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Silymarin and its effect on improving the health of cattle infected with liver flukes, a clinical and pathological study

Huda Hameed Kadhim Alabbody
Market Research and Consumer Protection Center, University of Baghdad, Iraq.
Corresponding author Email: huda@bccru.uobaghdad.edu.iq
https://orcid.org/0000-0003-1566-534X

Abstract: Fascioliasis is a global parasitic disease with economic consequences. In Iraq, it represents a major health problem for ruminants. This study aimed to evaluate the therapeutic effect of the herbal extract (silymarin) in improving the health of cattle naturally infected with liver flukes and treated with an anthelmintic (rafoxanide). The study included 9 head of cattle (6 females and 3 males) aged 3 to 7 years, divided into three groups (G1, G2, G3), each containing 3 animals, 2 females and 1 male: G1 was untreated, G2 was treated with rafoxanide alone (7.5 mg/kg orally on days 1, 8, and 15), and G3 was treated with rafoxanide as in Group 2 with silymarin (1200 mg orally daily from day 1 to day 22). The efficacy of the two drugs was evaluated by liver function tests using serum parameters such as bilirubin, total protein, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT). In addition to evaluating the histopathological changes in the livers of slaughtered males, a light microscope was used. Liver histopathological showed the main lesions: inflammation, necrosis, fibrosis, and hyperplasia of bile ducts in groups G1 and G2, biochemical analysis showed significant increases in AST, ALP, GGT, bilirubin, and total protein levels. Group G3 treated with rafoxanide and silymarin showed significant improvements in both biochemical and histopathological parameters ($P < 0.05$). Therefore, it is concluded that silymarin had superior hepatoprotective and regenerative activity when administered with immunotherapy. Rafoxanide.
Key word: Silymarin, Rafoxanide, Pharmacological synergy, Fascioliasis

INTRODUCTION

Fascioliasis is a parasitic disease of animals and humans caused by the genus *Fasciola*, commonly known as liver fluke parasites. Two major liver fluke species cause it, *Fasciola hepatica* and *Fasciola gigantica*. These flukes use various species of freshwater snails of the *Limnidae* family as intermediate hosts to complete their life cycle (31). These snails live along river banks. *Fasciola hepatica* is distributed globally but is more prevalent in temperate regions, while *Fasciola gigantica* has been found in tropical areas on two continents (Africa and Asia) (25). Differential diagnosis is crucial between *Fasciola gigantea* and *Fasciola hepatica* due to their similar modes of transmission and epidemiological characteristics across different hosts. Each liver fluke species has unique characteristics and is transmitted by different snail species. However, studies have shown that clinical, pathological, and immunological methods cannot be used to classify Fasciola species. Serological findings fail to differentiate between these species (1, 13). Due to the limitations of morphological methods, the distinction between *F. hepatica* and *F. gigantica* relies on morphological studies or the application of advanced molecular methodologies using various molecular targets (6). This disease is globally widespread, and its prevalence varies depending on the control plan and environmental factors of each country. In Iraq, both types of liver flukes are present, and several studies have been conducted on *Fasciola* in animals (28, 30). Recent studies have indicated a high prevalence of *Fasciola* in cattle, goats, and sheep in most Iraqi governorates. This disease is capable of causing significant damage to the livestock sector in many countries of the world. Through the presence of this parasite in the liver, gallbladder, and bile ducts of the host (19), it causes chronic liver deterioration, decreased milk, meat, coat, and fertility production (15). The migration of immature liver flukes leads to liver damage, and sometimes liver lesions may lead to acute liver failure which can lead to death (23). In other studies, it has been observed that liver fluke infestation increases the risk of rumen displacement, ketosis, immune suppression, and uterine inflammation (22). Studies have shown that the liver fluke is a serious health problem for humans, with human cases reported in 51 countries, infecting more than 17 million people (16). Several anthelmintics have been used to

combat *Fasciola* , Rafoxanide is one of the most important and effective anthelmintics. It binds closely to blood proteins and therefore has a long-lasting effect on the blood. The recommended oral dose in cattle, sheep, and goats is 5–10 mg/kg body weight; treatment is repeated after three weeks. Trials have shown that using 15 mg/kg body weight expels 90% of worms in 4-week-old calves. Rafoxanide is effective against all adult and immature stages of the parasite and is used to control adult and immature parasites (*F. hepatica* and *F. gigantica*). In cattle and sheep. Rafoxanide is also used to control several nematodes such as *Bonostrum* and *Haemonchus* torsion, all larval stages of *Oestrus ovis* in sheep, and *Oesophagostomum spp*. . Rafoxanide is well absorbed in cattle and sheep, reaching peak plasma levels within 24–28 hours after administration. The half-life of rafoxanide is 5–10 days in cattle (2).

