Anthelmintic Drugs and Resistance

Subjects: Parasitology

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Helminth parasitic infections are a considerable constraint to the livestock industries worldwide. Nematode parasites cause the major proportion of harm to livestock. The infections caused are accountable for severe economic losses in cattle, goat and sheep farming industries. Morbidity and mortality in livestock due to parasitic diseases are increasing alarmingly. Also, their zoonotic influence on human health is considered significant. Anthelmintic drugs have been developed occasionally to curb this disease and prevent major losses. But the development of resistance against these drugs has put another constraint on this flourishing industry. Helminth parasites have developed resistance against three main classes of anthelmintics: benzimidazoles, macrocyclic lactones and nicotinic agonists. With the intensification of resistance, various screening and confirmatory tests have been developed for the speedy introduction of newer drugs in the livestock industry. At the same time, designing and launching novel anthelmintics is time-consuming and economically restrained. Phytochemicals attract much attention because of their pharmacotherapeutic potential, least toxic profile and low environmental hazards.

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1. Introduction

Livestock plays an undeniable role in the human life cycle and ecosystem balance. In traditional and contemporary agriculture, cattle are a valuable blessing, providing meat, milk, skin, wool, hides, manure and draught power. Moreover, in a traditional society, they are a quintessential part of the social structure, depicting a family asset, and they are appraised as a survival tool by the nomads. Compared to the distribution of land, the distribution of animal assets is significantly more egalitarian [1]. Worldwide, livestock has a significant impact on improving rural economies. Livestock has the potential to create jobs, particularly for small farmers and landless peasants [2]. Thus, livestock contributes to equitable revenue distribution by alleviating regional and societal poverty [2][3]. Livestock animals can become infected with harmful pathogens just like humans. Gastrointestinal helminthosis is a substantial obstacle in breeding for goats, sheep and cattle [4]. It is defined as a disease caused by the presence of helminth parasites like cestodes (tapeworms), trematodes (flukes) or nematodes (roundworms) in the gastrointestinal tract (GIT) of an animal. Almost all animal species can be infected with helminth parasites, but the infection often is far more severe in very young and old or immunosuppressed animals. Certain adult animals can flourish satisfactorily despite being infected with a low parasite load. Helminth parasitism is responsible for the loss of economy in many ways which sometimes go unnoticed to the proprietor, such as decreased fertility, decreased milk yield, reduced work capacity, lack of appetite, diarrhoea, anorexia, anaemia, decreased growth rate, and

mortality and morbidity of heavily parasitized animals [5]. Helminth parasitic infections significantly hinder ruminants' sound and satisfactory productive efficacies [6]. Occasional ruminant mortality due to parasitic diseases probably may not be considered panicking. Still, its indirect effects on livestock productivity and their zoonotic impact on human beings are considered alarmingly significant [7][8]. Losses indirectly about nematode infections involve the decreasing potential of productivity due to weight loss, diarrhoea, decreased growth rate, anorexia, and anaemia [5]. Considering the effect of certain groups and species of GIT parasites on cattle populations at risk, the economic losses were estimated to be $7107.97 million in 2011. The potential financial losses caused in 2011 by the significant five ectoparasites and GIT parasites of cattle in Brazil was a surprising amount of $13.9 billion. [9]. Therefore, the effective management and control of parasitic helminth diseases are critical in increasing livestock production yield from a diminishing foundation of natural resources to fulfil the necessities of an upsurging world population nutritionally and dietarily more demanding [10].

