in sterile rooms with 55% humidity and a temperature of 22 ± 2°C. Additionally, a 12-hour light/dark cycle was provided. Pairs of rats were kept in standard cages and fed ad libitum with a normal diet and water.

Control implant group (n = 20): Resorbable blast material surface implants that were 2.5 mm-diameter and 4 mm-long (Implance Dental Implant System, AGS Medical, İstanbul, Turkey) were surgically placed in the metaphyseal parts of the right tibia bones of the subjects. No additional processing was applied during the experimental setup. At the end of each of the second and fourth weeks, 10 rats were sacrificed.

ABS implant group (n = 20): Resorbable blast material surface implants that were 2.5 mm-diameter and 4 mm-long were surgically placed in the metaphyseal parts of the right tibia bones of the subjects. The implants were placed in surgically prepared sockets by locally applying as much ABS as the socket could accommodate. At the end of each of the second and fourth weeks, 10 rats were sacrificed.

Surgical Procedures

The rats were not fed for 8 hours before surgery and general anesthesia. Maximum attention was paid to sterile conditions in all surgical procedures. General anesthesia was applied intramuscularly—with the help of an insulin injector—using xylazine hydrochloride (Rompun®, Bayer HealthCare AG, Animal Health Division, Leverkusen, Germany) and ketamine hydrochloride (Ketasol®, Richter Pharma AG, Wels, Austria). Mepivacaine hydrochloride (0.3 ml/kg, 2% with scandicaine epinephrine 1:100.000, (Septodont, Saint-Maur-des-fossés Cedex, France) was infiltratively applied to the treated area to control bleeding during the surgical procedure. The area where the surgical procedure was to be performed was shaved and then washed with povidone iodine.

A 1.5-cm incision was made over the tibial crest using a scalpel Number 15. The proximal part of the tibia was reached using a periosteal elevator. In the Ankaferd group, implants were placed in the implant sockets prepared by surgical methods by applying ABS locally as much as the socket could take. In the control group, 2.5 mm-diameter and 4 mm-long implants were surgically placed in the metaphyseal parts of the right tibia bones of the subjects (Figure 1A, B). No additional processing was applied throughout the experimental setup.

After the implants were applied, the flaps were closed using absorbable threads (4/0 vicryl, Ethicon, Inc., Somerville, NJ, USA) on soft tissues and monofilament suture (Nylon 4.0, Ethicon, Inc.) for the skin. To avoid negative situations that might occur after surgery, the rats were checked daily for signs of pain, dilation, infection, restricted movement, loss of appetite, and weight loss. Antibiotic (50 mg/kg penicillin) and analgesic (0.1 mg/kg tramadol hydrochloride) for the prevention of infection and pain were administered intramuscularly every 24 hours for 3 days. All subjects were sacrificed after a four-week recovery period. The implants were taken for biomechanical analysis, together with the surrounding bone tissues.

Biomechanical Analysis

To evaluate the osseointegration of the implants, the reverse torque test was performed on rats sacrificed after the two and four-week recovery period. The samples were kept in a liquid solution (10% buffered formalin). An evaluation was performed immediately to prevent dehydration. All implants were placed in polymethylmethacrylate blocks for analysis. After the rejected parts of the implants were screwed in, a digital torque tool (Mark-10, Cap Torque Tester, Model MTT01-12, NY, USA) was fixed for each implant. Next, a counterclockwise ejection force was slowly and progressively applied manually.

The reverse torque application was complete when the implant rotated in the bone socket. When the stabilization of the implants was completed, the highest torque value (Ncm) obtained on the digital torque screen was automatically recorded (Fig. 2).

