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REVIEW ARTICLE

COMBINED STRATEGIES TO CONTROL ANTINEMATICIDAL -RESISTANT GASTROINTESTINAL NEMATODES IN SMALL RUMINANTS ON ORGANIZED FARMS IN PAKISTAN

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Antinematicidal resistance has been rooted on all the continents particularly in areas where ovine and caprine are being reared intensively due to frequent annual use of broad-spectrum dewormers. Farmers rely on mono-strategic scheme by using synthetic drugs to treat their livestock which is deemed the easier way to control gastrointestinal nematode infections as compared to the other strategies. On the other hand, recurrent employment of antinematicidal chemotherapeutics has conduced to development and prevalence of resistance among nematode populations. In this regard, other advocating strategies such as grazing management, rotation of antinematicidal drugs (although it is too late), amelioration of animal immunity, genetic approaches, biological control, nutritional supplementation, avoidance of mass treatment, improvement of management, eradication of concurrent diseases, and phytotherapy should be considered too. Although, by far there are no commercialized substantial alternatives to chemotherapy, but the current substitutes could decrease the parasitic burden, which, in turn, restrict indiscriminate use of synthetic drugs. The resistance is more rampant on organized farms as compared to non organized farms in rural areas in Asian, African and South Latin American countries because tamed animal raisers in those areas depend on ethnobotanicals to treat parasitism due to high cost of allopathic drugs. Therefore, in this review, the different strategies to control the antinematicidal resistance on organized farms in Pakistan will be elaborated.

Keywords: Worm control, antinematicidal resistance, gastrointestinal nematodes, small ruminants, organized farms, medicinal plants

INTRODUCTION

Generally, the emergence of resistance is expressed as "unresponsiveness of resistant individuals within populations of parasitic nematodes to standard doses of a chemotherapeutic agent being compared to normal populations of the same species". It is inheritable (Prichard *et al*., 1980) and genetically determined (Sangster and Gill, 1999). Currently the dilemma of antinematicidal resistance is one of the serious impediments limiting sheep and goat productivity in most countries of the world (Waller, 1997) including Pakistan (Babar, 2005; Saddiqi, 2005; Hamad, 2013). In addition to small ruminants, the resistance has become a great menace to human health as well (Beech and Silvestre, 2010; Harhay *et al*., 2010; Poole and Sheffield, 2013; Kashif *et al*., 2013).

Parasitic nematodes have evolved resistance mainly against the major broad-spectrum anthelmintic classes which include benzimidazoles (BZs), imidazothiazoles and macrocyclic lactones (MLs), whilst resistance to narrow-spectrum dewormers is relatively less common in most countries (Bartley *et al*., 2004).

For this reason, some alternatives such as grazing management, nutritional supplements, vaccination, genetic approaches and biological control have been advocated by researches (Stear *et al*., 2007). Practically these substitutes can not offer magic salvations and additionally each one has some advantages and disadvantages (Stear *et al*., 2007). In recent years, ethnobotanicals (as novel alternative) have drawn attention of veterinary parasitologists to control ecto- and endo-parasites particularly in developing countries and probably they will be an incisive sword to fight parasites in near future (Jabbar *et al*., 2006; Zaman *et al*., 2012). It is noteworthy to mention that retarding or avoiding development and rampancy of antinematicidal resistance among gastrointestinal (GI) nematodes is too late (Waller, 2006) because it has been originated every where (Waller, 1997). Therefore, it should be dealt with the phenomenon of resistance as an existing problem requires exploitation of more than one strategy at the same time to control it.

ANTINEMATICIDAL RESISTANCE AS A PHENOMENON

Antinematicidal resistance (AR) has been diagnosed most frequently among GI nematodes of ovine and caprine particularly *Haemonchus* (*H.*) *contortus* and *Teladorsagia* (*T.*) *circumcincta*. Even though nematodes categorized under *Trichostrongylus*, *Nematodirus*, *Cooperia* genera have

evolved resistance too (Taylor and Hunt, 1989). The date of development of resistance against GI nematodes is back to the mid- 1950s when phenothiazine, which was discovered in 1938 by Harwood and workers at the US bureau of animal industry, failed to control *H. contortus* infection in a flock of sheep in Kentucky, USA (Drudge *et al*., 1957). After commercialization of thiabendazole (a first generation of benzimidazole group) in 1961 (Brown *et al*., 1961), the AR was developed by parasitic nematodes few years later against it (Drudge *et al*., 1964).