The annual integrated cost of the three helminth infections in 18 countries participating in COMBAR (2020) (Combatting Anthelmintic Resistance in ruminants) was estimated to be €1.8 billion [€1.0–2.7 billion] [11]. Nearly 81% of this cost (€1.46 billion [€0.84–2.10 billion]) comprised of charges owing to production losses and 19% (€0.35 billion [€0.14−0.57 billion]) accredited to treatment costs. Currently, known public expenditure in research on controlling helminth infections is approximately 0.15% of the annual expenses for parasitic diseases [11]. The severity of this disease and the drop off of production depends on the severity of the infection and nutritional position [12]. Pregnant females and young animals are susceptible to a greater extent to helminthosis than adult ones because of their intricate nutritional condition and abject degree of immunity [13]. Animal diseases will remain a significant threat to livestock productivity if not taken care of in time and rationally. Hence, a major economic profit can be made in the agricultural sector by strengthening the control of various crucial parasitic diseases [14].

Despite the advantages of these synthetic drugs in treating and eradicating diseases, they may have adverse effects on various non-target species when released into the environment. Due to the increased production pressure, more medications are being administered to animals, raising the environmental risks of these potential chemical pollutants [15]. A considerable rise in synthetic antihelmintic drug usage worldwide has led to the build-up of drug residues in animal body organs, rendering the life of consumers at risk, especially children, the most vulnerable risk group in the population [16]. Various hazards include embryotoxicity, teratogenicity, and other harmful consequences of benzimidazoles in many animal species [17]. Increased concentrations of levamisole have proven to cause hematological problems in people consuming foods containing its residues for more extended periods [18].

2. Anthelmintic Drugs and Resistance

Vaccines are used to prevent a disease rather than cure it. EG95 is a vaccine designed against the zoonotic disease echinococcosis or hydatid cyst [19]. Various other vaccines are being developed, such as TSOL-18 against neurocysticercosis [20] caused by *Taenia solium* and Hc-23 against *Haemonchus contortus* [21], but there are still many other parasitic diseases, where vaccines have not been developed, or their development is in the infancy. Their treatment broadly relies on chemotherapy. However, these chemotherapeutic agents are prone to resistance.

Anthelmintic resistance is losing sensitivity to the parasitic populations previously sensitive to the drug. It is a heritable change because it is genetically transmitted, which makes it even worse [22]. Anthelmintic resistance has become a prevalent issue. It is noticed in the field ordinarily when helminthic control policies collapse. Anthelmintic resistance (AR) is thought to have appeared due to parasitic or management and handling factors. Genetic divergence is also considered an element in drug resistance development. Many reports suggest resistant alleles are present before the primary anthelmintic dosing [23]. The first case of anthelmintic resistance appeared in mid-1950 in sheep kept at a research centre in Kentucky, USA, where in the treatment of haemonchosis, phenothiazine failed as a drug [24]. The occurrence of resistance against most of the pre-eminent marketed anthelmintic drugs has become a grievous problem globally [25]. Resistance against all of the three broad spectrum families, the benzimidazoles, ivermectin and imidathiazoles, has been recorded worldwide [26]. Resistance against drugs of a narrow spectrum of activity, like salicylanilides, has also been observed [27]. An intensifying spread of AR has been confirmed by the latest investigations that have illustrated predominantly in nematode populations of livestock animals [26][27][28][29][30][31]. AR has acquired economic and clinical gravity in certain parts of the globe, especially in trichostrongyle species infecting sheep and goat populations. The problem seemingly has reached more significant levels coupled with the occurrence and expansion of multi-drug resistant species in small ruminants [30]. The evident discrepancy between the soaring evidence of AR, on the one hand, in the field, and unpredictability regarding the authentic status of the helminth population in any particular group of animals, on the other hand, is a problem that requires redressal.

