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Pharmacobiology of topical Ankaferd hemostat in neoplastic disorders

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ABSTRACT

Ankaferd Hemostat (ABS) is a hemostatic agent of plant-extract acting on red blood cells used for achieving hemostasis. ABS has anti-inflammatory, anti-microbial, anti-fungal, anti-oxidative and anti-neoplastic effects. Cancer treatment is a challenging clinical condition that can lead to numerous clinical complications of different severity. Antineoplastic features of ABS had been depicted in many solid and hematological tumors. Supportive treatment of cancer is very important to decrease the mortality and morbidity of the cancer patients. ABS prevents and treats chemotherapy associated mucositis with its unique effects on the blood cells, endothelium, angiogenesis, cellular regeneration, wound healing and vascular dynamics. Those features of ABS bring it to be also beneficial for necrotizing enterocolitis as well. Besides its supportive and preventative roles in the cancer patients, ABS can also be potentially utilized as a chemoembolization agent within intratumoral treatment modality. The aim of this review is to summarize current pharmacobiology of topical ABS in neoplastic disorders.

Keywords: Ankaferd hemostat, neoplastic disorders, pharmacobiology

Ankaferd Hemostat (ABS) is a plant-based hemostatic agent which is mainly used for achieving hemostasis. ABS has critical effects on angiogenesis, endothelium, hematopoietic cells, cellular reproduction, wound healing and vascular dynamics [1]. Moreover, ABS also has anti-inflammatory, anti-microbial, anti-fungal, anti-oxidative and anti-neoplastic roles [2-5]. Chemotherapy could lead to many complications, one of which is oral mucositis leading to morbidity [6]. Oral mucositis is defined as the ulcerative lesions in the mucosa of the patients who were given chemotherapy; mucositis is frequently encountered as a complication of anti-cancer chemoradiotherapy. Oral mucositis is seen in 40-80% of patients who are given chemotherapy [7]. ABS is a useful wound-healing agent in the treatment of chemotherapy associated severe oral mucositis in patients with hematological malignancies [8]. ABS had been administered to the patients with severe mucositis and with a median healing time was 6.6 days. Thus, ABS is quite effective in the treatment of cancer-related mucositis [8]. Gastrointestinal tract cancer bleedings are another major problem in cancer patients. The mortality rate is approximately 5-10% for peptic ulcer hemorrhage and 15-20% for variceal bleedings [9]. Endoscopic treatment decreases the rates of re-bleeding, surgery, and mortality in active bleeding; however early recurrence is still approximately 20% even with active early he-

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mostatic measures. ABS is also effective in the controlling of the gastrointestinal tracts bleedings in the cancer patients. The endoscopic use of ABS for bleeding gastrointestinal tumors is associated with immediate hemostatic response, easy application and minimum side effects [10]. ABS can be used as a treatment agent in peptic ulcer disease, radiation colitis, sphincterotomy bleeding, Mallory-Weiss syndrome, post-polypectomy bleeding, Dieulafoy's lesion, solitary rectal ulcer and other neoplastic gastrointestinal bleedings [9]. The aim of this review is to summarize the pharmacobiology of topical ankaferd hemostat in neoplastic disorders.

MOLECULAR BASIS OF TOPICAL ANKAFERD HEMOSTAT

The antineoplastic features of topical ABS depend on the unique transcriptomics, proteomics, metabolomics features of ABS. ABS stimulates the cellular factors that have important role in the regulate the cell cycle machinery, pro-apoptotic pathways, angiogenesis, signal transduction and other metabolic pathways. Some of those factors are nuclear factor-1 (NF-1), interferon-(IFN-) stimulated response element (ISRE), protein-2, androgen receptor, cyclic AMP response element binding protein, SMAD2/3,cyclic AMP response element or stimulating transcription factor-1, Myc-Max, E2F1-5, peroxisome proliferator-activated receptor, E2F6, EGR, protein 53, and Yin-Yang (YY1) [11] . ABS may prevent oxidative damage on DNA. The effect of ABS on superoxide dismutase, 8-hydroxy-2′-deoxyguanosine, myeloperoxidase levels over pleural adhesions in rabbits with pulmonary parenchymal damage was demonstrated [12]. The preventive effect of ABS on oxidative DNA damage was confirmed by the study.