The AR was recorded first in parasites of ovine and equine. Now-a-days resistance has emerged in parasites of several livestock animals as well as humans all over the world. It comprises various phyla of parasitic worms and comprehends the entire main broad- spectrum classes of anthelmintics (Sangster and Gill, 1999) particularly the major antinematicidal groups, BZs, MLs (i.e. ivermectin), and imidazothiazoles (i.e. levamisole HCL) (Kaplan, 2004). Resistance has also been reported against narrow-spectrum synthetic drugs such as salicylanilides (flukicides for cattle and sheep) (Scott and Armour, 1991) and organophosphates (Green *et al*., 1981).

Since the last three decades, AR has become a great menace to the small ruminant industry almost in all the regions or continents such as European Union countries, Africa, Australia, South-East Asia/ South Pacific, North America, and South Latin America (Waller, 1997). It is noteworthy to mention that climatological conditions, nematode species and adopted therapeutic policy play a significant role in developing of AR in different geographical regions of the world. For example, the emergence of resistance in northern hemisphere it seems to be slower than southern hemisphere (Waller *et al*., 1990).

FACTORS INVOLVING EVOLUTION OF RESISTANCE

An anthelmintic with faecal egg count reduction (FECR) percentage 98 is considered highly effective, whilst FECR percentage 80 and above is effective (Wood *et al*., 1995) against susceptible individuals of parasitic nematodes.

The rest numbers of existing helminths, which resist the therapeutic agent in the population, then move to the pasture producing resistant generations which conduce to evolution of AR owing to selection pressure. Explicitly, there are many factors which contribute the evolution of AR, but operational factors are most significant as compared to others because they can be operated by the livestock raisers (Jabbar *et al*., 2006). Of the numerous factors involving to AR, important ones are mentioned as under:

***Recurrence of therapy*:** It has been reported that recurrent administration of the same class of antinematicidal dewormer may lead to evolution of AR (Taylor and Hunt, 1989). There are records that resistance evolves in areas where livestock are drenched repeatedly. AR has been developed by *H. contortus* in some humid tropical regions where 10 to 15 annual drenches were employed to control this trichostrongylid worm in sheep and goats (Dorny *et al*., 1994). There is evidence that AR develops when merely two to three annual therapies are applied (Coles *et al*., 1995). In his study on sheep in Angora Goat Farm, Rakh Khairewala-Pakistan, Hamad (2012) has reported development of AR by *H. contortus* against BZs (oxfendazole), imidazothiazoles (levamisole HCL) and MLs (ivermectin) as a result of average annual use 5, 4 and 3 times respectively.

***Employment of sub-optimal dosage*:** Administration of drenches less than standard recommended doses to animals is deemed a significant factor in evolution of AR (Edwards *et al*., 1986) because sub-optimal doses might permit the existing of heterozygous tolerant helminths (Smith, 1990). In this respect, extra studies on the effect of underdosing on the evolution of AR are required. It has been reported that farmers in most developing countries adapted to treat their livestock with lower international standard doses to minimize the costs (Warren *et al*., 1993). Such practices definitely generate AR in small ruminants. Additionally, other factors that have been incriminated in evolving and rampancy of resistance in developing countries include poor-quality of local products, using of out of date anthelmintics and availability of repacked products in markets (Shakoor *et al*., 1997; Monteiro *et al*., 1998). On the other hand, on-shelf presence of anthelmintics and access of illiterate livestock raisers easily to them without veterinarian prescription in developing countries including Pakistan may also be significant factors in the evolution of resistance (Jabbar *et al*., 2006).

***Species variations*:** It has been approved that bioavailability of dewormers is varied in different animal species which, in turn, influences on the determination of precise doses that should be given to a certain species. For instance, the bioavailability of BZs and imidazothiazoles is much lesser in caprine than in ovine, thus, goats must take doses 1.5 to 2 times higher than those administered to sheep (Hennessy, 1994).

