Hepatotoxicity in sheep and goats caused by experimental feeding with foxtail millet (*Setaria italica*)

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Abstract:

BACKGROUND: Some species of grass cause poisoning and hepatogenous photosensitization in animals. **OBJECTIVES:** Feeding trials were conducted in sheep and goats to evaluate the hepatotoxic effects of *Setaria italica* (*S. italica*). **METHODS:** Twelve indigenous male sheep and goats were used in this study. The animals were kept outdoors against prevailing climatic conditions. They were fed with *S. italica* freely for 50 days. Some biochemical factors associated with liver function, such as total bilirubin (TBIL), direct bilirubin (BC), aspartate amino transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT) activities, blood urea nitrogen (BUN), total protein (TP), and albumin (ALB), were measured on day 0, 7, 14, 21, 28, 35, 42, and 49 of the experiment. On the 50th day, the animals were sacrificed and necropsied, then the gall bladder and livers were removed for pathological study. Blood samples on day 0 (prior to feeding with *S. italica*) were set as the control group. **RESULTS:** Three sheep and 3 goats showed signs of intoxication, including facial edema, mucus hyperemia, runny nose, lacrimation, and icterus. Post-mortem examination revealed varying degrees of generalized icterus, degeneration, necrosis and cell swelling of hepatocytes, formation of acidophilic bodies, and mild hyperplasia in biliary ducts. **CONCLUSIONS:** Clinical signs, laboratory findings, and necropsy findings, support the potential of *S. italica* in the induction of hepatotoxicity and secondary photosensitivity in sheep and goats.

Introduction

Setaria italic (*S. italica*), (foxtail millet) is one of the oldest cultivated cereal grains. It is the most economically important species of the Setaria genus. Other names of *S. italica* are Italian millet, German millet, Chinese millet, and Hungarian millet. The cultivation of *S. italica* dates back 5000 BC from China. It is found all over the world (Liu et al., 2012). *S. italica* is an annual grass with slim, vertical, leafy stems, which can reach a height between 100–150 Cm (Kazemi Arbat, 2005). *S. italica* is a quick growing species that is able to grow in many types of soil and climate conditions. The root system of *S. italica* is shallow, scattered and fragmented, making it suitable for growing in semiarid regions. *S. italica* is cul-

tivated in many parts of Iran such as Birjand, Kerman, Yazd, and Isfahan. *S. italica* is used as forage for hay, grazing or grain for birdseed. Consumption of millets can induce poisoning, hepatogenous photosensitization and sometimes death in animals (Nazifi et al., 2009). Hepatogenous photosensitization is the most common type of photosensitivity reaction seen in animals. Phylloerythrin is a derivative of chlorophyll produced in the body as a photodynamic substance. Normally, phylloerythrin is secreted into the intestine by the biliary system and excreted through the feces. Damage to the biliary transport prevents the excretion of phylloerythrin. Photosensitivity reaction occurs along with the accumulation of phylloerythrin under the skin. In sensitive animals, this reaction is most severe in non-pigmented skin, which has the least protection from UV or visible light exposure (Quinn et al., 2014). Different species of Panicum grasses cause poisoning and hepatogenous photosensitization in animals. They include Panicum miliaceum in sheep (Badeie et al., 2009; Nazifi et al., 2009), Panicum coloratum and Panicum maximum in sheep (Kellerman et al., 2005), and Panicum virgatum in sheep and horses (Lee et al., 2001). Based on available literature, it seems that there is no published report on *S. italica* poisoning from Iran. The main affected organ in most cases of photosensitization is the liver. Therefore, the aim of this study was to evaluate the liver function and health status of sheep and goats fed with *S. italica*.

Materials and Methods

Animals: Six male sheep and 6 male goats within the age of 4-6 months used in this study were selected from the farm of in the Faculty of Agriculture, during the spring and summer of 2010. Initial mean body weight (BW) of goats and sheep were 16.5±2.5 kg and 21±2 kg, respectively. *S. italica* was harvested, dried and stored in a dry place away from sunlight, moisture, and heat. The voucher number specimen (No. 625-626) was deposited in the herbarium of Birjand University, Iran for *S. italica*. The animals were fed alfalfa hay and *S. italica* based diet freely, in a two-week adaptation period and seven-week experimental period, respectively. They were housed in a pen without protection against climate conditions (sunlight) with free access to tap water. Animals were dewormed 28 days prior to the commencement of the experiment by oral administration of Albendazole (Damloran Co, Borujerd, Iran) and subcutaneous injection of Ivermectin (Razak Co., Tehran, Iran).