Although rafoxanide is beneficial in combating parasites, the effects of liver injury or parasitic complications remain in the host's liver, making the use of these drugs alone an inappropriate option (29). Therefore, using additional compounds is an excellent strategy have hepatoprotective properties, combating the parasite and its complications and promoting liver regeneration. Silymarin acts as an antioxidant and anti-inflammatory agent in clinical medicine. It is a mixture of phenylpropanoid isomers and flavonoids derived from milk thistle (Silybum marianum) extract (17). The use of this plant as an herbal remedy for liver and gastrointestinal diseases has been described in ancient medical books for 2,000 years. In folk medicine, it is used for gallbladder and liver disorders (jaundice, cirrhosis, and hepatitis) and to protect against environmental and chemical toxicity to the liver. Silymarin is widely used as a nutritional supplement or therapeutic agent in liver diseases without serious side effects in both animals and humans (7). Cattle may suffer from *Fasciola* infestation throughout their lives during pregnancy, birth, and milk production. It is used for dairy cows at the beginning of the lactation season and may lead to earlier peak milk production. Improvement and stimulation of liver function have been observed with silymarin treatments. Silymarin affects cell permeability and has antioxidant properties that prevent lipid peroxidation and membrane degradation. One study reported that the polyphenolic fraction of silymarin had positive effects on plasma lipoprotein levels and prevented the development of fatty liver in rats. Silymarin also significantly reduced the levels of gamma-glutamyl transpeptidase, alanine transaminase, and aspartate transaminase in the serum of rats with liver damage (9). Studies conducted on many organisms, including humans, pets, and poultry, indicate that silymarin positively reduces stress, accelerates metabolic adaptation, and repairs tissue damage caused by aflatoxins, especially in the liver. It has also been reported that silymarin has an anti-tumor effect against various types of tumors and cancers by stopping the cell cycle and inducing programmed cell death (3, 11, 21, 12)

This clinical study aimed to evaluate the therapeutic efficacy of the herbal extract (silymarin) supplemented with rafoxanide compared to the therapeutic efficacy of rafoxanide alone on bovines infested with Fasciolisis in rural areas of Taji district, Baghdad. By measuring some liver biochemical parameters (aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, and total protein), the two drugs were also evaluated using histological cross-sectional examination of the livers of slaughtered males.

MATERIALS AND METHODS

Experimental design

The study included 9 heads of Iraqi local cattle infested naturally with liver fluke, 6 females, and 3 males, aged (3 to 7 years), weighing 350 to 400 kg, divided into three groups (G1, G2, G3), . (G1) were left without treatment; (G2) treated only with suspension of rafoxanide, trade name Avidin (Aveco) Jordan, 25 mg/ml at an oral dose of 7.5 mg/kg body weight, equivalent to 50 ml orally in days 1, and 15 from the experiment; (G3) treated with rafoxanide as G2, and supplemented with silymarin herbal preparation at a dose of 500 mg orally daily from day 1 to day 15, 100 ml per animal, on days 1, 8, and 15 from the experiment….table 1.

Diagnosis

The initial diagnosis was made based on the case history, as the animal lived in a rural and grazed in open areas near swamps where snails are abundant. The clinical symptoms that appeared in the animals were emaciation, loss of appetite, pale mucous membranes, fatigue, decreased milk production, pale or yellowing of the mucous membranes and sclera, and the appearance of a bottle jaw in one animal.

Laboratory diagnosis was made based on the presence of eggs in fecal samples. Fecal samples were collected directly from the rectum and stored in a plastic bottle containing a 10% formalin solution. Diagnosis was made using the sedimentation technique (4)

Blood samples and biochemical analysis

Blood samples were collected from the external jugular vein of all studied animals on days 1, 8, 15, and 22 and stored at +4°C for biochemical analysis to separate serum, the blood was centrifuged at 3,000 rpm for 10 minutes. Due to the poor stability of enzymes and bilirubin in serum, samples were analyzed within six hours. Liver enzyme activities (AST, GGT, ALP), bilirubin, and total protein were measured according to standard procedures using a BT1500 automated analyzer (Philippines). Data were analyzed using IBM SPSS version 22 for the chi-square test, and the difference between means ($P < 0.05$) as shown in Table 2.