***Mono-drug policy*:** Recurrent and persistent employment of one antinematicidal dewormer conduces to the evolution of resistance. For instance, an anthelmintic, which is generally very efficacious at the beginning of its use, it will become ineffective due to continuous use (Pal and Qayyum, 1996). Recurrent employment of ivermectin without substitution with other antinematicidal drugs has led to rapid evolution of AR in *H. contortus* in South Africa and New Zealand (Van Wyk *et al*., 1989; Shoop, 1993).

***Targeting and timing of mass therapy*:** Prophylactic group therapies of small ruminants have enhanced in developing of resistance widely in parasitic worms. In order to control nematodiasis in sheep and goats, it has been approved that regular grazing of animals in uncontaminated pastures post-mass therapy and/or planning to drench in the dry seasons is

an ordinary practice to decrease swift re-infestation. Although, these procedures result in the next worm offspring consists approximately of helminths that existed treatment and, thus, might involve to the evolution of resistance (Taylor and Hunt, 1989).

***Miscellaneous factors*:** Other factors can also play a role in developing of AR such as parasites in refugia, gene frequency, genetic of AR, biological fitness of unselected worms (Coles, 2005), keeping ovine and caprine together (Jackson, 1993) and introduction of animals infected with resistant strains through smuggling from a country to another (Várady *et al*., 1994).

ADVOCATING SUBSTITUTES TO SYNTHETIC CHEMOTHERAPEUTICS

Due to widespread development of AR in parasitic nematodes infecting livestock around the world, some alternatives have been recommended to control these nematode populations without depending on antinematicidal dewormers (Stear *et al*., 2007). These substitute methods are as under:

***Grazing management*:** The most important objective of this policy is reducing the population of infective stage larvae (L3) on pasture through reducing egg deposition, reducing subsequent molting of larvae and their survival rather than keeping the pasture always less contaminated. This target can be achieved through exploitation of whole areas of available pasture properly for animal grazing (Stear *et al*., 2007). In this regard, some procedures and options should be pursued to reduce infectivity of parasitic nematodes on pasture. These include rotational grazing (Stear *et al*., 2007), moving of vulnerable animals to less contaminated fields after deworming (Sutherland *et al*., 2002), reducing of animal density in a given area and avoiding the build up multi-host nematodes through grazing different species of animals together or rotating young and older livestock (Stromberg, 1997).

***Exploitation of biological method*:** Using predators such as the nematode-trapping fungus, *Duddingtonia flagrans* which minimizes the intensity of infective larvae on pasture, and, in turn, it reduces the severity of infestation (Waller *et al*., 2004). Daily mixing of fungal spores to animal diets is the main bottlenecks in the employment of predatory fungi (Stear *et al*., 2007).

***Dietary supplementation*:** It has been approved that adding supplementary protein and some trace elements like copper, iron, molybdenum and zinc to animal fodder are an effective way to control nematodes infecting livestock (Stear *et al*., 2007). Principally, these supplementary materials modulate animal resistance against nematode infestation (Koski and Scott, 2003). The obstacles that restrict adoption of this approach are mainly financial.

***Vaccination*:** Pertaining availability of vaccines against parasitic nematodes, just irradiated infective stage (L3) vaccine against verminous pneumonia in cattle and sheep is commercially obtainable (Bain, 1999).

***Genetic approaches*:** Exploitation of genetic variation depends on three strategies: selection among breeds, selection within breeds and cross-breeding (Nicholas, 1987). The major drawback in the employment of this method is that it needs proficiency in quantitative genetics to execute more efficiently in addition to some worries over productivity (Stear *et al*., 2007).

