Nutritional consequences on the outcome of parasitic challenges on small ruminants

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Abstract. Host nutrition can affect the resident and incoming populations of pathogens and consequently ameliorate the detrimental consequences of an infectious challenge in small ruminants in four different ways: (i) affect the fitness of the parasite, through the ingestion of plant compounds, such as plant secondary metabolites; (ii) alter the conditions in the gut environment from beneficial to detrimental and even toxic for parasite survival; (iii) positively affect host resistance, i.e. the ability of the host to regulate gastrointestinal nematode establishment, development, fecundity and survival; and (iv) enhance host resilience to the parasitic infection. In this paper we address the effects of nutrition either directly on parasite fitness or through its influence on the environment of the parasite. We believe the nutritional consequences on parasitised hosts have not received appropriate attention so we focus on them in this paper. We first discuss how the excess or lack of nutrients can alter the physicochemical properties of the digestive tract making this environment more hostile for parasites transmitted through the oral route. We then concentrate on specific plants rich in secondary metabolites (PSM) and review evidence on the consequences of their consumption on resident or incoming nematode population. We conclude by discussing specific prerequisites for effectively using nutrition for parasite control.

Keywords. Gastrointestinal parasites – Nematodes – Plant secondary metabolites – Bioactive forages.

Manipulation nutritionnelle et conséquences sur le parasitisme chez les petits ruminants

Résumé. La nutrition de l'hôte affecte les populations de pathogènes existantes et nouvelles ce qui allège les conséquences négatives de l'infestation des petits ruminants à travers quatre voies différentes : (i) elle affecte la forme du parasite, à travers l'ingestion de composés de la plante, tels que les métabolites secondaires ; (ii) elle altère l'environnement intestinal qui passe de l'état bénéfique à l'état nuisible voire toxique pour la survie des parasites ; (iii) elle affecte positivement la résistance de l'hôte, c'est-à-dire la capacité de l'hôte à réguler l'installation du nématode gastro-intestinal, le développement, la fécondité et la survie ; et (iv) elle augmente la résilience de l'hôte à l'infection parasitaire. Cet article traite des effets de la nutrition sur la forme du parasite ou sur le milieu environnemental du parasite. On pense que les conséquences nutritionnelles sur les hôtes infestés par les parasites n'ont pas été étudiées auparavant, ce qui nous a encouragés à traiter cet aspect dans cet article. Dans une première étape on a discuté comment l'excès ou le déficit en nutriments peut altérer les propriétés physicochimiques du tube digestif rendant cet environnement plus hostile pour les parasites transmis par voie orale. On s'est concentré ensuite sur les plantes riches en métabolites secondaires et les conséquences de leur consommation sur la population de nématodes résidente ou attendue. On a conclu cette revue avec une discussion des conditions spécifiques permettant une nutrition efficace destinée au contrôle parasitaire.

Mots-clés. Parasites gastrointestinaux – Nématode – Métabolites secondaires – Fourrage bioactif.

I – Introduction

Small ruminants are constantly exposed to pathogens, such as gastrointestinal nematode parasites. They eventually acquire immunity to them and successfully regulate them, although their immunity may break down during certain stages of their lives. There is abundant evidence that

