Caprine haemonchosis: optimism of breeding for disease resistance in developing countries

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ABSTRACT
Haemonchosis is one of the major parasitic infestations in small ruminants and one of the significant causes for loss of production, morbidity and mortality in young sheep and goats. Conventional strategies for the control of haemonchosis involve breaking the life cycle of the worm using anthelmintic drugs, pasture management and animal management. However, indiscriminate use of anthelmintic compounds could contribute to the development of resistance in the parasites. Therefore, a sustainable strategy needs to be implemented to effectively control haemonchosis in goats. One of the ways to achieve this is to breed animals for disease resistance. There are various commercial strains and breeds that can be used as genetic markers to select for resistance. However, their direct utilization in developing nations and field situations may be difficult due to the higher cost of gene based selection and multifactorial nature of the trait. Hence, breeding for nematode resistance in goats will require a more integrated approach using indicator traits to identify resistant breeds/lines/animals and then adopting gene-based selection for organized farms.

Introduction
Productivity in animal rearing is affected by management and diseases. Gastro-intestinal parasitism has been one of the major problems in the small ruminant rearing system. Gastro-intestinal parasites mostly found in small ruminants are Trichostrongylus colubriformis, Teladorsagia (Ostertagia) circumcincta, Cooperia spp., Oesophagostomum spp., Strongyloides spp., Bunostomum spp. and Haemonchus contortus. Among these, Haemonchus spp. (or the Barber’s pole worm) is probably the most important parasite of sheep and goats. Haemonchus contortus is a blood-sucking parasite and is the major reason for morbidity and production losses in the goat-farming system, especially in the developing world (Selemon 2018). Various risk factors contribute to the development of haemonchosis, which can be grouped as extrinsic and intrinsic. The extrinsic factors include climate, vegetation, nutrition, worm load in pasture, etc. The intrinsic factors include age, physiological status, nutritional level and breed of animal (Selemon 2018).

Classical strategies for the control of haemonchosis involve breaking the life cycle of the worm using anthelmintic drugs, pasture and animal management. Anthelmintic drugs are the most widely and commonly used methods for gastro-intestinal nematodiasis in small ruminants. However, their widespread use may cause resistance in the target species of parasite(s). For e.g. in small ruminants, Teladorsagia, Trichostrongylus and Haemonchus are reported to be the most abundant anthelmintic-resistant nematodes (Papadopoulos et al. 2012). Apart from this, the environmental impact of excessive anthelmintic application and rising cost of labour and treatment further complicate the scenario (Shrivastava et al. 2018). In goats, anthelmintic resistance has been reported worldwide, ranging from the temperate and Mediterranean climate of European countries, such as France, Netherlands, Switzerland, Germany (Rose et al. 2015), to subtropical climate in Cuba (Arece-Garcia et al. 2017) and tropical climates of South Africa (Bakunzi et al. 2013), Pakistan (Jabbar et al. 2008), Kenya (Wanyangu et al. 1996), Malaysia (Dorny et al. 1994) and India (Das and Singh 2005; Dixit et al. 2017).

Alternative helminth control strategies include rotational grazing (Marley et al. 2006), nutritional immunomodulation (Strain and Stear 2001), the use of nematophagous fungi (Flores-Crespo et al. 2004) and vaccines (Tian et al. 2020). However, these methods are mostly employed in sheep farming, and their effect on the goat production system is yet to be analyzed. Also, the use of a vaccine, nutritional modulators and rotational grazing may not be pertinent as per the goat rearing practices of developing nations, especially Africa and Asia. Therefore, a sustainable strategy needs to be adapted for effective and widespread control of haemonchosis in goats. One of the ways to achieve this is to breed animals for disease resistance. This involves the identification of breeds that are naturally resistant to gastro-intestinal nematodes (GINs) or Haemonchus spp., and, the underlying causative genetic mutations that can be used as markers for selection and breeding of haemoncho-tolerant or resistant progeny. In sheep and goat, certain native breeds are resistant or tolerant to haemonchosis; these include sheep breeds such as Morada Nova, Red Maasai, Barbados Black Belly (Arsenopoulos et al. 2009).
In goat, there is one certain example of ‘haemonchotolerant’ breed, i.e. Nigerian West African Dwarf goat (Chiejinia and Behnke 2011), with some other Indian native breeds such as Barbari, Jamunapari, (Chauhan et al. 2003; Rout et al. 2011) and Rohilkhandi (Shrivastava et al. 2018) showing promising results. There are various genetic loci identified in these breeds that can be used as genetic markers to select resistant animals. Therefore, this review will focus on genetic loci or markers identified in goats, for resistance to gastro-intestinal nematodiasis, keeping *H. contortus* central to the discussion, and utilization of native breeds in sustainable control of haemonchosis in goats.