PHYTOTHERAPY: A NOVEL ALTERNATIVE TO CHEMOTHERAPY

Pursuant to the historical documents, medicinal plants have been used since thousands of years to cure human and animal diseases as part of Asian traditional medicine (Jabbar *et al*., 2006). Due to their importance as effective therapeutic agents to control human and livestock ailments, phytotherapeutics will continue to occupy their roles within therapeutic inventory, not merely in Asian, African and South Latin American countries, but in the developed countries as well (Waller, 2006). The therapeutic magnitude of medicinal plants to control GI nematodes of small ruminants is attributed to unavailability of highly effective substitutes to be used in place of synthetic drugs, firstly (Stear *et al*., 2007). And secondly, they possess some unique characters such as containing of many active constituents that preclude worms to develop resistance against them. Additionally, the kingdom of plant is rich with thousands of plant species and at least 25,000 of them occupy our planet (Borris, 1996). Unfortunately, just 5-15% of higher plants have been chemically analyzed for their contents of active ingredients against a wide range of infectious and non-infectious diseases of humans and animals (Pieters and Vlietinck, 2005). Different medicinal plants have been investigated by researchers in Asia, Africa and South Latin America for their adulticidal, larvicidal and ovicidal activity to GI nematodes (Hammond *et al*., 1997; Iqbal *et al*., 2001; Cala *et al*., 2012; Iqbal *et al*., 2012). On the other hand, herbal remedies are natural accepted items, pal to the environment, no residual effects and ecological pollution have been reported (Waller *et al*., 2001). Owing to the above reasons, it may be hypothesized that in future, success of any combined strategies to achieve sustainable control programs for nematodiasis in small ruminants may need an integrated policy incorporating medicinal plants as a main therapeutic factor in addition to other alternative sources. It is noteworthy to mention that mono-substitute strategy has not attained any progress in the field to control AR among nematode populations of livestock so far (Stear *et al*., 2007).Thus, incorporating of ethnobotanicals to treatment prescriptions could be fundamental.

COMBINATION OF APPROACHES

Undoubtedly, combination of more than one strategy plays a significant role to control GI nematode infection in sheep and goats, but astonishingly there are very few studies in combination of different methods (Stear *et al*., 2007). Perhaps the reasons back to some bottlenecks confronting application of such program pragmatically at the level of both parasitologists and farmers. Stear *et al*. (2007) have concluded that in spite of existence of a variety of approaches to control GI nematodes but no one method can be promoted to the avoidance of all others. Hence, combined policies are inevitable. It is noteworthy to mention that each livestock farm may require choosing the most suitable combined procedure from the proposing alternatives. Most of investigations in the field of combination approaches have been focused on nutritional supplementation and genetic resistance. In this regard, Abbott *et al*. (1985) have studied the influence of dietary protein additions on moderate infestation with *H. contortus* establishment and pathogenesis in two different breeds of sheep; one of them was comparatively susceptible Finn-Dorset and the other one was relatively resistant Scottish Blackface. In the same connection, the severest impacts were observed in the comparatively susceptible Finn-Dorset lambs deliberately infested with *H. contortus* after feeding the low protein diet. Interestingly, pathogenesis was not affected by the low protein in the resistant lambs so they behaved alike susceptible lambs on the diet rich with protein (Abbott *et al*., 2000). Significant impacts of dietary protein in genetically susceptible sheep were observed in Scottish Blackface as compared to Hampshire Down as well (Wallace *et al*., 1996). The majority of research works on diet supplementation and genetics have been with *H. contortus*, but an experiment with Scottish Blackface breed that were strongly infested with 10000 *Teladorsagia* (*T*.) *circumcincta* three times per week for nine weeks then butchered proposed that a combination of acquired immunity and concentrated diet would be most efficient to control infestation with *T. circumcincta* (Stear *et al*., 2000).

PRACTICALITY OF COMBINED STRATEGIES IN PAKISTAN

In spite of prevalence of AR among GI nematodes of small ruminants against almost all the major classes of anthelmintics (BZs, imidazothiazoles and MLs) in the public and private organized farms but surprisingly the existing alternatives have not been exploited for control purposes so far (Afaq, 2003; Hamad, 2012). Most veterinarians are dealing with the unresponsiveness to the standard doses of dewormers by using double and triple dosage, which, in turn, are not highly effective too (Hamad, 2012). Veterinarians and farmers are not aware as it should be with the consequence of rampancy of AR among nematode populations which poses a great threat to the animal resource through limiting the productivity of livestock which consequently causes an enormous economic loss to the country. This review article will manipulate the feasibility of using combination between four methods only which are genetic approaches, grazing management, nutritional supplementation and phytotherapy because other substitutes have not been adopted due to some reasons mentioned previously in this article.

