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Anthelmintic resistance: is a solution possible?

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ABSTRACT

More than 50 years after anthelmintic resistance was first identified, its prevalence and impact on the animal production industry continues to increase across the world. The term "anthelmintic resistance" (AR) can be briefly defined as the reduction in efficacy of a certain dose of anthelmintic drugs (AH) in eliminating the presence of a parasite population that was previously susceptible. The main aim of this study is to examine anthelmintic resistance in domestic herbivores. There are numerous factors playing a role in the development of AR, but the most important is livestock management. The price of AH and the need to treat a high number of animals mean that farmers face significant costs in this regard, yet, since 1981, little progress has been made in the discovery of new molecules and the time and cost required to bring a new AH to market has increased dramatically in recent decades. Furthermore, resistance has also emerged for new AH, such as monepantel or derquantel. Consequently, ruminant parasitism cannot be controlled solely by using synthetic chemicals. A change in approach is needed, using a range of preventive measures in order to achieve a sustainable control programme. The use of nematophagous fungi or of plant extracts rich in compounds with anthelmintic properties, such as terpenes, condensed tannins, or flavonoids, represent potential alternatives. Nevertheless, although new approaches are showing promising results, there is still much to do. More research focused on the control of AR is needed.

1. Introduction

Gastrointestinal nematodes (GINs) or "roundworms" are very common parasitic helminths in herbivores, especially ruminants and horses, which are both affected by a range of strongyle parasites, such as *Trichostrongylus axei*. GIN parasitosis has a significant health and economic impact on both industrialized and developing countries (Matthews et al., 2016). In small ruminant livestock, GIN cause productive losses and a deterioration in the animal's general state of health, with signs of diarrhoea, anaemia, and anorexia. In cattle, the effects are less serious, but include possible growth retardation and a variable impact on milk production (Raue et al., 2017). In humans, known ruminant parasites such as *Trichostrogylus* spp. or *Ostertagia* spp., have been reported in humans in European, Asian and African countries (Fuseini et al., 2009; Sato et al., 2011; Lattes et al., 2011; Gholami et al., 2015; Buonfrate et al., 2017; Karshima et al., 2018; Terefe et al., 2019). In tropical and subtropical countries, GIN parasitosis represents a major human health problem, with possible outcomes ranging from asymptomatic infection to death, and its presence has been related to other infectious pathologies in humans, such as tuberculosis or HIV (Pampiglione et al., 1987; Glickman et al., 1999; Adams et al., 2005).

The main anthelmintic drugs used – benzimidazoles (BZs), imidazothiazoles (IMs) and macrocyclic lactones (MLs) – were initially very effective, so their use spread rapidly (Kaplan 2020). This large-scale use has led to the emergence of resistance to these drugs, with the first cases of resistance being reported in sheep in 1964 (Drudge et al., 1964) with the first wide-ranging review of anthelmintic resistance (AR) in livestock coming some years later (Prichard et al., 1980). Despite attempts to optimize the efficacy of anthelmintics, over the last 20 years AR has increased rapidly, making helminth control a serious worldwide prob-

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lem (Kaplan and Vidyashankar 2012; Lanusse et al., 2018). Currently, AR affects all anthelminthic drugs, especially BZ (Traversa and von Samson-Himmelstjerna, 2016) and multidrug resistant has been reported in different European countries (Jackson et al., 1992; Sargison et al., 2001; Álvarez-Sánchez et al., 2006; Traversa et al., 2007; Höglund et al., 2009; Scheuerle et al., 2009; Geurden et al., 2014).

The increase in AR, the financial losses it causes for livestock farmers, and the possible zoonoses that may also result mean that research on alternative treatments is needed. To date, no alternative treatment to anthelmintic drugs possesses proven effectiveness. This review examines the causes of AR and the latest alternative treatments reported in the literature.

2. Causes of AR

AR can be defined as "parasite survival to treatment and pass on resistance-associated genes to their offspring" (Sangster et al., 2018). Resistant species are, a priori, morphologically non-differentiable from non-resistant species and AR must be distinguished from therapeutic failures in which the persistence of parasite is due to inappropriate administration of treatment (Woodgate et al., 2017). In the initial phase of AR, the number of resistant parasites within a population is low. Due to continuous exposure to the same or similar AH, an intermediate phase ensues, and the frequency of resistant heterozygous individuals within the population increases. Finally, the intensity of selection pressure intensity causes resistance to become widespread (Sutherst and Comins 1979). Therefore, AR is a heritable trait and rarely reversible, making detection and prevention essential (Prichard et al., 1980).