**Haemonchosis in goats: chemical and non-chemical control**

*Haemonchus* spp. is a blood-sucking nematode and is one of the most pathogenic parasites of small ruminants. Among the twelve species in the genus, *Haemonchus contortus* is most widespread and is found in small ruminants (Arsenopoulos et al. 2021). Adult parasites are found in the abomasum and transmitted horizontally by grazing on contaminated pasture. The adult worm lays thousands of eggs at a time that come out with faeces, and depending upon the external environment; it develops into an infective L3 larval stage. L3 can survive on the grass blades for months. These are then eaten up by the healthy host, in which they develop into adult parasites. *Haemonchus* spp. is a haematophagus parasite, and a single adult worm can suck up to 30 µl of blood per day (Emery et al. 2016). This causes massive blood loss, haemorrhagic lesions, anaemia, which ultimately causes a decrease in growth, production and even mortality, especially in severe infections (Wang et al. 2017).

*Haemonchus contortus* is primarily a parasite of tropical climate. Humidity and warm temperature(s) of the tropical and subtropical region favour the development of larval stages in adults (Arsenopoulos et al. 2021). However, it can resist the seasonal temperature and humidity changes by hypobiosis, a way of arresting development during unfavourable conditions (Waller and Thomas 1975). Rashid and Irshadullah (2018) reported that temperature around 28–32°C, with a relative humidity of 60–100% showed the maximum prevalence of haemonchosis in goats; similar trends were observed in Bangladesh (Nahar et al. 2015), Pakistan (Qamar et al. 2009), Benin (Attindehou et al. 2012), Nigeria (Josiah et al. 2015) and Mozambique (Atanásio-Nhacumbe and Sitoe 2019). Also, it should be noted that in temperate and arid regions, haemonchosis may only be a seasonal threat, as very high and low temperature increases the hypobiosis period, thus making the infective stage larva unavailable for a major period (Arsenopoulos et al. 2021).

The first line of control against haemonchosis (or gastrointestinal nematodiasis) is the application of anthelmintic compounds. Although these have been beneficial, especially in temperate regions, their prolonged use has led to the development of drug resistance in most of the parasite(s). A recent study on Polish goat herds showed that 88% of the herds were resistant to benzimidazoles; 95% were resistant to macrocyclic lactones, and 12% were resistant to levamisole (Mickiewicz et al. 2021). Benzimidazoles (BZ) are the most used anthelmintic drugs due to their broad-spectrum, low cost and short withdrawal period (Lanusse et al. 2016). However, most studies have shown benzimidazole resistance in *Haemonchus* spp. around the globe, with the identification of benzimidazole-resistant parasitic genotypes. In Brazil, the frequency of BZ-resistant allele in goats was 9% (Nunes et al. 2013); in India BZ-resistant genotypes in goats varied from 62% in central India (Dixit et al. 2017) to 55–85% in northern India (Chandra et al. 2015), in Greece, 100% population of *Haemonchus contortus* in goats was found to be of BZ resistant type (Arsenopoulos et al. 2020). Similar findings of benzimidazole resistance were also reported in semi-extensive and medium to large scale goat farms in South Sudan (Mohammedsalih et al. 2019) and India (Ghalsasi et al. 2012). Apart from benzimidazoles, there are reports of the development of multi-drug resistance in *Haemonchus* spp. in goats. Multi-drug resistance was observed in the Atlantic region (Crook et al. 2016), France (Chartier et al. 2001; Bordes et al. 2020), Switzerland (Schnyder et al. 2005), India (Easwaran et al. 2009), China (Wang et al. 2017), Germany (Scheuerle et al. 2009), Czech Republic (Vadlejch et al. 2021), Cuba (Arece-Garcia et al. 2017), Kenya (Mungube et al. 2015), etc.