***Combined genetic approaches and grazing management*:** Apparently this combined strategy has not been investigated extensively by researchers in the world. A comparison of different breeds for resistance to nematodes has shown that some breeds of sheep and may be also goats resist the infection with GI nematodes than others. In Pakistan, the native Lohi breed of sheep is relatively more resistant to *H. contortus* than other indigenous breeds such as Kachhi and Thalli (Saddiqi, 2010). The benefit that might be obtained from this strategy includes lower parasite burdens (low helminth egg production) which consequently reduce the infectivity of pastures by worm larvae (Eady *et al*., 1996). So, promotion of such policy has some favourable epizootiological impacts through decreasing the epidemicity of infective larvae (L3). Although, mating between susceptible animals to infection with GI nematodes and relatively resistant animals has achieved some progress but still it is far from ambitions of farmers (Gray, 1997). It is noteworthy to mention that studies on this method are very rare in Pakistan or might be not yet available. In this regard, it is useful to point out to the cross-breeding that has been carried out in Glasgow University Veterinary School by mating relatively resistant single sire (Scottish Blackface) with pure-bred flock which is presently being validated on commercial farms in Scotland (Keatinge, 1996). Accordingly, mating of Lohi rams with Kachhi, Thalli and Pak Karakul ewes may produce progeny remarkably able to resist GI nematode infection and consequently low parasitic load, which, in turn, reduces faecal egg output. Thus, there will be less contamination of pasture with infective third-stage larvae, but this hypothesis should be investigated pragmatically. Practically, might be easy to convince farmers to adopt this method because they keep their own flock. The other strategy for utilizing genetic variation is selection among breeds. It has been revealed that some breeds of sheep are much more resistant to GI nematodes notably *H. contortus*. For example, in Kenya, the native Red Maasai is more resistant than imported Dorper breed (Mugambi *et al*., 1996) and also sheep of Texel breed are more resistant than sheep of the Suffolk breed (Good *et al*., 2006). Conceptually, this strategy is the easiest method to utilize genetic variation as compared to the other approaches. Small ruminants infected with GI nematodes can be replaced by a more resistant breed. Implementation of such amelioration genetically may be has some trade-off with respect to livestock productivity (Woolaston and Baker,

1996). Additionally, even when there is an obvious commercial benefit to one breed, livestock raisers can be hesitant to switch breeds. On the other hand, most of farmers are not well-educated or entirely unaware about the magnitude of genetically resistant animals to nematodes, hence, it will be difficult to persuade them to follow this approach (Stear *et al*., 2007). In spite of getting some advantages from genetic variation to control nematodes but definitely obtaining good results requires another strategy to combine this method. In this connection, pasture management could be helpful if adopted properly. The main objective of present grazing management is exploiting all the pasture areas for grazing livestock. As genetic approaches, grazing management also minimize the number of infective larvae to infest grazing animals. The rate of development and survival of free-living stages of nematodes are largely affected by temperature and moisture (Callinan, 1978) which vary among different geographical regions in accordance with prevailing weather (Kao *et al*., 2000). In this regard, researchers have recommended that the useful way to control nematodiasis in small ruminants is performing local studies on ecology of parasites. Virtually, adopting this combined strategy in Pakistan, although currently is encountering some difficulties to carry out, may find its way practically in near future if enough funds ensured for researches and education of farmers.

