THE USE OF TANNIN-CONTAINING RESOURCES IN THE CONTROL OF GASTRO INTESTINAL NEMATODES IN RUMINANTS.

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Summary

Parasitic infections with gastrointestinal nematodes (GINs) remain a worldwide major pathological threat associated with the outdoor production of ruminant species. Because of the widespread resistance to synthetic chemical anthelmintic drugs, there is now a strong need to explore novel approaches to design a more integrated management of these parasitic infections. Tannin containing resources to control GINs represent one of these alternatives which has been under investigation for the last 20 years.They illustrate the concept of nutraceuticals in veterinary parasitology, which can be defined as a feed which combines nutritional value and positive effects on animal health. Results are presented to describe the possible botanical resources to use,the anthelmintic effects on the biology of GINs, the hypotheses explaining the mode of action and the diverse modes of exploitation.

Introduction

Infections with gastrointestinal nematodes (GINs) still represent a worldwide parasitic threat when ruminantsare bred outdoors. Up to now, the control ofthese parasitic diseases has essentially relied on the repeated use of commercial anthelmintic (AH) drugs. However, there are now serious limits to the exclusive reliance on these chemical solutions, including: **i)** the increasing demand of consumers for a general reduction of chemicals in agriculture in order to reduce possible residues in food products and in environment; **ii)**the increasing constraints in regulation to address these demands of consumers and more important; and**iii)**the constant widespread diffusion of resistance to AH drugs in worm populations, and the occurrence of multi-resistant strains, which is a serious problem in small ruminants in an increasing number of areas in the world(Van Wyck et al., 1997, Torres-Acosta et al., 2012, Jackson et al., 2012,).

There is thus a strong impetus to explore alternative solutions which can help at achieving an integrated and more sustainable control of GINs infections (Hoste and Torres-Acosta, 2011). One of these alternative approachesis the use of bioactive plants to modulate the biology of worms. The use of tannin containing plants as nutraceuticals is one of the most studied examples worldwide.

What is a tannin-containing nutraceutical?

The term “nutraceutical” results from a combination /contraction between the two words “nutrition” and “pharmaceutical”. Anutraceutical in veterinary science can be defined as “a livestock feed which combines nutritional value with beneficial effects on animal health, including the prevention and treatment of disease,”(Andlauer and Fürst, 2002).In contrast to classical AH drugs, nutraceuticals are not synthetic compounds, but they are plant-based products that contain nutrients and bioactive compounds that can be used either directly as part of the plant diet or added in a concentrated form to another diet after extraction from the bioactive plant. By comparison to synthetic chemical AHs, the concept of nutraceutical is defined by the following points:

- *The main objective when using tannin–containingnutraceuticals is the prevention of GIN infections;*
- *A nutraceutical is at first a feed with nutritional value;*
- *A nutraceutical is proposed and not imposed on the animals. The effects on health depend on the animal’s feeding behaviour and on their voluntary feed intake;*
- *The impact of nutraceuticals against the parasites depends on the presence of bioactive planr secondary metabolites (PSMs);*
- *The anti-parasitic impact of nutraceuticals depends on their consumption for several days (at least one week);*
- *The effects of tannin-containing nutraceuticals differ from synthetic AH.*

Do tannin containing plants have anthelmintic effects?

The first evidence to support the use of tannin containing plants as nutraceutical feeds against GINwas obtained in New Zealand. These early empirical results reported significant reduction of GIN faecal egg counts in sheep when grazing pastures with different legumes, i.e. birdsfoot trefoil and big trefoil (*Lotus corniculatus, L. pedunculatus*), and sulla (*Hedysarumcoronarium*). One common feature of these legumes was the fact that they contained condensed tannins (CTs) (Niezen et al., 1995, 1998, 2002).

The information generated by these early field trials has given the impetus to seek other tannin containing legumes (Fabaceae) with properties against GINs in small ruminants elsewhere in the world. Some of the most extensive studies have been dedicated to sericea lespedeza (syn. Chinese bushclover) (*Lespedeza cuneata*) in the USA and South Africa (Shaik et al., 2006, Terrill et al., 2007, 2009).