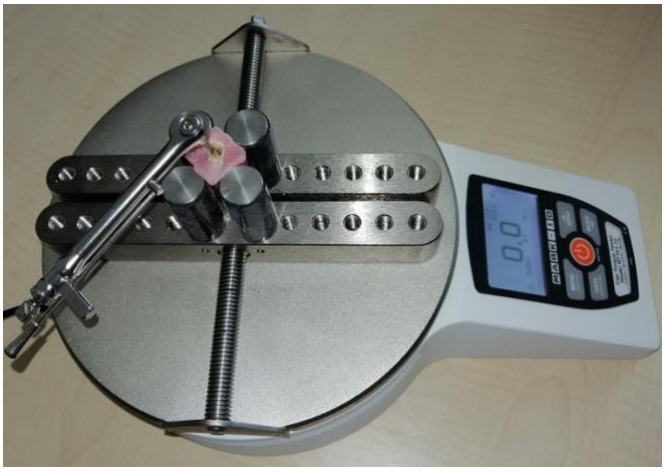

Figure 2. Reverse torque analysis of the samples

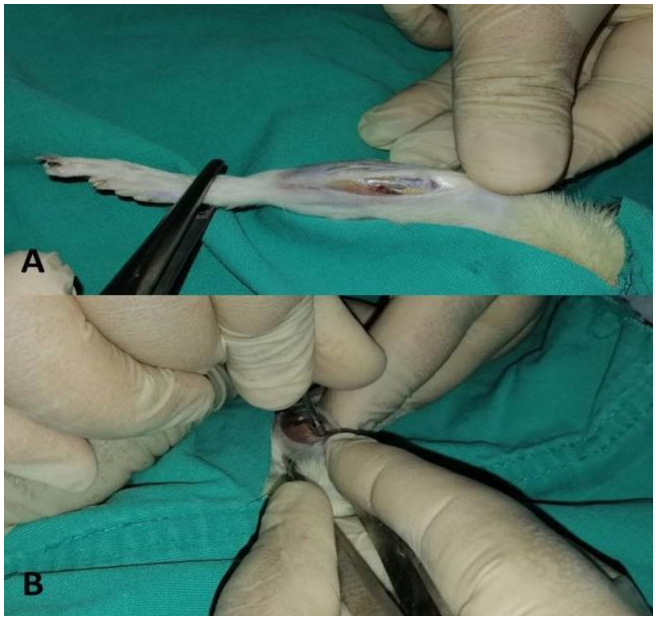

Figure 1. **A.** Surgical approach of the metaphyseal part of the right tibial bone after crestal incision and dissection of the soft tissues. **B.** Creation bone cavities and insertion the titanium implants.

Biochemical Analysis

Biochemical analyses were performed in the central biochemistry laboratory of Fırat University, Faculty of Medicine. Blood samples from the rats were obtained under deep anesthesia. Glucose, serum alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P) values were analyzed with blood samples taken by cardiac puncture without anticoagulant. The biochemical data were measured individually in rats.

Statistical analysis

Analysis of the data was carried out with IBM SPSS Version 22 (IBM SPSS Inc., Armonk, NY, USA). Whether the data were normally distributed was determined using the Kolmogorov - Smirnov test.

The data were first evaluated with the between-groups Student's t-test, then the One-Way ANOVA test was applied between all groups for all parameters. One-Way ANOVA was used in groups with normal distribution. Tukey's honestly significant difference (HSD) test was used to determine the group that caused the differences, and $p<0.05$ was considered statistically significant in the analyzes.

Results

As shown in Table 1 and Table 2, the analysis revealed no significant difference in the biomechanical bone-implant contact (BIC) value between the ABS group and the control group at week two and week four. As shown in Table 3; however, in the comparison between the ABS group in week two and the ABS group in week four, the BIC value was found to be higher in week four, and this difference was found to be statistically significant ($p<0.05$).

As shown in Table 1 and Table 2, the biochemical analyses showed no statistically significant difference between the groups in the second week, while calcium (Ca) and phosphorus (p) values were found to be lower in the groups in which ABS was applied at the fourth week, and this difference was found to be statistically significant ($p<0.05$).

Table 1. Biochemical and biomechanic (BIC: Bone Implant Connection) parameters of the groups after two weeks surgical insertion of the implants.

