



Veterinary Anthelmintics and Anthelmintic Drug Resistance

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Abstract

Helminths are a diverse group of parasitic worms in the body of animals and human. Infection of livestock with parasitic worms poses a great burden on the health of animals that eventually leads to great losses in the productivity of these animals and economic losses to the farmers. The control of helminthiasis is dependent almost solely on the use of anthelmintic drugs, due to the ease of implementation and low cost of therapy, compared to other methods of control. However, chemotherapy of parasitic worms is burdened with such problems as the development of anthelmintic resistance (AR). Many of the currently available anthelmintic drugs have been in use for quite a long time and reports exhibiting the development of AR against them are increasing.

Improving livestock management and, hence, productivity is a requirement in order to compensate for the increasing world population, which will eventually lead to increased demands for animal products. The tackling of AR needs to implement such methods as: (i) the systematic use of the currently available drugs, (ii) control of animal pasture, (iii) promoting the breeding of animals that are naturally resistant to certain types of helminths and (iv) development of new anthelmintic drugs by the pharmaceutical industry that have novel modes of action. Although each of these methods plays a part in the control program, chemotherapy will remain the cornerstone in the control program of helminth infections. Hence, the continuous supply of new antiparasitic compounds to the currently available anthelmintic pool is the best strategy to be implemented in the fight against helminth infections.

Introduction

Parasitic worms or helminths occur worldwide parasitizing the body of humans and domesticated and wild animals [1, 2]. They often belong to the phyla Platyhelminthes (flat worms), including the trematodes and cestodes, and Nematoda (round worms) [3-5]. Helminth infections are causing major health problems to humans and are considered among the major public health concerns throughout the globe [6, 7]. Despite the progress in the public health and sanitary conditions in the last two decades [8], soil-transmitted helminthiasis (e.g. *Ascaris lumbricoides* (the roundworm), *Trichuris trichiura* (the whipworm) and *Necator americanus* or *Ancylostoma duodenale* (the hookworms) still affect more than two billion people worldwide [6]. However, helminthiasis are arguably of even greater relative importance in our domestic animals [9].

Generally, helminth infections have the impact of decreased productivity in livestock animals through: (a) damage to the infected tissues, leading to decreased performance of the affected organ; (b) consuming the energy that is supposed to be utilized in production in immune and defense mechanisms, and (c) a decrease in feed consumption [9].

The direct life cycles and access by grazing to infective stages of the parasites, aided by intensive farming practices, make herbivores an easy target for many nematode species. This is particularly true in areas where extensive grazing is practiced causing serious economic losses by millions of pounds each year through losses in productivity and the costs of control measures [10].

Although the impact of helminthiasis could be reduced dramatically by improved sanitation and pasture control in domestic animals, such methods are not sufficient to eradicate these parasites. In the absence of vaccines, the control of these parasites is mostly reliant on chemotherapy [11].

The first discovered anthelmintic agents were phenothiazine and piperazine, which were discovered in 1940 and 1954, respectively. These agents provided activity against target parasite species and with acceptable tolerance in the host animal species. The following years, between 1960 and 1980, witnessed an extraordinary achievement in the development of anthelmintic drugs [10]. Despite this, very few anthelmintic drugs were discovered in the recent years to combat helminth infections [12]. However, a variety of diseases caused by helminths, including larval cestode infections in animals, still await satisfactory treatment and, unfortunately, the extensive use and improper dosage of anthelmintics in conjunction with other factors has resulted in drug resistance, causing a serious threat to effective control of helminth infections [13].

Diversity of Helminths

Helminths are a diverse group of parasitic worms in humans and animals which belong to the phyla Platyhelminthes and Nematoda [1]. The phylum Platyhelminths contains 29488 species of flat worms [5]. The parasitic worms in this phylum belong to three main groups: (a) Cestoda, or the tape worms, containing about 3500 species, (b) Trematoda, or the flukes, comprising around 20000 species, and (c) Monogenea, that includes about 1000 species of parasitic worms [3]. Many species of the parasites are relevant to human and animal health.