Factors related to the management include repeated use of a single drug or a congener drug belonging to the same category repeatedly, mass treatments of all farm animals as a prophylactic measure, inappropriate dosing and under or over-dosing [31]. According to Andrew C Kotze and co-workers [32], AR might be induced by various factors like deletion or mutation of any amino acids in the gene of the target or a reduction in the total number of receptors, decreased affinity of receptors for the target drugs, and absence of enzymes required in the process. The time of resistance development against an introduced anthelmintic drug has shrunk to less than 10 years [33]. AR has developed against various groups of anthelmintic drugs on many continents [34]. The most commonly used three classes of anthelmintic drugs in small ruminants include macrocyclic lactones (MLs), benzimidazoles (BZs), and cholinergic agonists (especially levamisole; LVM). The most accepted mechanism of resistance is that of BZ; however, the mechanisms of resistance of some other anthelmintics have not been well understood [35]. Resistance against LVM, ML and BZ among ruminants was recorded in *Cooperia* sp. *Haemonchus* sp., *Teladorsagia circumcincta*, *Trichostrongylus* sp. and *Ostertagia ostertagi* [36]. Hamed [37], highlighted the development of resistance against ivermectin of the GIT parasites, specifically of *Trichostrongylus* sp., *Ascaris* sp., *Trichuris* sp. and *Moniezia* sp. in camel hosts. Mphahlele and coworkers [38] successfully measured the effective resistance of BZ and LVM in ruminant nematode species. Bartley and Co-workers [39] successfully measured the resistance against monpental in *H. contortus*, *T. circumcincta* and *T. axei*, Coles and co-workers [40] detected resistance against BZ. In contrast, Dolinska and co-workers [41] reported resistance against Ivermectin in livestock nematodes. A study by Mickiewicz and coworkers [42] showed the existence of AR against BZ, LEV and ML in Polish goat farms, where the resistance was extensive against BZ and ML but comparatively low against LEV. Potarinche and co-workers [43] studied the resistance of GIT nematodes in goats against BZs and MLs, in

Romania. Van den Brome and co-workers [44] revealed the occurrence of AR against the newest groups of anthelmintic drugs by *Haemonchus contortus* against monepantel C and an amino acetonitrile derivative. Studies have shown that AR develops briefly after the drug is launched. In certain countries, unfortunately, various goat and sheep farms have been closed down because of the increasing anthelmintic resistance [45]. In sheep, AR against tetrahydro pyrimidines, imidazothiazoles, and avermectin/milbemycins, developed in three to nine years. The severity and the range of this problem, especially concerning the multi-drug resistant (MDR) nematode population, is predicted to upsurge further [33]. Various researchers have outlined the ubiquitous occurrence of MDR populations of *H. contortus*, *Trichostrongylus* and *Teladorsagia* against imidazothiazoles, benzimidazoles, and macrocyclic lactones in the European sheep populations [46].

Macrocyclic lactone (MLs) resistance was found to have developed in trichostrongyle species of cattle in Europe [47]. The same results also appeared in South and North America [28][48]. Two studies reported multi-drug resistance against ML and BZ [28][49]. Resistance is frequently found in small strongyle species of horses against BZs and, to a considerably lesser extent, against pyrantel (PYR) [50]. Despite these alarming discoveries, it is to be ascertained that these anthelmintics still perform adequately in a considerable percentage of stables [51][52]. **Table 1** outlines the different classes of anthelmintic drugs and their drug action and resistance mechanisms.

Table 1. Various classes of anthelmintic drugs with their mechanism of action and drug resistance.

Anthelmintic Standard Drug	Mechanism of Action	Mechanism of Resistance	References
Benzimidazoles	Inhibition of Polymerization of microtubule subunits leading to disarrangement of microtubules.	Changes in the β tubulin isotype 1 target site in the nematode parasite. Continued polymerization of microtubules.	[53][54]
Macrocyclic Lactones	Modulating the glutamate-gated chloride channel.	Mutation in glutamate-gated chloride channel or gamma-aminobutyric acid receptor gene.	[54][55]
Imidazothiazole	Agonists of nicotinergic acetylcholine receptor	Altered Nicotinic acetylcholine receptor.	[54]
Monepantel	Act on Nicotinic acetylcholine receptor genes.	Increased expression of P-glycoproteins. Mutation in Hco-des-2H, Hco-acr-23H, Hco-MPTL-1 genes	[54]

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