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REVIEW

# An Insight into Different Strategies for Control and Prophylaxis of Fasciolosis: A Review

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ABSTRACT

Fasciolosis is one of the important diseases of livestock and has zoonotic importance. Fasciolosis can cause huge economic losses due to decrease in milk and meat production, decreased feed conversion ratio, and cost of treatment. Treatment and prophylaxis strategies for *Fasciola* infection are formed based on epidemiological data. The control of *Fasciola* infection can be attained by treating the animals with active anthelmintics. The use of different combinations of anthelmintics with a possible rotation is more effective against immature as well as adult flukes. Control of the intermediate host (snail) is vital for the reduction of fasciolosis. Due to the rapid growth of snails, the eradication is quite difficult in waterlogged and marshy areas. The use of different grazing methods and treatment of grazing areas can also help to control fasciolosis. A variety of antigens generated by *Fasciola* spp. have been shown to protect against liver fluke infection. The crude antigens, excretory/secretory, and refined antigens and their combination can be used as prophylactic treatment for the control of fasciolosis. The use of any of the single or combination of these methods can be very effective for the control of fasciolosis.

## 1. Introduction

Fasciolosis is a zoonotic disease caused by the species of the genus *Fasciola* belonging to Platyhelminthes, Digenea, and Fasciolidae. In animals and humans, fasciolosis is transmitted through food and drinking water. Fasciolosis is prevalent all around the world and is reported more frequently in the tropics [1]. Treatment and prophylaxis strategies for *Fasciola* infection are formed based on epidemiological data. The effective treatment

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of fasciolosis during the prepatent period will be helpful in reducing the *Fasciola* infection. It also helps to reduce pasture contamination to a very low level and requires treatments less frequently for a considerable time [2]. The successful control of fasciolosis can be achieved, by treating the animals with effective anthelmintic drugs or their combinations with a possible rotation against both immature and adult flukes [3]. Grazing management like rotational grazing and treatment of grazing areas (biological and chemical) can also be effective for the control of fasciolosis. The use of a combination of flukicide along with the control of snails, proper sanitation practices, and environmental manipulation is thought to be more efficacious.

The efficient control of mortality in fasciolosis can be ensured by the early diagnosis of the disease. The control of infection at the early stage by administration of effective anthelmintic can reduce the pathogenesis [4]. Traditional diagnostic methods are not very sensitive and sometimes give false-negative results. Such kinds of results can lead towards the production losses and even mortality of animals. To overcome the limitation of traditional methods, various molecular techniques have been developed which are more sensitive. For the control and prevention of fasciolosis, a variety of methods are available, and this review highlights the possible methods.

## 2. Epidemiology and Financial Loss due to Fasciolosis

Fasciolosis is prevalent in various parts of Asia, including the Middle East (Pakistan, Nepal, Iran, Turkey, Vietnam, Iraq, Russia, Thailand, Bangladesh, China, Japan, Korea, Saudi Arabia, Cambodia, and the Philippines). In Bangladesh, the prevalence of fasciolosis in cattle has been reported about 14.28 percent to 21.54 percent [5]. The higher prevalence of the parasite may be associated with high rainfall, as moist environments are best for snail reproduction and survival [6]. The overall prevalence of these helminths was estimated to be 28.5 percent in a research done on sheep in China, and the greater prevalence suggested the need for better managemental practices [7]. In India, varying figures have been recorded for sheep (2.78%~8.98%), goats (2.35%~15%), cattle (10.79%), and buffaloes (10.79%) [8]. The increasing incidence of fasciolosis may be attributed to good weather for snail populations, the availability of well-irrigated, low-lying marshy ground, and pastures beside water bodies that are appropriate for intermediate host reproduction [9]. In Europe, 11 countries (UK, Ireland, France, Portugal, Spain, Switzerland, Italy, Netherland, Germany, and Poland) have revealed fasciolosis prevalence, with cattle (0.12 percent~86.0 percent) having the highest prevalence and goats (0.0 percent~0.8 percent) having the lowest. In bovines, covered regions by meadows and wet environments and the density of big lakes are connected with fasciolosis risk. This helminthic infection has been found in 48 percent of England's cow herds [10]. The high frequency of fasciolosis is linked with summer rains and sheep migrations in endemic fluke areas. The seasonal occurrence has been observed as high as 57.10 percent in Germany [11].