The phylum Nematoda comprises 25,043 species of round worms in both aquatic and terrestrial environments [4, 14]. Nematodes parasitizing the gastrointestinal tract of animals are found worldwide and are considered of significant importance in domesticated and wild animals.

Economic and Health Impact of Helminth Infections in Animals

Helminth infections are an important group of diseases in grazing ruminants affecting their health conditions and productivities. Parasitic nematodes have major economic impacts on livestock throughout the world [15]. Other domesticated and wild animals are also susceptible to helminthiasis from the subarctic to the tropical regions of the globe [16]. Although helminthiasis are of a considerable importance in humans, they are of even greater significance to the health and productivity of the livestock throughout the world [17]. The level of helminth impact on the productivity of the animal herds and flocks is largely influenced by the type of parasite species, the number of helminths inside the host's body, the immunological and health status of the host, management conditions of the farm such as diet and stocking rate of the animal herd, environmental conditions such as climate and type of pasture [15].

The effect of helminthiasis in animals comprises three main aspects: (i) direct tissue damage that is caused by the adult and larval stages of the parasites such as the liver (e.g. infection by *Fasciola hepatica*) and lungs (e.g. *Dictyocaulus* infection in hoofed animals) leading to reduced activities of these organs [18], (ii) deprivation of the host from energy and nutrients and diversion of much of the intake of energy and protein towards defense and regeneration of the lost tissues [19], and (iii) reduction the amount of feed consumption which is a common feature of all helminth infections [9]. The economic and health effects of some common helminth infections are illustrated in Table-1.

Table-1: Economic and Health Impacts of Some Common Helminth Infections in Domestic Animals

Type of helminth	Hosts infected	Health impact	Ref.
<i>Cooperia oncophora</i>	Cattle	Decreased weight gain of up to 13.5%. Reduced milk production.	[20]
<i>Dictyocaulus viviparus</i>	Cattle with a prevalence rate of 70-80% of herds infected.	Mortality, decreased weight gain and milk production.	[21, 22]
<i>Fasciola hepatica</i>	All ruminants with a prevalence level of 30-80% in susceptible areas.	Reduced appetite, decreased weight gain and milk production. Reduced fertility and carcass quality.	[23, 24]
<i>Haemonchus contortus</i>	All grazing ruminants	Severe anemia, reduced food intake and weight gain, reduced wool production.	[15, 25, 26]
<i>Ostertagia ostertagi</i>	Cattle	Decreased weight gain, milk production and carcass quality.	[19, 27-29]
<i>Teladorsagia circumcincta</i>	Sheep and goats	Reduced weight and wool production, mainly due to loss of energy and nutrients for immune response.	[18, 30]
<i>Toxocara canis, T. cati</i>	Humans and other mammals such as rodents and domestic livestock from subarctic to the tropics, with a prevalence rate from 0.7% in New Zealand to 81% in Nepal.	Hepatitis, endomyocarditis, endophthalmitis, asthma and leukocytosis.	[16, 31-36]

The clinical infection of cattle with gastrointestinal nematodes causes a reduced body weight gain per day in all circumstances [37]. Lower milk production (1kg/day) is also reported in cattle herds that are infected with GI nematodes (e.g. *Ostertagia ostertagi*) [27]. Infection with *Fasciola hepatica* or liver fluke leads to a 6% decrease in weight gain of cattle in the untreated herds [17]. Infection of cattle with *Dictyocaulus viviparus* has been reported to cost €163 per cow due to a total decrease in milk production of 15-20% in herds infected with this nematode. Mortality rates of up to 6% caused by *Dictyocaulus viviparus* has also been reported [21].

Experimental infection of Merino lambs with the round worm *Haemonchus contortus* has been reported to cause a 38% decrease in live weight gain and 6.8% decrease in wool growth [25]. Infection of sheep with GI strongyles in southern Italy has been reported to cause 1.4-13.0% decrease in milk production [38]. The aforementioned information is suggestive that helminth infection poses a big burden on the health and productivity of animals leading to great economic losses throughout the globe. In order to increase the health and welfare conditions of animals and, hence their productivity, systematic helminth control should be one of the priorities in animal industry.