host's nutrition can contribute to regulating parasite populations in a host, either by acting independently or through enhancing immunity at times of increased susceptibility to parasites (for reviews see Coop and Kyriazakis, 2001; Houdijk and Athanasiadou, 2003; Sykes and Kyriazakis, 2007). Although not all mechanisms have been investigated in depth, various ways have been proposed to account for such effects of nutrition on the parasitised host. Firstly, nutrition may directly affect the fitness of the parasite, through the ingestion of plant compounds, such as plant secondary metabolites. Secondly, the excessive consumption or the lack of certain nutrients may alter the conditions in the gut environment from beneficial to detrimental and even toxic for parasite survival. Thirdly, certain nutrients, such as protein, can affect host resistance, i.e. the ability of the host to regulate gastrointestinal nematode establishment, development, fecundity and survival. Host resistance to gastrointestinal nematodes is mainly mediated through acquired immunity and thus, host nutrition has the potential to affect gastrointestinal nematodes by affecting the rate of acquisition and the degree of expression of immunity. Finally, the nutrition of the host can ameliorate the detrimental effects of the parasitic infection on production by improving the resilience to parasitic infection. A number of reviews have been published on the effects of nutrients, such as protein, on the resistance and the resilience of parasitized hosts, and they will not be considered further in this paper (Coop and Kyriazakis, 1999, 2001; Houdijk and Athanasiadou, 2003; Kyriazakis and Houdijk, 2006; Sykes and Kyriazakis, 2007).

In this paper, we concentrate on the effects of nutrition either directly on parasite fitness or through its influence on the environment of the parasite, as we believe such nutritional consequences on parasitised hosts have not received appropriate attention. We focus on the gastrointestinal nematodes, as they are the most pervasive challenge to health and welfare of small ruminants, although similar consequences may be experienced in other type of infections. Table 1 shows epidemiologically important gastrointestinal nematodes of ruminants and their main effects on parasitised hosts.

Table 1. Epidemiologically important gastrointestinal nematodes of sheep, goats and cattle, their site of infection and main effect on the parasitised host

	Site of infection	Nematodes	Consequences of parasitism
Sheep, goats	Abomasum	*Haemonchus contortus*	Anaemia
		Teladorsagia circumcincta	Reduced food intake
	Small intestine	*Nematodirus battus*	Dehydration
		Trichostrongylus colubriformis	Reduced food efficiency
		Trichostrongylus vitrinus	Reduced food efficiency
Cattle	Abomasum	*Haemonchus placei*	Anaemia
		Ostertagia ostertagi	Reduced food intake
	Small intestine	*Cooperia oncophora*	Reduced food efficiency
		Cooperia punctata	Reduced food efficiency

Source: Adapted from Houdijk and Athanasiadou (2003).

In the first part of this paper we discuss how the excess or lack of nutrients can alter the physicochemical properties of the digestive tract, making this environment more hostile for parasites transmitted through the oral route. Although most experimental evidence is from monogastrics, we use this evidence to extrapolate on relevant mechanisms in ruminants. In the second part we concentrate on specific plants rich in secondary metabolites (PSM) and review evidence on the consequences of their consumption for resident or incoming nematode populations. As many PSM are also known for their anti-nutritional properties, we further explore the prerequisite that should be met in order for parasitised hosts to benefit from the anthelmintic properties of PSM-rich plants. In some cases, interactions may occur between these two different influences on the parasitic infection. For example, certain PSM may create an unsuitable environment for the establishment and development of parasites. We will identify such interactions when evidence is available; however, we have chosen to separate the two issues in the present

review for the sake of clarity. We conclude by making recommendations on the potential incorporation of plants in nutritional regimes that can improve the health and welfare of small ruminants.

II – Consequences of nutrition on the parasite environment

Nematodes identify and select precise locations to reside within their hosts. Although the exact reasons for the specific choice of habitat are still not clear, the specificity of the location is so consistent that can not be disputed (Sukhdeo and Bansemir, 1996). Consequently, we may assume that any changes in the environment of the parasites may affect the incoming or the resident parasite population in two ways. The first one is by influencing the ability of incoming parasites to identify their niche thereby inhibiting their abilities to feed and reproduce. The second one is by creating a hostile/toxic environment for the incoming or resident parasites, with detrimental consequences on their survival. For example, changes in the levels or types of sugars in the diets of parasitized rats resulted in parasites changing location in the gut and consequentially experiencing penalties in their growth and reproduction (Parshad *et al.*, 1980; Crompton *et al.*, 1983). Unfortunately this research did not explore the mechanisms that underlined these observations or the manner in which the specific carbohydrates affected the environment of the parasites.

