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Immunohistochemical Alterations of Syndecan-1 in Sheep Liver with Cystic Echinococcosis

Nihat YUMUŞAK[1,a,*]

[1]Department of Pathology, Faculty of Veterinary Medicine, University of Harran, Sanliurfa, Turkey.

[a]ORCİD: 0000-0002-9299-2902

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***Correspondence:** Nihat YUMUŞAK
Department of Pathology, Faculty of Veterinary Medicine, University of Harran, Sanliurfa, Turkey.e-mail: nihatyumusak@harran.edu.tr

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Abstract: Cystic echinococcosis is formed by the larval forms of *Echinococcus granulosus*, causes health problems in humans and different species of animals worldwide. There is still limited information about the pathophysiological response to cystic echinococcosis in the liver. Syndecan-1 (Sdc1) is a cell surface proteoglycan of the liver. It has a crucial role in the pathophysiology of various liver diseases. This study aimed to investigate the immunohistochemical expression of Sdc1 in the liver with cystic echinococcosis in sheep. A total number of 51 liver tissue samples with cystic echinococcosis and ten healthy livers were examined. The tissue samples were stained with hematoxylin-eosin (HE) for histopathological examinations. Sdc1 was determined in the same liver tissues by immunohistochemistry. Infected liver tissues mainly showed severe inflammatory reactions, congestion, diffuse degeneration, and necrosis of hepatocytes around the cysts. The results indicated severe Sdc1-positive staining in hepatocytes around the cysts. Liver tissues of the control group showed relatively mild immunopositive reactions. This study determined that the Sdc1 significantly increased in the sheep livers with cystic echinococcosis infection.
Keywords: *Echinococcosis, Liver, Sheep, Syndecan-1.*

Kistik Ekinokokkozlu Koyun Karaciğerlerinde Sindekan-1'in İmmünohistokimyasal Değişiklikleri

Özet: Karaciğer kistik ekinokokkozisi *Echinococcus granulosus*'un larval formları tarafından oluşturulur. Dünya çapında insanlarda ve farklı hayvan türlerinde sağlık problemlerine neden olur. Kistik ekinokokkozisin patofizyolojisi hakkında hala sınırlı bilgi mevcuttur. Sindekan-1 (Sdc1) karaciğer hücre yüzey proteoglikanıdır. Farklı karaciğer hastalıklarının patofizyolojisinde önemli rolleri vardır. Bu çalışmada kistik ekinokokkozisli koyun karaciğerlerinde Sdc1 salınımındaki değişiklerin immünohistokimyasal olarak belirlenmesi amaçlanmıştır. Toplam 51 hidatid kistli karaciğer dokusu ve 10 sağlıklı karaciğer dokusu incelendi. Histopatolojik incelemeler amacıyla doku örnekleri hematoksilen-eosin (HE) ile boyandı. Aynı karaciğer dokularında Sdc1 immünohistokimyasal olarak belirlendi. Enfekte karaciğer dokularında başlıca şiddetli yangısal reaksiyon, konjesyon ve kist duvarları çevresindeki hepatositlerde yaygın dejenerasyon ve nekrozlar görüldü. Kist duvarları çevresindeki hepatositlerde şiddetli Sdc1 immünpozitif reaksiyon belirlendi. Kontrol grubuna ait karaciğer dokuları ise hafif immünopozitif reaksiyon gösterdi. Bu çalışmada ekinokokkozisli koyun karaciğer dokularında Sdc1 salınımın belirgin şekilde arttığı tespit edildi.
Anahtar Kelimeler: *Ekinokokkozis, Karaciğer, Koyun, Sindekan-1.*