Iraq suffered a financial loss of US$ 8801.69/year as a result of the condemnation of contaminated animal parts [12]. The overall economic loss in Turkey due to fasciolosis was assessed to be US$ 63.03 based on the company's wholesale rates [13]. The average yearly cost of liver condemnation in Saudi Arabia has been reported to be US$ 0.2 million [14]. In 2001, the Kingdom of Cambodia suffered a loss of about 17.02 million US dollars due to fasciolosis in cattle and buffaloes [15]. In Bangladesh, the financial losses owing to liver condemnation were US$ 2374.9/year [16]. The median financial loss owing to bovine fasciolosis in Switzerland has been estimated at over 52 million dollars due to lower milk supply and fertility, with low costs due to reduced meat production and liver condemnation [11].

## 3. Control of Snails

Control of the intermediate host (snail) is vital for the reduction of fasciolosis. Due to the rapid growth of snails, the eradication is quite difficult in waterlogged and marshy areas. The snail poisons come in a variety of forms, but they require greater attention and accuracy in their application. Different molluscicides are used for snails' control and some of them are more effective, such as the combination of molluscicides such as a pyrethriod (Deltamethrin), N-octyl bicycloheptene dicarboximide, sodium pentachlorophenate, niclosamide, pyrethroids, N-tritylmorpholine, and thiodicarb [17]. It has been reported that molluscicides' properties come from the different plant extracts like leema toxins or endod that are obtained from the fruits of the shrub, *Phytolacca dodecandr* [18]. Lemma toxins or "Endod" were shown to be quite effective for the control of *Lymnaea* (*L.) truncatula*, *L. natalensis*, and *Fasciola* transmitting snails.

However, due to their poisonous nature to the environment, many ecosystems are topographically unfavorable for the application of molluscicides, making them difficult to apply properly. Because they are not species-specific and may eliminate all types of snails, which are of great value as food in certain communities. Moreover, the frequent application and collaboration between adjoining properties are essential for successful cover [17]. Different compounds used as molluscicides for the control of trematode infection and their possible risks are given in Table 1. Other beneficial approaches to control fasciolosis include snails' biological control and fencing of the waterlogged region to prevent infected snails from direct contact with final hosts [19]. Other than chemical compounds, a variety of medicinal plants have been used as molluscicides around the world (Table 2).

**Table 1.** Different compounds used as molluscicides for the control of trematode infection and their possible risks

| Compound | Risks | Formulation |
|---|---|---|
| Bordeaux Mixture | Lime and copper sulfate combination; it causes an acute but moderate oral poisonousness risk. Harmful to aquatic life, fish and invertebrates. Brush a Bordeaux combination onto tree trunks to prevent snails; one treatment should continue for a year. | Spray, Dust |
| Boric Acid | Different borates as well as boric acid occur normally in the eating regimen and have somewhat low but acute toxicity. Through the skin they remain unabsorbed; nonetheless, ingestion of modest quantities of boric acid consistently more than several months has been displayed to decrease sperm count in lab creatures. Borates are harmful to plants. | Bait pellets, Dust, Granules |
| Diatomaceous Earth | When breathed in it causes lung disturbance. In occupational settings lung cancer is caused by prolonged exposure to diatomaceous earth dust. | Dust |
| Iron Phosphate | Low but acute poisonousness to wildlife, pets and people. Pets that eat lure might get an upset stomach. | Granules, Bait pellets |
| Carbaryl | Poisonous to the nervous system of bees, pets and humans. The EPA named it as a cancer-causing agent. To increase the poisonousness of metaldehyde bait, carbaryl is frequently added into it. Profoundly poisonous to beneficial bugs and bees. | Bait Pellets |
| Metaldehyde | For humans, metaldehyde is a cause of moderate but acute oral toxicity. It is also poisonous to birds, canines and felines. Pelleted lures can be a reason of non-target poisoning in wildlife and pets. | Dust, Bait Pellets, Spray, Granules, |
| Methiocarb | Moderate acute inhalation toxicity and high but acute oral toxicity. Methiocarb is highly harmful to beneficial insects, bees and birds. For aquatic species it is also profoundly toxic. | Bait Pellets, Granules, Powder |
| Spinosad | To expand the quantity of pests controlled, sinosad is frequently added to iron phosphate bait.<br>It causes a low intense poisonousness hazard to people and isn't probably going to cause cancer or other prolonged illness. No prolonged experiments have been conducted. Moderately harmful to beneficial bugs, fish and aquatic invertebrates. | Bait pellets |