Chemical means of control using anthelmintic compounds have resulted in widespread resistance among parasites. Hence, other non-chemical methods have been suggested to control haemonchosis in small ruminants. Intensive rotational grazing, in which the animals were exposed to short grazing period (and subsequent natural parasitic infections) (Colvin et al. 2008), alternate grazing of sheep and cattle (Mahieu and Aumont 2009), and intensive cell grazing system (Ruiz-Huidobro et al. 2019) are useful for the control of haemonchosis in sheep. A mixed grazing strategy between cattle and sheep was most beneficial for growth rate in lambs when they were treated with anthelmintic after weaning (Marley et al. 2006). Grazing management, using mixed or alternate grazing, is based on minimizing the intake of infective larva, thus decreasing the risk of getting an infection (Hoste et al. 2011; Arsenopoulos et al. 2021). However, goats are browsers, and they, inherently are at lower risk of ingesting L3 infective larva; hence, they can be reared under an extensive system. Hoste et al. (2011) suggested using goats in combination with anthelmintic plants for browsing to reduce overall pasture load also mixed grazing has shown reduced worm load in goats. However, the scope of such strategies gets restricted, as goats are mostly reared in small stocks, and nutritional requirements and availability of grazing grounds are limited (Colvin et al. 2008). Apart from this, some plants and nematophagous fungi have been advocated for parasitic control. Plants with bioactive compounds and condensed tannins are antiparasitic and help improve production performance (Athanasiadou et al. 2005; Hoste et al. 2012). However, their use becomes limited, as in tropical countries, grass contains less protein and more fibre; hence the inclusion of condensed tannins can further lower the protein absorption leading to reduced growth (Waghorn 2008). Nematophagous fungi like *Duddingtonia flagrans* have been tried for the control of *H. contortus* in sheep and goats. Although it has given promising results in sheep (Chandrawathani et al. 2004), its effects and applicability...
in goat under field conditions remain to be elucidated (Maingi et al. 2006; Rahmann and Seip 2007). Nutritional supplements and dietary alterations have also been proposed to control Haemonchus spp., like using a high protein diet (Strain and Stear 2001) and paraprobiotic-treated bacterial proteins (Sanders et al. 2020). Although these approaches are effective to some extent, most of them have been tested in sheep. Second, goat rearing is a major component of agriculture activities in developing nations, that too at small scale; therefore, the sustainability of these methods under an extensive system of rearing remains to be evaluated.

**Genetic control strategies**

One of the main reasons behind the optimistic approach towards genetic control is its sustainability and availability of huge breed diversity/goat genetic resources. Breeding for enhanced disease resistance offers several advantages over other methods of control. It can be an inexpensive and relatively simple way to improve animal health, welfare and productivity. Goats are natural browsers, and this has led to greater avoidance of infective L3 larva than sheep (Hoste et al. 2011). Due to this behaviour, in goats, the immune response against nematodes is differently developed than in sheep. In goats, the immune response is weakly expressed for the establishment of L3 larva and persistence of adult worms (Hoste et al. 2011), due to which goats can act as carriers of the between breed variation in sheep and goat. Identifying resistant/susceptible goats, either within or between breeds, requires some ‘phenotypic indicator traits’. These traits can be broadly grouped as parasitological, haematological, biochemical and immunological.

**Identification of resistant animal(s)**

For identifying the resistant animal, the most common phenotypic trait is faecal egg count (FEC). FEC has been the most reliable indicator of gastro-intestinal parasitism, and it has been reported to be highly correlated to worm count in sheep and goats (Cabaret et al. 1998; Cringoli et al. 2008; Kemper et al. 2010; González-Garduño et al. 2013). FEC can be easily and efficiently used for within and between breed variability for resistance/susceptibility to gastro-intestinal parasitism (Eady 1995). FEC has heritability values ranging from 0.7 to 0.4; it was estimated to be 0.07 in dairy goats (Heckendorn et al. 2017), 0.39 in Malabari and Attapady black goat (Aparna et al. 2011), 0.05–0.13 in Barbari goats (Mandal and Sharma 2008), 0.13 in Galla goat (Baker 1998) and Creole goat (Mandonnet et al. 2001, 2006). Although there are reports of FEC varying with physiological status (Agrawal et al. 2015; Notter et al. 2017), differences in FEC may also arise due to age, season, time, previous exposure, the proportion of male to female worms and most important innate immune response of animal or breed (Saddiqi et al. 2012). Apart from these differences, the basic advantage that FEC estimation provides is its non-invasiveness and relative ease of quantification. However, in the case of Haemonchus spp., especially during natural infections, identification of worm/larval type may also be required using secondary assisting techniques (larval culture and identification). This is because most of the eggs from genus Trichostrongylus (mainly Haemonchus spp., Trichostrongylus spp., Ostertagia spp., Teladorsagia spp., Oesophagostomum spp., and Cooperia spp.) are identical in appearance (Storey 2015). Other parasitological indicator traits include worm count at necropsy (worm burden) and worm length. FEC and worm burden are highly correlated; hence, worm count at necropsy can be used to assess resistance/susceptibility, particularly when the FEC values are not very conclusive (Mugambi et al. 2005). Worm length is another important parasitological indicator trait, which represents the fecundity of parasites (Strain and Stear 2001). However, worm-related traits like number and length are expensive to study and require animal slaughter, and hence, are not in routine use.