2.1. Genetic factors

Nematodes have genetic and biological parameters that facilitate the emergence of AR, such as short life cycles, high rates of reproduction, high speed to evolution and large populations. Consequently, these parasites present exceptional genetic diversity, facilitating the appearance of genetic mutations which can reduce their susceptibility to AH (Anderson et al., 1998). Concretely, mutations in the isotypes 1 and 2 β-tubulin gene (F200Y, E198A, E198L, F167Y and F200Y) determine the resistance of BZs for many GIN species of ruminants (Kwa et al., 1993; Avramenko et al., 2015; Baltrušis et al., 2020). Genotyping studies in BZ-resistant strain of *H. contortus* isolated from sheep and goat presented 26% resistant alleles in the β-tubulin codon, suggesting a potential underestimation of low-levels of resistance (Königová et al., 2021). In the group of IMs, several candidate genetic markers for resistance are known and resistance has been demonstrated in studies with *Caenorhabditis elegans* (Fleming et al., 1997; Culetto et al., 2004; Towers et al., 2005). Orthologues of some of these genes, as Cel-unc-38, Cel-unc-63, Cel-unc-29, Cel-lev-1 and Cel-unc-8 have been found in different species of GIN (Neveu et al., 2010). Moreover, the presence of the truncated Hco-acr-8 transcript has been related to levamisole resistant phenotype in *H. contortus* (Williamson et al., 2011; Sarai et al., 2013; Barrère et al., 2014; Kotze et al., 2020). More studies will be necessary to verify if this deletion confers resistance to other IMs and if it is present in other GIN species. Resistance against MLs has been deeply investigated, mainly in the species *H. contortus*. Most of the studies are based on the candidate gene strategy. So far, a quantitative trait loci (QTL) has been related to ivermectin resistance in *H. contortus* chromosome V (Doyle et al. 2019, 2020; Redman et al., 2019).

2.2. Drug factors

Inappropriate use of AH, such as incorrect concentrations or the administration of broad spectrum AH, has also been reported as a frequent cause of AR development by FAO (FAO 2004, p. 2). Certain AH drugs present a prolonged elimination curve, maintaining the selection pressure over time and, therefore, favouring the selection of alleles which confer AR in GN populations (Vercruysse and Dorny 1991; Woodgate et al., 2017).

2.3. Management factors

Livestock management is probably the most important contributory factor to the appearance of AR, particularly with regard to widespread and excessive use of AH in small ruminants or increases in treatment frequency (Traversa and von Samson-Himmelstjerna 2016; Woodgate et al., 2017; Williams et al., 2021). Two examples of the wayward use of AH concern underdosing: dose calculation is often based on the average weight of individuals in a herd, with larger animals thus receiving a low dose; or goats may receive doses on the basis of calculations undertaken for sheep, but the higher metabolic activity of goats means that they require a higher AH dose (Leathwick et al. 2008, 2012; Woodgate et al., 2017; Babják et al., 2018). Furthermore, animals of different origins often harbour cohorts of parasites with different genetic backgrounds, and if they are carriers of resistant alleles, these can be transmitted to parasites indigenous to the herd. Therefore, quarantine is essential to reduce AR (Fleming et al., 2006; Shalaby 2013).

2.4. Other factors

There are further factors which may facilitate the emergence of AR. Certain climatic conditions may make the establishment of sustainable methods for parasite control more difficult. For example, a high parasite load during the wet season requires the most effective AH groups to be employed to avoid severe parasitosis, but this may contribute to an increase in AR (French 2018; Kaplan 2020).

Recently, Kaplan (2020) has published a review with a series of management recommendations to avoid the increase of AR in herds.