**Table 2.** Medicinal plants used as molluscicides against different species of snail around the world

| Molluscicide | Species of Snail | Country | Lethal Concentration | References |
|---|---|---|---|---|
| *Citrullus colocynthis* | *Galba truncatula* | Tunisia | $LC_{50}$=12.6 mg/L | 20 |
| *Euphorbia splendens* | *Lymnaea columella* | Brazil | $LC_{90}$=1.51 mg/L | 21 |
| *Atriplex stylosa* | *Biomphalaria alexandrina* | Egypt | $LC_{90}$=180 ppm | 22 |
| *Atriplex stylosa* | *Bulinus truncates* | Egypt | $LC_{90}$=167 ppm | 22 |
| *Atriplex stylosa* | *Lymnaea cailliaudi* | Egypt | $LC_{90}$=162 ppm | 22 |
| *Agave ferox* | *Biomphalaria alexandrina* | Egypt | $LC_{90}$=192 ppm | 22 |
| *Agave ferox* | *Bulinus truncates* | Egypt | $LC_{90}$=185 ppm | 22 |
| *Agave ferox* | *Lymnaea cailliaudi* | Egypt | $LC_{90}$=179 ppm | 22 |
| *Alternentherase ssilis* | *Bulinus globosus* | NA | $LC_{50}$=40.42 ppm | 23 |
| *Balanites aegyptiaca* | *Biomphalaria pfeifferi* | Saudia Arabia | $LC_{50}$=56.23 ppm | 24 |
| *Caesalpiniapulc herrima* | *Biomphalaria pfeifferi* | NA | $LC_{50}$=614.8 ppm | 25 |
| *Calotropis procera* | *Monacha cantiana* | Saudia Arabia | $LC_{50}$=34.35 mg/L | 26 |
| *Calotropis procera* | *Bulinus truncatus* | Sudan | $LC_{50}$=619 ppm | 27 |
| *Jatropha curcas* | *Ampullaria gigas* | China | $LC_{50}$=50 ppm | 28 |
| *Jatropha curcas* | *Schistosoma haematobium* | Germany | $LC_{100}$=25 ppm | 29 |

## 4. Chemotherapeutic Control of *Fasciola* Spp.

Flukicide is particularly successful in controlling most trematode infections when used strategically [30]. Triclabendazole (TCBZ) is very efficacious against all stages of flukes e.g., adults as well as the parenchymal stages of *Fasciola* spp. The most used drugs for fasciolosis include diamphentide, rafoxanide, nitroxynil, brotanide, and closantel. Chemotherapy helps in the reduction of infection severity and prevalence, as indicated by fecal egg counts [31].

The efficacy of closantel (a salicylanilide antiparasitic compound) in goats with naturally-acquired fasciolosis was determined, which elicited 80.3%, 97.8%, and 92.7% efficacy at the second, third- and fourth week, respectively. A comparative study of ethnoveterinary plant extracts *viz. Caesalpinia crista*, *Fumaria parviflora, Saussurea lappa*, and *Nigella sativa* with triclabendazole was conducted. The extracts of *Fumaria parviflora* and triclabendazole were most effective as compared to the *Caesalpinia crista* and *Nigella sativa,* however, the *Saussurea lappa* showed low flukicidal activity in comparison to plant extracts [32]. The result of the study determined the efficacy of different drugs like oxyclozanide, rafoxanide, and triclabendazole, and showed that the treatment with oxyclozanide in animals presented a maximum reduction of EPG as compared to the treatment of animals with triclabendazole and rafoxanide [33]. The percentage efficacy of various drugs used to control fasciolosis around the world is given in Table 3.

## 5. Management of Grazing Environment

Pasture rotations have been used in various parts of the world for the last four decades for the production of goats

