



SAGA OF ANTHELMINTIC RESISTANCE: MECHANISMS OF DEVELOPMENT, METHODS OF DETECTION AND WAYS OF MITIGATION – A REVIEW

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Abstract

Nowadays, antimicrobial resistance is a burning issue all over the globe and has been addressed with higher priority. Anthelmintic resistance (AhR) is also becoming a threatening issue since control of helminths mainly depends on deworming using anthelmintics. Therefore, anthelmintics are frequently used around the year. However, the issue regarding AhR has not been focused properly when compared with anti-microbial resistance (AMR). The occurrence of AhR in livestock is very common and increasing rapidly. There are lots of evidences of AhR developed against various anthelmintics. The intensive and indiscriminate use of anthelmintics like benzimidazoles (BMZ), tetrahydropyrimidines (THP) and macrocyclic lactones (MCL) has led to the development of AhR. Therefore, researchers should devise and implement new strategies for helminth control, and control should increasingly incorporate alternative and evidence-based control strategies to limit the development of AhR. This review describes the mechanism of AhR, recent advances in developing resistance, diagnostic tests and worm control strategies.

Key words: anthelmintic resistance, mechanism of anthelmintic resistance, resistance diagnostic tests, worm control strategies, herbal anthelmintic

Helminths are diverse groups of parasitic worms that include nematodes, trematodes and cestodes and are serious threats to both human and animal health in many parts of the world (Kaplan, 2004; Hotez et al., 2008; Ali et al., 2024). Humans, animals and poultry are infected with a variety of helminths on pastures, the most prevalent of which are gastrointestinal (GIT) nematodes and flukes, by ingesting the infective larvae or metacercariae, the encysted infective stage of flukes on the contaminated grass, or by skin penetration (e.g., hookworms, *Strongyloides* or *Schistosoma*) (Van Dijk et al., 2010; Labony et al., 2022 a, b; Dey et al., 2022; Anisuzzaman et al., 2023). Helminths have constantly been a problem and undoubtedly a long-standing issue that poses a threat to the livestock and poultry industry (Waller, 2006; Shohana et al., 2023). These parasites impair animals' or birds' productivity and welfare, negatively affecting feed consumption, growth rate, milk and egg production (Charlier, 2014; Anisuzzaman et al., 2022; Ritu et al., 2024).

Helminth infections are treated with a number of drugs, such as macrocyclic lactones (MCL), benzimidazoles (BMZ), imidazothiazoles (ITZ), and praziquantel (PZQ). Due to frequent use, administration for a long time and substandard dose, anthelmintic resistance (AhR) may develop. Animals quickly developed resistance to anthelmintics once they were introduced (Shalaby, 2013; Hasan et al., 2022; Parvin et al., 2022, 2023). AhR to the broad spectrum anthelmintics was detected nearly three decades ago and this phenomenon has changed from being considered merely a parasitological curiosity to a state of industry crisis in livestock sectors and human health (Waller, 1997). The presence of AhR in parasites of various animal species has been observed, including cattle (Lifschitz et al., 2010; Geurden et al., 2015), sheep, goats (Coles, 2005; Domke et al., 2012) and horses (Geurden et al., 2013; Wolf et al., 2014; Saes et al., 2016). The annual cost for parasitic diseases has been calculated at 1 billion dollars in Australia (Roeber et al., 2013), 7.11 billion dollars in Brazil (Grisi et al.,

2014), and believed to be 10 billion dollars worldwide (Roeber et al., 2013). Even though AhR in livestock species is a global problem; true prevalence, diagnostic tools, and other useful management strategies to slow down its spread are yet to be addressed properly. If the spreading of AhR can be prevented, then the currently available anthelmintics will remain effective in the long term. Wherever possible, competent authorities, the veterinary pharmaceutical industry, veterinarians, independent organizations, and academia should collaborate to determine the needs of farmers for parasite control programs as well as to improve parasitology research (OIE, 2021; Anisuzzaman et al., 2023). Such resistance in livestock is a persistent and growing issue in all parts of the world and requires immediate attention. In this review, we describe the mechanism of development of AhR along with the methods used for the detection of AhR.

What is AhR?

