Chapter 16

Plant as Anthelmintic Allies in the Fight against Fasciolosis: A Review

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ABSTRACT

Plants are the primary food source for ruminating mammals; therefore, using different medicinal plants (extracts, oils, and bioactive compounds) could be effective fasciolicides to prevent economic losses due to fasciolosis. The problem of anthelmintic resistance in flukes due to the excessive and inappropriate use of fasciolicides poses an alarming threat and urges the development of new and alternative fasciolicides. Now, the focus is diverging towards plant-based fasciolicides because of their safe and environment-friendly nature. Different plants' essential oils and active compounds are effective in controlling egg hatching and causing the mortality of adult flukes. The *Artemisia* and *Etlingera* extracts exhibited significant efficacy against eggs and adults of *Fasciola spp.* The plants (*Zingebar officinalle* and *Potentilla fulgens*) also showed considerable efficacy against miracidia, sporocyst, rediae, and cercarial stages. The use of plant oils in controlling parasitism has been practiced all over the world. Oils from (*Pelargonium graveolens*, *Citrus aurantium*, *Helianthus annuus*, and *Cuminum cyminum*) plants actively inhibit egg development. Moreover, plants' active compounds, diterpenoids, thymoquinone, curcumin, flavonoids, acids, artemisinin, and saponins also show promising effects on egg development and adult fluke productivity.

KEYWORDS		
Fasciola, Fasciolosis, Anthelmintics, Phytotherapy, Medicinal Plants	Received: 04-Jun-2024 Revised: 01-Jul-2024 Accepted: 05-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Fasciolosis (Fascioliasis) is a zoonotic disease that affects animals and humans worldwide. A trematode parasite, *Fasciola* (*F. hepatica* and *F. gigantica*) also called liver fluke, causes the disease and can be transmitted to animals and humans through its infective stage (metacercariae). The life cycle of this parasite consists of two hosts. The eggs are shed in the faeces of ruminants as sheep, cattle, and goat, and are hatched into the miracidia that infect the first host snail (Lymnid). There, it progresses asexually into its two stages, sporocysts and rediae, after which snail starts shedding cercariae in the water. These cercariae swim randomly, and after a few hours, they lose their tail, get enclosed in a wall and become metacercariae (infective stage) and attached to the watercress or leaves. When the final host mammals (sheep, cattle, and goat), ingest watercress, undercooked vegetables or leaves, the infective metacercariae become converted into immature flukes which excyst in the duodenum, penetrate the intestinal wall and migrate through liver parenchyma to biliary ducts (FAO, 2020; Mia et al., 2021).

Prevalence of Fasciolosis

Fasciola hepatica is prevalent worldwide, while *Fasciola gigantica* is distributed in the tropics (Urquhart et al., 1996). The overall infection rate is increasing due to climate change, drug resistance, and its ability to intrude new areas. It infects more than 2.4 million people worldwide, with 180 million at risk of infection in 66 countries. In livestock, it is hard to quantify, but according to an estimate, it infects over 600 million domestic ruminants annually, which causes heavy economic losses (Collado et al., 2019). The global prevalence of fasciolosis in livestock ranges from 0.72 to 94% (Khan et al., 2013). Humans are accidental hosts which may be due to the ingestion of raw or undercooked vegetables. The infection rate in humans is low with an estimated 4.5% of people worldwide are thought to have fasciolosis (Infantes et al., 2023).