Control of Helminth Infection in Animals

Control of helminth infections in animals is an important factor towards increasing the productivity of livestock to meet the raising demands on animal products. Global health has improved considerably in the last two decades and the population is increasing continuously so that the world population is expected to increase to

9 billion by 2050 [8, 39]. Hence, the demand for animal meat and other products will be increased with the same pace.

Improving the animal health management has a direct impact on improving livestock productivity. However, helminth infections are among the major constraints (e.g. protozoan diseases, ectoparasites, and management problems) on achieving this goal [40].

On a global scale, the control of worms is approached through the implementation of four different strategies; (i) using anthelmintic chemotherapy in infected populations, (ii) public education pertaining how to lead a healthy lifestyle, (iii) following hygienic and sanitary lifestyle and (iv) using vaccines and remote sensing [41].

Public and environmental health education is required for long-term control of helminthiasis in human and animals [42]. Development of a better economic and sanitary state of the populations is the unequivocal step in the control of infectious diseases. These eventually aim at reducing the rate of contamination of the environment with the eggs and larvae of the helminths.

Animals infected naturally with different helminths develop an immune response against reinfection by the same parasite and development of vaccines that provide protection against some cestode infections have given successful results and efforts are still ongoing towards the development of new effective vaccines [43-45]. However, the successful development of vaccines for nematodes and other parasitic helminths infecting ruminants and other domesticated animals seems to encounter many difficulties [43, 46, 47].

In areas of high-transmission, using anthelmintic chemotherapy remains the mainstay towards the control of helminthiasis and is still the preferred method of helminth control. The treatment strategy can include the entire population irrespective of age, sex and infection status, or it can target the individuals that are infected with the helminth parasite. Many anthelmintic compounds were developed between 1960 and 1981 that provided novel anthelmintic activities yet highly safe to the health of animals [10]. Anthelmintic market is the largest sector of veterinary pharmaceutical industry and due to the vast diversities of the anthelmintic classes; the next section will review only the most important drug classes.

Anthelmintic Drugs for Veterinary Use

Veterinary anthelmintics available to treat veterinary helminthiasis belong to the classes of probenzimidazoles and benzimidazoles, macrocyclic lactones, imidazothiazoles, salicylanilides and substituted phenols, tetrahydropyrimidines, spiroindoles, amino-acetonitrile derivatives and Cyclooctadepsipeptides [10, 12, 48-50].

The probenzimidazole (e.g. febantel and netobimin) and benzimidazole (thiabendazole, cambendazole, albendazole, etc.) anthelmintics are effective against the GI nematodes and act via binding to the worm cell tubulin, preventing the formation of microtubules inside the helminth cells. Hence, the cells become unable to transport secretory granules resulting in cell lysis [51].

The macrocyclic lactones include the avermectins (ivermectin, abamectin, etc.), milbemycins (e.g. moxidectin, nemadectin and milbemycin oxime) and spinosyns (spinosyn A and D) [48], which are effective against GI nematodes and insects. Avermectins and milbemycins exert their anthelmintic activity via binding specifically to the inhibitory glutamate-gated chloride ion channel (GluCl⁻) receptors of the helminths that are found only in invertebrates (such as helminths and insects). This binding results in increased permeability of the nerve cell to chloride ions (Cl⁻). The influx of Cl⁻ causes hyperpolarization of the nerve cell membrane that eventually

results in paralysis of the worm muscles [52-56]. The mechanism of action of spinosyns seems to differ from that of the avermectins and milbemycins, as they inhibit the nicotinic acetylcholine receptor (nAChR) functions of the worms [57, 58].