Anthelmintic resistance is the capability of parasites to endure at the therapeutic doses of an anthelmintic that would normally kill parasites of the same species and stage. The phenomenon of AhR is inherited and parent worms pass the genetic material to their progeny in a vertical fashion that controls the process of AhR. These resistant genes are initially uncommon in the population or develop as rare mutations, but as selection progresses, both their frequency in the population and the number of resistant parasites rise (Geary et al., 2012; Nielsen, 2022). Different anthelmintics exhibit different types of resistance. The first type of resistance, known as cross-resistance, allows a parasite strain to withstand therapeutic doses of anthelmintics with distinct chemical structures or modes of action. One example of cross-resistance is resistance to anthelmintics belonging to BMZ. The second sort of resistance is called side resistance, and it refers to a situation in which an anthelmintic is resistant because another anthelmintic with a similar mechanism of action has been selected for it. It has been claimed that Levamisole-resistant strains also develop side resistance to morantel. The third kind of resistance, known as multiple resistance, occurs when parasites become resistant to two or more anthelmintics as a result of selection by either each group independently or concurrently (Nipane et al., 2008; Ahuir-Baraia et al., 2021). AhR is increasing and becoming a major global barrier in livestock production. Future livestock production and grazing animals' welfare will be seriously threatened by the emergence of AhR (Shalaby, 2013; Vineer et al., 2020). For farmers using only conventional deworming with commercial anthelmintics, AhR leaves very few options to control the foe (Rios-de Alvarez et al., 2021; Charlier et al., 2022). It is common for nematode parasites of sheep, goats, and horses to exhibit AhR. AhR is also common for nematode parasites of pigs and cattle (Prichard, 1994). However, the prevalence of AhR in livestock-infecting parasitic worms has increased steadily over time (Mukherjee et al., 2023). In the year 1980, a

study assessed the information regarding the detection of AhR. Based on their analysis, they anticipated the spread and long-term effects of AhR and also established objectives for future research (Prichard et al., 1980). The first report of AhR against a contemporary medicine used in animal production was made in 1964 for *H. contortus*, a parasite that was resistant to BMZ in sheep (Drudge et al., 1964). Within ten years of the first report of AhR, scientists revealed AhR in sheep parasites on a regular basis followed by resistance in horse and cattle nematodes subsequently (Jackson et al., 2006; Kotze and Prichard, 2016).

Mechanism of AhR

AhR mechanisms typically involve one or more of the following: (1) up-regulation of cellular efflux mechanisms, (2) an increase in drug metabolism, (3) modification of drug-receptor sites that reduce drug binding or the functional consequences of drug binding, or (4) a decrease in drug-receptor abundance through reduction of expression or another route for down-regulation. The relationship between the aforementioned changes and resistance varies between helminth species (Sarai et al., 2014; Kotze and Prichard, 2016; Fissiha and Kinde, 2021).

BMZ

BMZ inhibit the polymerization of β -tubulin which is essential to form microtubules. It is well known that resistance is linked to point mutations in the β -tubulin genes which prevent drug binding. However, a number of distinct β -tubulin gene polymorphisms have been linked to BMZ resistance (Feng and Yates, 2003). Though BMZ-resistant strains of *H. contortus* have a change in the β -tubulin isoforms but not in the α -tubulin isoforms (Lubega and Prichard, 1991). However, restriction fragment length polymorphism (RFLP) pattern for individual worm DNA when cut with *Hpa*I, a restriction enzyme and hybridized with a *H. contortus*-tubulin DNA probe (isotype 1), this pattern also provided evidence that a change in α -tubulin may be related to BMZ resistance (Roos et al., 1990). Cloning and sequencing of β -tubulin genes from *Brugia pahangi* and *H. contortus* showed that there are at least two different isotypes of β -tubulin genes in these parasites (Guenette et al., 1991, 1992; Geary et al., 1992). Recently, with BMZ resistance, the RFLP patterns for both isotype 1 and isotype 2 β -tubulin genes are reduced, and isotype 2 may not even be present in extremely resistant strains of *H. contortus* (Kwa et al., 1993 b). Using isotype 1 or isotype 2 specific primers-based polymerase chain reaction (PCR) analysis of individual *H. contortus* has shown a decrease in the number of alleles for each isotype linked with BMZ resistance in this nematode (Prichard et al., 1993). Additional PCR study has revealed that in *H. contortus* there is a reduction from at least 6 isotypes 1 allele to a single isotype 1 allele, and for isotype 2 there is also a marked reduction from over 12 different alleles, with the development of BMZ resistance (Beech et al., 1994).