It is worth noting that, besides these various legume (Fabacea) species, many other plant candidates which contain CTs, from a wide range of botanical families, have also been examined for their potential AH activity (Sandoval-Castro et al., 2012) and that studies are now exploring the possible use of these tanniniferousnutraceuticals against cattle nematodes (Novolbisky et al, 2013) and also some other gastrointestinal parasites (e.g. coccidia) (Sarastis et al., 2012; Burke et al, 2013; Kommuru et al., 2014).

To address the question of the identification and scientific validation of tannin-containing plants,an overall experimental schemehas been developed which relies on 3 successive levels:

- *Level 1: In vitro studies*

The main aim is **to screen the potential AH effects** of different tannin-containing plants. Except for the Larval Exsheathment Inhibition Assay (LEIA) (Bahuaud et al., 2006), most of these*in vitro* assays for primary screening of plant products have been adapted from those developed to evaluate the efficacy of synthetic AHs against GINs in ruminants (Wood et al., 1995, Jackson and Hoste, 2010). In addition, it is worth mentioning that the model of the free living nematode, *Caenorhabditiselegans*, can also be exploited to screen the AH properties of different plant resources (Katiki et al., 2012).

When calculation of EC 50 values is feasible, one of the main interests of these *in vitro* assays is to provide tools **for a primary comparison** of the AH effects,either for the same tannin containing resources against a range of nematode species and/ or isolates (e.g. resistant or susceptible to AHs), or for a range of different tannin containing resources against the same GIN isolate.

These different *in vitro*assays are also highly valuable either to explore the mode of actions of the different PSMs (e.g. by comparing tannin rich extracts, isolated fractions, or pure compounds) (Hoste et al., 2012) and their possible interactions (Klongsiriwet et al., 2014) on different stages of GIN and to better understand the consequences on either the biological and structural changes in different GIN stages (Hoste et al., 2012)

- *Level 2: In vivo studies in controlled conditions*

The main aim is**to confirm the possible AH effects** of identified, selected resources based on step 1, in GIN infected sheep or goats and cattle.These studies should provide a better understanding of the role of different factors, identified by *in vitro* studies, such as differences in effects on different nematode species and /or stages, and requiredconcentration of PSMs in the resource and in the animal diet to obtain the AH effects. These studies can also help to gain information on the role of factors which cannot be addressed by *in vitro* studies, e.g. differences in the AH effects for the same resource between different ruminant species (Alonso Diaz et al., 2010).

- *Level 3: Systemic*in vivo *studies to examine the optimal conditions to exploit tannin-containing resources in different ruminants' breeding systems.*

The main aim is**to explore the best mode of exploitation** of various tannin-containing resources, corresponding to different ruminant breeding systems, in a range of climatic/ecological/epidemiological conditions for parasitic GIN infections. These are relatively long term studies (at least designed for a grazing season = several months) which can allow researchers to obtain information on GIN control, but also on animal production. Despite their ability to better define the conditions of use of tannin-containing nutraceuticalsunder farm conditions, these holistic studies are far less abundant that those corresponding to steps 1 and 2.

What are the main AH effects associated with the consumption of tannin-containing resources on the GIN life cycle?

- *On the worm populations*

In contrast with synthetic AHs whose main goal is to totally interrupt,for a short time, the parasitic life cycle by eliminating 100 % of the wormpopulation, the effects related totanniniferousnutraceuticals are less striking. Three main potential impacts have been linked to the intake of tanniniferous plants by infected ruminants (Hoste et al., 2012) on the GIN life cycle by interfering with three key biological stages

1/a lower establishment of the infective third-stage larvae (L3) in the host.

This first point contributes to reducing host invasion by the infective L3.

2/a lower excretion of nematode eggs by adult worms, related either to a reduction in worm numbers or a lower fertility of female worms; and

3/an impaired development of eggs into infective L3.