The specific conditions that carbohydrates create in the gastrointestinal tract of parasitised hosts attracted attention recently from Petkevicius *et al.* (2004, 2007). They noticed that changes in fermentation patterns in the large intestine of pigs altered pH in various compartments of the gastrointestinal tract and reduced parasite populations. They showed that the consumption of diets high in inulin, a highly degradable fructose polymer, reduced worm numbers and egg counts in pigs infected with the large intestine nematode *Trichuris suis* (Petkevicius *et al.*, 2007). Similarly, infusion of short chain fatty acids (SCFA) and lactate acid (LA), which are the fermentation products of inulin, also reduced populations of *Oesophagostomum dentatum* in pigs (Petkevicius *et al.*, 2004). The specific mode of action of the fermentation products in regulating the parasites is not clear. It was proposed that SCFA and LA may exert some direct effects on worm physiology, especially the females. High inulin diets were detrimental to parasites during the establishment of an infection and on patent infections. In addition, following the consumption of inulin and the infusion of the SCFA and LA, pH was reduced in the caecum and the proximal colon of the pig. The close association between increased levels of SCFA and LA, low pH and expulsion of nematodes suggests that changes in pH may play a major role in worm expulsion, perhaps by creating an unsuitable environment for mature and immature parasites.

To date there is no experimental evidence on whether and how the extensive dietary fibre fermentation that occurs in the rumen may influence the conditions in the gastrointestinal tract required for successful parasite establishment and survival. As with carbohydrate fermentation in monogastrics, changes in rumen pH may affect parasite establishment or survival. For example, the ekdysis of infective larvae, otherwise known as exsheathment, is a process necessary for the successful establishment in the host. Exsheathment generally occurs in the rumen for many of the gastrointestinal nematodes of small ruminants, including *Haemonchus contortus*, *Teladorsagia* spp. and *Trichostrongylus* spp. (Hertzberg *et al.*, 2002). Changes in pH of the rumen, as well as bicarbonate concentrations, influence this process. In addition, dietary changes affect the exsheathment kinetics of gastrointestinal nematodes in ruminants (De Rosa *et al.*, 2005). Dietary changes associated with changes in rumen pH, such as excessive carbohydrate ingestion, should be further considered for their antiparasitic potential. However, this should be done in combination with their antinutritional effects, modulated via negative consequences to rumen microflora, prior to advocating them as potential means for parasite control.

In addition to carbohydrate consumption, dietary protein may influence conditions in the gastrointestinal tract thereby affecting parasite survival in ruminants. This effect of protein would be

in addition to the well-established role of protein in resistance and resilience (Coop and Kyriazakis, 2001; Houdijk *et al.*, 2001). Datta *et al.* (1998) showed that protein supplementation reduced the level of parasitism in lambs and also that high-protein diets increased production of ammonia in rumen digesta. They suggest accumulated ammonia in the rumen might directly influence the rumen microenvironment by exhibiting toxic effects on *Haemonchus contortus*. High rumen ammonia also increases the pH of the rumen, which may also affect the exsheathment of the infective larvae as discussed earlier.

In addition to protein excess, extreme protein deficiency may create an unfavorable environment for parasites. Contrary to expectations, sheep fed a food low in metabolisable protein (MP) (mean: 1.7 g MP per kg body weight) had lower parasite burdens than sheep fed a food adequate in MP (Athanasiadou *et al.*, 2001b). The very low protein content of the food may have altered the structure and/or the physiology of the gut and may have created an unsuitable and hostile environment for the survival of parasites. Low-protein diets may change the morphology of the gastrointestinal mucosa (Brown *et al.*, 1963), influence local blood flow (de Aguilar-Nascimento, 2005) and increase epithelial cell apoptosis (Bodiga *et al.*, 2005), all of which may affect parasite establishment and survival. However, as none of the above hypotheses were further investigated to elucidate the possible mechanisms, it is not possible to reject or accept them. Consequently, there may be more to the role of protein in parasite regulation than the effects on resilience and resistance, and future efforts should explore the full potential of protein nutrition in parasite control.