Ivermectin (IVM)

Levamisole (LEV)

nematode neuromuscular junction and induces spastic paralysis. However, the mechanism of resistance to this class of medications is still unknown. Nevertheless, one possible resistance mechanism has been proposed as the reduction in the number of receptors (Geerts et al., 1997). LEV-resistant nematodes are also resistant to other nicotinic agonists such as pyrantel and morantel. Membrane preparations from resistant nematodes have decreased binding affinity for a LEV analogue at a low affinity (Waller, 2006). Lacking nAChR, resistant mutants (such as *C. elegans*) do not respond to cholinergic agonists such as acetylcholine, nicotine, carbamyl chloride, and LEV, which cause flaccid paralysis (Lewis et al., 1980).

Praziquantel (PZQ)

PZQ is commonly used against all trematodes except *Fasciola* spp., however, it is a drug of choice against schistosomes. Precise mode of action of PZQ is unknown, therefore, it is uncertain how schistosomes develop a resistance to it. Immature schistosomes, particularly skin stage schistosomula, are resistant or less susceptible to the medicine, which is a complicating aspect regarding PZQ resistance that should be highlighted (Frahm et al., 2019; Anisuzzaman et al., 2021). The low cure rates may therefore be caused by the presence of immature worms in the patients at the time of therapy (Renganathan and Cioli 1998; Gryseels et al., 2001). Various groups have successfully established PZQ resistance in the lab by sustaining schistosomes in mice for numerous generations at increasing sub-lethal and ultimately lethal doses of PZQ as well. These isolates lack long-term stability and also exhibit decreased genetic diversity, similar to field-derived bacteria with reduced sensitivity, but the molecular processes underlying induced resistance are still unknown (Coeli et al., 2013; Hoekstra et al., 2020, 2022; Alemu et al., 2024).

Methods for detection of AhR

In vivo tests

Fecal egg count reduction test (FECRT)

FECRT is the main method for detecting AhR in worms with veterinary significance (Calvete and Uriarte, 2013). Fecal egg counts (FEC) are performed before therapy and after treatment at different time points. Therefore, FECRT is calculated to estimate the effectiveness of the anthelmintic used (Coles et al., 1992). The data are interpreted using the arithmetic mean of FEC, and resistance is thought to exist if the percentage of reduction is less than 95%, and the 95% lower confidence limit is less than 90%. Resistance is suspected if just one of the two criteria is met (d'Assonville et al., 1996). FECRT has been used successfully to detect AhR in many countries, including Zimbabwe (Mukaratirwa et al., 1997), Zambia (Gabriel et al., 2001), Brazil (Fortes et al., 2013), Kenya (Mwamachi et al., 1995), Switzerland (Artho et al., 2007), and Bangladesh (Dey et al., 2020). FECRT has the advantage of being compatible with all currently available anthelmintic groups. The disadvantage is that the number of adult worms present inside the animals does not always match the FEC levels (Vatta and Lindberg, 2006; Coles, 2002). FECRT only indicates the number of fecund adults. However, FECRT has been used for over 30 years, and more recent work has revealed shortcomings in the diagnosis of resistance based on proportional reduction (Lejeune et al., 2023; Kaplan et al., 2023; Krücken et al., 2024).

Controlled anthelmintic efficacy test

The test is regarded as the gold standard for the detection of AhR, and the most accurate and reliable method for determining an anthelmintic's effectiveness against a mixed infection. In this method, one group of animals receives the anthelmintic while the second group are kept as untreated controls. The effectiveness is determined by comparing post-mortem worm counts between the two experimental animal groups and by identifying surviving (resistant) helminths (George et al., 2017). The helminths are regarded as resistant when the worm burden reduction is less than 90%. Laboratory animals might be the greatest option due to their high-cost involvement (Hasan and Ghazy, 2022).

Critical anthelmintic test

Hall and Foster (1918) described this test first which is based on the collection of animals' feces for at least four days following the anthelmintic treatment. The expelled worms are recovered and their number is estimated. Then the animals are slaughtered, residual worm burdens are estimated, and the percentage efficacy is calculated by dividing the number of expelled worms by the residual number and multiplying by 100 (Gordon, 1950). The main advantage of this technique is that each animal acts as its control. Therefore, fewer animals are needed in this method than in the controlled efficacy test. Unfortunately, in addition to the aforementioned drawbacks, the

critical test requires a lot of time and labor (Johansen, 1989).