Biochemical analysis: Blood samples were obtained between 8 and 9 am, to avoid diurnal influences, by jugular venipuncture into bottles containing EDTA (in a 10:1 ratio) as an anticoagulant from day 0 to day 50, at weekly intervals. After centrifugation at 750 g for 15 min at room temperature, plasma was separated and stored at -21°C until analysis. Total bilirubin (TBIL), direct bilirubin (Conjugated or BC), aspartate amino transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT) activities, blood urea nitrogen (BUN), total protein (TP), and albumin (ALB), were measured by autoanalyser (prestige 24i model, Japan), using standard methods (Thomas, 1998), by Pars Azmoon Co. (Iran) kits.

Histopathological analysis: At the end of the experiment (day 50), animals were sacrificed and necropsied. Tissue samples were collected from the liver and gall bladder. The samples were washed in saline solution, and fixed in 10% formalin buffer (Merck, Germany) at room temperature for 72 h. After fixing the tissue, it was thoroughly washed under running water and dehydrated in ascending grades of ethyl alcohol, cleared, and embedded in soft paraffin. Tissue sections of about 5 µm were prepared, stained with hematoxylin and eosin (H&E), and observed under a light microscope.

Statistics: The data were expressed in SI

units and presented as mean, standard error of mean (SEM). The raw data were tested for normal distribution using the Kolmogorov-Smirnov method and analyzed by descriptive statistics and repeated measurement of the ANOVA procedure, using the SPSS 16/ PC software. Data were measured at eight different time points. One of these groups is the control group (day 0). Significance level was set at $p<0.05$.

Results

Clinical findings: Three of the sheep and three of the goats showed clinical signs of intoxication. These signs include face edema, mucus hyperemia, runny nose, shedding of tears, and yellow eye mucus in sheep. In goats, symptoms of hepatogenous photosensitisation are hyperemia on ears, slight yellow discoloration of the eyes, mucous membrane and facial swelling. Slight weight loss (Table1), intermittent diarrhea and inappetence were seen in all animals.

Laboratory findings: In sheep, TBIL and BC showed an increasing trend during the experiment. TBIL and BC increased significantly from the 21st and 14th day, until the end of the experiment, respectively. AST, ALT and ALP tended to increase gradually during the experiment. The activity of ALT increased significantly on the 35th and 42nd day. There was a tendency for serum GGT activity to decrease during the experiment and a significant decrease was observed on the 35th and 42nd day. TP increased slightly during the experiment. ALB concentration increased on the 7th day, but was approximately constant in other days (Table 2). In goats, TBIL showed an increasing trend. BC increased until the 28th day and decreased throughout the period of the experiment. AST increased and reached the peak on the 21st day and then gradually decreased on the 28th, 35th, 42nd and 49th day. Statistically significant increases in ALT and ALP activities were observed from the 14th and 28th day, respectively, while no significant change was seen in the serum GGT activity. Goats fed with *S. italica* had significantly higher TP and ALB concentrations compared to Day 0 of the experiment as the control (Table 3). BUN levels significantly decreased during the experiment in sheep and goats.

Table 1. Weight of sheep and goats during the study (n=12).

Day/weight	Sheep(kg)	Goats (kg)
0	21.00±2.0	16.5±2.5
7	21.83±1.63	17.62±1
14	22.83±1.70	17.6±1.2
21	22.91±1.43	17.6±1.3
28	22.66±0.98	17.42±0.8
35	22.08±0.96	17±0.7
42	21.08±0.73	16.85±0.6
49	20.66±0.60	16.25±0.6

Pathological findings: At necropsy, all animals showed varying degrees of generalized icterus in tissues, especially around the livers and kidneys. In addition, there were moderate to severe yellow discoloration in mucous membranes. Histopathological examination revealed various lesions in the livers of animals. Degeneration, necrosis and cell swelling of hepatocytes, formation of acidophilic bodies, and mild hyperplasia in biliary ducts were observed (Figs. 2, 3, and 4). The gall bladders were enlarged and contained bile, but biliary obstruction was not observed.