3. Anthelmintic resistance in the world

3.1. Small ruminants

Anthelmintic-resistant GIN have been reported in sheep and goats in different countries around the world, with Brazil, Argentina, USA, Australia, New Zealand and South Africa showing particularly high rates of AR (Overend et al., 1994; Leathwick et al., 2001; Schnyder et al., 2005; Pomroy 2006; Cringoli et al., 2007; Ahmed 2010; Cristel et al., 2017; Oliveira et al., 2017; Hodgkinson et al., 2019). These data suggest that the most widely used drugs (BZs, IMs and MLs) are frequently ineffective, with widespread multiple anthelmintic resistance (MAR) and even resistance against more recently developed molecules, such as monepantel and derquantel (Kaminsky et al., 2008). *Haemonchus cortortus* is the most resistant GIN, although there are also resistant strains of *Teladorsagia* spp. and *Trichostrongylus* spp. across different continents, including Asia (Tsotetsi et al., 2013; Sutherland 2015; Han et al., 2017). In Europe, studies show a lower prevalence of AR than in other regions of the world, although resistance against BZs and MLs has been reported in most European countries (Traversa and von Samson-Himmelstjerna 2016).

Although most ARs seem to be found in sheep, some studies have also observed it in other species such as goats (Holm et al., 2014; Singh et al., 2017; Babják et al., 2018; Mickiewicz et al., 2019).

3.2. Cattle

AR in cattle has developed more slowly than in small ruminants. This fact seems to be a consequence of a higher frequency of deworming and other handling factors in small ruminants, such as frequent incorporation of animals into the flock, semi-intensive farming systems, whole-flock treatment lack of the dose-and-move practice or anthelmintic rotation after each application, among others (Niciura et al., 2012). However, in recent years the increase in the prevalence and distribution of AR has accelerated in all species. The major increase of AR in *Ostertagia* spp. is a concern for veterinary clinicians, as they represent an important pathogen in bovids, causing serious production losses and zoonoses (Gasbarre et al., 2009; Edmonds et al., 2010). In the USA, Australia, and New Zealand, ARs are common in pathogenic GIN such as *Cooperia* spp., *Ostertagia ostertagi* and *Haemonchus* spp. In the USA more than 90% of farms have had ML-resistant *Cooperia* spp. (Kaplan 2020) in the last five years, and Waghorn et al. (2006) reported AR in 94% of farms in New Zealand.

In Europe, ARs for ML have been found in *H. contortus*, *Cooperia* spp. and *O. ostertagi* in countries such as Germany, France and Italy (Geurden et al., 2014).

3.3. Horses

The most common GIN in horses are *Strongylus vulgaris* and *Parascaris equorum* (Reinemeyer and Nielsen 2009) and they can cause a poor body condition, a distended abdomen, retarded growth, weakness, and poor digestion and malabsorption (Slocombe 1985). As with small ruminants and cows, digestive nematodes in horses have developed AR to the main drugs in use, such as BZs or MLs (Geurden et al., 2013; Wolf et al., 2014; Saes et al., 2016). Although less common than in ruminants, resistance in horses has been reported in countries such as the USA, Cuba, New Zealand and Germany (Scott et al., 2015; Salas-Romero et al., 2018; Nielsen et al., 2018).

4. Possible solutions and alternative treatments

Despite the consolidation of the animal health industry, the extensive research undertaken into AR does not seem to have yielded results in practice (Vande Velde et al., 2018). New molecules, such as monepantel (Zolvix®, Novartis Animal Health) and derquantel (Startect®, Zoetis), have been brought to market, with high manufacturing costs, and yet AR to these new drugs have already been reported in sheep in Australia, UK, Netherlands and France (Van den Brom et al., 2015; Bartley et al., 2015; Sales and Love 2016; Niciura et al., 2019). Moreover, the later emergence of AR in cattle and horses indicates that AR prevention measures are not being used appropriately (Kenyon and Jackson 2012; (Charlier, 2014; Verschave, 2014). Other formulations have been recently tested *in vitro* showing promising results, for example aminoalcohol and diamine derivatives (Valderas-García et al., 2021). However, the later emergence of AR in cattle and horses indicates that prevention measures are not being used appropriately (Hodgkinson et al., 2019; Kaplan 2020). Thus, a change in strategy is needed involving all stakeholders to bring the problem under control and the necessary openness to the adoption of alternative AR-prevention measures already exists (Takeuchi-Storm et al., 2019).