The imidazothiazoles (levamisole and tetramisole) are effective against GI and lung nematodes. These drugs exert their anthelmintic effects through the agonistic action at the nAChR of the nematode muscle cells, which leads to first opening and then blocking the receptor [2, 50].

The salicylanilides (closantel, niclosamide, oxclozanide, rafoxanide, etc.) and substituted phenols (bithionol, nitroxynil, nitroscanate, hexachlorophene, etc.) are active mainly against adult liver flukes (*F. hepatica* and *F. gigantica*) and *H. contortus* and used extensively against haemonchosis and fasciolosis in cattle and sheep [10, 59]. The mechanism of action of these drugs is through the selectively uncoupling the mitochondrial oxidative phosphorylation of the parasite [60, 61].

The tetrahydropyrimidines (e.g. pyrantel and morantel) are effective against GI nematodes in ruminants, horses, dogs, cats, and pigs [10]. These drugs are potent agonists at acetylcholine (ACh) receptors on nematode muscle cells that eventually cause spastic paralysis of the nematode muscle fibers [62].

The spiroindoles (e.g. derquantel) are antagonists at the nAChR of nematode neuromuscular junction, causing flaccid paralysis of the worms [63]. Derquantel is active against the adult and fourth larval stage (L4) of nematodes such as *Trichostrongylus*, *Nematodirus* and *Haemonchus* spp [64, 65].

Monepantel represents the first drug in the amino-acetonitrile compounds that is effective against nematodes in cattle and sheep [66]. This drug binds to the ACh receptor MPTL-1, which is unique to nematodes, forcing it to open. The receptor then fails to close, eventually resulting in spastic paralysis of the worms muscles [67, 68].

Emodepside is a cyclooctadepsipeptide that is considered as a fairly new anthelmintic drug [69]. This drug acts via stimulation of pharyngeal paralysis through inhibition of Ca^{2+} influx into the muscle cells of the pharynx and eventual death of the parasite [70]. It is available as a spot-on for cats and tablet for dogs for the treatment of GI nematodes [12].

Emergence of Anthelmintic Resistance

Currently, the control of helminthiasis in human and animals relies mainly on the use of anthelmintics [6, 42]. The intensive use of anthelmintic compounds to get rid of helminth infections in livestock animals throughout the world will eventually lead to the emergence of resistance against the currently available drugs [11]. Anthelmintic resistance (AR) is said to have developed when an anthelmintic drug fails to kill the exposed population of parasites using the dose that is recommended therapeutically [11, 13, 71]. Emergence of AR is a raising problem in human and livestock farming that threatens the success of anthelmintic therapy in humans and reduces livestock productivity [72] (Table-2).

Table-2: Mechanisms of Resistance Formation of the Commonly Used Anthelmintic Classes

Anthelmintic class	Drug example	Anthelmintic spectrum	Proposed mechanism of resistance formation
benzimidazoles probenzimidazoles	Albendazole, thiabendazole Febantel, netobimin	GI and lung nematodes of ruminants GI and lung nematodes of many host species, liver flukes, tape worms	Mutation in the gene coding for β -tubulin isotype 1 [73].
Imidazothiazoles Tetrahydropyrimidines	Levamisole, tetramizole Pyrantel, morantel	GI and lung nematodes of ruminants GI and lung nematodes of ruminants, horses, dogs and cats. Pyrantel is also effective against tapeworms	Decrease in the number of nicotinic acetylcholinesterase receptors or by a reduced affinity of these receptors for the drug [13].
Amino-acetonitrile derivatives	Monepantel	GI and lung nematodes of ruminants.	Loss of part of nAChR superfamily member ACR-23 [74, 75].
Macrocyclic lactones:			Changes in the P-glycoproteins that are involved in export of the drug, leading to reduced concentration of the drug inside the cell [76].
Avermectins Milbemycins spinosyns	Ivermectin, abamectin Moxidectin, milbemycin oxime Spinosyn A and D	GI and lung nematodes of many host species	

The main cause the development of AR is the extensive use of anthelmintic drugs, through the selection of the resistant individuals [11, 72, 77]. Helminths carrying drug resistance genes are given a better chance to flourish as the competing drug-susceptible individuals are eliminated from the host body. Hence, they are no longer competing for the predilection sites inside the host body. Moreover, the proportion of the helminth eggs carrying resistance genes will become higher in the environment, giving a higher chance of spreading the resistance alleles in the environment [11].