III – PSM-rich plants

1. Anthelmintic effects

Plant secondary metabolites are organic compounds that do not seem to have a role in the primary plant metabolism, i.e. in growth, reproduction or development of plants. More than 80,000 different PSM compounds have been described, whereas more than 100,000 compounds are believed to exist in plants resulting in a great compound diversity (Acamovic and Brooker, 2005). Although PSM are present in all plants in small and moderate amounts, only a small proportion of plant species contain PSM in high amounts and those we call PSM-rich plants (Gershenzon, 2002). In many cases, PSM-rich plants have anthelmintic activity, which in most cases is attributed to the PSM. Table 2 shows some examples of PSM-rich plants and the suggested anthelmintic compounds.

Saponins, lactones, glycosides and polyphenols are PSM with reported anthelmintic activity towards animal and human gastrointestinal parasites (Guarrera, 1999; Satou *et al.*, 2002). One of the PSM most systematically investigated is the polyphenolic compounds collectively called condensed tannins (CT) or proanthocyanidins. They are located inside the vacuole of the plant cell and may be present in many parts of the plant, but are usually present in higher concentrations in the woody tissues (Bernays *et al.*, 1989). Evidence of the antiparasitic activity of CT-rich plants comes from both animal experimentation and *in vitro* studies. Early observations from grazing experiments showed that CT-rich forages such as *Lotus* spp. or *Hedysarium* spp. (Niezen *et al.*, 1994, 1995, 1998) could affect Trichostrongylides infections in sheep by reducing nematode egg excretion and worm burdens. In addition, Athanasiadou *et al.* (2000a,b, 2001a) investigated CT-parasite interactions *in vivo* using quebracho (a CT-extract from *Schinopsis* spp.) as a supplement to *T. colubriformis* infected sheep. They found tannin-rich food lowered the nematode egg excretion and parasite worm burdens by 50% compared to non-tannin supplemented animals. *In vivo* data from sheep (Butter *et al.*, 2000; Niezen *et al.*, 2002; Hordegen *et al.*, 2003; Marley *et al.*, 2003), goats (Paolini *et al.*, 2003; Min *et al.*, 2004), and deer (Hoskin *et al.*, 1999) confirmed antiparasitic effects of either CT extracts or CT-rich plants. Further support of antiparasitic activity has come from *in vitro* studies where crude or purified plant extracts were tested against larval parasitic stages. Such studies, which used extracts from leguminous species such as *Lotus pedunculatus*

(greater birdsfoot trefoil), *Hedysarum coronarium* (sulla), *Onobrychis viciifolia* (sainfoin), *L. caeneata* or *Schinopsis* spp. (Molan *et al.*, 2000a,b, 2002; Athanasiadou *et al.*, 2001a; Paolini *et al.*, 2003) or woody plants, such as *Rubus fructicosus*, *Quercus robur* and *Corylus avellana* (Paolini *et al.*, 2004), all demonstrated dose-dependent anthelmintic effect against immature stages of several nematode species including *Dictyocaulus* spp., *Ostertagia* spp. as well as *H. contortus*, *T. colubriformis* and *T. circumcincta.*

Table 2. Examples of PSM-rich plant extracts with reported anthelmintic properties, and the potential active compounds