Traditional solutions, such as reducing selection pressure (by keeping a part of the herd untreated in "refugia", or the simultaneous use of different groups of AHs), reducing larval density in pastures by reducing the number of animals, or through mixed pastures of sheep and cows, do not seem to be effective. However, other host-focused solutions, such as improved feeding, have been tested with relatively good results (Burke and Miller 2020). The development of vaccines could be a long-term solution, and research is taking place both into vaccines themselves and on achieving a better understanding of the different immune responses of GIN (Zhan et al., 2014; Traversa and von Samson-Himmelstjerna 2016; Albuquerque et al., 2019).

The best long-term solutions for AR seem to be genetic selection of animals which are resistant to GIN infection and the use of alternative AH treatments. A number of genetic selection programmes have been carried out, with promising results (Albers et al., 1987; Windon 1990; Bisset et al., 2001; Vanimisetti et al., 2004b, a). Molecular studies have also been carried out to determine how resistance to GIN infection is generated and this can be used to accelerate the results of genetic selection (McManus et al., 2014; McRae et al., 2014). Recently, Estrada-Reyes et al. (2019) discovered a large number of single nucleotide polymorphisms (SPNs) within 7 genes, in sheep and goats, related to resistance to infection by *H. contortus*. This means that resistance to infection is polygenic, and so selection results will be slow.

Regarding alternative treatments, despite the fact that natural formulations are rarely as effective as synthetic AH (Castagna et al., 2019), phytotherapy remains an interesting field of research, so its use in a comprehensive parasitological control program may contribute to a gradual reduction in AH use to a more acceptable level. Molecules such as condensed tannins, terpenes, or flavonoids are secondary metabolites with well-established anthelmintic properties and they are increasingly important for helminth control in ruminants (Burke and Miller 2020).

5. Phytotherapy

5.1. Condensed tannins

Condensed tannins, or proanthocyanidins, are phenolic polymers synthesized by many plants – such as *Lespedeza cuneata, Onobrychis viccifolia, Hedysarum coronarium, Lotus pedunculatus* and *L. corniculatus* – and they possess proven anthelmintic effects in small ruminants (Hagerman and Butler 1981; Hoste et al., 2012). These molecules can have a directly anthelmintic effect, or they may act indirectly, by improving the nutritional status and immune response of the host (Lanusse et al., 2018). Anthelmintic effects in sheep have been demonstrated *in vitro* and *in vivo* in studies focusing on different GINs, such as *Haemonchus contortus* and *Strongyloides venezuelensis* (Iqbal et al., 2007; Cabardo and Portugaliza 2017; Soldera-Silva et al., 2018; Acevedo-Ramírez et al., 2019; Carvalho et al., 2019). However, their effect in other species such as goats or cows is not yet known. For example, Kalmobé et al. (2017) reported an anthelmintic effect *in vitro* against *Onchocerca ochengi*, a bovine GIN, but an *in vivo* effect has not been yet been reported. Furthermore, the AH activity of condensed tannins can be significantly enhanced by the addition of other molecules, such as flavonoids (Klongsiriwet et al., 2015). Thus, although these biomolecules could open a new area of study in anthelmintic treatments, there is still some work to be done before they can be widely used.

5.2. Terpenes

Terpenes are the most common plant-derived volatile components in essential oils used in human and animal medicine, and they possess a variety of different properties. The effects of different terpenes in human diseases, such as cancer or depressive disorders, are well known (Kumar et al., 2019; Kis et al., 2019; Chong et al., 2019). In the case of parasitic diseases, artemisinin (obtained from the herb *Artemisia annua*) plays a critical role in malaria treatment (Talman et al., 2019). The anthelmintic properties both *in vitro* (Macedo et al., 2015; Katiki et al., 2017) and *in vivo* (de Aquino Mesquita et al., 2013; Andre et al., 2016) of different terpenes has been demonstrated, but their AH effect against particular species of GIN is still unclear. For example, Peña-Espinoza et al. (2016) observed an anthelmintic effect of a chicory (*Cichorium intybus*) diet on *O. ostertagi* in cattle. However, no effect of this diet against *C. oncophora in vivo* was found, although a certain effect was observed *in vitro* (Peña-Espinoza et al., 2017). Recently, the anthelmintic effects and molecular mechanisms of other terpenes, such as carvacrol, thymol and eugenol, have been studied (Hernando et al., 2019). Terpenes interact with P-glycoprotein (P-gp), a protein related to genetic resistance to AH, and that may explain their AH effect (Prichard and Roulet 2007; Eid et al., 2013), but, at this time, the specific mechanism of their anthelmintic effect on different GNs remains unknown (Lanusse et al., 2018).