Introduction

Cystic echinococcosis (hydatidosis) is a zoonotic parasitic disease caused by the larval forms of *Echinococcus granulosus.* It causes human and animal health problems in many regions of the world (McManus et al., 2003). In addition, it causes significant economic losses in meat, milk, fleece quality, and fertility (Budke, 2006; Widdicombe et al., 2022). Canids play a role in the transmission and spread of the infection. The infection has a high incidence in sheep breeding areas where dogs are common (Craig et al., 2007; Eckert et al., 2004). The cyst formation depends on the host's innate immunologic activity and the parasite's immunosuppression strategies (Cabrera et al., 1995; Rogan and Craig, 1997; Al Malki and Ahmed, 2022). It reacts to the parasite through free radicals that cause oxidative stress in the host. Free radicals cause oxidative damage to the liver when produced in excess (Derda et al., 2004; Kilic et al., 2010; Mert et al., 2019; Saleh, 2008). The main microscopic findings are degeneration and necrosis of hepatocytes, calcifications, and inflammation around the cyst in the infected liver (Heidarpour et al., 2012; Shoulah et al., 2023).

Sdc1 is the major cell surface heparan sulfate proteoglycan of the liver. It is predominantly expressed on the sinusoidal surface of hepatocytes. It provides cell-cell and cell-matrix connections as a regulator of cell behavior against various effectors (Afratis et al., 2017; Kim et al., 1994; Teng et al., 2012). They have many different functions, such as cellular adhesion, migration, and proliferation, with coreceptor in chemokines. The shedding of Sdc1 is triggered by tissue injury, inflammatory conditions, and mediators (Gopal et al., 2021; Teng et al., 2012). Sdc1 consists of a transmembrane, an intracellular, and an extracellular domain. In particular, the extracellular domain of this protein interacts with different ligands and promotes pathogenesis by facilitating pathogen attachment and invasion of cells (Nam et al. 2017; Palaiologou et al. 2014). Recent studies have shown that Sdc1 has a crucial role in the pathophysiology of various liver dysfunctions (Regos et al. 2020; Reszegi et al. 2022). Data have indicated that liver cells Sdc1 shedding in mice is activated during Schistosoma infection (Jacobs et al., 1999). Another study showed that in mice brains with infected toxoplasmosis, the brain cells overexpressed Sdc1 (Etewa et al., 2021). Beiting et al. (2006) observed that in muscle infection by Trichinella spiralis, the infected muscle cells produce Sdc1. A recent study demonstrated that Sdc1 overexpressed in sheep liver with natural fluke infection (Yumusak and Filikci., 2022). However, Bhanot and Nussenzweig (2002) concluded that Sdc1 does not play a role in experimental liver infection by Plasmodium sporozoites. On the other hand, Regos et al. (2020) found that Sdc1 was markedly expressed in cirrhotic liver. Matsumoto et al. (1997) observed a diffuse immunoreaction in hepatocellular carcinoma.

To our knowledge, no study has investigated before a possible relationship between Sdc1 and liver infected with *E. granulosus*. In this study, Sdc1 were investigated whether there is a significant difference between healthy and infected liver with cystic echinococcosis by immunohistochemistry.

Material and Method

Sample collection: A total of 51 sheep liver samples with hydatid cysts were used. And ten uninfected liver tissues taken from the slaughterhouse were examined as a control. The tissue samples were fixed in formaldehyde (pH 7.0) through immunohistochemical and histopathological studies. All stages of the study were carried out with the approval of the National Ethics Committee and under the supervision of the Local Ethics Commission (App. Number: 2023/002-01.17).

Gross and Histopathological Method: The affected livers were investigated for gross changes associated with the cysts. After routine pathologic tissue procedures, five micron- thick sections were stained with hematoxylin and eosin (HE). All slides were examined at x40-x100 objective magnifications under a light microscope (Olympus BX53-DIC; Tokyo, Japan).