Parameters	Groups	N	Mean	Std. Deviation	p*
Glucose	Control	10	107,20	7,74	0,67
	ANK	7	109	9,22	
ALP	Control	10	54,5	14,30	0,42
	ANK	7	50,43	4,39	
Ca	Control	10	9,26	0,54	0,2
	ANK	7	9,66	0,67	
P	Control	10	5,7	0,54	0,07
	ANK	7	6,2	0,49	
BIC	Control	10	0,9	0,42	0,053
	ANK	10	0,58	0,26	

* Student T Test. P: Phosphor, Ca: Calcium, ALP: Alcaline phosphatase, ANK: Ankaferd.

Table 2. Biochemical and biomechanic BIC parametes of the groups after four weeks surgical implant insertion.

Parameters	Groups	N	Mean	Std. Deviation	p*
Glucose	Controls	10	111,4	10,95	
	ANK	10	116,4	12,08	0,35
ALP	Controls	10	53,8	34,69	
	ANK	10	69,4	30,93	0,3
Ca	Controls	10	9,81	0,43	
	ANK	10	9,2	0,64	0,02
P	Controls	10	6,13	0,74	
	ANK	10	5,46	0,41	**0,025**[α]
BIC	Controls	10	1,05	0,35	
	ANK	7	1,47	0,87	0,26

* Student T Test. [α] Statistically highly in Controls compared with the ANK group in 8 weeks. P: Phosphor, Ca: Calcium, ALP: Alcaline phosphatase, ANK: Ankaferd.

Table 3. Biochemical and biomechanic BIC parameters all of the groups.

		N	Mean	Std. Deviation	Minimum	Maximum	p*
Glucose	Control-2	10	107,2	7,74	97	126	
	ANK-2	7	109	9,22	97	121	
	Control-4	10	111,4	10,95	90	124	0,236
	ANK-4	10	116,4	12,08	101	133	
ALP	Control-2	10	54,5	14,3	35	75	
	ANK-2	7	50,43	4,39	45	57	
	Control-4	10	53,8	34,69	32	150	0,394
	ANK-4	10	69,4	30,93	38	132	
Ca	Control-2	10	9,26	0,54	8,39	10,1	
	ANK-2	7	9,66	0,67	8,66	10,65	
	Control-4	10	9,81	0,43	9,26	10,37	0,06

	ANK-4	10	9,2	0,64	8,21	9,93	
P	Control-2	10	5,7	0,54	5,2	6,7	
	ANK-2	7	6,2	0,49	5,4	6,9	
	Control-4	10	6,13	0,74	5,2	7,4	0,05
	ANK-4	10	5,46	0,41	5,1	6,3	
BIC	Control-2	10	0,9	0,42	0,3	1,8	
	ANK-2	10	0,58	0,26	0,2	1	
	Control-4	10	1,05	0,35	0,6	1,7	0,007
	ANK-4α	7	1,47	0,87	0,5	2,9	

*One Way Anova. α Statistically significantly difference compared with the ANK 2-week group. P: Phosphor, Ca: Calcium, ALP: Alcaline phosphatase, ANK: Ankaferd.

Discussion

Goker et al. (1) reported that the hemostatic network created by ABS is related to the functions performed by proteins in the blood and red blood cells. The mechanism of action realized by ABS also includes the protein network that enables the formation of focal points for erythrocyte aggregation. They report that the blood cells in the erythrocytes and thrombocytes gather together and form a mass and network formation takes place. The use of ABS prevents individual coagulation factors and reportedly provides tissue oxygenation and a physiological hemostatic process. The fact that ABS consists of active plant extracts is an advantage that enables this unique mechanism (25).