Discussion

Clinical signs of hepatogenous photosensitisation in goats were slight, probably because of the protection effect of hair and skin pigmentation from sunlight. Darker skin containing melanin or pigment serves as protection to prevent additional photosensitization (Knight and Walter, 2001). The reaction is most severe in non-pigmented skin that has the least protection from light exposure (Quinn et al., 2014). Secondary (hepatogenous) photosensitization with damage to the liver or bile duct is the

Table 2. Effect of feeding *Setaria italica* on the levels (mean ± SD) of some biochemical parameters in sheep (n=6). D a: day;TBIL: total bilirubin; BC: direct bilirubin; AST: aspartate amino transferase; ALT: alanin amino transferas; ALP: alkaline phosphatase; GGT: gama glutamyle transferase; BUN: blood urea nitrogen; TP: total protein; ALB: albumin; Significant difference with first sampling time ($p<0.05$).

Da	TBIL (µmol/l)	BC (µmol/l)	AST (IU/l)	ALT (IU/l)	ALP (IU/l)	GGT (IU/l)	BUN mg/dl)	TP (g/l)	ALB (g/l)
0	± 2.61	± 1.19	102.67	± 18.83	292.17	± 88.85	± 34.5	8.0 ± 83.3	2.4 ± 25.0
	0.63	0.17	13.82 ±	7.02	66.35 ±	18.51	7.34		
7	± 2.27	± 1.30	101.50	± 20.66	274.17	± 78.36	± 24.83	4.2 ± 86.1	± 30.0
	0.51	0.56	30.16 ±	8.11	63.94 ±	14.55	*1.94		*3.8
14	± 3.76	± 2.23	115.00	± 22.33	288.83	± 83.08	± 22.33	4.1 ± 88.4	1.4 ± 29.8
	1.81	*0.66	7.09 ±	6.34	54.99 ±	14.95	*6.12		
21	± 3.84	± 2.70	± 116.50	± 23.33	± 304.83	± 79.68	± 23.33	3.7 ± 92.3	0.9 ± 28.8
	*1.00	*0.51	18.94	4.54	106.52	14.78	*2.16		
28	± 3.69	± 2.27	124.00	± 25.00	± 318.67	± 73.65	± 23.16	8.9 ± 89.3	4.0 ± 27.1
	*0.54	*0.27	14.07 ±	5.65	133.64	15.53	*3.71		
35	± 4.36	± 2.82	131.50	± 27.33	± 274.00	± 62.06	± 15.83	4.8 ± 92.0	2.8 ± 28.6
	*0.97	*0.37	24.67 ±	*10.91	106.78	*17.72	*3.92		
42	± 3.64	± 2.36	138.33	± 25.50	± 327.17	± 73.25	± 12.16	5.0 ± 91.6	1.4 ± 27.8
	*0.64	*1.09	33.01 ±	*7.86	138.56	*20.98	*2.92		
49	± 3.64	± 2.78	141.33	± 22.50	± 343.83	± 74.01	± 10.83	8.0 ± 89.1	3.0 ± 27.1
	*0.17	*0.47	32.36 ±	14.29	133.46	18.19	*1.16		

Table 3. Effect of feeding *Setaria italica* on the levels (mean ± SD) of some biochemical parameters in goats (n=6).D a: day; TBIL: total bilirubin; BC: direct bilirubin; AST: aspartate amino transferase; ALT: alanine amino transferase; ALP: alkaline phosphatase; GGT: gama glutamyle transferase; BUN: blood urea nitrogen; TP: total protein; ALB: albumin; Significant difference with first sampling time ($p<0.05$).