Following the introduction of a new anthelmintic compound, emergence of resistance against that particular drug appears fairly soon after marketing. Sometimes the resistance develops after only a few years of marketing of the anthelmintic compound (Table-3). The first report of AR development was published in 1957 when phenothiazine showed varying degrees of efficacy against different strains of nematodes in sheep [78]. Since then, the incidence of resistance development against different anthelmintic agents continued to rise at a steady pace and reports showing failure of different anthelmintic compounds are emerging from different parts of the globe (Table-4).

Table-3: Years of approval and first report of resistance development for some anthelmintic drugs

Drug	Year of drug approval	First report of resistance	Ref.
Thiabendazole	1961	1964	[79]
Levamisole	1970	1979	[80]
Pyrantel	1974	1996	[81]
Ivermectin	1981	1988	[82]
Moxidectin	1991	1995	[83]
Monepantel	2010	2013	[84]
Derquantel	2010	2012	[85]

The continuous rise in the incidence of AR is not a problem of livestock farming in the poor countries only. Reports of failure of anthelmintic agents to eliminate helminth infections continue to emerge even from the economically developed countries such as the US [86], Canada [87], Australia [88] and Europe [89]. The extensive use of anthelmintics and the rapid pace at which AR develops in different parts of the world threatens the future of livestock management and productivity. The posed burden on the old anthelmintic therapies currently available calls for urgent development of new drugs. Moreover, long-term strategies should be adopted to reduce the occurrence of resistant helminths in livestock.

Table-4: Selected reports of anthelmintic resistance in different countries

Species of helminth	Anthelmintic agent	Host animal	Country	Year	Ref.
<i>Ostertagia circumcincta</i>	Ivermectin, levamisole, thiabendazole	Sheep	Australia	1997	[90]
<i>Trichostrongylus, Ostertagia</i>	Thiabendazole, levamisole	Sheep	Denmark	1997	[91]
<i>Trichostrongylus, Ostertagia</i> spp	Thiabendazole, levamisole	Goat	Denmark	1996	[92]
Gastrointestinal nematodes	Ivermectin	Sheep	Slovak Republic	2003-2004	[93]
<i>Teladorsagia</i>	Thiabendazole	Sheep	Scotland	2000	[94]
Gastrointestinal nematodes	Ivermectin, albendazole, levamisole	Goat	United States	2001	[95]
<i>Haemonchus contortus</i>	Levamisole, thiabendazole	Sheep	Kenya	1998	[96]
<i>Oesophagostomum</i> spp	Pyrantel citrate	Pigs	Denmark	1987	[97]
<i>Haemonchus contortus</i>	Doramectin, albendazole	Sheep	Netherlands	2007	[98]
<i>Trichostrongylus</i>	Thiabendazole, ivermectin, levamisole	Sheep	Spain	1999-2003	[99]
<i>Cyathostominae</i>	Fenbendazole, oxibendazole, pyrantel pamoate	Horses	United States	2004	[86]
Nematodes	Thiabendazole	Sheep	Slovak Republic	2006	[100]
<i>Trichostrongylus</i>	Fenbendazole, pyrantel	Horses	United States	1999	[101]
<i>Haemonchus contortus</i>	Benzimidazole, levamisole and ivermectin, closantel	Sheep	Brazil	1996	[102]
<i>Trichostrongylus</i>	Benzimidazole, levamisole	Sheep	Uruguay	1996	[103]
<i>Haemonchus contortus, Ostertagia, Trichostrongylus</i>	Benzimidazoles, levamisole, ivermectin	Sheep	Argentina	1996	[104]
<i>Haemonchus, Cooperia</i>	Ivermectin, ricobendazole	Cattle	Argentina	2004	[105]
<i>Cooperia</i>	Ivermectin, fenbendazole, levamisole,	Cattle	Argentina	2007	[106]
<i>Cooperia, Haemonchus</i>	Ivermectin, albendazole, levamisole	Cattle	Brazil	2002-2004	[107]
<i>Teladorsagia, Haemonchus, Trichostrongylus</i>	Benzimidazole, levamisole	Sheep	France, Greece, Italy	2012	[89]
<i>Haemonchus</i>	Ivermectin, fenbendazole, levamisole	Sheep	Canada	2013	[87]
<i>Teladorsagia, Trichostrongylus, Haemonchus</i>	Ivermectin, abamectin, moxidectin	Sheep	Australia	2009-2012	[108]
<i>Cooperia onchophora</i>	Ivermectin	Cattle	Australia	2015	[88]
Gastrointestinal nematodes	Benzimidazole, ivermectin	Sheep	Slovakia	2014	[109]
<i>Haemonchus, Calicophoron</i>	Albendazole, levamisole, ivermectin	Cattle, sheep, goats	South Africa	2013	[110]
Small strongyles	Fenbendazole, pyrantel	Horses	Brazil	2013	[111]