Immunohistochemical Staining Method: Five-micrometer-thick sections were carried out on standard streptavidin-biotin peroxidase complex (ABC) technique protocol (Zymed, Histostain Plus Kit, California, USA) under 37°C and in humidity cabinets. The section was pre-treated with sodium citrate buffer (pH 6.0) using heat-mediated antigen retrieval for 20 min. Protein blocking was performed by incubating tissue sections with 5% normal bovine serum for 30 min before the primary antibody. The sections were incubated with Syndecan-1 (DL-101, sc-12765, Santa Cruz, USA), diluted at 1:50, overnight at 4°C. Biotinylated secondary antibody (TP-125-BN, Lab Vision, USA), was used to detect the primary antibody for 30 minutes, and diaminobenzidine (DAB, TA-125-HDS; Lab Vision Dako/Denmark) was used as the chromogen. The section was stained with hematoxylin for counterstain. The slides were semi-quantitatively scored according to the intensity of positive staining (-: no immunoreactivity; +: limited immunoreactivity; ++: strong immunoreactivity) (Jacobs et al., 1999).

Results

Gross Examination: The grossly multiple irregular spherical cysts were seen as superficial and fully deep embedded in the liver. Varying sizes of cysts were single or multiple. The cysts were generally soft and clear fluid-filled, ranging in size from 3 to 12 cm. Some cysts were firm, calcified, and hard to cut. The cut section of cysts was characterized by a white cyst membrane consisting of fibrous connective tissue.

Histopathological Findings: Liver tissues taken as control showed typical structures. The cyst wall had a thick, eosinophilic outer laminated membrane and a germinal epithelial layer (Figure 1a) in the infected liver. The cysts

were surrounded by the proliferating fibrous tissue, mononuclear cells, and eosinophils. In some chronic cysts were caseous or calcified. Diffuse degeneration and necrosis were observed in the hepatic lobules around the cyst structures. Hepatic parenchyma was congested and showed multiple small hemorrhages. Severe, multifocal inflammatory cell reactions were seen in nearby the cyst and portal areas, mostly of lymphocytes, macrophages, plasma cells, multinucleated giant cells, and a few eosinophils (Figure 1b). In addition, sinusoidal spaces and central veins were congested. Multifocally, proliferating fibrous tissue replaced adjacent hepatic parenchyma. The adjacent hepatocytes showed hypereosinophilic cytoplasm and necrosis. Vacuolar degenerative changes in hepatocytes were commonly seen in these areas. Pyknotic nuclei were detected in some hepatocytes. An increase in Kupffer cells was also observed in these areas. In addition, degeneration and hyperplasia were observed in the biliary epithelium, along with a few inflammatory cells.

Immunohistochemical Findings: Sdc1 mildly immunopositivity was detected in control liver samples (Figure 1c). In the livers of sheep with hydatid cysts, severe Sdc1- positive staining was seen, especially in the hepatocytes around the cyst wall (Figure 1d). It was determined that hepatocytes in areas of inflammation gave a severe Sdc1 immunoreaction. Hepatocytes in areas of degeneration and necrosis were found to have strongly positive staining. In addition, fibrous tissue cells around the cyst wall were mildly positive. However, immunopositivity was not detected in the cyst capsule and bile ducts.