**Table 3.** The percentage efficacy of various drugs used to control fasciolosis around the world

| Drug | City | Country | Animal | % Efficacy | References |
|---|---|---|---|---|---|
| Oxfendazole | Sargodha | Pakistan | Sheep | 72.85% | 4 |
| Oxyclozanide | Sargodha | Pakistan | Sheep | 80.40% | 4 |
| Triclabendazole | Sargodha | Pakistan | Sheep | 83% | 4 |
| Levamesole | Sargodha | Pakistan | Sheep | 74.32% | 4 |
| Triclabendazole (Flukare C) | Gippsland | Australia | Cattle | 0% | 34 |
| Clorsulon (Virbamec) | Gippsland | Australia | Cattle | 100% | 34 |
| Oxyclozanide (Nilzan) | Gippsland | Australia | Cattle | 100% | 34 |
| Albendazole | NA | Sweden | Sheep | 67% | 35 |
| Triclabendazole | NA | Sweden | Sheep | 97%-100% | 35 |
| Nitroxynil | Iringa/Arumeru | Tanzania | Cattle | 100% | 36 |
| Triclabendazole | Iringa/Arumeru | Tanzania | Cattle | 100% | 36 |
| Oxyclozanide | Iringa/Arumeru | Tanzania | Cattle | 96.7%-100% | 37 |
| Oxyclozanide | NA | Sudan | Sheep | 86% | 38 |
| Triclabendazole | Chad lake | Chad | Cattle | 98% | 39 |
| Triclabendazole | Cajamarca | Peru | Cattle | 31% | 40 |
| Triclabendazole | Cajamarca | Peru | Sheep | 25% | 40 |
| Closantel | NA | Netherlands | Cattle | 100% | 41 |
| Nitroxynil | Patagonia | Argentina | Cattle | 100% | 42 |
| Triclabendazole | Patagonia | Argentina | Cattle | 18% | 42 |
| Closantel | Patagonia | Argentina | Cattle | 100% | 42 |

and proper grazing management. This process is very helpful to minimize the spread of helminth infection. The dose of an effective anthelmintic and the movement of animals to a less contaminated pasture was found to be a good strategy for the control of helminths infection [43].

The grazing management was also done by alternate hosts, cropping and aftermaths, clean grazing, and rotational grazing for the control of helminths infection. Grazing management without anthelmintics treatment is very effective during defined circumstances however, grazing management with anthelmintics treatment requires some care for sufficient refugia, if treated animals and pasture have some unexposed worms, then there can be a strong selection for drug resistance [44].

Predatory fungi, e.g., *Duddingtonia flagrans* have also been used as an alternative approach to the management of pasture for the control of free-living parasite populations [45]. Under optimum conditions (fungal growth and larval development occurring at the same time), a great reduction in the larval population was observed by using this approach.

Snail-borne helminth and water-borne infections can be controlled by applying different techniques like providing clean water supplies and proper sewage systems and control of draining swamps. However, chemotherapy is cheaper than all the above control methods of helminths infections [46].

## 6. Immunological Control

A variety of antigens generated by *Fasciola* spp. have been shown to protect against liver fluke infection. These antigens can also be used for the detection of fasciolosis [47]. Effective vaccines have been developed using both crude and refined antigens. These antigenic vaccinations aid in the reduction of fluke loads as well as fluke proliferation. As a result, both the number of eggs produced and the liver disease were decreased, dramatically. Purified glutathione S-transferase (GST) antigen is also being utilized to produce the fasciolosis vaccine. Vaccination of young ruminants with irradiated *Fasciola* spp. metacercariae provided protection which ranged from 45% to 68% [48].

Antigenically varied components found in *Fasciola* spp. are capable of activating host immunological responses. These antigens have been used to explore the host's immune response and can be used as potential vaccine components. *Fasciola* spp. produce many antigens which were already used as protection against liver fluke infections. For the development of the effective vaccine, crude and purified antigens have already been used. And these antigenic vaccines help to reduce the fluke growth and infection rate and egg production, which ultimately reduces the liver pathology by reducing the fluke's growth. Purified glutathione S-transferase (GST) antigen has been used as a vaccine to control fasciolosis. After those effects have been observed in vaccinated and non-vaccinated animals, the infection rate was very low in the vaccinated animals. Vaccinating young ruminants with irradiated *F. gigantica* metacercaria provided 45% to 68% protection against the parasite [49].

Irradiated metacercaria of *F. hepatica* protected ruminants from *F. hepatica*. Glutathione-S transferase (GST) and *F. gigantica* cathepsin L were shown to be ineffective in protecting cattle from *F. gigantica* infection [50]. These proteins were protective against *F. hepatica* with the vaccinated cattle, sheep, and goats showing a greater level of protection [51]. The fact that animals responded differently to immunization with GST, cathepsin L, and FABP from *F. gigantica* and *F. hepatica* showed that the parasite-host-parasite interactions are different.

Antigenically varied components found in *Fasciola* spp. are capable of activating host immunological responses. These antigens have been used to explore the host's immune responses as well as potential vaccine components. Somatic antigens and ES Ag are examples of these antigens [50].