Studies have reported that ABS has positive effects on new bone formation, antibacterial activity, cytotoxicity, and blood clot formation during the wound healing process (18, 26). In a study, alveolar osteocyte evaluation was made of ABS applied to the mandibular third molar tooth socket. According to the results of this randomized clinical trial, using ABS to the sockets for hemostasis after surgery on the affected mandibular third molar does not increase the incidence of alveolar osteitis. This appears to favor the surgical procedure and possibly reduce the number of postoperative visits by the patient. ABS application to sockets for hemostasis has been reported to increase postoperative pain, but this occurs within the first two days after surgery only. No other discomfort was reported as a result of ABS use in these patients. It further appears that ABS can be safely applied as an agent in hemostasis after mandibular third molar surgery (27).

ABS is a hemostatic agent containing plant extracts from Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum, and Urtica dioica. All of these plant extracts have been shown to have effects on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics, and mediators. In addition, ABS can be used as a hemostatic agent to control bleeding after tooth extraction, periodontal and other surgery, and subgingival curettage procedures (27-29).

Studies on ABS have also indicated its suggested positive effects on new bone formation and soft tissue wound healing (27, 29). In a study, augmentation was applied on the sinus floor using a bone graft, and the effects of ABS and the bone graft on bone healing were evaluated (30). No evidence was found that new bone formation occurred in the first week. However, while an increase in new bone formation was observed in all groups in the following weeks, the highest increase was detected in the ABS + heterograft group. In a study conducted by Tanik et al. (31), the histological scores of new bone formation in rats on the 28th day were compared between ABS and β-TCP + ABS groups. There was no statistically significant difference found between them. However, it was reported that it-new bone formation was significantly higher between the control group and β-TCP + ABS (31).

The histopathological results of the study revealed that more than 60 percent of those treated with ABS after a tibial defect occurred in rats did not suffer inflammation. This is thought to be related to the anti-inflammatory activity of some components of the hemostatic agent. Although fibrosis formation was statistically similar in both groups, the group treated with ABS had a lower rate of fibrosis than the untreated control group. More dense new bone formation and less necrosis were reported in defects treated with ABS, possibly as a result of an increase in healing speed and a decrease in inflammation associated with the antioxidant activity of ABS components (18, 32).

In our study, the value of BIC in rats with dental implants was evaluated. Biomechanical and biochemical tests were performed in the second and fourth weeks. The analyses also compared the control group and the ABS group in the second week, finding that the value of BIC was higher in the control group, but no statistically significant difference was observed. In the fourth week, although the value of BIC was higher in the ABS applied group, no significant difference was found. In the comparison between the ABS group in the second week and the fourth week, the BIC value was found to be higher in the fourth week ABS group, the difference being statistically significant ($p = 0.007$). In addition, Ca and P values in the fourth week were found to be significantly lower in the ABS group than in the control group.

Conclusions

It may thus be concluded that the use of ABS during surgery is of benefit to both the patient and the physician, thanks to its ability to control bleeding. Moreover, its use has no long-term negative effects. In dental implant applications, it is believed to have only a limited effect on osseointegration. More studies are needed to understand better the advantages of using ABS in such procedures.

Ethical Approval: Ethics committee approval was received for this study from Fırat University, Animal Experiments Local Ethics Committee in accordance with the World Medical Association Declaration of Helsinki, with the approval number: 2020-396483).

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – E.C.Ö.; Design – E.C.Ö., M.G., A.T.; Supervision – T.T.Y.; Materials – M.Ö., A.B.; Data Collection and/or Processing – E.C.Ö., H.E.Ö.; Analysis and/or Interpretation – H.E.Ö., S.D.; Literature Review – M.G., A.T., T.T.Y.; Writer – E.C.Ö.; Critical Review –E.C.Ö., T.T.Y., S.D.