***Combined genetic approaches and nutritional supplementation*:** As mentioned previously in this review, just this combined scheme has been investigated to control GI nematodes in Scotland. Pertaining diet supplementation, it has been confirmed that extra feeding of animals with additional protein and trace elements such as copper, iron, molybdenum and zinc can modulate the host resistance against nematodes and also enhance the ability of infested host to repair mucosal damage in addition to compensation of lost protein as a result of parasite pathogenicity (Sykes and Coop, 2001; Koski and Scott, 2003). Though adding supplementary protein to animal diets is costly, but exploiting animal by-products could be a cheap source of protein. In Pakistan, thousands of tones of inedible offal and entrails are produced annually from slaughtering of different species of animals other than poultry because this country possesses a big livestock population (cattle 36.9, buffalo 32.7, sheep 28.4, goat 63.1 and camel 1.0 million) as well as domestic poultry (79.68 million) and broilers (34.82 million per annum) (Pakistan Economic Survey 2011-2012). Although there are some concerns about transmission of prion, the causative agent of Bovine Spongiform Encephalopathy (Mad Cow Disease) in cattle and Scrapie in sheep and goats, through feeding extracted proteins from uneatable parts of carcasses to ruminants in some countries particularly United Kingdom. The second source of protein which could be utilized easily in Pakistan is vegetable protein because in this country, agriculture is well-developed. But, at the same time, particular attention should be given to protein quality, protein yield and costs of the resultant protein. In this regard, barley is an energy-rich diet grain cultivated throughout the world including Pakistan. This agricultural crop is considered a good source of energy and protein in lamb and ewe diets in most countries in the world. The crude protein content of barley (13.5%) is higher than that of other major feed grains such as corn (10.1%), sorghum (11.5%) and oats (13.3%). Non-degradable percentage of barley is approximately 20 to 30% (NRC, 1996). Additionally, this palatable crop for feeding small ruminants contains plethora of essential minerals and vitamins (NRC, 1996) which, in turn, boost the immune system of infected animals with GI parasites. For example, as compared to other major cereal grains, barley is too rich with vitamin A which is very necessary to repair damaged mucous membranes of parasitized organs of alimentary tract. Moreover, in addition to barley, there are some other sources of protein (by-products of seeds after extraction of oil) which can be utilized as supplementary diet to improve immune hypo-responsiveness of young small ruminants (Coop and Holmes, 1996). These sources include cottonseed cake (approximately contains 41% protein) (Boodoo *et al*., 1990), sunflower meal (usually contains 26-40% crude protein) (Jabbar *et al*., 2009) and brassica (mustard) seed cake (contains 30-35% protein) (Nasar *et al*., 2006). Among the above mentioned by-product seeds, sunflower meal is a cheaper protein source that can be used in feeding small ruminants as compared to the other protein sources (Yunus *et al*., 2004). Additionally, this by-product is increasingly cultivated on wide areas and was grown on 937000 acres during 2006-2007 with total production of 65600 tons (Anonymous, 2006-2007). Animals taking supplementary diets may get an enhanced resilience against GI nematode infections. However, the resistance amelioration of ovine and caprine against GI nematodes can be influenced by other factors such as presence of concurrent diseases (particularly ectoparasites), nutritional status of the flock, management condition of the farm and development of acquired immunity (Keatinge, 1996). Virtually, both methods work on the immune system, genetic approach increases the acquired innate immunity while supplementary diet ameliorates the immune response through increasing the ability of humoral immunity. It might be concluded that this combined strategy, if followed properly, could be an efficient method and appropriate option to control nematodiasis in Pakistan.

***Combined genetic approaches and phytotherapy*:** In spite of unavailability of sufficient researches about pharmaco-dynamic, pharmacokinetic and pharmacognosy of different medicinal plants that being used by farmers in developing countries against GI nematodes in livestock, but interestingly a big number of them has been documented and validated for their efficacy towards parasitism in Indo-

Pakistan subcontinent, South Latin America , Africa and even industrialized countries (Waller, 2006). In accordance to Wood *et al*. (1995), majority of therapeutic botanicals could be categorized as effective anthelmintics because results that obtained by researchers have revealed that antinematicidal medicinal plants can reduce the faecal egg count reduction percentage (FECR %) above 80 but less than 98. Even though, some workers have reported highly effective results of some ethnobotanicals with FECR% more than 98, but their claims should be exposed to extra investigations and trials. It is noteworthy to mention that control of antinematicidal-resistant GI nematodes could be executed by phytotherapeutics in place of major classes of anthelmintics which resistance has been evolved against them in most organized sheep and goat farms in Pakistan (Hamad, 2012). For instance, *Nicotiana* (*N.*) *tabacum* leaf (2g kg^{-1} BW) and *Azadirachta* (*A.*) *indica* seed kernel (4g kg^{-1} BW) extracts have reduced the FECR% in Pak Karakul breed of sheep infected naturally with resistant *H. contortus* to 87.5 and 85.14 respectively, whilst the FECR% for synthetic chemotherapeutics such as oxfendazole, levamisole HCL and ivermectin were -56, 75 and 78 respectively which indicate that they were less effective than medicinal plants (Hamad, 2012; Hamad *et al*., 2012). It would be concluded that herbal medicines are appropriate alternative to control antinematicidal-resistant nematodes in small ruminants. On the other hand, absolutely one substitute strategy can not achieve the requested target to control nematodes, thus it should be underpinned with another approach, say genetic method (Stear *et al*., 2007). Logically, it would be predicted that genetically resistant animals are harbouring less adult worms as compared to genetically susceptible animals (Eady *et al*., 1996), so using phytotherapeutic medicines instead of chemotherapeutic drugs for treatment once or twice during late winter/early spring (lambing time) and monsoon seasons may lead to attain considerable results through minimizing egg deposition and pasture contamination with infective larvae (L3).