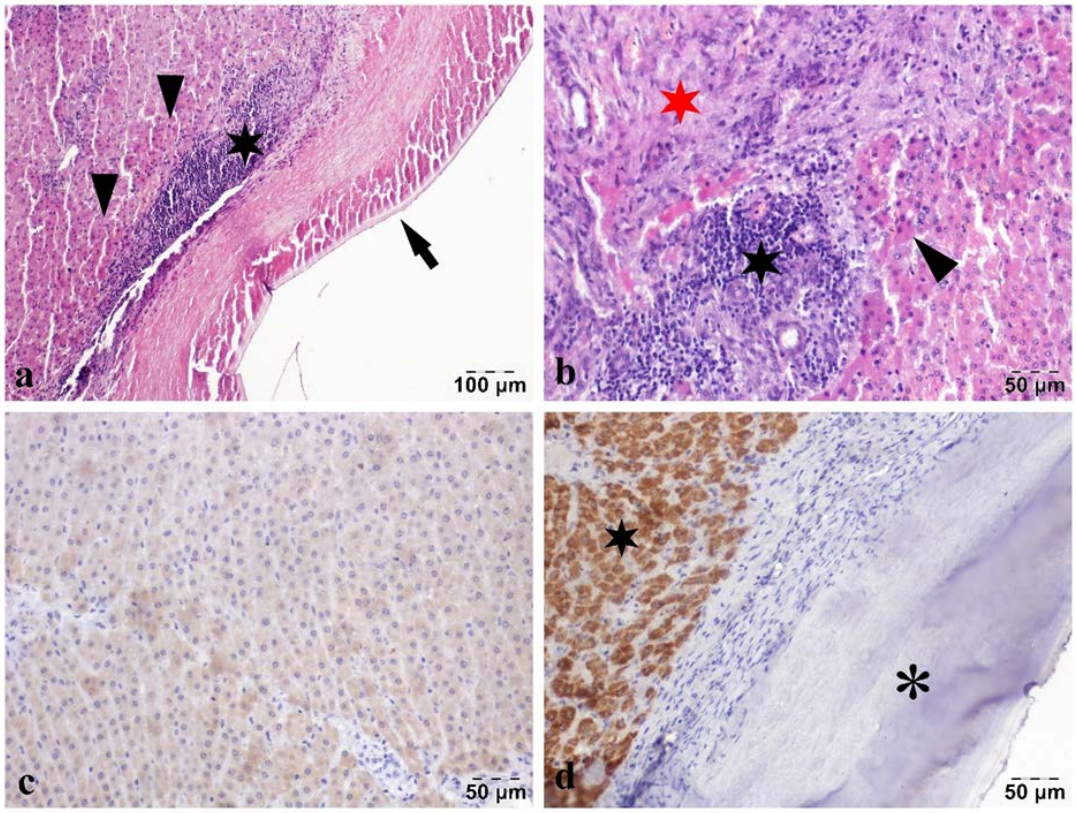

Figure 1. a) Severe inflammation around of cyst wall (star), degenerated hepatocytes (arrow heads) and cyst wall (arrow), HE. b) Severe inflammation (black star), fibrosis (red star) and degenerated hepatocytes (arrow head), HE. c) Mild Sdc1 immunpositive cells in control liver, DAB. d) Severe immunoreaction in infected liver cells (star) around of cyst wall (asterisk), DAB.

Discussion and Conclusion

In the present study, our main findings were *E. granulosus* caused severe hemorrhage, inflammatory cell infiltration, cellular degeneration, necrosis, fibrosis and, biliary hyperplasia, leading to significant liver damage as in previous studies. In addition, markedly increased levels of Sdc1 immunoexpression were determined in the infected liver, especially adjacent hepatocytes around the cysts. According to this limited study, overexpression of Sdc1 may play a role in *E. granulosus* induced liver damage in sheep.

Echinococcosis is an endemic zoonotic disease in several worldwide countries - larval forms *of E. granulosus* mainly cause illness of sheep. The larvae migrate through the circulatory system to several organs, especially the liver and lungs. The larvae in the liver destroyed the parenchyma, bile ducts, and vessels. Many studies documented these histopathological effects in sheep infected with *E. granulosus* (Al Malki and Ahmed, 2022; Budke, 2006; Widdicombe et al., 2022). The chronic granulomatous inflammatory process occurs as a characteristic finding of the disease. The cysts cause inflammatory reactions in the host, and severe congestion, hemorrhage, degeneration, and necrosis are

evident in the infected liver (Al Malki and Ahmed, 2022; Kebede et al., 2009; Serefettin et al., 2003). In some cases the cysts present an abscess or can be ruptured, producinf a pleural effusion or metastasis in the lungs and brain (Gerazounis et al. 2002). Ibrahim and Gameel (2014) have reported that severe fibrosis of the portal area in infected liver was detected. Singh et al. (2014) said that neighboring the cyst wall showed hepatocyte atrophy and cellular infiltration of lymphocytes, macrophages, and plasma cells around the fibrous capsule. Also, dilatation of sinusoids and central veins has been described. Khadidja et al. (2014) mentioned that extensive cirrhosis was observed in the infected liver in some cases. In the current study, disease's distinctive histopathological features were similar to the above-mentioned studies. Unlike this, we did not see severe cirrhosis, abscess or metastasis.