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References

1. Goker H, Haznedaroglu IC, Ercetin S, Kirazli S, Akman U, Ozturk Y et al. Haemostatic actions of the folkloric medicinal plant extract ankaferd blood stopper. J. Int. Med. Res. 2008;36(1):163-70. (Crossref)
2. 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):329-36.
3. 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. (Crossref)
4. 4Hasgul R, Uysal S, Haltas H, Akyol S, Yuksel Y, Gurel A, et al. Protective effects of ankaferd blood stopper on aspirin-induced oxidative mucosal damage in a rat model of gastric injury. Toxicol. Ind. Health 2012;30(10):885-95. (Crossref)
5. Koçak E, E Akbal, Taş A, Köklü S, Karaca G, Can M, et al. Anti-inflammatory efficiency of Ankaferd blood stopper in experimental distal colitis model. Saudi J. Gastroenterol. 2013;19 (3) 126-30. (Crossref)
6. Kuru S, Kismet K, Bag YM, Barlas AM, Senes M, Durak M, et al. Does the application of Ankaferd Blood Stopper rectally have positive effects on the healing of colorectal anastomosis and prevention of anastomotic leakage? An experimental study. Biomed. Pharmacother 2017;96:968-73. (Crossref)
7. Tasdelen FN, Tanriverdi CY, Coban AY, Ozatli D, Tanyel E, Durupinar B, et al. Antimicrobial activity of plant extract Ankaferd Blood Stopper. Fitoterapia. 2009;80 (1):48-50. (Crossref)
8. Bilgili H, Kosar A, Kurt M, Onal IK, Goker H, Captug O, et al. Hemostatic efficacy of Ankaferd Blood Stopper in a swine bleeding model. Med. Princ. Pract. 2009;18(3):165-69. (Crossref)
9. Uğur A, Saraç N, Çankal DA, Özle M. The antioxidant and antimutagenic activities of Ankaferd blood stopper a natural hemostatic agent used in dentistry. Turk. J. Med. Sci. 2016;46(3):657-63. (Crossref)
10. Sen V, Uluca U, Ece A, Güneş A, Zeytun H, Arslan S, et al. Role of Ankaferd on bacterial translocation and inflammatory response in an experimental rat model of intestinal obstruction. Int. J. Clin. Exp. Med. 2014;7(9):2677-86.
11. Akkoc N, Akcelik M, Haznedaroglu IC. In vitro anti-bacterial activities of Ankaferd medicinal plant extract. Turk. J. Med. Sci. 2009;29 (2);410-15.
12. Buyuktiryaki M, Tayman C, Koyuncu I, Cakir U, Turkmenoglu TT, Cakir E, et al. Therapeutic and preventative effects of ankaferd blood stopper in an experimental necrotizing enterocolitis model. Biomedicine & Pharmacotherapy 2019;110:105-10. (Crossref)
13. Barka EA, Gognies S, Nowak J, Audran JC, Belarbi A. Inhibitory effect of endophyte bacteria on Botrytis cinerea and its influence to promote the grapevine growth. Biol Control. 2002;24:135-42. (Crossref)
14. Yamakoshi J, Kataoka S, Koga T, Ariga T. Proanthocyanidinrich extract from grape seeds attenuates the development of aortic atherosclerosis in cholesterol-fed rabbits. Atherosclerosis.1999;142:139-49. (Crossref)
15. Zhao J, Wang J, Chen Y, Agarwal R. Anti-tumor promoting activity of a polyphenolic fraction isolated from grape seeds in the mouse skin two-stage initiation-promotion protocol and identification of procyanidin B5-3'-gallate as the most effective antioxidant constituent. Carcinogenesis. 1999;20:1737-45. (Crossref)
16. Matsuda H, Ando S, Kato T, Morikawa T, Yoshikawa M. Inhibitors from the rhizomes of Alpinia officinarum on production of nitric oxide in lipopolysaccharide-activated macrophages and the structural requirements of diarylheptanoids for the activity. Bioorg Med Chem. 2006;14:138-42. (Crossref)
17. Testai L, Chericoni S, Calderone V, Nencioni G, Nieri P, Morelli I, et al. Cardiovascular effects of Urtica dioica L. (Urticaceae) roots extracts: in vitro and in vivo pharmacological studies. J Ethnopharmacol.2002;81:105-9. (Crossref)
18. İşler SC, Demircan S, Çakarer S, Çebi Z, Keskin C, Soluk M, et al. Effects of folk medicinal plant extract Ankaferd Blood Stopper® on early bone healing. Journal of Applied Oral Science 2010;18(4):409-14. (Crossref)
19. Albrektsson T, Dahl E, Enbom L, Engevall S, Engquist B, Eriksson AR, et al. Osseointegrated oral implants. A swedish multicenter study of 8139 consecutively inserted nobelpharma implants. J. Periodontol. 1988;59(5):287-96. (Crossref)
20. Haiat G, Wang HL, Brunski JB. Effects of biomechanical properties of the bone-implant interface on dental implant stability: From in silico approaches to the patient's mouth. Annu. Rev. Biomed. Eng. 2014;16: 187-213. (Crossref)
21. Franchi M, Bacchelli B, Giavaresi G, De Pasquale V, Martini D, Fini M, et al. Influence of different implant surfaces on peri-implant osteogenesis: Histomorphometric analysis in sheep. J. Periodont. 2007;78:879-88. (Crossref)
22. Mathieu V, Vayron R, Richard G, Lambert G, Naili S, Meningaud JP, et al. Biomechanical determinants of the stability of dental implants: Influence of the bone-implant interface properties. J. Biomech. 2014;(47):3-13. (Crossref)
23. Javed F, Romanos GE. The role of primary stability for successful immediate loading of dental implants. A literature review. J. Dent. 2010;(38):612-20. (Crossref)
24. 24.Vayron R, Nguyen VH, Lecuelle B, Albini Lomami H, Meningaud JP, Bosc R, et al. Comparison of resonance frequency analysis and of quantitative ultrasound to assess dental implant osseointegration. Sensors 2018;18(5):1397. (Crossref)
25. Gao J, Hooker BS, Anderson DB. Expression of functional human coagulation factor XIII A-domain in plant cell