It is necessary to produce and purify recombinant cathepsin protease that mimics the levels of immunogenicity generated by natural protease. The generation of physiologically active, native-like recombinant cathepsin protein can be achieved by expressing cathepsin B and L in yeast [49]. Recombinant cathepsin L obtained in Pichia (*P.) pastoris* was utilized as a vaccine in sheep and goats, resulting in 35% to 45% protection and a 50% anti-fecundity effect. Baculovirus and Saccharomyces (*S.) cerevisiae* were used to produce recombinant procathepsin L3. In rats, baculovirus-encoded protease provided 52% protection, whereas yeast-encoded protease provided no meaningful protection [50]. Intranasal vaccination of large ruminants with recombinant cathepsin W cysteine protease elicited 54 percent protection against infection, whereas intranasal immunization of small ruminants elicited 56.5 percent protection against infection. Because native cathepsin B from immature liver flukes is only produced in trace levels, conducting vaccination trials is challenging. As a result, rats were immunized with recombinant FhCatB. In vaccinated animals, the yeast-produced protein was formed in either Quil A or Freund's adjuvant and generated IgG antibody titers of 106 and 105, respectively [52]. The percentage efficacy of various antigens used as immunoprophylaxis for the control of fasciolosis is given in Table 4.

**Table 4.** The percentage efficacy of various antigens used as immunoprophylaxis for the control of fasciolosis

| Antigens | Parasites | Country | Animal | % Efficacy | References |
|---|---|---|---|---|---|
| FhCL1 | *F. hepatica* | Denmark | Goat | 38.70% | 53 |
| FhCL1 | *F. hepatica* | Spain | Sheep | 0% | 54 |
| FhCL1 | *F. hepatica* | Spain | Goat | 0% | 55 |
| FhPrx | *F. hepatica* | Spain | Goat | 33.10% | 56 |
| FhLAP | *F. hepatica* | Uruguay | Rabbit | 78% | 57 |
| FhLAP | *F. hepatica* | Uruguay | Sheep | 83.80% | 58 |
| FhCL1 | *F. hepatica* | Ireland | cattle | 47% | 59 |
| FABP(Fh12) | *F. hepatica* | Spain | Sheep | 42.00% | 60 |
| FABP + GST | *F. gigantica* | India | Buffalo | 35% | 61 |
| rPrx | *F. hepatica* | Spain | Goat | 0.00% | 53 |
| rPrx | *F. gigantica* | India | Buffalo | 0% | 62 |
| rPrx | *F. hepatica* | Spain | Goat | 0.00% | 56 |
| RHbF2 | *F. hepatica* | Belgium | cattle | 0% | 63 |
| rLAP | *F. gigantica* | India | Buffalo | 0.00% | 62 |
| rLAP | *F. hepatica* | Uruguay | Sheep | 49%-86% | 58 |
| CatL1 Mimotopes | *F. hepatica* | NA | Goat | 46%-79% | 64 |
| CatL1 Mimotopes | *F. hepatica* | Mexico | Sheep | 51% | 64 |
| rCatL1 | *F. hepatica* | Spain | Goat | 0% | 55 |
| rCatL1 | *F. hepatica* | Spain | Goat | 0% | 53 |
| rCatL1 | *F. hepatica* | Ireland | cattle | 48% | 59 |
| Sm14 Peptide | *F. hepatica* | Spain | Goat | 0% | 65 |
| rFABP | *F. gigantica* | India | Buffalo | 0% | 61 |

## 7. Conclusions

Fasciolosis is one of the important diseases of livestock and has zoonotic importance. Fasciolosis can cause huge economic losses due to decreases in milk and meat production, decreased feed conversion ratio, and cost of treatment. For the control of death and to improve the production of animals, it is necessary to control the infection. Early detection of fasciolosis, treatment of animals with the best anthelmintics, strategic control of the intermediate host, effective use of grazing methods, and use of different antigens as a prophylactic treatment are the best strategies to control the disease. The use of chemical compounds without their proper knowledge and dose rate to control the intermediate host and immature and adult flukes can lead to the development of resistance. The use of the same compound, again and again, can also be responsible for the development of resistant worms. To avoid the development of resistant worms, the strategic use of chemical compounds is very crucial. The development of an effective vaccine to control fasciolosis is necessary to stop infection and production losses.

## Author Contributions

HMR and MSS contributed to the conception and design of the article, HA, SG and MA drafted the article and revised it critically.

## Conflict of Interest

Authors declare that there is no conflict of interest.

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