Histopathological analysis

The three males from the three groups were slaughtered about two weeks after the end of the experiment. Liver biopsies were collected, fixed in a 10% buffered formaldehyde solution, embedded in paraffin, and sent to the histopathology laboratory. Five-micrometer sections were stained using the hematoxylin-eosin (H&E) technique and examined under a light microscope. Histopathological changes in the liver tissues of the three groups were examined. The levels of inflammation, bile duct hyperplasia, necrosis, and fibrosis were also assessed (14).

Results

Overall, gradual improvement was observed in the animals in G3, particularly after the 15th day of the trial. This improvement was evident in improved appetite, activity, and appearance, with pink mucous membranes appearing in the eyes. One cow's bottle jaw also disappeared. Twenty-two days after the start of the experiment, a significant difference was shown in the serum biochemical analysis of mean levels of AST, ALP, and GGT, and a decrease in bilirubin and increase total protein in G3. Untreated animals G1 compared to groups G2 and G3. ($P < 0.05$)...table 2

Histopathological examination of the livers of the slaughtered males of the three groups (G1, G2, G3) showed a significant improvement in the histological changes and lesions in G3. While G1 and G2, there was no significant difference, but the liver fluke infestation disappeared in G2 in animal's feces examination, while the infestation persisted in G1.

As for the histopathological changes in both groups G1 and G2, there was dilatation of the bile duct surrounded by fibrosis, hepatocellular necrosis, loss of visceral tissue structure and change in the shape of the liver histological section to fibrous connective tissue (cirrhosis), infiltration of red blood cells (hemorrhage), infiltration of inflammatory cells around the blood vessels in the hepatic portal vein, Kuepfer cells/macrophages and lymphocytes mixed with dead hepatocytes (Fig. 1).

Conversely, histopathological examination of liver tissue in G3 after 22 days of treatment, as demonstrated by the appearance of remission and the presence of normal hepatocytes, as well as the reduction and remission of pathological lesions such as inflammatory cells, necrosis, and fibrosis. Hepatocytes surrounding the portal tracts (junction) have a normal, somewhat ordered structure and large nuclei. Red blood cells are relatively scarce throughout the sinusoids. Inflammatory cells are present, as well as hepatic Kupffer macrophages, which play a fundamental role in maintaining liver function and are an indicator of recovery... Figure 2

Table 1: Experimental design of the study

Experimental design			
9 heads of Iraqi local bovine (6 females and 3 males) aged 3 – 7 years infested with fascioliasis			
1	G1 2 females and 1 male They were left without treatment	G2 2 females and 1 male were treated with rafoxanid 7.5 mg/kg body weight On the 1st and 15th day of the experiment	G3 2 females and 1 male were treated with rafoxanid as G2, plus sylimarin 500 mg orally daily 1-15

2	Blood serum samples for biochemical analysis (hepatic enzyme activities & Bilirubin and Total protein) from each group in days 1st, 8th, 15th and 22th				
	AST	GGT	ALP	Bilirubin	Total protein
3	Liver histopathological analysis The 3 males of the 3 groups were slaughtered after two weeks from the completion of the experiment.				

Table 2: Mean of serum parameters of bilirubin, total protein, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) on the 1st, 8th, 15th, and 22 st day of beginning the trial.

Period	Parameter	G1 (F)	G2 (FR)	G3 (FRS)	Normal values	P- value
1st day	AST, U/L	175.5	150.1	155	54-135	> 0.05
	ALP U/L	200	190.5	145.5	27-127	> 0.05
	GGT, U/L	6.3	50.5	10.7	17-54	> 0.05
	Bilirubin mg/dl	3.25	3.1	2.16	0-0.1	> 0.05
	Total protein mg\dl	9.5	10.2	11.5.	6.7-8.8	> 0.05
8th day	AST, U/L	174.2	150.1	76.5	54-135	> 0.05
	ALP U/L	526.2	504.6	145.5	27-127	> 0.05
	GGT, U/L	51.3	50.5	20.8	17-54	> 0.05
	Bilirubin mg/dl	3.25	3.1	1.5	0-0.1	> 0.05
	Total protein mg\dl	4.5	5.2	11.0	6.7-8.8	> 0.05
15th day	AST, U/L	175.5	150.1	76.5	54-135	<0.05*
	ALP U/L	526.2	504.6	145.5	27-127	> 0.05
	GGT, U/L	51.3	50.5	32.3	17-54	> 0.05
	Bilirubin mg/dl	3.25	3.1	1.16	0-0.1	< 0.05*
	Total protein mg\dl	4.5	5.2	6.5	6.7-8.8	> 0.05
21st day	AST, U/L	175.5	150.1	70.5	54-135	<0.05*
	ALP U/L	526.2	504.6	135.5	27-127	<0.05*
	GGT, U/L	51.3	50.5	37.2	17-54	<0.05*
	Bilirubin mg/dl	3.25	3.1	0.16	0-0.1	<0.05*
	Total protein mg\dl	4.5	5.2	8.5	6.7-8.8	< 0.05*