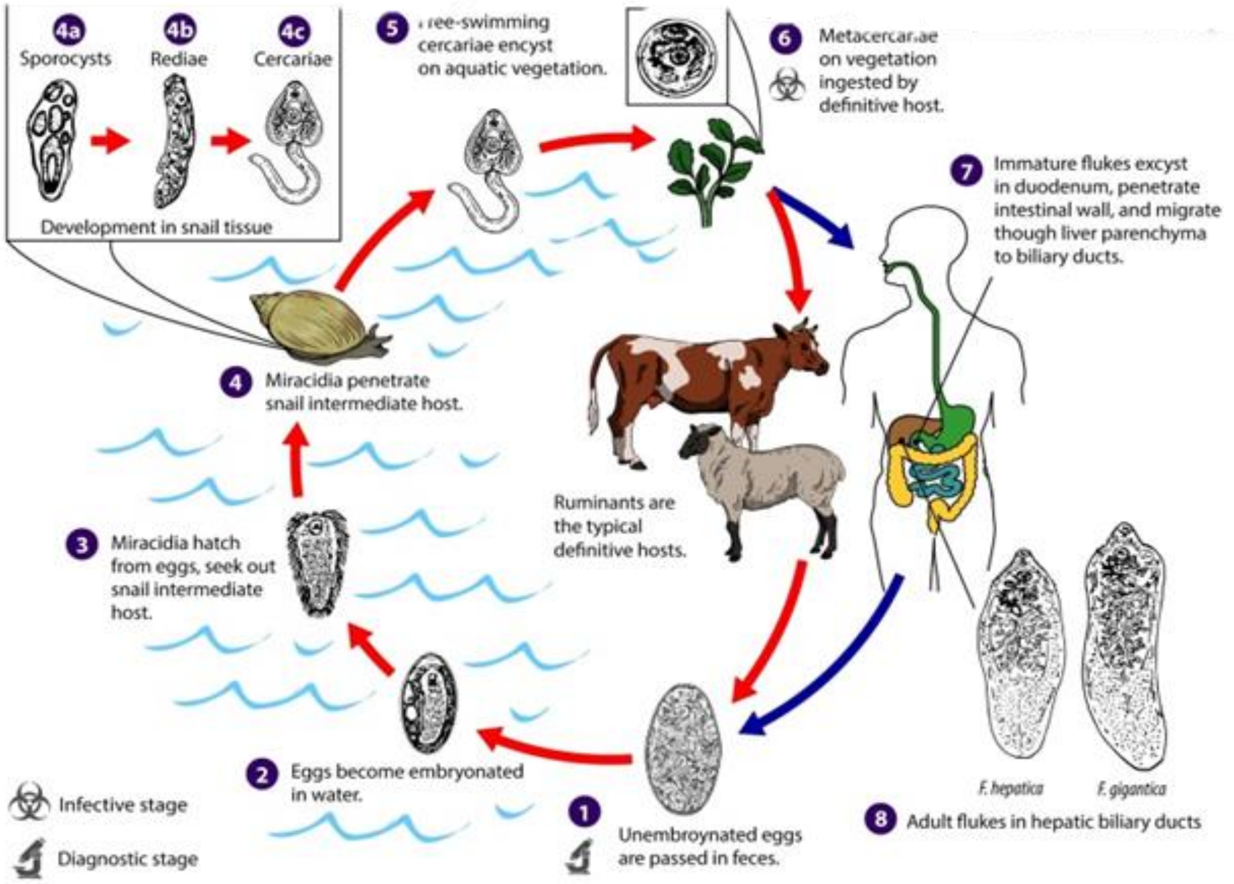

Fig: Life cycle of *Fasciola* spp.

The prevalence of fasciolosis in Pakistan from 2000-2020 was reported in a study. It was 42.70% in Sindh, 25.20% in Baluchistan, 17.70% in Punjab, 10.70% in KPK, and 1.50% in Islamabad. The prevalence was highest among sheep in Punjab at 65.7%, in Baluchistan cows at 28.5%, and in KPK buffalo at 15.9% (Rizwan et al., 2022).

Economic Impact

Helminthes infection costs the agriculture sector an annual loss of US$20 billion towards animal productivity, out of which, the liver fluke infection was predicted to cause annual losses of about US$3.20 billion worldwide (Mehmood et al., 2017; FAO, 2020). The following Table 1 summarizes the economic losses throughout the world due to *Fasciola* infection.