ABS has also antioxidant and antimutagenic effects. Those effects of ABS had been tested with two different methods [13]. β-carotene-linoleic acid tests and 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging were used to analyze the antioxidant features of ABS. The Ames Salmonella/microsome mutagenicity test with the bacterial mutant strains Salmonella typhimurium TA98 and TA100 was used to analyze the antimutagenic features of ABS. The antioxidant and antimutagenic effects of ABS was demonstrated with these test in a previous study [13].

The main mechanism behind the antineoplastic effects of ABS is apoptosis. Protease-activated receptor 1 (PAR1) is a part of proteinase-activated receptor (PARs) family which is found in seven transmembrane G-protein-coupled receptors group [14]. Increased PAR1 alters intra-cellular signaling by coupling G proteins. PAR1 and EPCR expression in K-562 and Jurkat cells is controlled by ABS. The effect of PAR1 and p21 in pro-apoptotic pathways was demonstrated in Jurkat cells. ABS controls PAR1- and p53-independent p21 involvement in pro-apoptosis in leukemia cells [5].

ABS has also various pleiotropic features, like antineoplastic and antimicrobial roles and tissue supportive features. ABS increases the expression of CREBZF leading to activation of the antineoplastic protein p53 [15]. Moreover, HNF-4a is a component of ABS and has antineoplastic features [16]. ME-1 is also a component of ABS which has significant effects of cancer metabolism [17]. ABS increases the UCHL1 and RPL5 which are tumor suppressor proteins [18]. The transcription factors of TRE/AP1, E2F6, AP2, AR, CREB, CREATF1, E2F1-5, EGR, ISRE, HNF1, MycMax, NF1, NF-κB, p53, PPAR, GATA, SMAD2/3, SP1 and YY1 which were involved in different biological mechanisms, such as hemostasis, infection, cellular growth, and inflammation; were stimulated by ABS [19]. Likewise, ABS increases several transcription factors that controls cell growth scuh as AP2, AR, SMAD2/3, CRE-ATF1, CREB, E2F1-5, ISRE, E2F6, EGR, Myc-Max, NF1, NF-κB, TRE/AP1, p53, PPAR, SP1, and YY1 [19].

ANKAFERD HEMOSTAT IN THE CANCER MANAGEMENT

ABS has anti-neoplastic and anti-proliferative effects on solid tumors as well as hematological tumors (Table 1). ABS has antineoplastic features on the lymphoid cells [20]. ABS showed anti-proliferative effects of chronic lymphoid leukemia cell lines at higher doses (> 0.5 µg/mL); whereas ABS had been found to increase of cellular differentiation at lower doses (< 0.5 µg/mL) (Fig. 1) [20]. The anti-proliferative effects

of ABS on myeloma cell lines were also demonstrated [21]. ABS exerts anti-cancer effects of melanoma cells via reactive oxygen generating (ROS), genotoxic, cytotoxic, pro-apoptotic mechanisms [22]. Anti-tumoral features of ABS on SaO_2 osteosarcoma cell lines were shown by previous studies [23]. Human CaCo-2 colon cancer cells lost cellular proliferative features with the administration of ABS [24]. ABS exert its antineoplastic effects on bladder cancer cells. A decrease in the viability of bladder cancer cells decrease was detected with ABS [25]. ABS induces necroptosis in breast cell cultures [26]. HEPG2 hepatocellular carcinoma cells were inhibited when the cells were exposed to ABS [27]. ABS may have a role in the treatment of solid and hematological cancer cells. Future human studies are needed to clarify the clinical efficacy of ABS in the cancer treatment.

ANKAFERD HEMOSTAT IN CANCER SUPPORTIVE TREATMENT

Cancer treatment could lead to many complications. The conventional cytotoxic chemotherapy agents could exert damage to normal tissue cells. ABS may be helpful in reducing the cancer related complication by its chemopreventive, antioxidant, and supportive features. Oral mucositis is a major chemotherapy associated problem in cancer patients. It affects 40-80% of cancer patients. The role of ABS in the treatment of