Sdc1 is a proteoglycan containing transmembrane heparan sulfate (HS). Sdc1 is released mainly from liver and other epithelial cells and plays a role in epitheliogenesis. Sdc1 studies in the literature still need to be improved, and the topic that has been mainly studied is the role of Sdc1 in the pathophysiology of liver diseases (Roskams et al., 1996; Zvibel et al., 2009). Recently, several authors have examined the anti-inflammatory effects of Sdc1 in clinical and experimental studies, while others have attempted to determine the potential antitumor effects of Sdc1 in liver carcinomas (Matsumoto et al., 1997; Nam et al., 2017; Regos et al., 2020; Roskams et al., 1996; Zvibel et al., 2009). Studies have shown that they are immunoexpressed in liver cirrhosis, infectious diseases such as hepatitis-c, hepatocellular carcinoma, and their metastases, as well as metastases of cholangiocellular carcinomas (Couchman, 2021; Reszegi et al., 2022). Roskams et al. (1996) determined that Sdc1 positivity is severe, especially in chronic cholestatic liver disease. They determined that Sdc1 immunoreactivity overexpressed the lateral and sinusoidal cell membrane of hepatocytes and the basolateral membrane of bile ductules. They suggested that Sdc1 may be critical in accompanying fibrogenesis and ductular reaction. In patients with HCV (chronic hepatitis C), especially in patients with cirrhosis and hepatitis, Sdc1 expression was significantly higher than in healthy individuals (Zvibel et al., 2009). Yılmaz et al. (2012) found that levels of Sdc1 significantly increased in serums of patients with nonalcoholic fatty liver disease. However, they found that this increase was not associated with histopathological liver damage, and similarly, they could not detect a correlation between immunohistochemical staining and serum Sdc1. Aquino et al. (2020) determined that in mice with Listeria monocytogenes, Sdc1 is expressed abundantly in the liver. Beiting et al. (2006) showed overexpressed Sdc1 in the Trichinella spiralis infection muscle cell cytoplasm. Yumusak and Filikci. (2022) demonstrated that Sdc1 was overexpressed in sheep liver infected by liver flukes. On the other side, Bhanot and Nussenzweig. (2022), declared that Sdc1 does not have a role in hepatocytes infected with Plasmodium yoelii.

In this study, we focused on the alteration of Sdc1 developed in cystic echinococcosis, and its alteration as the response to infected liver parenchyma. In our study the amount of Sdc1 varies in the liver infected with *E. granulosus* and healthy livers. The increased amount of Sdc1 were observed in all liver areas in infected livers. However, we observed strong immunoreactivity of Sdc1 in adjacent hepatocytes of cystic structures. On the contrary, mild immunoreactivity was seen fibrotic areas surrounding the cysts. Identifying targets for *E. granulosus* induced liver damage would be a basis for developing effective treatment strategies. The study with limited results concluded that Sdc1 release increased in the liver with cystic echinococcosis. These findings showed that Sdc1 proteins may have a role in that infection. However, more comprehensive molecular-related studies would clarify the pathogenesis of cystic echinococcosis in the liver.

Conflict of Interest

The authors stated that they did not have any real, potential, or perceived conflict of interest.

Ethical Approval

This study was performed with the permission of the Experimental Animals Local Ethics Committee in Harran University with (HRÜ-HADYEK) 10.05.2023 date and 01-17 approval number.

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Similarity Rate

We declare that the similarity rate of the article is 8% as stated in the report uploaded to the system.

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References

Afratis NA, Nikitovic D, Multhaupt HA, Theocharis AD, Couchman JR, Karamanos NK, 2017. Syndecans key regulators of cell signaling and biological functions, *FEBSJ*, 284, 27–41.

Al Malki J, Ahmed N, 2022: Epidemiological and histomorphic studies in sheep infected with hydatid cyst in Taif area. *Saudi J Biol Sci*, 29, 886-893.