Apart from parasitological traits, some haematological parameters are also used to assess resistance/susceptibility. For haemonchosis, packed cell volume (PCV) percentage is a highly informative parameter (Gauly and Erhardt 2001). PCV is indicative of anaemia caused by blood-sucking nematodes (like Haemonchus spp.), and a lower level of PCV is indicative of high parasite count (Baker et al. 2003). PCV has been employed extensively with FEC to assess the extent of parasitism and its effects. PCV has a little higher in resistant animals, and it is negatively correlated with FEC (Costa et al. 2000; Vanimisetti et al. 2004; Onzima et al. 2017; Alam et al. 2019). However, some reportsshows that PCV has been less useful for determining resistant status between groups, especially in goats (Retee et al. 2019; Makun et al. 2020). It was also suggested that in caprine haemonchosis, PCV values might not be much informative if worm burden is low to moderate (Heckendorn et al. 2017). Another haematological parameter frequently used is the eosinophil count. Eosinophilia or an increase in eosinophil count is a prominent feature of parasitic infection (Bambou et al. 2013), and eosinophil count has been negatively correlated with FEC in sheep (Davies et al. 2005). However, Bambou et al. (2013) reported a higher eosinophil count in susceptible Creole kids; also, more recently, Basripuzi et al. (2020) reported no association between peripheral eosinophilia and FEC in Boer goat experimentally infected with low-dose H. contortus larvae. This was mainly because goats, in general, lack an effective eosinophil response against H. contortus infection. Hence, they don’t always follow the classical negative correlation pattern with FEC (Basripuzi et al. 2018).

Besides these, there are some other phenotypic traits too that are frequently employed with parasitological traits for the assessment of resistance/susceptibility to haemonchosis in sheep and goats. The important one among these is the estimation of immunoglobulin level, mostly IgA and IgE. de la Chevrotière et al. (2011) reported a positive correlation between IgA and FEC in Creole goat. They also observed a negative correlation between IgE and L3 larva of H. contortus and FEC. GIN infestation is mostly marked with the production of parasite-specific IgA, IgG1 and IgE (Saddiqi et al. 2012). A recent study has shown that experimental infection of Boer goat with H. contortus larva produced increased parasite-
specific IgA, but this increase was not associated with FEC and worm burden (Basripuzi et al. 2020). IgE, the antiparasitic antibody, is another important marker that can be utilized with worm-related traits for the identification of resistant animals (Bricarelo et al. 2007). Increased local IgE levels have been found in GIN-resistant sheep and goats (Pernthenner et al. 2005; de la Chevrotière et al. 2011). Similarly, IgG levels were also postulated to indicate resistance/susceptibility in GIN infections in sheep (Muñoz-Guzmán et al. 2006). Imran et al. (2020) reported significantly different levels of IgG and IgE in two native goat breeds of Pakistan, infected with equal doses of H. contortus larva, and concluded that reduced levels of these immunoglobulins might have an effect on susceptibility towards H. contortus in one of the native goat breeds. Apart from these, there are some other minor traits, such as abdominal histology, mast cell and tissue eosinophil counts, total plasma protein, albumin level, etc., but due to the availability of infections that can frequently produce related symptoms, these are mostly used in concordance with parasitological and immunological traits for the assessment of resistant/susceptibility to GINs.

**Genetic loci for GIN resistance in goats**

In natural infections, GINs are seldom found pure; thus, for efficient identification of resistant/susceptible animals, genetic markers linked to the indicator traits have to be identified as means for indirect selection. Recently, there has been an abundance of genetic markers identified in sheep. These are mostly either QTLs (quantitative trait loci) or single nucleotide polymorphism (either regions or genome-wide) or identification of genomic regions using genome-wide association studies (Marshall et al. 2009; Sallé et al. 2012; Periasamy et al. 2014; Sallé et al. 2014; Benavides et al. 2015; Atlija et al. 2016; Guo et al. 2016; Niciura et al. 2019). In goats, the exploration of genomic regions that can be used for the selection of resistant animals has been slow. In this section, we will focus on gene(s) and regions identified in goats that are proposed to be potential candidates for the selection for Haemonchus spp. (or GIN) resistance.

The MHC (major histocompatibility complex) is one of the most studied regions for disease resistance research, including resistance/susceptibility to gastro-intestinal nematodiasis (Dukkipati et al. 2006). MHC is one of the most polymorphic and gene-dense regions in the genome, and its function is to present foreign antigens to immune cells (Grossen et al. 2014). Goat MHC is called caprine leucocyte antigen (CLA), and it is located on chromosome 23 and is, similar to ovine leucocyte antigen (OLA) in an overall organization (Ballingall and Todd 2019). Many studies report polymorphism in CLA; these have mostly focussed on the DRB region, as it is highly polymorphic and is involved in the formation of antigen-binding groove in MHC cluster (Tizard 2004; Shrivastava et al. 2015). Yakubu et al. (2017) studied polymorphism in Nigerian native goat breeds using PCR RFLP and advocated its use for selection and breeding for heat stress in tropical goats. Asif et al. (2016) studied polymorphism in DRB1, IGF1 and IL 32 in native Chinese goats infected naturally by H. contortus, and they reported that missense SNP at DRB1 locus was significantly associated with FEC. Balamurugan et al. (2021) studied polymorphism in the MHC DRB region and its effect on natural infection of H. contortus, in two native Indian goat breeds: Salem Black and Tellicherry goat. Although they reported a difference in mean values of FEC and PCV, the effect of genotypes on both the indicator traits was non-significant (P ≤ 0.05). Estrada-Reyes et al. (2016) reported SNP at OLADR20 having a significant effect on the square root of mean FEC and production traits in sheep and goats, thus playing an important role in resistance/susceptibility towards H. contortus infection in small ruminants. Shrivastava et al. (2018) used SNP and intronic microsatellite of CLA for its possible association with mixed natural infection of H. contortus in Rohilkhandi goat. The SNPs at TaqI and Bsal locus of MHC DRB gene and microsatellite loci DYA and ODRB1.2 were associated with one or the other indicator traits, indicating their importance in resistance/susceptibility to H. contortus in Rohilkhandi goat (Shrivastava et al. 2018). A characteristic feature of MHC in small ruminants in the presence of microsatellite repeats (Dukkipati et al. 2006), these regions have been extensively used in sheep for their association with resistance/susceptibility (Luffau et al. 1990; Buitkamp et al. 1996; Charon et al. 2002; Castillo et al. 2011; Hassan et al. 2011a). However, reports of their use for parasitic resistance studies in goats are scanty.