5.3. Flavonoids

The structural diversity of flavonoids make the study of their anthelmintic properties difficult and the number of studies concerning the anthelmintic effect of flavonoids is lower in comparison with those on condensed tannins or terpenes (Spiegler et al., 2017). Recently, Delgado-Núñez et al. (2020) identified the flavonoid isorhamnetin in *Prosopis laevigata* and tested its AH effect on *H. contortus.* Another flavonoid, quercetin, has demonstrated an *in vivo* AH effect on *C. punctata* in cattle when used alone and in combination with other natural compounds such as caffeic acid or the flavonoid rutin, and an *in vitro* effect was also found when combined with ivermectin on *H. contortus* (Escareño-Díaz et al., 2019; Borges et al., 2020). *Acacia farnesiana* is a shrub legume with a potent AH effect on *H. contortus* and it contains flavonoids and other natural compounds (Zarza-Albarrán et al., 2020). In some cases, the AH effect of these flavonoids seems to derive from their influence on nitric oxide synthase activity (Chetia and Das 2018). Nevertheless, the AH effect of flavonoids is difficult to demonstrate, since many of the studies that have been carried out concern plant extracts that contain flavonoids and also other natural compounds (Swargiary et al., 2016; Váradyová et al., 2018; Yadav et al., 2020; Dkhil et al., 2020; Davuluri et al., 2020).

5.4. Other alternative natural molecules

Research has also been carried out on the AH effect of other natural molecules. The macrolide elaiophylin has demonstrated an AH effect in *in vitro* studies, but its effect on GIN remains to be determined (Gui et al., 2019). Natural peroxides have shown AH activity in parasites such as *S. stercoralis* and others, but not in GIN (Panic et al., 2014; Vil' et al., 2017). Surveys of other natural molecules also indicate an AH effect on GIN. For example, cyclotide variants extracted from *Viola odorata* inhibited larval development of *H. contortus* and *T. colubriformis* in an *in vitro* study (Colgrave et al., 2008). Other alternative plant extracts have proved to be ineffective. Burke et al. (2009) studied the AH activity of garlic and papaya, and found no effect on blood packed cell volume and faecal egg counts in goats. Matthews et al. (2016) reported no effect for supplementing food with ginger or pumpkin seeds on faecal egg counts in sheep and goats.

6. Biological control

The biological control of GINs can also be carried out using nematophagous fungi (Jackson and Miller 2006; Healey et al., 2018; Canhão-Dias et al., 2020). The mechanism consists of the trapping and consumption of parasitic larvae in faeces by the fungi (Grønvold et al., 1993). Various species of fungi have been tested and spores from *Duddingtonia flagrans* seem to have the best ability to survive in gastrointestinal tract of ruminants and horses without a negative impact on the environment (Saumell et al., 2016). In the USA, two formulations of *D. flagrans* recently became commercially available: BioWorma® and Livamol® (Burke and Miller 2020). Even though these biological control methods work well, GIN control should be carried out by means of a comprehensive programme instead of via a single method.

7. Conclusion

AR is a serious problem affecting small ruminants, cattle and horses. Many years of use of anthelmintic drugs have generated great resistance to them in GIN. Although sound herd management is essential, this is not enough to combat GIN, making it necessary to carry out studies on alternatives to traditional drugs. New synthesized molecules do not eliminate the problem of AR, as these new AH also produce resistances. An approach to the problem must take in other perspectives, such as genetic selection or new natural treatments and methods. The genetic selection of animals resistant to GIN infection is a safe but slow system to resolve the problem of AR, since genetic selection gives results after many generations. Given that the host species are non-prolific and have long generation times, and that resistance to infection is quantitative and, therefore, of a complex nature, other solutions must also be sought. Biological control using nematophagous fungi seems to be working well in the USA, but a combined approach is recommended. Some natural anthelmintic molecules have shown efficacy, but further studies are needed to verify this efficacy in different species of GIN and also in different hosts.

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Writing – original draft, A.E.A. and F.C.; writing – review, editing and supervision, L.L. and M.M.G. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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