suspensions and whole plants. Protein Expr Purif. 2004;37:89-96. (Crossref)
26. Mihmanli A, Ulker Z, Alpsoy L, Ezirganli S. Evaluation of cytotoxicity of a new hemostatic agent Ankaferd Blood Stopper® using different assays. Hum Exp Toxicol 2012;31:780 7. (Crossref)
27. Tek M, Akkas I, Toptas O, Ozan F, Sener I, Bereket C. (). Effects of the topical hemostatic agent Ankaferd Blood Stopper on the incidence of alveolar osteitis after surgical removal of an impacted mandibular third molar. Nigerian journal of clinical practice, 2014;17(1):75-80. (Crossref)
28. Şimşek HO, Tüzüm MŞ, Baykul T, Gürer İE, Başsorgun Cİ. Experimental investigation of the effects of a blood stopper agent (Ankaferd Blood Stopper) on bone surfaces. Turk J Hematol 2013; 30: 177-83. (Crossref)
29. Erçetin S, Haznedaroğlu IC, Kurt M, Önal IK, Aktaş A, Kurt ÖK, et al. Safety and efficacy of Ankaferd Blood Stopper in dental surgery. Int J Hematol 2010; 20: 1-5. (Crossref)
30. Cakir M, Karaca IR, Firat A, Kaymaz F, Bozkaya S. Experimental evaluation of the effects of Ankaferd Blood Stopper and collagenated heterologous bone graft on bone healing in sinus floor augmentation. Int J Oral Maxillofac Implants 2015;30: 279-85. (Crossref)
31. Tanik A, Doğru AG, Akpolat V, Kaya FA, Saribaş E, Gül M, et al. Investigation of the effect of combined use of alloplastic-based tricalcium phosphate bone graft and antihemorrhagic plant extract (ABS) on bone regeneration in surgically induced bone defects in nondiabetic rats: an experimental animal study. Turkish Journal of Medical Sciences 2018;48(6):1302-14. (Crossref)
32. Gül M, Günay A, Tanik A. An evaluation of the effects of caffeic acid phenethyl ester and Ankaferd blood stopper on secondary wound healing of oral mucosal tissue. Turkish Journal of Medical Sciences 2020;50(1):248-57. (Crossref)