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Exploitation of Host Resistance: A Promising Alternative Approach to Control Gastrointestinal Nematodoses in Small Ruminant: A Review

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ABSTRACT

Gastrointestinal nematodes (GINs) are the most insidious pathogens causing severe economic losses to the livestock industry. Among GINs *Haemonchus contortus* is the most pathogenic and predominant parasite of small ruminant livestock. Although the use of chemical anthelmintics is still the corner-stone of control method for GINs, the increasing rate of prevalence of anthelmintic resistance has made it less reliable control option. Anthelmintic resistance together with global demands for chemical residue free animal product has led to search for alternative sustainable control strategies which rely less on chemical anthelmintics. One of such strategy is the exploitation of host resistance against the GINs including *H. contortus*. The resistance of animals to GINs varies within and between breeds of sheep and goats. Host immune response plays an important role in host resistance but the immune mechanisms responsible for resistance are not fully known. Studies on identification of gene/(s) responsible for host resistance are also being carried out to find out the molecular mechanism of GINs resistance in sheep and goats all over the world. Selective breeding for GINs resistance is the ultimate solution for the problems of anthelmintic resistance. This article reviews the published reports on GINs resistance in relation to immunological response and genetic studies in small ruminants and discusses the prospects for selective breeding of GINs resistance in sheep and goat.

Key words: Gastrointestinal nematodes, Host resistance, Immunological response, Selective breeding, Small ruminants.

Small ruminants are important components of rural Indian economy. Profitable sheep and goat rearing is inhibited mainly by different disease conditions and out of which parasitic gastroenteritis caused by various types of nematode parasites is the major culprit. Gastrointestinal nematodes (GINs) generally occur as chronic and sub-clinical infection and remain unnoticed and thereby causing huge economic losses to the farmers due to reduced appetite, decreased weight gain, milk production and reduction in body weight and sometime death (Kaladeh *et al*., 2019; Jas and Ghosh, 2009). The gastrointestinal tract of sheep and goat are inhabited by variety of nematode parasites under field condition. The commonly occurring species are *Haemonchus* sp., *Trichostrongylus* sp., *Oesophagostomum* sp., *Bunostomum* sp., *Teladorsagia* sp., *Strongyloides* sp., *Nematodirus* sp., *Cooperia* sp. and *Trichuris* sp. infecting sheep and goats all over the world (Tesfaye, 2021; Chali and Hunde, 2021) including India (Jas and Pandit, 2017; Malathi *et al*., 2021). Out of these *Haemonchus contortus* is the most pathogenic (Tesfaye, 2021; Chali and Hunde, 2021) and predominant nematode species in most parts of world including India (Jas *et al*., 2017).

Gastrointestinal nematodoses are mainly controlled by use of broad spectrum anthelmintics in small ruminants (Reyes-Guerrero *et al*., 2022). The indiscriminate and unwise use of anthelmintics among the ruminants has resulted in the emergence of anthelmintic resistance in GIN (Mickiewicz *et al*., 2021). Resistance against almost all the anthelmintic groups has been recorded in most of the GIN species all over world (Martins *et al*., 2017).Widespread prevalence of anthelmintic resistance together with increasing market demand for ecological or "green animals" products (Waller and Thamsborg, 2004) has led to search for a sustainable alternative approach to control GI parasitism in small ruminant livestock.

Alternative control measures include the use of animal breeds with enhanced disease resistance (McRae *et al*., 2014; Emery *et al*., 2016), dietary protein supplementation (Lopez-Leyva, 2022), biological control using nematophagus fungi (Braga and de Araujo, 2014) and vaccines (Smith, 2014), herbal anthelmintics (Liu *et al*., 2020), neutraceutical

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(Vardyova *et al*., 2018), feeding of copper wire particle (Needleman *et al*., 2022) and grazing management (Sanyal and Sadaf, 2011). In this context exploitation of host resistance to regulate its own parasite population would be a promising sustainable approach to control GIN as well as management of anthelmintic resistance.

Alternative control strategies

Antinematodal vaccine

Successful commercial vaccines against nematode parasite are very limited. The major constraints for effective vaccine development include difficulty in production of parasite antigen fraction in commercial quantities, complexity of host immune response and natural unresponsiveness (Waller and Thamsborg, 2004) in young animals. A vaccine against *H. contortus* (Barbavex®) using parasite's concealed antigen was commercially available in 2014 (Smith, 2014). The problem associated with this vaccine could be related to the cost and frequency of the vaccination which needs 4-5 times vaccination annually and protection lasts for only 6 months.