* A significant difference at P value < 0.05

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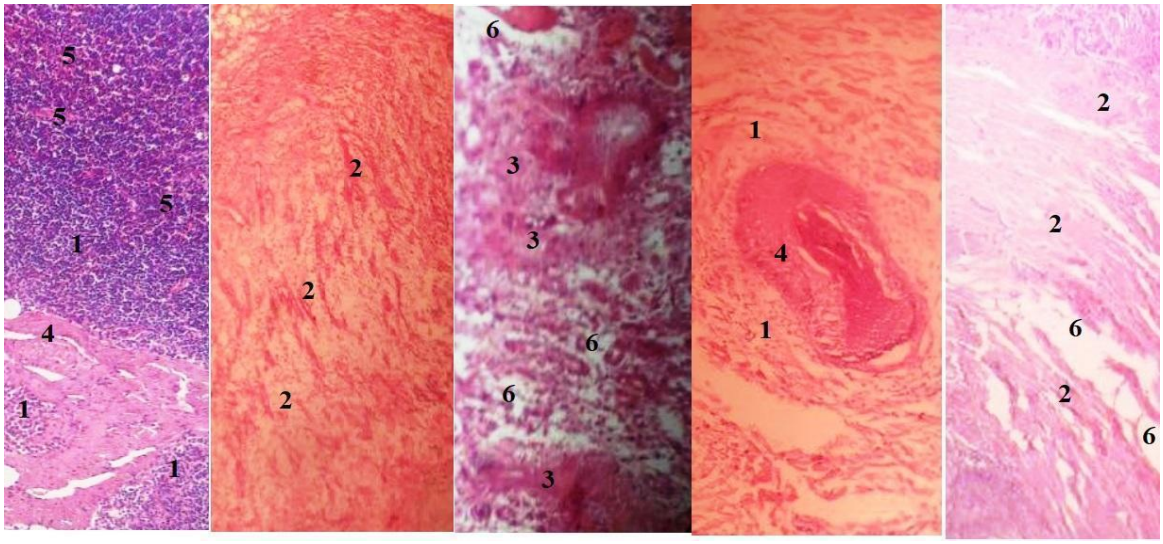

Figure 1. cross section of liver tissue in animals in G1 and G2 showed the same histopathological changes, revealing perivascular inflammatory cell infiltration, inflammatory cell infiltration of Kupffer cells/macrophages and lymphocytes in the hepatic portal vein (1), fibrosis and fibrovascular septa connecting the portal tracts (2), necrosis (3), bile duct hyperplasia surrounded by fibrosis (4), red blood cell infiltration and extensive hemorrhagic lesions (5), loss of visceral tissue architecture, liver tissue destruction and hepatocyte necrosis (6)... H&E stain (200×)

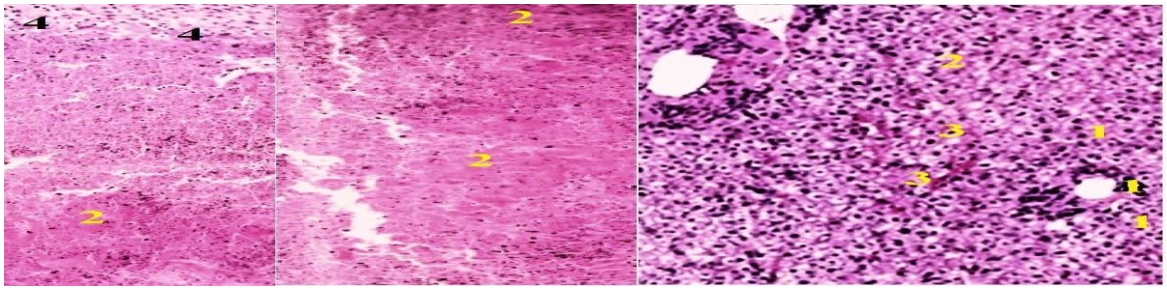

Figure 2 cross section of liver tissue of animal in G3, shows the positive effect of silymarin and rafoxanide therapy on histopathological changes after 5 weeks of the trial beginning, including the appearance of repair and re-healing tissue as the presence of normal hepatocytes, the regression of pathological lesions such as inflammatory cells, necrosis, and fibrosis, show hepatocytes in the centrilobular zone (1), with some degeneration or necrosis (2). Hepatocytes surrounding the portal tracts (junctions) have a normal, somewhat ordered structure and have large nuclei. A relative scarcity of red blood cells is observed throughout the sinusoids (3). Inflammatory cells are present, as well as hepatic Kupffer macrophages (4), which play a key role in maintaining liver function and are an indicator of recovery... H&E stain (200 x) (100 x)