Da	TBIL (µmol/l)	BC (µmol/l)	AST (IU/l)	ALT (IU/l)	ALP (IU/l)	GGT (IU/l)	BUN (mg/dl)	TP (g/l)	ALB (g/l)
0	± 1.82	± 0.71	± 96.23	20.83	204.67	± 59.78	± 37.16	± 72.3	± 27.6
	0.32	0.18	9.86	2.3 ±	12.62 ±	3.05	1.77	3.06	0.98
7	± 1.94	± 0.77	± 144	± 25.21	374.82	± 75.28	± 26.5	± 79.8	± 31.6
	0.10	0.18	28.67	1.44	68.22 ±	9.37	*2.14	*1.7	*0.7
14	± 2.57	± 0.83	± 145	± 25.52	345.20	± 73.53	± 25.2	± 80.2	± 31.3
	0.96	0.17	15.18	0.09	*33.2 ±	6.69	*2.98	*0.8	*1.2
21	± 2.38	± 1.03	± 210	1.23 ± 26	454.50	± 75.31	± 26.5	± 82.8	± 31.1
	0.25	0.21	*20.15		*95.8 ±	7.76	*3.11	*2.0	*0.9
28	± 2.74	± 1.23	± 170.8	*1 ± 28.16	510.80	± 76.6	± 20.5	± 82.3	± 30.5
	0/19	*0/11	*19.4		*34.5 ±	8.73	*3.31	*1.6	*0.5
35	± 2.59	± 1.06	148.5	*3.09 ± 36	534.57	± 66.2	± 11.66	± 84.6	± 34.5
	0.31	0.28	*±15.8		*43.9 ±	6.49	*3.33	*1.6	*2.2
42	± 2.19	± 0.97	130.33	*1.84 ± 33	550.80	± 62.45	± 10.66	± 85.6	± 32.8
	0.26	0.11	*1o ±		*39.1 ±	8.33	*2.67	*2.0	*1.9
49	± 2.57	± 0/74	± 126.2	± 34.5	596.75	± 64.28	± 14.5	± 85.5	± 31.3
	0.10	0.21	*6.64	*2.03	*37.2 ±	6.43	*3.04	*2.4	*0.4

most common type of photosensitivity. Field outbreaks of hepatogenous photosensitization are caused by the hepatotoxic agents usually present in plants (Minervino et al., 2010). In many parts of the world, hepatogenous photosensitization of animals is associated with grazing on plants containing steroidal saponins. Different species of *Panicum*, including *Panicum miliaceum* in sheep (Badeie et al., 2009; Nazifi et al., 2009), *Panicum coloratum* and *Panicum maximum* in sheep (Kellerman et al., 2005), and *Panicum virgatum* in sheep

Figure 1. *Setaria italica* is used in the experiment to induce hepatotoxicity in sheep and goats.

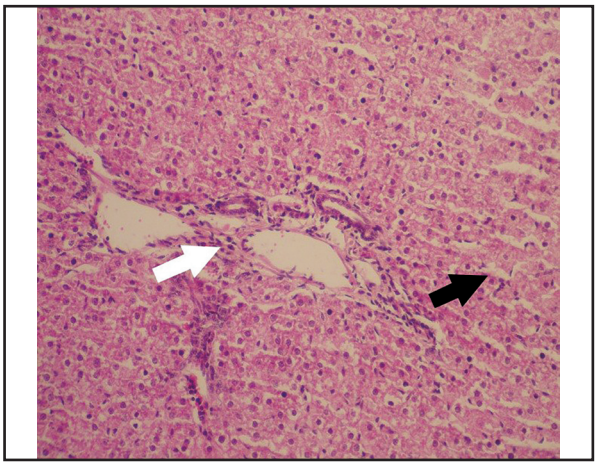

Figure 2. Hyperplasia of the bile ducts (white arrow) with hepatocytes necrosis (black arrow) in the liver of sheep fed *Setaria italica* (H&E stain, X 40).

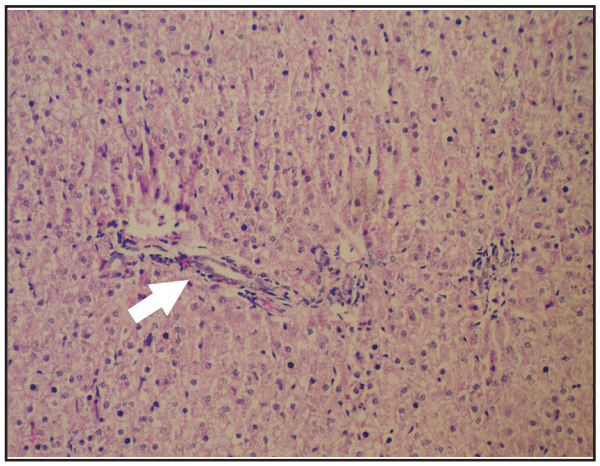

Figure 3. Mild hyperplasia of the bile ducts (white arrow) in the liver of goats fed *Setaria italica* (H&E stain, X 40).