PSM-rich plants	Parasite	Suggested active compound (s)	Reference
Catica papaya	Nematodes	Papain and lysozyme	Satrija *et al.*, 1994; Stepek *et al.*, 2006
Ananas comosus	Nematodes	Cysteine proteinases	Stepek *et al.*, 2006
Hedera helix	Cestodes	Saponic extract	Julien *et al.*, 1985
Macleaya cordata	Nematodes	Isoquinoline alkaloids	Satou *et al.*, 2002
Mallotus philippinensis	Cestodes	Glycosides	Akhtar and Ahmad, 1992
Chenopodium ambrosioides	Nematodes	Ascaridol	Guarrera, 1999
Azadirachta indica	Nematodes	Tannins	Chandrawathani *et al.*, 2006
Punica granatum	Helminths	Polyphenols	Guarrera, 1999
Artemisia vulgaris	Helminths	Tannins	Guarrera, 1999
Artemisia maritima	Nematodes	Santonine	Waller *et al.*, 2001
Paeonia suffriticosa	Nematodes	Gallotannins, condensed tannins	Mohamed *et al.*, 2000
Rubus idaeus	Nematodes	Polyphenols	Taylor and Murant, 1966
Sesbania sesban	Nematodes	Condensed tannins	Ibrahim, 1992
Schinopsis spp.	Nematodes	Condensed tannins	Athanasiadou *et al.*, 2000a
Balanites aegyptiana	Nematodes	Saponin	Ibrahim, 1992
Quercus robur	Nematodes	Condensed tannins	Paolini *et al.*, 2004
Plagiochila stephensoniana	Nematodes	Polyphenols	Lorimer *et al.*, 1996
Chicorium intybus	Nematodes	Condensed tannins, sesquiterpene lactones	Molan *et al.*, 2003

Source: Modified from Houdijk and Athanasiadou, 2003.

The anthelmintic properties of PSM may be attributed to a number of mechanisms. Firstly, the *in vitro* results point towards a direct anthelmintic effect through inhibition of motility, feeding, development and survival (Taylor and Murant, 1966; Athanasiadou *et al.*, 2001a; Molan *et al.*, 2003; Paolini *et al.*, 2004). For example, Molan *et al.* (2000a) showed that CT extracts from greater birdsfoot trefoil, birdsfoot trefoil (*Lotus corniculatus*), sulla and sainfoin forages reduced: (i) the rate of larval development (eggs to L3 larvae); (ii) egg hatching ability; and (iii) the motility of L3 larvae. In almost all the previous *in vitro* studies, the magnitude of the anthelmintic effect was directly related to the increasing CT concentration. In some cases the activity could not be attributed to CTs alone, as crude extracts contained other compounds as well. The restoration of the inhibitory effects following the addition of specific tannin-inhibitors supports the hypotheses that at least part of the activity was due to CTs.

These *in vitro* results were supported by *in vivo* evidence, where the experimental design enabled the investigation of the specific, directly mediated anthelmintic effect in parasitised sheep (Athanasiadou *et al.*, 2000a,b, 2001a; Tzamaloukas *et al.*, 2005a). Several suggestions have been put forward to account for the possible *in vivo* anthelmintic activity of PSM. For example, CTs may

bind to L3 larvae and inhibit establishment and/or their motility (Lorimer *et al.*, 1996; Hoskin *et al.*, 1999). Furthermore, CTs may interfere with the motility of the parasite as noted from *in vitro* studies, which may inhibit development (Molan *et al.*, 2000b) or exhibit toxic effects when in direct contact with the parasite (Butter *et al.*, 2001). Electro-microscopy has shown that condensed tannins may destroy the parasite sheath making parasites more susceptible to hosts defences (Hoste *et al.*, 2006). Although there is no direct evidence, PSM may also affect the environment in which the parasites reside, for example by affecting the pH of the rumen (Villalba *et al.*, 2006; Osoro *et al.*, 2007). This is of particular importance in light of recent evidence suggesting that certain PSM delay exsheathment of the gastrointestinal nematode *H. contortus* in goats (Brunet *et al.*, 2007), which may be mediated through changes in pH in the rumen.