Aquino RS, Hayashida A, Park PW, 2020: Host syndecan-1 promotes listeriosis by inhibiting intravascular neutrophil extracellular traps. *PLoS Pathogens*, 16 (5), e1008497.

Beiting DP, Park PW, Appleton JA, 2006: Synthesis of syndecan-1 by skeletal muscle cells is an early response to infection with Trichinella spiralis but is not essential for nurse cell development. *Infect Immun*, 74 (3), 1941-1943.

Bhanot P, Nussenzweig V, 2002: Plasmodium yoelii sporozoites infect Syndecan-1 deficient mice. *Mol Biochem Parasitol*, 2 (123), 143-144.

Budke CM, 2006: Global socioeconomic impact of cystic echinococcosis. *Emerg Infect Dis*, 12, 296–303.

Cabrera PA, Haran G, Benavidez V et al., 1995: Transmission dynamics of Echinococcus granulosus, Taenia hydatigena and Taenia ovis in sheep in Uruguay. *Int J Parasitol*, 25, 807–813.

Couchman JR, 2021: Syndecan-1 (CD138), carcinomas and EMT. *Int J Mol Sci*, 22, 4227.

Craig PS, McManus DP, Lightowlers MW et al., 2007: Prevention and control of cystic echinococcosis. *Lancet Infect Dis*, 7, 385-394.

Derda M, Wandurska-Nowak E, Hadas E, 2004: Changes in the level of antioxidants in the blood from mice infected with Trichinella spiralis. *Parasitol Res*, 93, 207–210.

Eckert J, Deplazes P, 2004: Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. *Clin Microbiol Rev*, 17, 107-135.

Etewa S, Sarhan M, Moawad H, Mohammad S, Samir M, Kandil A, Mostafa E, 2021: Behavior and neuropsychiatric changes in experimental chronic toxoplasmosis: Histopathological and immunohistochemical studies. *Parasitologists United Journal*, 14 (2), 183-192.

Gerazounis M, Athanassiadi K, Metaxas E, Athanassiou M, Kalantzi N, 2002: Bronchobiliary fistulae due to echinococcosis. *Eur J Cardiothorac Surg*, 22 (2), 306-308.

Gopal S, Arokiasamy S, Pataki C, Whiteford JR, Couchman JR, 2021: Syndecan receptors: pericellular regulators in development and inflammatory disease. *Open Biol*, 11, 200377.

Heidarpour M, Mohri M, Borji H, Moghdass E, 2012: Oxidative stress and trace elements in camel (Camelus dromedarius) with liver cystic echinococcosis. *Vet Parasitol*, 187, 459–463.

Ibrahim SEA, Gameel AA, 2014: Pathological, histochemical and Immunohistochemical studies of lungs and livers of cattle and sheep infected with hydatid disease. In: Proceedings of 5th annual conference-agricultural and veterinary research–February 2014, Khartoum, Sudan, 2, 1–17.

Jacobs W, Bogers J, Van Marck E, 1999: Distinct B-cell populations are present in hepatic and intestinal Schistosoma mansoni granulomas. *Acta Gastroenterol Belg*, 62 (2):178-81.

Kebede N, Mitiku A, Tilabun G, 2009: Hydatidosis of slaughtered animals in Bahir Dar abattoir, northwestern Ethiopia. *Trop Anim Health Prod*, 41, 43-50.

Khadidja H, Achour Y, Houcin B, Vasile C, 2014: Histological Appearance of Echinococcus Granulosus in the Camel Species in Algeria. *Bulletin UASVM Vet Med*, 71, 79–84

Kılıç E, Yazar S, Başkol G, Artiş T, Ersayit D, 2010: Antioxidant and nitric oxide status in patients diagnosed with Echinococcus granulosus. *Afr J Microbiol Res*, 4, 2439- 2443.

Kim CW, Goldberger OA, Gallo RL, Bernfield M, 1994: Members of the syndecan family of heparan sulfate proteoglycans are expressed in distinct cell-, tissue-, and development-specific patterns, *Mol Biol Cell*, 5, 797–805.