In vitro tests

Egg hatch test (EHT)

The EHT is an *in vitro* test and can be performed to assess AhR (Le Jambre, 1976). EHT was developed to differentiate between the strains of gastrointestinal tract nematodes (GIN) that are susceptible to BMZ and LEV. It is comparably quicker and less expensive than FECRT. The principle is based on calculating the percentage of eggs that do not hatch in solutions of increasing drug concentrations in comparison to the control wells, enabling the test user to develop a dose-response line plotted against the drug concentration (Taylor, 1990). Dose-response lines are generated in the EHT and other *in vitro* tests (Sangster and Dobson, 2002). This enables the calculation of parameters, such as the EC₉₅, a single parameter used to compare isolates that can destroy 95% of eggs. Resistant worms will have a higher EC₉₅ because a higher drug concentration is required to kill them. These tests are underutilized tools for assessing resistant phenotypes. However, they have become fundamental tools for researching the outcomes of experimental genetic crosses (Elard et al., 1999; Fairweather et al., 2012; Robles-Pérez et al., 2014; Calvete et al., 2014).

Larval development assay (LDA)

The LDA was described in detail by Hubert and Kerbouf (1992), which is conducted in a 96-well plate. Each well of a 96-well-microtiter plate is filled with the counted number of eggs in 0.5 mL of egg suspension. The well contents are then mixed, and the plates are then incubated in an incubator with humidified conditions at 27°C for 48 hours. Anthelmintics are then added to the plates and incubated further for 5 days. Plates are examined to determine the development of eggs and survival of the larvae at various concentrations of anthelmintics. Therefore, the percentage of inhibition of larval development in each well is determined using the following formula (Cala et al., 2012):

$$E = ((\text{Eggs} + LI) - LI / (\text{Eggs} + LI) \times 100)$$

Larval motility, migration and paralysis test

By this method, the effects of anthelmintics on larval motility and migration capability are evaluated. Larvae are incubated for 24 hours at 25°C in the dark with varying drug concentrations. Then, they are exposed to light for 20 minutes to stimulate the unparalyzed larvae. The number of non-motile larvae is then calculated and percent of non-motile larvae is estimated as a proportion of total larvae present at each drug concentration (Kohler, 2001). The motility of the larvae can be monitored by light microscopy or by a high throughput real-time cell monitoring equipment x-CELLigence which was successfully used to detect and evaluate AhR. By x-CELLigence, a larval motility test has already been performed in *H. contortus* (Rinaldi et al., 2015). It has also been

used to distinguish between strains that are susceptible to BMZ and pyrantel. The larval migration test has also been utilized to test AhR in adult pig nematode, *Oesophagostomum dentatum*. In the assay, adult worms were incubated in anthelmintic at different concentrations and then transferred to the migration chambers. The migration chamber had polyamide nets with mesh sizes ranging from 300 to 500 μm , and the worms were free to migrate through them for 30 minutes. Therefore, migrated larvae were counted and data were used to create a dose-response curve (Petersen et al., 1997, 2000).

Tubulin binding assay

It is a specific technique used for the identification of BMZ-resistant helminths. It is based on the differences in binding of the BMZ to tubulin (an intracellular structural protein) isolated from susceptible and resistant nematodes (Nega and Seyum, 2017). Tritium-labeled BMZ is incubated with crude tubulin extract harvested from several stages of parasites (adult, larval, and eggs) until equilibrium is obtained. Charcoal is used to remove any extra medication, and a liquid scintillation spectrometer is used to measure the amount of tritium-BMZ/tubulin complexes present in the test milieu. Tubulin extracted from BMZ-resistant strains binds with BMZ less strongly than that obtained from BMZ-susceptible strains (Lacey and Snowden, 1988). The degree of binding depends on the structure of the specific BMZ. The tubulin-binding assay overcomes many of the issues that other *in vitro* assays have because it is based on biochemical changes in the parasites. Since it is vigorously standardized, inter-laboratory comparisons can be done with more certainty than other *in vitro* techniques, and they can be related to field conditions. This process is incredibly quick, sensitive, and accurate when sources of parasite material are readily available.

Molecular techniques for AhR detection

Nowadays, a range of novel techniques and tools, most of which are molecular, have been added to the old parasitological diagnostic approaches, which mostly involve microscopy. Even while using conventional methods might be laborious and time-consuming, they are nonetheless often utilized today. It has been demonstrated that PCR-based procedures are more sensitive and specific than “traditional” diagnostic methods that rely on microscopy and/or immunological detection (Garcia et al., 2018). Studies on the origin of the BMZ-resistant alleles in worm populations have been conducted. For instance, it has been discovered that several BMZ-resistant alleles exist in various resistant populations of *H. contortus*, which can easily be detected by RFLP-PCR on the isotype 1 β -tubulin gene (Kwa et al., 1993 a). Using the same method on two BMZ-resistant populations, it has been also discovered that the BMZ-resistant alleles were probably already present in two *H. contortus* populations before this class of drugs was