In addition to direct anthelmintic effects, PSM may also indirectly mediate immunological effects. PSM-rich forages may enhance immune response to parasites, either as an outcome of the PSM having immunomodulatory effects or through the nutritional value of the plant. A limited number of studies have monitored immunological parameters following the consumption of either PSM-rich forages (Tzamaloukas *et al.*, 2006) or CTs extract (Paolini *et al.*, 2003). The consumption of PSM-rich forages increased the number of mucosal mast cells and globule leukocytes, whereas CTs extracts increased the number of mast cells on the mucosa. Although it was not clear how this effect was mediated, it may have been due to the higher crude protein content of the bioactive forages compared to the grass/clover control. Consequently, parasitised hosts experienced the beneficial effects of protein supplementation on the development of resistance in parasitised hosts (Coop and Kyriazakis, 2001; Houdijk and Athanasiadou, 2003).

Furthermore, the consumption of PSM-rich plants improves resilience of parasitised hosts, i.e. their ability to cope with the parasitic infection without penalising their performance, when compared with conventionally fed animals (Niezen *et al.*, 1998; Marley *et al.*, 2006; Athanasiadou *et al.*, 2007). Although the mechanisms that underline such effects on resilience are not known, they may be related to the nutritional superiority of many PSM-rich forages. It is thus evident that the beneficial effects observed in parasitised hosts maybe the outcome of multiple actions of PSM-rich plants that are not always easily distinguished. We believe further understanding of the mechanisms that regulate their anthelmintic activity will ensure the efficient utilisation of PSM-rich plants in parasite control strategies. This is particularly relevant, because as explained in the next section, PSM are also responsible for many detrimental effects, which may further complicate their use in parasite control schemes.

2. Anti-nutritional effects

The consumption of PSM-rich plants has been associated with various detrimental consequences in both invertebrate and vertebrate herbivores. The severity depends on the concentration, the type and the structure of the PSM, and the concentration of other nutrients, such as proteins and carbohydrates in the diet (Mueller-Harvey, 2006). In general, herbivores that do not regularly include PSM-rich plants in their diets, such as various monogastrics and sheep (sheep generally eat plants rich in PSM) and cattle, may get more severely penalised by the consumption of PSM-rich plants. The consumption of PSM-rich plants by ruminant herbivores can result in reduced intake, weight loss, toxicity and death (Milgate and Roberts, 1995; Waghorn and McNabb, 2003). For example, condensed tannin consumption has been associated with reduced food intake, digestibility and impaired rumen metabolism (Barry and McNabb, 1999; Min *et al.*, 2003). Some types of condensed tannins are also responsible for mucosal toxicity and consequently a reduction in nutrient absorption (Reed, 1995; Dawson *et al.*, 1999; for review: Mueller-Harvey, 2006). Saponins have also reduced food intake and impaired growth (Applebaum and Birk, 1979; Milgate and Roberts, 1995), and they have additional been associated with haemolytic action and bloat in ruminants. Excessive consumption of alkaloids, glycosides and terpenoids can cause lesions in the nervous system (Conn, 1979; Mabry and Gill, 1979).

On the other hand, herbivores that usually include PSM-rich plants in their diets have developed