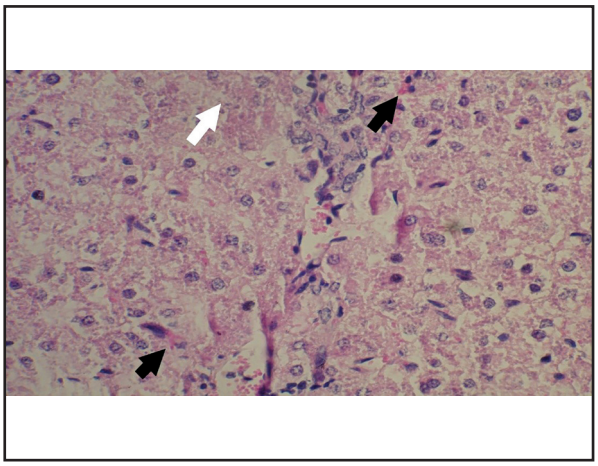

Figure 4. Degeneration of hepatocytes (white arrow) and acidophilic bodies (black arrow) formation in the liver of goats fed *Setaria italica* (H&E stain, X 40).

and horses (Lee et al., 2001) have been reported to cause photosensitization. In the present study, clinical signs of *S. italica* intoxication were consistent with those of *Panicum miliaceum* poisoning in Iranian fat-tailed sheep (Badeie et al., 2009; Nazifi et al., 2009). TBIL and BC showed an increasing trend (hyperbilirubinemia). Bilirubin is produced as a breakdown product of hemoglobin. TBIL includes both unconjugated (BU) or indirect bilirubin and BC. BU is transported in the blood bound to albumin to the liver. BU is taken up by hepatocytes, conjugated (BC), and excreted into bile (Sticova and Jirsa, 2013). The main gross lesions in animals of the present study were varying degrees of icterus in tissues associated with hyperbilirubinemia. Increased concentrations of BC and TBIL were detected in cases of natural and experimental plant poisoning in cattle, sheep and goats (Aslani et al., 2004; Mendonça et al., 2008; Nazifi et al., 2009; Saturnino et al., 2010). AST activity is high in many cells, including hepatocytes (De Oliveira et al., 2013). The cytosol of hepatocytes contains little ALT activity in large animals (Kiran et al., 2012). In this study, an increase in AST and ALT activities indicates damage to the parenchymal cells of the liver; this finding is in agreement with the report of Badeie et al. (2009) in sheep. Also, ALP activity increased during this experiment. In more chronic cases, ALP activity could have increased to a greater