Table 1. Anti-neoplastic features of Ankaferd Hemostat

Authors	Cancer Type	Study Summary
Akalın *et al.* [20]	Lymphoid neoplastic cells	ABS administrated chronic lymphocytic leukemia cells stopped proliferation. Transformation of lymphocytic leukemia cells to the blastic aggressive lymphoid forms was inhibited by ABS.
Avcu *et al.* [21]	Multiple myeloma cells	ABS exerts anti-neoplastic effect on myeloma cells which was detected by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide-dye reduction assay in Balb/c mice
Turk *et al.* [42]	Melanoma cells	A decrease in cell viability was observed after ABS administration to SK-MEL-10 (CVCL_6020), SK-MEL-9 (CVCL_ U934), A2058 (ATCC® CRL-11147™), and MeWo (ATCC HTB-65™) melanoma cell lines.
Kocyigit *et al.* [22]	Melanoma cells	ABS stimulate DNA injury, apoptosis, and ROS levels in melanoma cells.
Goker *et al.* [23]	Osteosarcoma cells	Following the ABS administration, a dose-dependent reduction was observed in cell proliferation and survival of Saos-2 cells.
Goker *et al.* [24]	Colon cancer cells	ABS exerts inhibitory effects on cellular reproduction of CaCo-2 cells and CaCo-2 cells lose their viabilities after ABS exposure.
Nenni *et al.* [43]	Colon cancer cells	ABS effects the glucose, fatty acids, and protein metabolism and cell cycle machinery. ABS increases cancer suppressor proteins such as carboxyl-terminal hydrolase 1, 60S ribosomal protein L5, Tumor protein D52-like2, karyopherin alpha 2, and protein deglycase DJ-1 in Caco-2 cells.
Sarı *et al.* [25]	Bladder cancer cells	ABS induces apoptosis and decreases cell viability of bladder cancer cells. Necroptosis was observed following ABS administration to the bladder cancer cells.
Fidan *et al.* [26]	Breast cancer cells	ABS decreases the cell viability ratio in breast cancer cells. Necroptosis and apoptosis were detected in breast cell cultures. The cytotoxic role of ABS on breast cancer cells were observed.
Nenni *et al.* [27]	Hepatocellular carcinoma	ABS inhibited cell viability of HEPG2 hepatocellular carcinoma cells