***Combined grazing management and phytotherapy*:** As previously reviewed the significance of grazing management and phytotherapy separately in this article, combination of the both approaches could be another option for farmers to reduce parasitic burden, which, in turn, keeps the pasture less contaminated with infective larvae. Certainly, drenching animals with an effective antinematicidal medicinal plant such as *N. tabacum* (or mixed with *A. indica*) before releasing animals for grazing is a main factor to control nematodiasis (Hamad, 2012). But, the pasture should be prepared properly according to the grazing management policy in order to get successful control program. Also, here should be pointed out to an important step which is checking the infectivity of pastured animals after exposure to medicinal plants through performing FECR test. This *in vivo* assay can determine accurately the need of animals for administration of phytotherapeutics once or twice before grazing.

***Combined grazing management and nutritional supplementation*:** In this article, the role of each approach to control resistant GI nematodes has been elaborated. Both alternatives have no any direct effect to kill nematodes, but undoubtedly, they contribute effectively to reduce epidemicity, infectivity of nematodes in addition to parasitic loads of sheep and goats through improvement of immune response (Sykes and Coop, 2001). Definitely, implementation of such combined strategy will experience some bottlenecks educationally and might be financially, but as explained formerly, Pakistan has many sources to produce affordable plant proteins which could be utilized to feed animals. Stand to reason, it will be hard to persuade uneducated livestock raisers and even inexperienced veterinarians to follow such scheme because they have been adapted since several years to get prompt results from using synthetic dewormers. On the other hand, they are unaware about the evolution and prevalence of antinematicidal resistance among GI nematode population or grazing management (for example: pasture rotation) (Afaq, 2003). In such situation, encouragement and education of both veterinarians and farmers to adopt this combined policy could bring considerable consequences to control parasitism in Pakistan.

***Combined nutritional supplementation and phytotherapy*:** Perhaps this combined approach is more practical, feasible and suitable for the situation of Pakistan as compared to the other combined strategies. Unquestionably, there are strong reasons justify exploitation of this policy such as: (i) presence of indirect synergism between both substitutes (supplementary diets improve immune system of infected animals, whilst ethnobotanicals kill worms) (ii) both alternatives are easily available (iii) economically reasonable (iv) culturally acceptable by farmers (v) pal to the environment (vi) relatively safe (vii) no residual effects on food chain (Bennet-Jenkins and Bryant, 1996). We believe strongly that this combined approach will solve the essence of the problem if accompanied with pasture rotation.

***Conclusion*:** Conspicuously, AR is a heavy load to animal resources worldwide and is starting to affect public health (Beech and Silvestre, 2010). AR has been developed by GI nematodes and extensively spread on organized livestock farms against the renowned broad-spectrum dewormers such as BZs, imidazothiazoles and MLs in Pakistan (Afaq, 2003; Saddiqi, 2005; Hamad, 2012). Unfortunately, AR has reached catastrophic level towards BZs in some farms due to discriminate use of these antinematicidal family members for along time (Hamad *et al*., 2012). Although, the advocated alternatives like dietary supplementation, grazing management and genetic approaches are not highly effective

(except phytotherapy) if applied solitary, but apparently, have not been utilized on organized farms in Pakistan so far. Veterinarians and livestock raisers are not acquainted with the magnitude of these substitutes and still they rely on synthetic chemotherapeutics, so, in this respect, providing them essential knowledge and education could be very useful. On the other hand, combination of these alternatives may play an enormous role in controlling resistant nematodes, but each farm may require choosing the most suitable combined approach. The best combined strategy for Pakistani environment may be the combination of nutritional supplementation and phytotherapy because they are easily available and culturally acceptable. Indeed, availability of synergy is impeccable among other proposed combined schemes, but definitely, should be confirmed pragmatically. Ultimately, further studies and investigations are required, especially in the application of suggested combined policies to local circumstances.

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