Host nutrition

Host nutrition plays a vital role in the development of the immunity against GINs which is greatly influenced by the quantity of nutrition. Higher resistance to GINs was observed in the sheep supplied with high metabolizable protein (Lopez-Leyva, 2022). Better nutrition is known to modulate host responsiveness as demonstrated by increased IgA production in *H. contortus* infected sheep (Amarante *et al*., 2005). Use of copper oxide wire particle hasbeen used to control *H. contortus* in small ruminants (Torres-Acosta and Hoste, 2008) but copper toxicity is a problem particularly in sheep (Hoste and Torres-Acosta, 2011).

Nutraceuticals

Nutraceuticals refers to the plant secondary metabolites (nutracines) which have beneficial effect upon the health rather than nutrition. In this context the condensed tannins have been paid attention as studies showed that sheep grazing on leguminous crop rich in condensed tannins harbour lower burden of GIN. Condensed tannins have been reported to be effective against intestinal nematodes (*Trichostrongylus colubriformis*) but not against abomasal worms *H. contortus, Teladorsagia circumcincta* (Vardyova *et al*., 2018). Thus, the nutraceutical approach using tannin rich legumes is promising but it is still under investigation and detail research is needed before commercial use.

Herbal anthelmintics

A wide range of plant products as herbal anthelmintics is used effectively particularly in Asian and African countries but there is lack of scientific validation of the proposed efficacy of those products. The plants such as papaya, pineapple and neem have shown anti-parasitic efficacy against a variety of GIN parasites (Liu *et al*., 2020). The active ingredients of those plants contain cysteine proteinase which might damage the cuticle of the nematodes (Stepek *et al*., 2004). But their mode of action is not well defined and their safety index should be properly addressed before wide field use.

Biological control

Biological control of GINs using the nematophagus fungi, *Duddingtonia flagrans* have shown good efficacy to trap infective larvae of GINs and thereby reducing pasture contamination (Szewc *et al*., 2021). Although field evaluation of this concept has been conducted in many regions but promising results have not been achieved in many cases. One of main hurdle in using fungi is that fungus spores need to be continuously passed through the faeces and for this a good delivery device/technique is required. Uses of fungi at feed block and fungal controlled release devices have been tried but they failed to show effective parasite control under field condition (Vieira *et al*., 2017).

Grazing management

Rotational resting and grazing as a means of parasite control restricts the host parasite contact thereby reducing pasture contamination. The strategy of rotational resting and grazing has been considered either preventative, evasive or dilution (Maqbool *et al*., 2017). However, these methods are difficult to apply especially in extensive production system and also in systems with common grazing. Rotational grazing has not been applied successfully in rural India where there is no definite pasture land for livestock.

Sheep breed resistant to gin infection

Resistance and resilience are the two terms closely related and widely used in the study of genetic resistance of the host against GIN infection. Resistance to GIN infection may be exhibited mainly by three ways: there will not be establishment of patent infection, there will be very low worm burden compared to susceptible animal or there will be spontaneously elimination of adult worm after certain period (McRae *et al*., 2015). Resilience is the ability of an infected host to compensate the negative effect of parasite and continue to production. Resilience is mainly by adaptive immune response of the host.

Many breeds of sheep showed resistance to naturally occurring as well as experimental GIN infection. Some of resistant breeds of sheep are Florida Native (Amarante *et al*., 1999), Saint Croix (Burke and Miller, 2004), Red Maasai (Mugambi *et al*., 2005), Barbados Blackbelly (Gruner *et al*., 2003), Katahdin (Becker *et al*., 2020), Gulf Coast Native(Amarante *et al*., 1999), Santa Ines (Amarante *et al*., 2005), Garole (Michael *et al*., 2020, Brahma *et al*., 2022a), Pelibuey (Morteo-Gomez *et al*., 2004), Lohi, Pakistan (Saddiqi *et al*., 2010). Both within and between breed resistances to GIN have been reported in many breeds of sheep. Within breed resistance has been observed in Australian Merino (Kemper *et al*., 2010), INRA 401(Gruner *et al*., 2004a), Scottish Black face (Pettit *et al*., 2005), Rasa Aragonesa (Dervishi *et al*., 2011) and Garole sheep (Brahma *et al*., 2022a,b; Ghosh *et al*., 2012; Bordoloi *et al*., 2012).The use of genetically resistant animals can minimize the use of anthelmintics and the selection of such animals would favour a reduction in pasture contamination in periparturient period and in monsoon, the most favourable time for GIN survival in many parts of world including India.