discovered (Blouin et al., 1995). The majority of molecular assays have been directed toward examining the molecular basis of BMZ resistance of *H. contortus*. A thymine (T) to adenine (A) transition (TTC-TAC) is the most often reported sign of nematode resistance to BMZ in sheep. A single nucleotide polymorphism (SNP) in the isotype 1 β -tubulin gene causes the encoded protein to have the F200Y substitution (Kwa et al., 1994). A phenylalanine was changed into a tyrosine at amino acid 200 of the isotype 1 β -tubulin gene in *Teladorsagia circumcincta*, *Trichostrongylus colubriformis*, and *H. contortus* (Elard et al., 1999). The F167Y (TTC to TAC) and E198A (GAA to GCA) SNPs are also responsible for BMZ resistance but are expected to be less prevalent than the F200Y (TTC to TAC) mutation (Chaudhry et al., 2019).

AhR prevention and control strategies

Chemotherapy

The majority of farms only use anthelmintic treatments to control worms, as opposed to management techniques that incorporate integrated strategies. The currently available anthelmintics belong to various drug classes, such as BMZ, MCL, tetrahydropyrimidines/imidazothiazoles, amino acetonitrile derivatives (AAD) and spiroindoles. These anthelmintics are effective against a variety of nematode species. In addition, MCL is effective against a number of arthropod parasites, whilst BMZ is also efficacious against some flatworm species (Traversa and von Samson-Himmelstjerna, 2016). These drugs are used to treat clinical cases as well as in mass drug administration (MDA) programs in an endemic area or a particular farm. In general, there are two types of MDA, namely strategic and tactical MDA. In strategic MDA, an anthelmintic is administered in a susceptible population or herd in a regular pattern based on a pre-designed schedule. For example, in the highland in Bangladesh, anthelmintics are recommended to be administered thrice a year whereas in the low-lying areas four times a year. On the other hand, in tactical MDA, anthelmintics are administered after a natural disaster such as heavy rainfall or flood. However, MDA is criticized and is thought to be linked to the development of AhR due to the indiscriminate use of anthelmintics since an effective anthelmintic vaccine is yet to be developed (Anisuzzaman and Tsuji, 2020).

Targeted selective treatment (TST) is a method to select individual animals for treatment based on specific criteria (Hodgkinson et al., 2019). In contrast to MDA, only diseased animals are selected in TST. Thus, it lowers treatment costs, drug residues in milk and meat, and the spread of drug resistant genes. Faffa Malan Chart (FAMACHA) system is the first tool used to make deworming decisions (Edith et al., 2018). In the FAMACHA system, operators determine the severity of parasitism based on a conjunctival color chart that correlates to anemia to select the infected animals for targeted treatment. As targeted treatment offers numerous potential advantages,

the use of FAMACHA has been a pivotal example of a practical strategy for managing resistance. One advantage is that it aids in worm removal from the most severely infected and affected animals, hence reducing production losses in the most infected animals. A targeted treatment of a small section of the flock can significantly minimize pasture contamination because these animals also shed more eggs than other animals. By reducing chemical use, it reduces selection and maintains refugia which means the proportion of the worm population escaping exposure to anthelmintics, which is the most important thing. The level of refugia is now regarded by the majority of parasitologists as the single most significant factor influencing the selection of parasites with anthelmintic resistance. Maximizing parasite kill is desired to decrease selection for resistance (Van Wyk, 2001).

It is necessary to provide some proof that nematode infections are fundamentally distinct from infections with other types of pathogens (or from cancer) to deny the principle of using combination products for treating nematode infections. The required therapeutic coverage is one exception. The goal of treatment for cancer, bacterial, fungal, and viral infections is to completely eradicate the pathogen (including tumor cells) in every treated patient. These infections are treated as individual cases unlike the population treatment paradigms commonly used in anthelmintic treatment procedures for ruminants (and sometimes horses). The removal of the parasites to the greatest extent possible from severely infected animals while ensuring that any remaining parasites are diluted into a population of susceptible, untreated parasites in the local environment known as a refugial population is, in fact, a key principle for slowing the emergence of AhR in parasitic nematodes of ruminants or horses (Dobson et al., 2001, 2011; Bartram et al., 2012). In both MDA and treatment of clinical cases, it is better to use a combination of two or more separate anthelmintics (e.g., anthelmintics from different chemical classes with distinct mechanisms of resistance, or different mechanisms of action). However, before using such a combination, it must be ensured that they are pharmacologically compatible. It is believed that such use of combined anthelmintics will provide efficacy in the presence of AhR to one class of anthelmintic and will delay the spread of AhR (Geary et al., 2012; Bartram et al., 2012; Abbas et al., 2021). To achieve this, full doses of veterinary medical products (VMPs) should always be administered. To treat a group of animals at the volume required for the heaviest animal, users must follow label instructions, calibrate application devices (such as oral drench applicators), and estimate animal weights. The three main routes of application are oral, injectable, and pour-on. According to certain reports, using various pour-on anthelmintic chemical formulations results in a relative under-dosing and there is concern that this will be selected for resistance (OIE, 2021; Leathwick et al., 2021).