Factors Contributing to the Spread of Anthelmintic Resistance

Resistance to a drug with a particular mode of action seems to confer resistance against other anthelmintic compounds with the same chemical structure [10, 112]. Genes conferring resistance against a

specific group of anthelmintics with the same mechanism of action sometimes exist in a small proportion of the helminths even before the introduction of that particular group of anthelmintic agents [113]. Development of resistance occurs when a particular anthelmintic drug eliminates the susceptible helminths, while it fails to get rid of the resistant ones. Hence, worms that are resistant to the anthelmintic agent continue to develop and reproduce [11]. For better understanding of how AR could be circumvented, the factors that facilitate the spread of resistance genes should be determined first. Although the pace of resistance development is influenced by operational, genetic and biological factors, the most important elements accelerating the rate at which AR develops are the operational factors [13]. Farmers play an important role in the management of AR through the selection of different anthelmintic drugs and drenching protocols implemented. The important factors contributing to the rapid development of AR are the frequent employment of the same chemical group in the therapy of helminth infections [114] and using of anthelmintics in a lower dose than is required therapeutically [115].

Therapy of helminth infections using the same chemical group will accelerate the rate of resistance development in the flock [116]. Resistance develops faster in the farms that follow a regular deworming program [117]. Using the same drug or group of drugs with similar mode of actions will eliminate the susceptible worms while the resistant ones grow and reproduce which eventually results in the spread of helminth eggs carrying resistant alleles in the environment.

Using of anthelmintic therapy in subtherapeutic dose is another factor contributing to the development of AR [118, 119]. Drugs show different bioavailabilities in the different animals. For example, benzimidazole and levamisole have a lower bioavailability in goats than in sheep. Hence, goats should be given approximately twice the dose of these drugs given to sheep. But during helminth control programs, both species are drenched with the same dose of the mentioned drugs which is considered as half of the dose required for goats [120].

Another factor contributing to the spread of AR is the introduction of new animals that are carriers of resistant helminths, which result in the spread of the resistance. Also keeping sheep and goats together in the same flock seems to facilitate resistance development, which could be due to the same reason mentioned in the previous paragraph [121].

Control of Anthelmintic Resistance

Development of anthelmintic resistance in livestock animals is usually not detected early since routine screening of AR is not undertaken by farmers. Moreover, the methods usually employed to detect AR under field conditions are not very sensitive [13]. Hence, for most of the times, detection of AR occurs after a considerably long time of its development.

Various classes of helminth parasites exist that have different lifecycles and follow different modes of transmission of the helminth infective stages to the final hosts. Hence, farmers and veterinarians must choose the helminth control strategies that are suitable to each particular situation of a livestock farm [114]. The circumvention of AR can be approached through either attempting to delay the onset of its development or using alternative methods of controlling helminth infections in livestock animals [13].