Indictors of GIN resistance

Resistance to GIN infection in host is a genetically determined character and it is polygenic in nature (Zvinorova *et al*., 2016) and is quantitative means large set of gene or Loci influence this trait with small effects (Karrow *et al*., 2014). The selection of resistant animals could be done directly through identifying the genes or alleles by molecular genetics techniques or indirectly through phenotypic indicators such as worm burden and FEC (Good *et al*., 2006). Packed cell volume (PCV), immunoglobulins; IgA and IgE (Karrow *et al*., 2014), peripheral eosinophil count (Michael *et al*., 2020) or many other variables are related to immune response. Among these the FEC is the most important phenotypic indicator of resistance and the FEC is moderately heritable and highly repeatable character (Saddiqi *et al*., 2010). The heritability of FEC ranged from 0.15 (Vanimisetti *et al*., 2004) to 0.63 (Miller and Harohov, 2006). Consistent low FEC has been used as marker for selection of GIN resistance in sheep in Australia and New Zealand (Bishop, 2012).

In case of blood feeding parasite like *H. contortus,* PCV may be a useful marker (Brahma *et al*., 2022b). Both FEC and PCV are important traits, as the FEC is an indirect measure of resistance and PCV is an indicator of resilience. Therefore, it would be beneficial to select both low FEC and increased PCV. Besides FEC and PCV, IgA, IgE and IgG concentrations, mast cells, eosinophils, globule leucocytes and concentration of histamine can also be used as indicator / marker of resistance as host immune response plays an important role in the host resistance against GIN (Burke and Miller, 2004).

Immune response behind the resistance

The immunological mechanism of host resistance against GIN infection has been a study of interest but the actual mechanism is not very clear. Both the innate and acquired immune responses are found to be involved in host resistance. Series of immunological events including activation of non-specific defence mechanism (innate response), recognition of parasitic antigens and activation of the specific acquired immune response are involved in elimination of nematodes from the GI tract of resistant animals. The acquired immune response is dependent on previous exposure and characterised by specific antigenic memory (Gonzalez-Garduno *et al*., 2021). Both the cellular and humoral immune responses are considered important because GI parasites have the capabilities of producing immune modulatory substances to evade the host's immune response. The cellular immune events involved in resistance or susceptibility in the host depend on stimulation of T-lymphocytes which are responsible for directing immune effector mechanism. Activated CD4+ T cells differentiate into two groups of helper T cells; Th_1 and Th_2 (Miller and Horohov, 2006). Both the Th_1 and Th_2 cells are responsible for increased production specific cytokines as well as increased mRNA expression of theses cytokine genes. Humoral immune response involving production of parasite specific IgG, IgA and IgE are responsible for intestinal contractility and thereby expulsion of worms (Hayward, 2013). Reduction in the fertility and length of *H. contortus* as well as intestinal worm burden were associated with higher level of IgA in the abomasal mucosa (Hernandez *et al*., 2016). Some studies also reported that plasma IgA was associated with low FEC (Brahma *et al*., 2022b). The IgE levels are responsible for regulation and activation of mast cells, eosinophils and expulsion of adult worms (Alba-Hurtado and Munoz-Gunzman, 2013).

The susceptibility and resistance to GIN infection depend on the type of immune response activated against the infection. Susceptible sheep produce relatively more IFN-γ compared to resistant sheep infected with *H. contortus* and less Th_2 cytokines and parasitic specific antibodies (Saddiqi *et al*., 2010) and therefore assumed that susceptibility is associated with Th_1 type response while the resistance involves a Th_2 type response (Andronicos *et al*., 2010). Recently an inter play between Th_1 and Th_2 and the involvement of regulatory T cells (Treg) has been suggested rather than a straight forward Th_1 or Th_2 type response for susceptibility or resistance (Arsenopulous *et al*., 2017). The resistant sheep express the genes for IL-4, IL-5, IL-13 and TNF-α and do not express those of IL-10 and IFN-γ (Pernthaner *et al*., 2006). The expression of IFN-γ gene as well as the serum concentration of IFN-γ was found to be higher in resistant Garole sheep compared to susceptible sheep (Brahma *et al*., 2022b). Higher concentration of IFN-γ in cell culture supernatant was also recorded in resistant Garole sheep compared to susceptible Sahabadi sheep (Michael *et al*., 2020).