Besides the use of MHC as a candidate gene, other loci are studied for gastro-intestinal resistance/susceptibility in small ruminants. IgE (immunoglobulin E) and its increased level are the hallmarks of parasitic infestation. They are implicated in the control of worm numbers in some infections such as Trichinella spiralis, Haemonchus contortus (Lee et al. 2011). The binding of the parasite to IgE triggers mast cell degranulation and hence are increased during parasitic infestations (Huntley et al. 2001). Polymorphism at IgE gene was explored for its possible association with GIN resistance. Clarke et al. (2001) studied polymorphism at 5’ UTR (untranslated region) gene in sheep, although one of the IgE alleles was associated with resistance to Trichosanthes colubriformis, the same could not be detected with H. contortus. The region was also studied in Rohilkhandi goat for the presence of polymorphism and its association with mixed natural infection of H. contortus (Shrivastava et al. 2018). While there were differences in mean FEC among the different haplotypes, the effect of IgE haplotypes on LFEC (Log FEC) was non-significant (P ≤ 0.05).

More recent studies have utilized a cluster of putative candidate genes, most of the immune regulation pathways, for the identification of causative mutation(s), resistance/susceptibility to GINs. Bressani et al. (2014) explored SNPs at IL13 (exon 2, 3 and 4), IL2 (exon 1, 2 and 3), IL 4 (exon 3) and IFN-γ (interferon-gamma) (exon 1, 2, 3 and 4 partial) loci for their association with H. contortus infection in F2 population of goats (produced by F1 inter-crossing of Saanen x Anglo Nubian cross). They identified 10 SNPs, out of which three (IL2, IL13 and IFN-γ) had a significant effect on FEC values. Recently, a genome-wide association study was performed on Creole goat, using FEC as an indicator trait (Silva et al. 2018). The goats were experimentally infected with L3 larvae of H. contortus, and after the challenge, FEC was evaluated at regular intervals. The study identified seven QTLs on chromosomes 4, 6, 11, and 17 to be associated with FEC. Also, these QTLs were identified in regions of genes associated
with intestinal damage, immune response, haemorrhagic control and muscle weakness (Silva et al. 2018). Alam et al. (2019), targeted 129 SNPs from 84 immune response-related genes in goats for their possible association with *H. contortus* infection. Ten polymorphism had a significant effect on FEC. These SNPs were found in CIITA (two SNPs; the coding region), ATP2A3 (two; 3’ UTR), HSPA8 (two SNPs; intron 8–9), STAT5B (one SNP; 3’ UTR), ESY1 (one SNP; intron 5-6) and SERPING1 (two SNPs; intron 6–7 and 7–8) genes. Also, the resistant animals had significantly higher expression levels for all candidate genes (except CIITA) (Alam et al. 2019). Estrada-Reyes et al. (2019) identified potential SNPs at IL5RA and IL12RB2 genes in Kiko, Boer and Spanish goats, associated with ADG (Average Daily Gain) and IgM levels for a selection of resistant animals. Omar et al. (2019b) explored polymorphism in NOD1 and NLRP9 genes in Chinese goat, having natural mixed infection of *H. contortus*. Two polymorphisms within these genes (NOD1_146.A > G and NLRP9_43.A > G) were significantly associated with FEC. NOD1 and NLRP9 are immune response-related genes, and their role in disease resistance has been studied in humans, pigs and aquaculture species. Also, the mRNA study exhibited over-expression of NOD1 and NLRP9 genes (in addition to IFNG, TLR8, IL32, and IGF1 genes) in resistant goats compared to the susceptible ones (Omar et al. 2019a). Omar et al. (2020) scanned a cluster of 12 innate immunity candidate genes for SNPs related to FEC in Chinese and Bangladeshi native goats. Eleven novel SNPs in NLRC3, NLRC5, HIP1, and LRP8 genes, were identified, which were significantly associated with FEC in goats. Also, the expression levels of NLRC3, HIP1, and LRP8 were significantly higher in the resistant group than the susceptible group, whereas expression of NLRC5 was lower in the resistant group (Omar et al. 2020). Bhuiyan et al. (2017) performed mRNA expression profiling in two distinct populations of Yichang goats (resistant and susceptible lines). From 2369 genes, 1407 were upregulated and 962 were downregulated, in which 298 genes were highly expressed in resistant animals. From these highly expressed genes, KEGG pathway analysis revealed the majority were from endocytosis, transforming growth factor (TGF)-β, mitogen-activated protein kinase (MAPK) and cell adhesion molecules (CAMs) pathways. Thus, Th2 related genes were upregulated in the resistant group (Bhuiyan et al. 2017), a characteristic feature of *H. contortus* infection in resistant goats (Guo et al. 2016). It has been reported previously that GIN infection in sheep is characterized by a differential expression of Th1 and Th2 types of immune response (Hassan et al. 2011b). Hepworth et al. (2012) reported that, in mouse models, during helminth infection, the Th2 type immune response is mediated by mast cells via the regulation of type 2 cytokines (IL-25, IL-33 and TSLP). Previous experimental studies have also advocated that resistance to *H. contortus* (or gastro-intestinal helminths) is mediated by a strong Th2 type of immune response (Perntha ner et al. 2005; Lacroux et al. 2006; Shahya et al. 2009). Aboshady et al. (2019) showed that resistance to *H. contortus* in Creole goats is due to differential expression of genes, which causes a reduction in worm fecundity probably mediated by MHC class I genes. Furthermore, it was observed that, in the case of haemonchosis, the onset of Th2 response is earlier in resistant kids compared to susceptible ones (Aboshady et al. 2020). Recently, the same group explored genomic variants affecting phenotypic traits for resistance/susceptibility to GIN infection in Creole goats (Aboshady et al. 2021). The KEGG pathway analysis of the RNA seq data showed T cell signalling, hepatitis B and MAPK signalling pathway to be most significantly different in their expression in resistant animals. Further analysis of T-cell signalling pathways in resistant animals revealed 78% of the genes showing genomic variants, thus confirming the role of T-cell immune regulatory genes in imparting resistance against GIN infections, in particular, towards haemonchosis (Aboshady et al. 2021).