One of the currently accepted approaches towards the postponement of the onset of AR is the use of a combination of anthelmintic drugs that have different modes of action [13, 122]. A combination of albendazole and levamisole has been recommended for the treatment of soil-transmitted nematode infections [123]. Drugs having different mechanism of anthelmintic actions act synergistically to minimize the number of helminth populations inside the host animal. Helminths resistant to the action of one anthelmintic agent develop mechanisms to by-pass the pathways that this particular drug inhibits, hereby this pathway becomes less

important for the survival of the parasite. Using two anthelmintics simultaneously will help the elimination of those helminths that are resistant to the effect of one agent and prevents the chance of spreading the resistant trait.

The enforcement of strict quarantine measures in the farm will help in delaying the onset of AR. The introduction of new animals carrying resistant helminths into the flock should be preceded by treating the newly arrived animals with two anthelmintic drugs acting through different modes of action such as levamisole and ivermectin. The animals are then quarantined for 48 hours before being mixed with the herd [124]. This technique doesn't make sure that the animal is free from helminthes. However, the worms that survive the treatment will be mixed with other helminth eggs present in the environment and, hence, the genes providing AR are diluted [13], minimizing the widespread dispersal of resistant eggs on the pastures.

Animals show different rates of susceptibilities towards parasitic helminths. In Australia, it was noticed that Merino sheep exhibit significant genetic variations in resistance towards *Haemonchus contortus* and *Trichostrongylus colubriformis* [125]. This has been promoted to the sheep breeders to encourage them to breed those sheep that exhibit resistance towards helminth infections [13]. Besides the advantage of reducing the probability of infection in the sheep, breeding resistant animals has also the advantage of reducing the production of helminth eggs and, therefore, reducing the contamination of pastures. However, effectuation of this method in the control of resistance formation did not reach the level that can help in the reduction of AR as breeding resistant sheep will trade-off for the productivity of the animals [126].

Control of pasture can reduce the impact of worm infection in livestock. Using of crop stubble instead of grazing on contaminated pastures prevents the infection of livestock animals with the infective stages of the parasites. Another approach is through the use of the pasture for different animals at different times such as bringing equine or cattle to the pasture for one season and using the pasture for sheep grazing in the next season [13]. The reason is that sheep and cattle or equines do not share much of the important helminth parasites such as *Haemonchus contortus*. However, implementation of this method needs a good knowledge about the epidemiology of the helminth parasites that are endemic to that area, such as the knowledge about the time at which the helminth eggs are hatched and the larval populations reach the infective stage [127].

Conclusion

Drug therapy of helminth infections is the preferable method in the control of helminthiasis, owing to the comparably low cost and immediate effect on the productivity of livestock. However, dependence on therapy as the sole means for prevention of helminthiasis eventually results in the development of resistance against the majority of these drugs currently available. Some of the old anthelmintic drugs have been used for a very long period and reports about the development of AR are emerging. Resistance development against the currently available drugs is increasing continuously. Hence, the anthelmintic pool needs to be reinforced by developing new compounds with novel mechanisms of anthelmintic activities in order to compensate for the enormous burden posed on the old drugs. Lately, three compounds; monepantel, derquantel and emodepside were marketed as new anthelmintics that provide novel mechanisms of anthelmintic activities. However, evidence shows that resistance develops after only a few years of the introduction of any new anthelmintic agent and it will not take long until resistance develops against the new drugs too.

Besides the discovery of new anthelmintic drugs, the old ones need to be implemented in a way that can delay the onset of resistance development. Using a combination of drugs with different modes of actions will help in the delaying of AR development. The available drugs should be used alternately, i.e. if one chemical group was used in one year, another group should be used in the next year, hence, preventing the spread of resistance

alleles among the helminths. AR development is inevitable; however, strategies that can delay its onset of appearance should be planned and implemented by veterinarians and farmers as well.

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