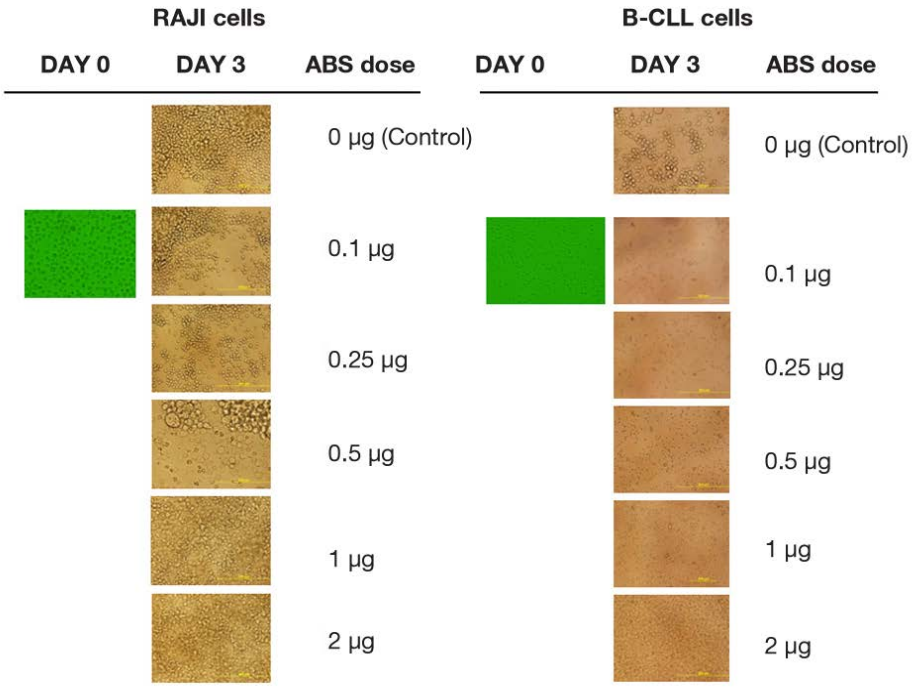

Fig. 1. RAJI (Human Burkitt's lymphoma cell line) and BCLL (B-chronic lymphoid leukemia) cells. Ankaferd treated B-CLL cells (at doses 0.5, 1 and 2 µg/mL) ceased to inflate and more than 50% of tumor cells were died compared to 0.1 and 0.25 µg/mL doses. ABS exerts anti-neoplastic effects at higher doses (> 0.5 µg/mL) whereas it stimulates the cellular differentiation at lower doses (< 0.5 µg/mL).
Reproduced from: Akalın, Ibrahim, et al. Acute in vitro effects of ABS (Ankaferd Hemostat) on the lymphoid neoplastic cells (B-CLL and RAJI tumor cell lines). Int J Hematol Oncol 2014;24:253-9, doi: 10.4999/uhod.13026.

chemotherapy-associated oral mucositis in the patients with hematological malignancies was clarified previously. ABS is efficient in the treatment of oral mucositis due to anti-cancer agents in childhood cancers [29]. Moreover, ABS is beneficial in the chemotherapy-associated oral mucositis in adult patients also [8]. ABS may decrease epithelial dysplasia. ABS has been shown to reduce the 7,12-dimethylbenz[a]anthracene associated oral epithelial dysplasia [28]. Cancer patients may also suffer from necrotizing enterocolitis which increases morbidity and mortality of the cancer patients. Inflammation, prematurity, oxidative stress may induce the development of necrotizing enterocolitis. ABS has preventive effect on intestinal damage in necrotizing enterocolitis with its anti-inflammatory, antioxidant, and antiapoptotic features on intestinal tissue cells [30]. On the other hand, hepatocyte cell is also positively affected with the antioxidative and hepatoprotective features of ABS since it has high levels of vitamin E and other trace elements such as magnesium, vitamin B12, vitamin D, vitamin B9, vitamin A, calcium [31-35].

ANKAFERD HEMOSTAT IN THE INTRATUMORAL TREATMENT

Intratumoral treatment of cancers is preferred in selected patients because of the minimal systemic toxicity with this method. Transarterial chemoembolization (TACE) aims to localize chemotherapeutic agents specially to the cancer site [36]. Conventionally, ethanol and lipiodol embolization is the preferred method for TACE in order to ablate the tumor. Although TACE is safe method that directs the tumor site, it has also several complications [37]. Local complications in TACE method is generally expected but also systemic complications such as tumor lysis syndrome or metabolic problems may develop [38]. ABS has a potential in intratumoral treatment. The antineoplastic features of ABS on myeloma cell line were analyzed by intraperitoneal preterm injection in vitro in Balb/c mice [21]. Moreover, ABS was given as an embolizer in splenic and renal arteries for medical nephrectomy and splenectomy in experimental animal models [39, 40]. In a previous study, ABS depicted success in the he-

patic embolization when compared to the alcohol [41]. According to those data, ABS may be potentially useful for intratumoral treatment since it has unique antineoplastic features on several cancers. ABS may be a superior chemoembolization agent than ethanol and lipiodol which are used frequently in TACE method. There is a need for future clinical studies that will clarify the role of ABS in intratumoral treatment as an embolizing agent.

CONCLUSION AND PERSPECTIVES

Cancer treatment is a challenging clinical condition which can lead to several serious clinical complications. ABS is shown to possess antineoplastic features along with other anti-inflammatory, anti-microbial, anti-fungal, anti-oxidative effects. Anti-neoplastic features of ABS have been proven in many solid and hematological tumors. Supportive treatment in cancer is very important to minimize the morbidity and mortality of patients. ABS prevents and treats chemotherapy associated mucositis with its unique effects on endothelium, blood cells, angiogenesis, cellular reproduction, vascular dynamics and wound healing. These features of ABS bring it to be also beneficial for necrotizing enterocolitis. Besides its supportive and preventative roles in cancer patients, ABS can also be utilized as a chemoembolization agent in intratumoral treatment modality.

Authors' Contribution

Study Conception: ÜYM, İCH; Study Design: ÜYM, İCH; Supervision: ÜYM, İCH; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ÜYM; Statistical Analysis and/or Data Interpretation: ÜYM, İCH; Literature Review: ÜYM; Manuscript Preparation: ÜYM, İCH and Critical Review: İCH.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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