**Selection for resistance or resilience?**

The confrontation of terms, resistance and resilience, often occurs when there is a discussion of parasitological infestations. Resilience is the ability of animals to maintain their production performance even when they are faced with a parasitic infestation (Bishop 2012). On the other hand, resistance can be acquired either actively or passively, and it is the ability of the animal to prevent parasitism (Saddiqi et al. 2012). Morris et al. (2010) reported selection for resilience in Romney sheep in New Zealand. They defined resilience in terms of first anthelmintic treatment as ‘the age at first anthelmintic treatment required to maintain acceptable growth rate in lambs’. When resilience was selected for about 10 years, the average ‘age-at-first-drench’ in the resilient line was increased by 23.6 days (compared to the control line) with a 4.5 kg increase in 6-month body weight. However, there were practical difficulties in scoring for such traits in field conditions (Morris et al. 2010), and selection for resilience does not provide any additional benefit over resistance. Also, selection for resilience may provide a source for pasture contamination, as the actual worm burden in the animal does not get reduced (McManus et al. 2014). On the other hand, resistance is either active or passive and can suppress the development of any infection (Albers et al. 1987). It is the innate property of a breed or individual and it also reduces pasture (or cross) contamination. Kemper et al. (2013) postulated that when resilience was selected for about 10 years, the worms did not adapt to genetically resistant or susceptible sheep breeds such as Barbados Blackbelly, St Croix, Florida.