Genes responsible for host resistance

Identification of specific genes responsible for resistance to GINs is critical for better understanding of genetic resistance as well as host response to GINs (Andronicos *et al*., 2010). Exploration of genes responsible for resistance/susceptibility relies on many factors which include an animal population with well-defined pedigree information; the exact estimate of resistance trait and specific tools for mapping of that trait on the host's genome. The accurate identification of genes for the host resistance and the specific function in this direction will aid in understanding of molecular mechanism of host resistance to GINs. The relative expression of genes varies between resistant and susceptible breed after infection and between infected and non-infected animals (Brahma *et al*., 2022b; Dervishi *et al*., 2011). The major histocompatibility complex (MHC) is a highly polymorphic region which includes several closely linked genes and these genes have been found to be involved in the antigen presentation to the host immune system.Relation of the FEC to the MHC I and MHC II regions close to chromosome 20 of sheep has been reported by many authors (Zvinorova *et al*., 2016; Karrow *et al*., 2014). The DRB1 locus of MHC II has been found to be associated with reduced FEC, increase in IgA and IgE and thereby associated with host resistance to GINs (Karrow *et al*., 2014; Hayward, 2013). The interferon gamma (IFN-γ) gene is considered as a candidate gene for immune response and in the study of disease resistance it has received much attention because of its proposed association with nematode resistance (Daries *et al*., 2006; Dominik, 2005).

A strong association between one allele of IFN-γ gene located on the chromosome 3 and reduced FEC and increase in the levels of specific antibodies (IgA) against *Ostertagia circumcincta* infection in sheep (Karrow *et al*., 2014). Coltman *et al*. (2001) reported a significant association of the host resistance against GINs with the IFN-γ gene. The expression of IFN-γ gene in infected sheep was also found to be associated with resistance (Brahma *et al*., 2022b). However, some authors did not observe any influence of the expression of IFN-γ gene on the resistance of the sheep against GIN infection (Karrow *et al*., 2014). A strong Th_2 cell response with overexpression of IL-13, IL-5, IL-4 and TNF α has been reported in resistant sheep infected with GINs (Alba-Hurtado and Munoz-Gunzman, 2013).

Recently quantitative trait Loci (QTL) has been proposed to be associated with GIN resistance and several studies have been undertaken to detect QTL linked to GIN resistance in sheep (Ahbara *et al*., 2021). The QTL regions on chromosomes 1,2,3,6,14,19 and 20 were found to influence genetic resistance and were associated with low FEC for different nematodes and chromosomes 1 for haematocrit value in *H. contortus* infection (Bishop, 2012). Different QTL regions in sheep for *H. contortus* resistance have been found to be located on chromosome 1, 3, 6, 14, 20 and 22 (Miller and Horohov, 2006).

Recently putative genes responsible for host resistance to parasitic infections have been mapped using dense SNP markers for their functional significance (Saddiqi *et al*., 2011). Furthermore, it is expected that while genome sequencing of resistant and susceptible animals by next generation sequencing (Ondove *et al*., 2008) would be able to detect the genes for resistance and hence the genetic marker to identify animals resistant to GIN infection and those animals could be selected for breeding.

Breeding of resistant and susceptible animals

The studies on sheep with varying degree of resistance to GIN infection have been an area of research for more than four decades but till date no work has succeeded to acknowledge the global heterogeneity in the livestock genetics and production systems. The finding of individual studies is needed to be captured in a new frame work for the international community. The unveiling of superior genetics is the most useful for parasite resistance in host animal. For exploration of genetic resistance, divergent lines of sheep have been studied by many authors. Genomic regions controlling resistance (McRae *et al*., 2014), detection of differential gene expression between lines (Andronicos *et al*., 2010), detection of biomarkers (Andronicos *et al*., 2014) and interaction between genetics and nutrition (Doyle *et al*., 2014) are studied in sheep selected for resistance against GIN infection. The idea of genetic selection for increased resistance in sheep to GIN infection has been the focus of research. Even a small gain through genetic selection for a parasite resistance within flocks or selection line needs an untiring effort over many years (Kemper *et al*., 2010). In a breeding program, the contribution of parasite resistance to the selection index must be less than the production traits.