Matsumoto A, Ono M, Fujimoto Y, Gallo RL, Bernfield M, Kohgo Y, 1997: Reduced expression of syndecan-1 in human hepatocellular carcinoma with high metastatic potential. *Int J Cancer*, 74, 482-491.

McManus DP, Zhang W, Li J, Bartley PB, 2003: Echinococcosis. *Lancet*, 362, 1295–1304.

Mert H, Yaşar S, Mert N, 2019: Investigation of TAS and TOS levels in sheep with hydatid cyst. *EurasianJHS*, 2 (4), 164-168.

Nam EJ, Hayashida K, Aquino RS, Couchman JR, Kozar RA, Liu J, Park PW, 2017: Syndecan-1 limits the progression of liver injury and promotes liver repair in acetaminophen-induced liver injury in mice. *Hepatology*, 66, 1601-1615.

Palaiologou M, Delladetsima I, Tiniakos D, 2014: CD138 (syndecan-1) expression in health and disease, *Histol Histopathol*, 29, 177-189.

Regos E, Karászi K, Reszegi A, Kiss A, Schaff Z, Baghy K, Kovalszky I, 2020: Syndecan-1 in liver diseases. *Pathol Oncol Res*, 26, 813-819.

Reszegi A, Tátrai P, Regős E, Kovalszky I, Baghy K, 2022: Syndecan-1 in liver pathophysiology. *Am J Physiol Cell Physiol*, 323, 289-294.

Rogan MT, Craig PS, 1997: Immunology of Echinococcus granulosus infections. *Acta Tropica*, 67, 7-17.

Roskams T, Rosenbaum J, De Vos R, David G, Desmet V, 1996: Heparan sulfate proteoglycan expression in chronic cholestatic human liver diseases. *Hepatology*, 24, 524-532.

Saleh MA, 2008: Circulating oxidative stress status in desert sheep naturally infected with Fasciola hepatica. *Vet Parasitol*, 154, 262–269.

Serefettin M, Merih G, Tulay C, Astarcioglu H, 2003: The Pathology of Echinococcosis and the Current Echinococcosis Problem in Western Turkey (A Report of Pathologic Features in 80 Cases). *Turk J Med Sci*, 33, 369-374.

Shoulah SA, Gaballa MM, Marawan MA, Saqr SA, Abdelhady A, Alzahrani HA, Wakid M, Al-Jabr O, Selim A, 2023: Pathological Findings and Oxidative Stress Status Associated with Hydatidosis in Dromedary Camels. *Vet Sci*, 10, 74.

Singh BB, Sharma R, Sharma JK, Mahajan V, Gill JPS, 2014: Histopathological changes associated with E. Granulosus echinococcosis in food producing animals in Punjab (India). *J Parasit Dis*, 40, 1–3

Teng YHF, Aquino RS, Park PW, 2012: Molecular functions of syndecan-1 in disease. *Matrix Biol*, 31, 3-16.

Widdicombe J, Basáñez MG, Entezami M, Jackson D, Larrieu E, Prada JM, 2022: The economic evaluation of Cystic echinococcosis control strategies focused on zoonotic hosts: A scoping review. *PLoS Negl Trop Dis*, 16 (7), e0010568.

Yilmaz Y, Eren F, Colak Y, Senates E, Celikel CA, Imeryuz N, 2012: "Hepatic expression and serum levels of syndecan 1 (CD138) in patients with nonalcoholic fatty liver disease". *Scand J Gastroenterol*, 47 (12), 1488-1493.

Yumusak N, Filikci K, 2022: Immunohistochemical Evaluation of Syndecan-1 Expression in the Liver of Small Ruminants with Natural Liver Fluke Infection. *Harran Univ Vet Fak Derg*, 11, 73-77.

Zvibel I, Halfon P, Fishman S, Penaranda G, Leshno M, Or AB, Halpern Z, Oren R, 2009: Syndecan 1 (CD138) serum levels: a novel biomarker in predicting liver fibrosis stage in patients with hepatitis C. *Liver Int*, 29, 208-212.