Table 1: Economic Losses in Different Regions of the World

Regions	Countries	Economic Loss through	Economic Loss	Reference
Asia	Iraq	Liver condemnation	US$ 8801.69	Kadir et al. (2012)
	Saudi Arabia		US$ 0.2 M	Degheidy and Al-Malki (2012)
	Sudan		US$ 1.94 M	Abebe et al. (2010)
Africa	Uganda	Liver condemnation	US$ 92 M	Joan et al. (2015)
America	Brazil	Weight loss	35 US$ PH	Dutra et al. (2010)
	Mexico	Productivity loss through reduced milk and meat yield	US$ 4.2 M	Rodriguez et al. (2017)
Australia	Australia	Productivity loss through meat and milk, liver condemination	60–90 M A$	Toet et al. (2014)
Europe	Switzerland	Reduced milk yield, fertility and meat	52$ M	Schweizer et al. (2005)

Control of Fasciolosis

Chemotherapy

Chemotherapy has a primary role in controlling parasitic diseases as it is affordable and effective (Khan et al., 2017). The control of fascioliasis is mainly achieved using synthetic anthelmintics such as albendazole, triclabendazole, and nitroxynil (Nixon et al., 2020; Kouadio et al., 2021). Among the benzimidazole derivatives, triclabendazole (TCBZ) is the most important and widely used drug of choice that can effectively control fasciolosis (Castro Hermida et al., 2021). It is the only drug that has an efficacy of >98% against adults and especially immature flukes as compared to other flukicides that target only adult flukes (Kahl et al., 2023).

Resistance against Anthelmintics

The liver fluke infection is increasing due to climate change, changes in the land use, increased movement of livestock, and its ability to intrude into new areas, which is compounded by the rising issue of anthelmintic resistance in *Fasciola* spp. (Beesley et al., 2023). The problem with the triclabendazole (TCBZ) resistance may be due to the farmers using less effective substitutes or even administering the dose inadvertently (Fairweather et al., 2012). In the recent years, many studies have shown that TCBZ is ineffective against *F. hepatica* in ruminants all over the world. The threat of drug resistance requires serious attention, as many reports have demonstrated drug resistance worldwide, including Scotland **(**Sargison and Scott, 2011), Spain (Martinez Valladares et al., 2014), and New Zealand (Hassell and Chapman, 2012), Wales (Gordon et al., 2012), Peru (Ortiz et al., 2013), Australia (Brockwell et al., 2014), Ireland (Hanna et al., 2015), and Argentina (Larroza et al., 2023).

Besides the issue of anthelmintic resistance, chemical residues found in derived products like milk and meat and their environmental effects are additional crucial factors to be aware of (Da Silva et al., 2020). Thus, for sustainable livestock production, the management of fasciolosis towards TCBZ resistance and the development of new alternatives as flukicides are necessary.

Plants as Anthelmintic Allies

Currently, the livestock sector is under threat due to the problem of increasing resistance to anthelmintics, which is because of factors including inappropriate dosage and repeated exposure of anthelmintics for deworming. Hence, search for alternative anthelmintics is necessary. For this, plant-based anthelmintics could be a preference for coping with this problem. Plant-based anthelmintic are becoming a growing trend because they are safer than the synthetic ones. Moreover, plants provide cost-effective substitutes that are more effective than synthetic anthelmintics (Zirintunda et al., 2022).

Around 80% of people use traditional medicine all over the world, and out of them, about 85% depends on medicinal plants (Nascimento et al., 2000; Oyebode et al., 2016; Romero-Benavides et al., 2017; Sanchez et al., 2020). Plants have been used as medicinal agents from millennia and become the integral part of animal's life. Moreover, plants are also immune boosters that protects against many diseases and also provide many vital nutrients to animal's body. Plants have some of the nature's most effective medicinal compounds. Their extracts and bioactive substances have the potential to become new medicinal agents because of their diversity and environment friendly nature (Abbas et al., 2020; Nurlaelasari et al., 2023). Many medicinal plants can be used as antibacterial agents (Chassagne et al., 2021), antiparasitic (Benlarbi et al., 2023), and antifungal agents (Nigussie et al., 2021). Hence identifying and validating different compounds and their extracts as effective fasciolicide is also necessary. For this, during the recent decades, many plants and their extracts have been evaluated for their anthelmintic activity worldwide (Pessoa et al., 2002; Kozan et al., 2006; Eguale et al., 2011; Ahmed et al., 2013; Payne et al., 2013; Acharya et al., 2014; Esteban Ballesteros et al., 2019).