Management factors

Good management practices greatly help to control parasites. The ground should not be used to feed animals. Water should be pure and devoid of feces. The likelihood of parasites surviving is decreased in the animal shed by facilities for good drainage. Overstocked pens or pastures should be avoided. To avoid the introduction of drug-resistant worms, new animals should be kept isolated from the rest of the flock for days and aggressively dewormed after being bought (Shalaby, 2013; Verma et al., 2018, Martin, 2024).

Strategic supplementation

Although anthelmintics are crucial for removing helminths from the host, a high-quality, nutrient-rich diet is vital for the health and well-being of parasitized animals. It is commonly recognized that a healthy diet boosts an animal's immunity to diseases (Rios-de Alvarez et al., 2021). The majority of clinical helminthiasis occurs in hosts who have marginal nutrition. Without sufficient food, none of the anthelmintics will increase an animal's weight gain. During the periparturient and rapid growth stage, it is crucial to give animals enough dietary protein so they can tolerate the worm's burden and become more resistant to infection (Coop and Kyriazakis, 2001). Mineral (copper, zinc, iron, cobalt, phosphorus) and vitamin (A, B₁₂, E) supplements help the immune system respond more effectively to internal parasites. Surprisingly, the addition of molybdenum at a dose of 6–10 mg/day reduces worm loads in lambs that were not attributable to the expected copper deficiency. Molybdenum contributes to an increase in blood eosinophils and jejunal mast cell numbers (Sykes and Coop, 2001). Animals must be provided with a diet that will fulfil their nutritional needs, and well-nourished animals that are fed well are better equipped to resist parasitism. Bioactive forages or plants with secondary metabolites are used because these plant metabolites, such as tannins, saponins, lectins, and others can reduce the parasite loads of animals (Rios-de Alvarez et al., 2021).

Adequate paddock rotation/rest periods

To prevent the larvae of the preceding group of animals from infecting the subsequent group, enough time between groups of grazing animals must be given. The length of a resting period depends on the weather and season of the year. The third-stage larvae (L3) in the grass have a life span of 21 days in tropical climates and up to 6 or more months in temperate climates (Rios-de Alvarez et al., 2021). Therefore, enough rest periods will provide scope to reduce the burden of infection in pasture and eventually minimize the chance of infection in definitive hosts.

Avoid overgrazing

The lifecycle of most of the GIN affecting animals and birds is direct and follows the feco-oral route. Susceptible animals and birds get infections through contaminated food and water (Anisuzzaman et al., 2023). Livestock get infected during grazing on a contaminated

pasture. In most cases, the third larval stage (L3) is the infective stage, however, in some cases eggs containing the second larval stage (L2) (e.g., Ascarids) or infective eggs with L3 (e.g., *Ascaridia galli*) cause infection. In contrast L3 of hookworms and *Strongyloides* spp. infect animals by skin penetration (Anisuzzaman and Tsuji, 2020; Anisuzzaman et al., 2023). Infective larvae (L3) are highly motile and positively hydrotrophic but negatively phototrophic. Therefore, they are abundant on the upper strata in a pasture during the morning; thus, grazing in the early morning is more likely to get infections. According to the GIN's life cycle, the majority of L3s will be found in the lowest part of the forages, close to the soil and feces. Animals that overgraze and feed closer to the lowest strata, where there is a higher risk of L3 contamination, easily get infested. To have enough biomass during the grazing season, adjustment of stocking rate to paddock size is necessary. Young or weakly immune animals should be grazed in "clean" paddocks or pastures that have not previously been grazed by infected adult animals (Rios-de Alvarez et al., 2021).