various mechanisms to inactivate them and overcome possible adverse effects on their health. For example, the excretion of salivary proline-rich proteins (PRP) has been considered the major physiological adaptation to neutralise excess of dietary tannin (see review by Bernays *et al.*, 1989). Deer produce PRP that have great affinity to dietary tannins (Robbins *et al.*, 1991). As tannins form complexes with PRP that pass through the digestive tract and are excreted in the faeces of herbivores (Mole *et al.*, 1990), they do not bind to proteins. Consequently, these animals may not experience negative consequences from the PSM. Other mammals, such as goats, that usually include tannin-rich grazing in their diets have developed other adaptation mechanisms. For example tannin tolerant, resistant or degrading microbial populations enable feral goats to cope with tannin-containing forages (Acamovic and Brooker, 2005). As a consequence, goats do not seem to suffer toxic effects of tannins at levels that other animals would (Silanikove *et al.*, 1996). Sheep do not have any protective/adaptive mechanisms for consuming tannins (Robbins *et al.*, 1991), and thus are more susceptible to their anti-nutritional effects. Mammals that have developed mechanisms to cope with the anti-nutritional consequences of PSM consumption may experience the anti-parasitic effects of PSM in a different manner compared to those without such mechanisms. For example, studies performed in parasitised goats suggest that the administration of Quebracho extract, a condensed tannin extract, may reduce the fecundity of abomasal nematodes (Paolini *et al.*, 2003), which contradicts the findings from sheep (Athanasiadou *et al.*, 2001a). In the latter, consumption of Quebracho extract affected the numbers and the fecundity of intestinal, but not abomasal nematodes. Figure 1 shows the total worm population recovered in sheep infected with either an intestinal (*Trichostrongylus colubriformis*) or an abomasal (*Haemonchus contortus*) nematode species following or not the administration of Quebracho extract. The fecundity of the nematodes followed a similar trend. The differences between sheep and goats may be attributed to the different physiological adaptations of sheep and goats mentioned above. Such adaptations, developed by goats to counteract secondary metabolites present in browse plants, may modulate the bioavailability of tannins, i.e. the amount of free condensed tannins available to interact with nematodes, and thus goats may experience the anthelmintic effects of tannins in a different manner from sheep. On how different hosts experience the positive and negative effects of PSM, and whether they can use them for their own benefit, is an issue that requires further investigation, prior to incorporating PSM in parasite control schemes.

Fig. 1. Total worm population recovered from sheep infected with either an intestinal (*Trichostrongylus colubriformis*) or an abomasal (*Haemonchus contortus*) nematode on day 35 post infection. On day 28 sheep were drenched with 8% (▨) of food intake commercially available condensed tannin extract (Quebracho extract). Undrenched controls are also shown (■). The bars represent 95% confidence intervals (from Athanasiadou *et al.*, 2001a).

In order for parasitized ruminants to benefit from the anthelmintic properties of the PSM-rich plants, the antiparasitic effects should outweigh the anti-nutritional consequences on the performance of the parasitized host. The latter will depend on the severity of the consequences to the host and to the parasite, as discussed in two recent reviews (Houdijk and Athanasiadou, 2003; Athanasiadou and Kyriazakis, 2004). It will also depend on the duration of exposure to the PSM-rich plants and the species of parasitised host as discussed above. For example, parasitized hosts might be able to tolerate short-term negative consequences (e.g. toxicity) if they can attain long-term benefits (e.g. parasite reduction) (Kyriazakis and Emmans, 1992). Consequently, short-term exposure may be one option for including PSM in parasite management schemes and others will be suggested in the next part of this paper.

3. Suggested solutions for potential applications

Mediterranean rangelands largely consist of plants with moderate to high content of PSM, and particularly tannins (Papachristou *et al.*, 2005). Indigenous plants, such as kermes oak (*Quercus coccifera*), oriental hornbeam (*Caprinus orientalis*) and manna ash (*Fraxinus ornus*), could potentially be incorporated in low input, extensive parasite control schemes. The prerequisite is that their anti-nutritional effects are penalising the health of the herbivores to a lesser degree than does parasitism. One way of addressing this problem may be through simultaneous use of more than one PSM-rich plant. Such combined use may provide two advantages for the parasitised host. Firstly, it may dilute the potential toxic effects of the individual PSM and thus maintain the food intake of animals at high levels, providing that the different plants contain different PSM. Previous evidence has showed that lambs offered a choice of feeds that contain different PSM such as oxalates, tannins and terpenoids consume more than lambs offered a single food that contains only one of these compounds (Villalba *et al.*, 2004). Moreover, some PSM may neutralise the activity of others rendering the combination inactive, which apparently happens with tannins and saponins in mice (Freeland *et al.*, 1985), and tannins and terpenes in sheep (Mote, 2006). However, in the process of neutralising their negative activity, these interactions between different PSM may also reduce the impact of the antiparasitic activity; this is an important issue that merits further investigation.