Plant Extracts

Use of plants as a whole requires a lot of plant mass moreover these are not as much effective. Instead, plant extracts and purified fractions must be used which can provide effective alternative to fasciolicides. The efficacy of plant extract depends on the solvent (water, methanol, ethanol, etc.) used for the extraction and also the mechanism of extraction (hot or cold maceration, proclation, soxhlet extraction, etc.). The solvents provide a medium for the extraction of active phytochemicals like phenols, alkalines, tannins, saponins, etc., and these should be extracted in a preferred medium. Plant extracts provide a combination of different phytochemicals that collectively act as fasciolicide. There are many studies that use different plant extracts to validate their efficacy against *Fasciola spp*. Nurlaelasari et al. (2023) conducted an experiment to evaluate the antifasciolic activity of Mugwort (*Artemisia vulgaris)* extract on the both adult and eggs stages of *Fasciola gigantica.* They assessed the ovicidal efficacy by incubating the eggs with the *A. vulgaris* extract at 5%, 2.5%, and 1.25% for 5, 9, 11, 14, and 16 days. The adult mortality assays were performed after incubating with the extract for 5, 10, 20, 40, 80, 160, 320, and 640 min. All the extract concentrations show significant anti-fasciolic activities. Among these, a 5% concentration of extract showed high level of ovicidal activity, whereas a concentration of 20% extract inhibits 66.67% of eggs hatching after 40 min of exposure. The extract also had high flukicidal efficacy, causing disintegration of different physiological structures (vitelline follicles, intestine, acetabulum, tegument, and spine) of adult fluke. This study has indicated that *A. vulgaris* extract exhibits potential antifasciolic properties. In another study conducted by Wulandari et al. (2023), Torch ginger (*Etlingera elatior)* ethanolic extract was evaluated on eggs and adults of *Fasciola gigantica*. The egg-hatching assay was performed at different concentrations. The ova development was reduced by 56.67%, 56.67%, and 36.67%, at 5%, 2.5%, and 1.25% concentrations, respectively, on day 11 post-incubation, and after 14 days, these developed eggs were decreased by 70%, 50%, and 13.33%, respectively. The flukicidal efficacy was recorded at 10% and 20% of the extract concentration, and the death of flukes was noted after 640 min and 80 min, respectively. The skin was damaged, the inner membrane of spina has erosions and syncytium was detached from the tegument. The study showed that *E. elatior* extract has antifasciolic activity against different stages of flukes. The ginger (*Zingebar officinalle*) hydroalcoholic extract was evaluated on the miracicidal stage of *Fasciola hepatica* by Ghafari et al. (2021). The hatched miracidia was incubated at 2, 5, and 10 ug/mL concentrations. The extract concentrations of 10, 5, and 2 ug/ml cause the fatality of miracidia within 105, 275, and 520 sec. and reduce the speed of miracidia movement to 0.08, 0.77, and 0.82 mm/s, respectively. The comparative efficacy with triclabendazole shows that the extract has antimiracidial efficacy. Kumar et al. (2020) performed the *in-vitro* larvicidal assay on sporocyst, redia, and cercaria stages of *Fasciola*. The Lined Cinquefoil (*Potentilla fulgens*) organic extracts and column-purified fractions larval motility was time and concentration-dependent. The highest toxicity against sporocyst, redia, and cercaria after 2h (LC50) of exposure was column purified fraction 62.4, 59.5, and 45.1 mg/L, respectively. In contrast, the lowest toxicity at this time was of ethanol extract 66.2, 64.7, and 51.3 mg/L, respectively. The same trend was found after 8h (LC50) of exposure, where column purified fraction has the highest toxicity while ethanol extract has the lowest toxicity.