For selection and breeding of animals resistant to GIN infection, many studies have been conducted with an aim to have animals with superior genetic potential; however, the outcomes of those studies were variable with different effects. The cross-breeding of resistant and susceptible breeds resulted in F_1 offspring showing an intermediate response to the GIN infection (Amarante *et al*., 2009). The cross between F_1 offspring of Florida native (resistant) and Rambouillet (susceptible) and Rambouillet sheep resulted in susceptible lambs to *H. contortus* challenge than Florida native lambs (Amarante *et al*., 1999). Li *et al*. (2001) reported that F_1 line of sheep resulted from cross breeding of Suffolk (susceptible) and Gulf Coast Native (resistant) had intermediate levels of infection. Back crossing of F_1 offspring (50% Red Maasai × 50% Dorper) with their parent stock either Red Maasai or Dorper resulted in lambs which differed in their levels of resistance as well as resilience (Mugambi *et al*., 2005). The offspring with 75% Red Maasai were of superior genetic potential showing lower FEC and higher PCV than the 75% Dorper lambs. The F_1 lambs resulting from St. Croix and Barbados Black Belly Cross had lower FEC and higher PCV than the lambs with 50% Dorset, 25% Rambouillet and 25% Finn sheep in response to artificial infection (Notter *et al*., 2003). The cross-breeding between Barbados Black Belly (resistant) and INRA 40I (susceptible) resulted in offspring which had similar response like that of Barbados Black Belly after challenge infection (Gruner *et al*., 2003). This F_1 lambs also showed resistance to *T. colubriformis* and to a lesser extent against *T. circumcincta*. The F_1 lambs produced by crossing of Suffolk or Ile de France with the resistant Santa Ines exhibited similar resistance potential to GIN infections to that of their parental resistant breed (Amarante *et al*., 2009). The drawback of most of the resistant breed is low productivity as compared to those selected for other traits (higher weight gain and better meat quality). The extent of the sire difference can be the same as that of the breed difference and therefore difference in resistance between breeds might reflect a single sire effect and should be interpreted cautiously (Saddiqi *et al*., 2011).

Prospects of breeding of genetically resistant animals

Small ruminant showing resistant to GIN infection should be selected for breeding program in the regions where pathogenic nematodes like *H. contortus, T. circumcincta, T. colubriformis* are found to infect animals throughout year. Selection of resistant lines within a breed and/ or use of the resistant sire are the available options for the breeding program; however, this trait of parasite resistance has been ignored by many countries. Selective breeding of genetically resistant stock between and within the breed is a sustainable strategy and this has been practised successfully in Australia and New Zealand to produce flock of the sheep with greater level of resistance against GIN infection (Bishop, 2012). Rearing genetically resistant animals has a positive impact on epidemiology of GIN leading to the reduction in pasture contamination. Lower level of pasture contamination results in reduced rate of infection or re-infection to the animal which would ultimately lead to improvement of production (Saddiqi *et al*., 2011). Sheep selected for resistance to *H.contortus* also exhibited resistance to artificial as well as natural *T. colubriformis* infection (Gruner *et al*., 2003) indicating sheep resistant to one species might be resistant to other species (Gruner *et al*., 2004b). Thus a substantial improvement in the livestock population could be achieved by selective breeding of resistant animals (Amarante *et al*., 2009); however any breeding programme should be adopted to increase parasite resistance in livestock population only after cost benefit analysis. Breeding for increased resistance against GIN infection should be the most favoured alternative strategy to control GIN infection in the face of anthelmintic resistance as it could extend the effective life of anthelmintic by slowing the rate of developmentof drug resistant worms.

CONCLUSION

The selection of genetically resistant animals depends on the heritability of the markers of GIN resistance and FEC is the most important marker which is moderately heritable and highly repeatable. The immune response that protects against GIN infection is the expression of that genetic resistance. There is considerable genetic variation among individual in exhibiting resistance to GIN infection and this suggests that selective breeding for increased resistance could be an alternative option to complement the control strategy, but not replacing the existing control measures. Genetic selection would be helpful in the anthelmintic resistance and it also has an epidemiological benefit in reducing pasture contamination and it could also be useful in extending the sustainability other control strategies. Use of the multiple control strategies can reduce the risk of evolution of pathogen. Therefore, breeding of the sheep for increased resistance should be an integral part of sustainable GIN management in small ruminant production system.

Conflict of interest: None.

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