Avoiding manure piles and snail inhabitants

Freshwater snails of the family Lymnaeidae are the intermediate hosts of liver flukes, which live in moist, swampy regions. There are two ways to terminate the life cycle of liver flukes: (i) by preventing contamination of snail habitats by animals' feces containing fluke eggs; (ii) by preventing ruminants from ingesting infective stages (metacercariae) of flukes (Anisuzzaman et al., 2023). Snails release cercariae, the freely swimming stage of trematodes that encysted onto the grass near water bodies. Both can be accomplished by putting up fences to prevent animals from entering these areas; however, if access to open water is restricted, water troughs may need to be installed. It is better to avoid feeding on aquatic grasses. However, if it is essential to harvest green grasses from the marshy areas then it is better to cut grasses above 5–6 inches of the water level. Most of the metacercariae are found attached 5–6 inches above or below the water level. In addition, metacercariae can easily be destroyed by preparing silage because heat generated during fermentation readily kills the metacercariae present in grasses. On the other hand, metacercariae can survive in hay and straw since sunlight is not enough to kill them. In hot, dry weather, dragging or harrowing pastures to break up manure piles may aid in the desiccation of parasite eggs, limiting the number of larvae. Additionally, feces can be collected and composted to kill larvae and prevent the spread of infection (John et al., 2019, 2020; OIE, 2021).

Vaccines

Vaccines can increase an animal's protective immunity and reduce the load of worms. An anthelmintic, even with the highest efficacy, is unable to protect a susceptible individual from reinfection. However, an efficacious vaccine can prevent an invading pathogen. Therefore, an anthelmintic vaccine, a vaccine against helminth, is a sustainable

choice for controlling parasites when they are available. Currently, there are a few approved anthelmintic vaccines, but they have limited spectrum (e.g. against *H. contortus* in sheep, lungworm (*Dictyocaulus viviparus*) in cattle and *Echinococcus granulosus* in ruminants; Springer et al., 2022; Johnson et al., 2003; Carman et al., 2024; Yang et al., 2024). These vaccines typically need to be administered multiple times, and even then, they only help with control, therefore they must be used in conjunction with other parasite management tools (OIE, 2021). Very recently, a five-year phase IIIa cluster randomized control trial was conducted among 18 schistosomiasis-endemic areas using the SjCTPI bovine vaccine along with mollusciciding (trial registry: ACTRN12619001048178) by targeting *Schistosoma japonicum*. *S. japonicum* is a highly zoonotic blood fluke, which is endemic in China, the Philippines and Indonesia. Buffaloes and cattle are the main reservoirs of the parasite for human infection. The combined trial reduced 31% of human infection in the study area (Ross et al., 2023, Anisuzzaman and Tsuji, 2020)

Some alternative measures for sustainable parasite control

Nematophagous fungi

The idea of nematode-trapping fungi for controlling helminth populations on pasture has recently been studied by researchers (Grønvold et al., 1993; Waller and Larsen, 1993). Infectious larvae can be prevented from growing and migrating for a long time if fungal spores can be given to sheep in a controlled release device (CRD). Such a device was simulated by reducing fecal egg output by the percentage of fungus effectiveness for the duration of the CRD payout period. For periods of 30, 60, and 90 days, efficiencies of 50, 75, 90, and 100% were simulated. With an efficiency of at least 75% and a duration of at least 60 days, worm control was improved over the conventional program for fungal CRDs (Barnes et al., 1995).

Use of herbal anthelmintic

Medicinal herbs are a powerful source of many pharmacological activities. Many medicinal plants contain compounds having anthelmintic efficacy. Use of such medicinal plants has been proven to be efficacious against many helminths affecting humans and animals (Rajeswari, 2014) (Table 1).

Parasite-resistant breeds

Some sheep and goat breeds are more resistant to parasitism. For example, compared to other hair sheep breeds, St. Croix and Katahdin were found to have a stronger resistance to parasitism (Burke and Miller, 2004). Genetically resistant sheep are associated with increased serum levels of IgG1 and IgA (Gill et al., 1993). Likewise, the number of IgE-bearing cells may be related to the host's capacity to respond to helminth infection (Pettit et al., 2005). By grazing resistant breeds with susceptible breeds, pastures may be "swept" and susceptible animals' exposure to contamination is reduced (Verma et al., 2018).