Plant Oils

A number of plant derived natural products including the natural oils have been shown to possess anti parasitic activity, as they have been used against different parasites *in-vitro* and *in-vivo*. De Mello et al. (2023) evaluated the antifasciolic activity of essential oils (EOs) from two plants, Geranium *(Pelargonium graveolens)* and Sour orange (*Citrus aurantium)*, on *Fasciola hepatica*. The essential oils from both plants show 100% efficacy to inactive egg hatching. The Geranium extract showed a mean mortality time of 15 h at both concentrations tested 0.0675 and 0.03375 mg/mL, while Sour orange extract promoted death within 18 h of incubation at concentration of 0.06375 mg/mL. The accumulation of liquid in the tegument was observed. It indicates that essential oils have potential ovicidal and adulticidal activities. Another research conducted by Da Silva et al. (2020) evaluated the Sunflower (*Helianthus annuus)* fixed oil and Cumin (*Cuminum cyminum)* essential oil against *Fasciola hepatica*. The *in-vitro* assay was assessed at different concentrations both fixed and essential oils and also the combination of both oils. The essential oil at concentration of 0.03 mg/mL showed 99% efficacy and the combination of both oils at 0.035+0.03 mg/mL showed 94% effectiveness, while the fixed oil was active insufficiently as an ovicidal. Overall, the results of the experiment showed that the essential oil of Cumin could be used as a new alternative for fascioliasis control.

Plant Active Compounds

Plant compounds and their active ingredients have great potential in the control of various parasites, thus interest is increasing for the search and use of new alternatives. The botanical-derived compounds harboring potential parasiticidal properties are tested as therapeutic agents worldwide. The most common phytochemical constituents of plants are diterpenoids, thymoquinone, curcumin, carbohydrates, terpenoids, fats, enzymes, amino acids, flavonoids, chicoric acid, phenols, polyphenols, alkaloids, artimisinin, saponins, anthocyanins, tannins, isoflavones and carotenoids etc. Interest in the studies with bioactive compounds has been growing as they show direct or indirect negative effects against endoparasites. Several natural diterpenoid molecules have been studied against parasitic trematodes, and their anthelmintic properties have been evaluated. In a study, Chakroborty et al. (2022) evaluated the use of nineteen chemically modified natural active compounds, abietic acid diterpenoid analogues (MC001 to MC088) were first evaluated for their anthelmintic activities against newly excysted juveniles (NEJs) of *Fasciola hepatica*. The six analogues that were proven effective against NEJs (MC008, MC009, MC010, MC052, MC058, and MC061) were secondly evaluated for their anthelmintic activities against adult wild strain flukes. From these analogues MC010 was highly effective against 8-week immature- and 12-week mature Italian strain flukes. The damage to the dorsal side of the fluke was observed. They deducted that the use of abietic acids can be a potential candidate for the development of new anthelmintics. Thymoquinone and curcumin are the active ingredients of *Nigella sativa* and *Curcuma longa,* respectively. Ullah et al. (2017) used these active ingredients as flukicidal agents against *Fasciola gigantica.* The worm motility and egg shedding were both time and concentration-dependent. The adult flukes were exposed to different concentrations (20, 40, 60 µM) of thymoquinone and curcumin. The reduction in motility was observed at 60 µM, but the worms remained alive for 3h post-exposure. The tegumental disruptions and spine erosion were observed in the posterior region and around the acetabulum. Thus, thymoquinone and curcumin have the potential to have a flukicidal effect.

Conclusion

Fasciolosis control using plant-based medicines is proving to be more effective than synthetic anthelmintic, i.e. albendazole. Moreover, plant-based medicines are a growing trend towards a sustainable and nature-friendly environment. In phytotherapy, the time and concentration-dependent factors are the most important; hence, determining toxicity is necessary. Further research using different plant extracts, oils, and their active compounds in this field should be evaluated. However, to confirm which concentrations effectively control eggs, miracidia, larvae, and adult stages is required. Moreover, the mechanism of action should also be understood through different methods like the molecular docking method to eradicate fasciolosis from the livestock industry completely.

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