DISCUSSION

Numerous studies have been conducted to find a suitable preparation to reduce the toxic effects of drugs on the liver or to reduce the destructive effects of chronic diseases, thus restoring liver efficiency, vitality, and structure. Translocation of immature parasites in liver tissue causes damage to the hepatic cell wall, leading to liver tissue necrosis, bile duct hyperplasia, and obstruction (23). These histopathological changes lead to alterations in serum liver biochemical parameters, resulting in

elevated levels of liver enzymes such as AST, ALT, GGT, and bilirubin. A decrease in serum total protein levels in bovines is a diagnostic indicator of *Fasciola* infestation. Hepatocellular damage leads to the release of liver enzymes into the bloodstream. Hepatocellular damage leads to reduced production of the proteins in the liver, such as albumin and globulin, resulting in edema in several areas of the body, such as the lower jaw, which is known as the bottle jaw. However, when treated with antiparasitic drugs, the liver may take time to recover and regain its health, so supportive therapy is required to accelerate the recovery process (26,28). Parasites can digest liver tissue and cause extensive destruction. However, mechanical liver damage is often caused by the migration of immature trematodes. Previous studies have observed degenerating hepatocytes within the mouth and pharyngeal suckers of trematodes. Figure 1 shows the histological changes in the livers of groups G1 and G2 High rates of necrosis, fibrosis, hepatitis, immune cell infiltration, and bile duct hyperplasia were observed, while Figure 2 shows the histological changes in the livers of animal in G3 group of silymarin and rafoxanide, the positive significant changes were observed. Also, the results indicated a hepatoprotective effect in G3, resulting in a significant decrease in serum enzyme and bilirubin levels and an increase in total protein at the end of the experiment ($P < 0.01$) to reach normal levels. (Table 1). Migratory flukes impair liver function by damaging the liver, which is reflected in elevated enzyme and bilirubin concentrations and decreased plasma protein (albumin and globulin). Therefore, this damage causes changes in the levels of these compounds in the blood. It is worth noting that low protein levels may lead to low levels of some vitamins, such as vitamin A and vitamin B3, which increases the deterioration of animal health (25, 28).

After two weeks, rafoxanide successfully eliminated the parasite in both G2 and G3. Moreover in G3, liver tissue was partially restored, and the integrity of the plasma membrane of the hepatocytes was maintained by silymarin, thus suppressing the leakage of enzymes (AST, ALP, and GGT) and creating new hepatocytes capable of performing their function. Many studies have supported the importance of supplements such as silymarin as a hepatoprotective agent and its ability to promote liver recovery (5,20).

Furthermore, biochemical analysis showed that total bilirubin was significantly higher ($P < 0.05$) in G1 and G2 than in G3. This increase could be attributed to increased bilirubin production due to hemolytic toxins generated by liver fluke infestation. Since combined treatments can simultaneously affect parasite death and liver recovery, lower total bilirubin levels were detected starting from the second week ($P < 0.05$) in G3 (20). All biochemical analysis results were consistent with the pathological findings. Rafoxanide was effective in eliminating the parasitic infestation to some extent, but it did not significantly and rapidly reduce the tested biochemical parameters as clearly and rapidly as in the rafoxanide and silymarin G3, which was superior in terms of better biochemical and histopathological results. The absence of visible eggs and resolution of liver lesions demonstrated that the use of silymarin did not affect or interfere with the anthelmintic activity of rafoxanide, as previous studies have shown (10,18).

We conclude that the histopathological and biochemical parameters used in this study were useful for evaluating the efficacy of anthelmintic and hepatoprotective agents. The combination of rafoxanide and silymarin protects the liver and eliminates liver flukes in naturally infested domestic cattle. Silymarin can always be used in combination with rafoxanide because it accelerates the recovery process. The study results also confirmed that serum AST, ALP, GGT, protein, and bilirubin levels are reliable indicators of liver fluke disease in cattle and can be used to test the therapeutic effect of anthelmintics and the preventive effect of hepatoprotective agents such as silymarin.

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Conflict of Interest
The author declares that there was no conflict of interest in the preparation of this manuscript.
Ethics Approval
Approved by the Presidency of the University of Baghdad.

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