Table 1. Plants or plant parts with anthelmintic efficacy used in folk veterinary medicine

Name of plant	Ingredients	Target parasite	References
Betel nut (<i>Areca catechu</i>)	Arecaidine, arecoline, guvacine, guvacoline	<i>Fasciola</i> spp.	Chu, 2001; Yamson et al., 2019
Neem (<i>Azadirachta indica</i>)	Nimbinolin, nimbin, nimbidin, nimbidol, nimbiol, nimbandiol, nimbolide, sodium nimbinate, gedunin, salannin, quercetin, nimbanene, 6-desacetylnimbinene, ascorbic acid, n-hexacosanol, 7-desacetyl-7-benzoyl azadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione	<i>Fasciola</i> spp.	Ali, 1993; Hossain et al., 2011; Kokate et al., 2010; Yamson et al., 2019
Garlic (<i>Allium sativum</i>)	Quercetin, alliin, allicin, ajoenes, vinylthiins	<i>Strongyles</i> and <i>Trichostrongylus</i> spp.	Beshbishy et al., 2020; Masamha et al., 2010
Wormwood (<i>Artemisia vulgaris</i>)	Sabinene, b-thujone, chrysanthemone, camphor, borneol and germacrene D	<i>Trichinella spiralis</i>	Caner et al., 2008
Milkweed (<i>Calotropis procera</i>)	Calotropin, calotoxin, calactin, uscharin, procerain; β -amyrin, lupeol, quercetin-3-rutinoside, calotropenyl acetate, β -sitosterol and stigmaterol, multiflorenol	<i>H. contortus</i>	Cavalcante et al., 2016; Iqbal et al., 2005
Papaya (<i>Carica papaya</i>)	Benzyl isothiocyanate, alkaloids, carpaine	<i>Ascaridia galli</i> , <i>Capillaria</i> sp. and <i>Heterakis</i> sp.	Jean, 1999; Nadkarni, 1998; Dakpogan et al., 2019
Sulla (<i>Heyysarvum coronarium</i>)	Kaempferol, rutin, quercetin-7-O-R-L-rhamnosyl-3-O-glucosylrhamnoside, quercetin-3-O-R-L-rhamnosyl-7-O-glucoside, kaempferol-3-O- β -D-glucoside-dirhamnoside, genistein-7-O- β -D-glucosyl-600-O-malonate, formononetin-7-O- β -D-glucoside-600-O-malonate, and afformosin and the phenolic acid chlorogenic acid	<i>Haemonchus contortus</i> , <i>Ostertagia circumcincta</i> and <i>Trichostrongylus colubrifomis</i>	Tibe et al., 2011; Molan et al., 2000
Chinaberry (<i>Melia azadarach</i>)	Kaempferol, sendanin, salannin, nimbinene, vanillin acid	<i>Ascaridia galli</i> and <i>Haemonchus contortus</i>	Falbo et al., 2008; Shekhawat et al., 2014
Fever nut (<i>Caesalpinia crista</i>)	Flavonoids, tannins, proteins, alkaloids, carbohydrates, reducing sugars, phytosterols, saponins, coumarins and triterpenoids	<i>Trichostrongylid</i> spp.	Al Snafi, 2015; Jabbar et al., 2007
Babla (<i>Acacia nilotica</i>)	Gallic acid, dicatechin, quercetin, robidandiol, β -amyrin, hentriacontane, betulin, sitosterol, kaempferol-3 chlorogenic acid, and glucoside isoquercetin	<i>Trichostrongylid</i> spp.	Sanchez et al., 2018; Bachaya et al., 2009

Copper oxide wire particles (COWP)

Intraluminal copper particles, commonly known as COWP or copper needles, are highly effective in goats. These can be given as boluses to adult and young goats every three months (Vatta et al., 2012). According to farmer experience, applications of COWP even at six months intervals are successful. Only *H. contortus* and *T. circumcincta* (in some cases) are resistant to COWP. It has been demonstrated that COWP can protect ewes from *Haemonchus* infections. However, because sheep are prone to chronic copper toxicity, they should only be used with caution. They can be used only for sheep that are reared on farms, which have low copper content in soil (Burke et al., 2005 a, b; Rios-de Alvarez et al., 2021).

Conclusions and future directions

For controlling helminth infection in both animal and human populations all over the globe, anthelmintic is the main tool but anthelmintics are used arbitrarily which leads to the development of AhR. More holistic and sustainable approaches are needed to stop the occurrence and spreading of AhR. The processes underlying AhR

need to be well understood, and a lot of research needs to be done. Veterinarians around the world are encouraged to routinely monitor anthelmintic efficacy against helminths of different types. It is necessary to establish a governing body to set anthelmintic standards and guidelines for standardizing FECRTs with different kinds of helminths, then the findings can be compared with various areas of that country. A large-scale dataset should be generated about epidemiological patterns of AhR and its impact on animal health from different geographical locations worldwide. In order to effectively combat AhR, holistic and sustainable measures are crucial. In addition, continued exploration of alternative measures and research is necessary to find newer anthelmintics or dietary additives from natural resources.

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