degree than GGT activity (Chapman and Hostutler, 2013). In the present study, GGT activity tended to decrease during the experiment. Decreased tissue mass may be associated with decreased GGT activity or concentration (Teixeira et al., 2013). GGT in the liver is primarily associated with biliary epithelial cells and ALP is primarily associated with hepatocytes (Chapman and Hostutler, 2013). Based on the serum biochemistry, the rise in ALP, AST and ALT activities and increased TBIL and BC concentrations, coupled with the decrease in GGT activity, might be manifestations of damage and decrease in liver mass. Blood urea nitrogen (BUN) in the first sampling time (day 0) was 34.5±1.16 and 37.16±1.77 mg/dl in sheep and goats respectively, but decreased to 10.83±1.16 and 14.5±3.04 mg/dl in sheep and goats, respectively, during the last sampling time (day 49). Decreased BUN concentration also suggests decreased hepatic functional mass with failure to convert ammonia to urea via the hepatic urea cycle (Obitsu et al., 2011). Albumin (ALB) is produced exclusively by hepatocytes. The formation of ALB is relatively well preserved, and decreases are not significant until there is substantial loss of hepatocellular mass (Mann, 2013). However, the decrease in hepatic functional mass has not affected ALB synthesis. TP and ALB concentration increased gradually during the experiment. This finding is in agreement with the findings of Ajala et al. (2000), who reported a significant increase of TP in West African Dwarf bucks on *Millettia thonningii* poisoning. Ajala et al. (2000) reported that the increase in TP could be due to protein richness of *Millettia thonningii*. Aslani et al. (2003) reported that the elevation of TP in goats receiving *Tribulus terrestris*, might be due to dehydration. In the present study, increasing TP and ALB concentrations could be due to intermittent diarrhea and subsequent dehydration. At necropsy, the gall bladders were enlarged and contained bile; this may be due to anorexia and diarrhea. The presence of hepatic lesions may be due to the conversion of saponins to sapogenins by bacteria in the digestive tract or by biotransformation after absorption through the injured epithelium (Nazifi et al., 2009). The present findings seem to be consistent with other research. Aslani et al. (2003) and Badeie et al. (2009) reported the same clinical signs and necropsy findings in sheep that received *Tribulus terrestris* and *Panicum miliaceum*, respectively. Brum et al. (2007) reported cholesterol-like, needle-shaped, crystals in the lumen of some bile ducts, along with degeneration and necrosis in epithelial cells of the small bile ducts in sheep grazing *Brachiaria decumbens*. The effect of *Panicum dichotomiflorum* was investigated by Riet-Correa et al. (2009), and they reported hepatotoxicity in sheep. In the current study, damage to liver was significant; but cholestasis and biliary obstruction were not observed. However, this difference may be as a result of the presence of different toxic substances in the plants used for the experiments and different exposure time. In conclusion, based on the results of this study (clinical, laboratory and necropsy findings), it can be said that feeding on *S. italica* can lead to hepatogenous photosensitization in sheep and goats.

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سمیت کبدی ناشی از تغذیه تجربی با ارزن دم روباهی (*Setaria italica*) در گوسفند و بز

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چکیده

زمینه مطالعه: برخی گونه‌های علوفه ای موجب مسمومیت و حساسیت به نور با منشأ کبدی در نشخوارکنندگان می‌شوند. **هدف:** اثرات سمیت کبدی گیاه ارزن دم روباهی (*S. italica*) با تغذیه آن در گوسفند و بز مورد ارزیابی قرار گرفت. **روش کار:** دوازده گوسفند و بز بومی در این آزمایش استفاده شدند. حیوانات در محیط بیرون و در معرض آب و هوا و بدون محافظ نگهداری شدند و به مدت ۵۰ روز از ارزن دم روباهی تغذیه شدند. برخی فاکتورهای بیوشیمیایی مرتبط با عملکرد کبد شامل بیلی روبین تام (TBIL)، بیلی روبین مستقیم (BC)، آسپارتات آمینوترانسفراز (AST)، آلانین آمینو ترانسفراز (ALT)، آلکالین فسفاتاز (ALP)، گاماگلوتامیل ترانسفراز (GGT)، نیتروژن اوره خون (BUN)، پروتئین تام (TP) و آلبومین در روزهای صفر، ۷، ۱۴، ۲۱، ۲۸، ۳۵، ۴۲ و ۴۹ آزمایش اندازه گیری شد. در روز ۵۰، حیوانات ذبح و کالبدگشایی شدند. سپس کبد و کیسه صفرا برای مطالعات پاتولوژی خارج شدند. نمونه‌های خون روز صفر (پیش از تغذیه با ارزن دم روباهی)، به عنوان گروه شاهد در نظر گرفته شد. **نتایج:** سه گوسفند و سه بز علائم مسمومیت شامل ادم صورت، پرخونی مخاطی، آبریزش از چشم و بینی و زردی را نشان دادند. نتایج کالبد گشایی حاکی از درجات متفاوتی از زردی سرتاسری، دژنراسیون، نکروز و تورم هپاتوسیت‌ها، تشکیل اجسام اسیدوفیل وهایپرپلازی ملایم در مجاری صفراوی بود. **نتیجه‌گیری‌نهایی:** علائم بالینی، یافته‌های آزمایشگاهی و کالبدگشایی، از پتانسیل گیاه ارزن دم روباهی برای القای مسمومیت کبدی و حساسیت به نور ثانویه در گوسفندان و بزها حمایت می کند.

واژه‌های کلیدی: بز، ضایعات کبدی، ارزن دم روباهی (*S. italica*)، گوسفند

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