**Breeding for nematode resistance and role of native breeds**

Host genetic variation and environmental conditions affect the genetic control methods for selection against GIN (Zvinorova et al. 2016). There is sufficient evidence for within and between breed variability towards GIN resistance/susceptibility in sheep, and various native sheep breeds are known to be resistant to *H. contortus* (or GIN) infestation. The variation between breeds of sheep in levels of resistance to internal nematodes was described more than 80 years ago in the U.S.A (Stewart et al. 1937). Natural breed differences towards nematode resistance have been identified in various native sheep breeds such as Barbados Blackbelly, St Croix, Florida.
Native and Gulf Coast Native breeds (Bishop 2012), Indian Garole (Nimbkar et al. 2003), African Red Massai (Baker et al. 2004), Sabi breed of Zimbabwe (Matika et al. 2003), Santa Ines of Brazil (Amarante et al. 2009) and Polish long wool breed (Boux et al. 1998). However, fewer examples are available for goat breeds that are innately resistant to haemonchosis or GIN infestations. Some of the important native goat breeds that are advocated to be resistant to haemonchosis/GINs are Jamunapari (Chauhan et al. 2003), West African Dwarf (Chiejina et al. 2010), Creole (Bambou et al. 2009; Bambou et al. 2013), Angora (Vlassoff et al. 1999), Thai native (Pralomkarn et al. 1997), Chinese native goat breeds (Omar et al. 2019a, 2019b; Omar et al. 2020), Black Bengal (Retee et al. 2019) etc. Native breeds can play an important role in breeding GIN resistance in goats. A phenotypic-marker-based, between breed evaluation, was performed between Sri Lankan indigenous (SLI) goats and their Jamunapari crosses (JC) (Kurukulasuriya et al. 2017). It was observed that the SLI breed performed phenotypically better than the JC crosses when exposed to natural and field infections of H. contortus (Kurukulasuriya et al. 2017). Another worthwhile example is the West African Dwarf (WAD) goat of Nigeria. The breed is found in humid and drier regions of Nigeria, forming two ecotypes, which are ‘haemonchotolerant’ and ‘trypanotolerant’ breeds of goat (Chiejina et al. 2009). It was also postulated that WAD goats had an innate ability to resist/tolerate H. contortus infestations, and goats that are crossed with other native goats (Sahelian goat) had reduced the ability of ‘haemonchotolerance’ (Chiejina et al. 2015). Later on, Makun et al. (2020) phenotypically evaluated three native goat breeds from north-western Nigeria, and it was inferred that up to the age of 6 months, all the three breeds (Sokoto, Sahelian and West African Dwarf goat) developed a substantial amount of acquired resistance or tolerance against H. contortus, and there are possibilities of within breed selection for haemonchus resistance (Makun et al. 2020). Sonibare et al. (2017) evaluated the response of three native Nigerian goat breeds (Red Sokoto, West African Dwarf and Sahel White) against primary and secondary infection of H. contortus. Although all the three breeds were able to resist the infestation to some extent, WAD goats had better adaptability and resistance to H. contortus infection. In addition to these, some native goat breeds are advocated to be resistant to Haemonchus spp. or GINs. There are reports of within-breed or between-breed variability in resistant traits that can be utilized in breeding for nematode resistance. Some examples include Rohilkhandi goat of India (Shrivastava et al. 2018), Caninde, Biju and Anglo-Nubian goat of Brazil (Costa et al. 2000), Teddy and Beetal goat of Pakistan (Babar et al. 2015) and Dera Din Panah breed of Pakistan (Imran et al. 2018).

Conventional breeding strategy for gastro-intestinal parasite resistance involves estimation of FEC and PCV as indicator traits. FEC values are of prime importance because of their wide applicability and ease of estimation; however, a considerable level of worm load is required so that variation in FEC can be contrastingly expressed. This automatically increases the time gap, and early selection in goats may not yield the desired efficiency (Zvirnora et al. 2016). Vagenas et al. (2002) explored the relationship between GIN resistance and production traits in crossbred Cashmere producing goats. They observed a weakly positive genetic correlation between production trait and FEC, and it was suggested that breeding for nematode resistance in goats might be more beneficial in the later stages of life or for animals that have been kept for a year or more, so that the trait could develop completely. These findings were corroborated by Rout et al. (2011) in Indian Barbari and Jamunapari goats. They reported low heritability of FEC and PCV, with heritability of FEC increasing with age (and PCV maximizing at 9-month age), suggesting selection at later ages may be more beneficial (Rout et al. 2011). Similarly, in Creole goats, a strong positive correlation was observed between FEC at 11-month-old kids and FEC during periparturient goats (Mandonnet et al. 2006). It was also observed that selection of kids at 11-month-old age, for resistance to parasitic infestations, may also provide some degree of resistance in periparturient does; hence, it can be perceived as indirect selection for resistant female goats (Mandonnet et al. 2006). However, Onzima et al. (2017) reported that in Indigenous goat breeds of Uganda, sole FEC-based selection may not be useful. Three native goat breeds of Uganda (East African, Mubende and Kigezi goat) were studied for breed variability regarding resistance to GINs. The experimental animals were artificially infected with H. contortus L3 larvae. FEC and PCV were estimated periodically from 3-week post-infection to 10 weeks. There was no significant difference in FEC between the three breeds, and a significant variation was seen in PCV values. In addition, the Mubende breed was most resistant in terms of PCV values, and variations in PCV can be exploited for selection for resistance to Haemonchus spp. (Onzima et al. 2017).