The second benefit the parasitised host may experience from the tandem use of more than one PSM-rich plant is that their anthelmintic action may act in a synergistic and/or complementary manner and ensure better protection from the parasites compared to the one. In a recent study, the potential complementary effects of two PSM-rich forages, sulla and chicory (*Chicorium intybus*) were tested in sheep parasitised with an abomasal nematode (Tzamaloukas *et al.*, 2005b). The consecutive consumption of the two PSM-rich forages did not result in a complementary effect; the authors suggest that either such an effect was not present, or it might have been masked by the immune response of the parasitised hosts. Systematic investigation is necessary to characterise the relationships among various classes of the anthelmintic PSM. The concurrent use of more than one PSM-rich plant has the potential to offer many advantages and for this reason it should not be ignored. Acquisition of such knowledge will promote the efficient and safe use of PSM-rich plants for parasite control.

An alternative way of reducing the negative effects of PSM on the parasitised host is by manipulating the availability of certain dietary nutrients. Tannin consumption reduces food intake in sheep offered a low-protein food, but not in those offered a high-protein food (Athanasiadou *et al.*, 2001b). This effect was probably mediated through the regulation of the bioavailability of the tannins in the host; more tannins were freely available to exert their negative consequences on rumen microflora and thus penalise the performance of animals on low-protein foods. On the other hand, such increased bioavailability of tannins may result in greater penalties on the parasites. In another example, protein and/or energy supplementation increased the ability of animals to eat foods that contain PSM compounds such as terpenes, tannins, oxalates, and saponins (Provenza *et al.*, 2003; Papachristou *et al.*, 2007). This was probably mediated by facilitating detoxification processes. Thus, supplementation with macro-nutrients whilst offered PSM-rich foods, can help the

animals: (i) cope better with PSMs; (ii) influence their preferences for foods high in PSMs, and (iii) likely reduce the time animals require to adapt to PSM.

As mentioned earlier, short-term grazing on PSM-rich plants may offer another possibility of minimising the negative effects of PSM, but still experiencing the positive anthelmintic effects. This way, parasitised animals would be offered access to PSM-rich plants for short periods of time, in order to reduce their level of parasitism, and then return to conventional pastures (Athanasiadou and Kyriazakis, 2004). This option would be extremely attractive if effective, as potentially adverse effects of PSM consumption on the performance of parasitised hosts would only be experienced for short-term. Indeed, if short-term PSM consumption could reduce the level of parasitism, as shown for certain PSM (Paolini *et al.*, 2003; Min *et al.*, 2004; Tzamaloukas *et al.*, 2005a), then short-term penalties on animal performance could actually lead to long-term benefits. These long-term benefits would be translated as having an impact on parasite epidemiology through lower parasite excretion, exposure and greater protection from parasites in subsequent grazing seasons.

IV – Conclusions

Host nutrition has a role in parasite management strategies as a complementary intervention to more traditional control measures, such as the use of anthelmintics. Due to the increasing rate of development of nematode resistance towards anthelmintic drugs (Jackson and Coop, 2000), as well as increasing public concerns about potential drug residues in animal products and the environment, nutrition will be required to play a more strategic role in the control of parasitism in ruminants. In the present review we have shown that through direct effects on parasite fitness, host nutrition has the potential to impact animal health, affect the epidemiology of the parasitic infection and consequently ease public concerns over environmental contamination. A strategic combination of the various consequences of host nutrition in parasitised herbivores could greatly contribute towards non-chemical, sustainable parasite control in low input, extensive systems of herbivore production. It is anticipated that nutritional control of gastrointestinal nematodes will be part of an integrated approach for parasite control, including genetic selection for increased resistance, vaccination and biological control, rather than being applied in isolation (Coop and Kyriazakis, 2001; Houdijk and Athanasiadou, 2003). Thus, developments of non-chemical parasite control strategies would require a multidisciplinary approach and close collaboration among a range of specialists, including nutritionists, parasitologists, geneticists and veterinarians.

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