Future prospects

Resistance against parasites is a polygenic trait. As discussed, many novel genetic loci are identified for nematode resistance in goats. A comprehensive study was undertaken by the USDA National Institute of Food and Agriculture 1890 Institution Capacity Building Grant Program, using Dorper, Katahdin and St. Croix as sheep breeds and Boer, Kiko and Spanish as goat breeds, to identify genetic markers in sheep and goats for parasite resistance. The humoral response of the sheep population was much stronger than goat breeds against challenge infections. IL12RB2 (Interleukin 12 receptor beta 2 subunits) appeared to be a candidate gene for resistance in both species. Also, TR4, CD86, CSF and NOS2 genes had an important effect on immune pathways against Haemonchus spp. infection in sheep and goats (Estrada Reyes et al. 2022). However, earlier reports have supported strong expression of Th2 type cytokine (IL-13, IL-4 and IL-10) in animals resistant to Haemonchus spp. infection (Corley and Jarmon 2014; Shrivastava et al. 2018; Aboshady et al. 2020). Apart from these, other high throughput SNP mining reports have indicated potential SNPs at caprine NLRV5, NLRV5, HIP1, LRP8, NOD1 and NLRP9 genes with their respective higher expression level(s) in resistant animals (Omar et al. 2019a; Omar et al. 2020). The molecular mechanism behind resistance against Haemonchus spp. is complex and involves various levels that...
need to be precisely deciphered. Also, large scale genotyping using high throughput techniques may not be feasible in actual field conditions; therefore, to adopt breeding for nematode resistance, the best path would be to utilize indicator traits. However, employing the most common parasitic disease indicator trait (i.e. FEC) may not always give desired results (Onzima et al. 2017); hence, it is better to measure all the available traits for efficient selection of resistant animals. This approach may involve using faecal egg count in combination with the estimation of packed cell volume, immunoglobulin levels, worm counts at necropsy (if the farming system permits) etc., so that resistant animals within the breed can be efficiently identified.

Tsukahara et al. (2021) evaluated the performance parameters of meat goat and hair sheep breeds, selected using indicator traits for resistance to parasites. The animals were artificially challenged with *Haemonchus contortus* larva. They reported that PCV and FEC (including immunoglobulin levels) may not always be correlated, especially in goats, and there may be breed variation; hence, they should be used carefully and, if possible, not in isolation. Secondly, selection for parasite resistance based on indicator traits does not adversely affect the performance parameters of meat or hair animals (Tsukahara et al. 2021). A plethora of studies have indicated within and between breed differences in the indicator traits, especially in native goat breeds. These breed differences must be utilized first to reduce the anthelmintic burden on small ruminants. When such resistant lines/breeds have been identified, they can be utilized for deciphering the molecular mechanism behind resistance or susceptibility. These specialized lines/breeds can be reared under specialized farms, where infrastructure favours their gene-based selection. These animals can be selected based on their genotype vis-à-vis performance recording, and the germplasm can be propagated in field farms via farmers’ herd/associations.

**Conclusion**

Selection and breeding for resistance to *H. contortus* (or GINs) in goats is an attractive strategy, especially in developing and tropical countries concerning GIN-resistant traits. After ascertaining the resistance status of breeds in experimental conditions may be implemented in tropical and developing regions. There are various reports of the development of anthelmintic resistance in goats, from developed and developing regions, indicating that parasites might be adapted for the selection pressure due to the indiscriminate use of anthelmintic drugs. Hence, breeding for nematode resistance may be a sustainable option for nematode control in goats limiting the use of anthelmintics without having any untoward effect on the host (its produce) or development of worm resistance. Therefore, implementation of breeding strategies/policies related to nematode resistance in goats would require an integrated approach, as identification of genetically resistant breeds, causative mutations, and their utilization in breeding policies/schemes with the amalgamation of proper data recording, herd management and dissemination of elite germplasm in the field, to yield positive results.

**Literature analysis**

For the current study, we collected literature from search engines on gastro-intestinal nematodiasis in goats and sheep. After an exhaustive search, we finalized 303 relevant articles, out of which we included 153 in our review for discussion. From these 303 papers, as per the primary country of publication, 109 were from Europe, 67 from Asia, 45 from Oceania, 28 from Africa, 39 from North America and 15 were from South America. Species-wise break up of the literature gave 113 articles from sheep, 99 from goat, 57 from ruminants/livestock and 2 from animal models. Due to insufficient data in goats, we could only include 68 research articles, especially dealing with caprine gastro-intestinal nematodiasis. Our criteria for the inclusion of articles were based on the fact that we were required to cover research and opinions, especially dealing with caprines and their GINs, keeping *haemonchus* as a major parasite. A comprehensive review, which would cover genetic markers and breeding strategies in goats for parasite resistance, is lacking, and our current manuscript aims to fill that gap.

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SPT, APS and KS conceptualized the idea. KS, KJ and SS drafted the manuscript. APS and SPT checked the final manuscript. All authors read and approved the manuscript.

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