Together,point 2 and 3 help to decrease the pasture contamination with parasitic elements and thus to reduce the risks for the hosts.

Hence,the potential combined effects of such separate, diversified impacts can lead to slowing down the general dynamics of GIN infectionand to reduce the need for synthetic AHs to control GINs. The bulk of *in vitro* results and some acquired from *in vivo* studies strongly support the hypothesis of some direct “pharmacological-like” effects of condensed tannins against the worms in the different digestive organs (Hoste et al., 2012).

The effects of tannin containing nutraceuticals against GINs of small ruminants have been most extensively studied. Similar effects have been reported with the 3 main nematode genera that infect sheep or goats (namely *Haemonchusspp, Teladorsagiaspp, Trichostrongylusspp*). It is worth emphasizing that some recent results (Gaudin et al., 2015) suggest that significant reductions in egg excretion have been observed when lambs, infected with a multi-resistant isolate of *H.contortus,* were consuming sainfoin pellets. Hence,tanniniferousnutraceuticals might represent a valuable alternative solution to manage AH resistance in worm populations. However, this statement needs further studies to confirm it.

Last, it is important to underline that, because plant nutraceuticals are natural resources and thus, that their PSM content is not well-defined, the variability in the AH effects reported in different studies is a key issue to address

(Hoste et al., 2012). This question of variability of the resourcesto be exploited also represents a main difference between the AH effects observed with non-standardised nutraceuticals when compared with the effects described with the use of the well-defined synthetic chemical AHdrugs.

- *On the host*

The effects on biological traits of parasitic populations have regularly been associated with positive effects on host resilience (e.g. better production parameters, less severe clinical signs, lower mortality under parasitic challenge) (Niezen et al., 1995, Paolini et al., 2005). In addition, several studies report an improved resistance in ruminants when fed on tannin containing legumes (Hoste et al., 2012). The mechanisms explaining this improved host resilience and/or resistance are still unidentified. They can partly be explained by the nutritive value of legumes (i.e. higher protein content) and the ruminal by-pass effect that occurs in the presence of tannins, which can protect dietary proteins from ruminal degradation (Waghorn, 2008,Rochfort et al., 2008, Hoste et al., 2012).

How to exploit tannin containing nutraceutical resources in outdoor ruminant breeding systems?

- *Tannin containing Legumes*

Thefocus for tannin-containing legumes as nutraceuticalscan probably be explained by 2 reasons:

1/*the occurrence of previous successful experience and agronomic knowledge acquired*to develop the production of*non-tannin containinglegumes* (e.g. the production of alfafa/lucerne) in Europe. Therefore, information on thepossible organisation for production and for on-farm cultivation on a large scale were yet available, namely by producing seeds, bycultivating them efficiently in regards to economic issues and by developing various modes of exploitation by ruminants for animal (meat or milk) production.

2/ *the "bonus" expected effects* for nutrition and health of ruminants and environmental issues when ruminants are fed *with tannin-containing nutraceuticallegumes* (see reviews by Rochfort et al., 2008, Mueller Harvey, 2006, Wang et al., 2015). The different benefits associated with the consumption of tannin-containing legumes include the following points**:** **i)** a reduced use of chemical fertilisers because of biological nitrogen fixation; **ii)**a high palatability for ruminants and feeding values; **iii)** some favourable effects to reduce ruminal methane emission and Greenhouse Gas effects;**iv)** anti bloat effects; **v)** a switch of nitrogen excretion from urine to faeces, and **vi)** and bee attraction for some legume species (e.g. sainfoin).

Results on the AH effects of tannin containing nutraceutical against GINs have been obtained when consumed either in direct grazing, or in conserved forms (e.g. hay, silage or dehydrated pellets). Some examples of these different modes of exploitation and related references are listed in the Table 1. The criteria to be considered to evaluate the pros and cons of these different modes of exploitation are: **i)** the autonomy for on-farm production; **ii)**the possibility to measure the bioactive PSM content before use; **iii**) the ability to store the resource before use; **iv**) the possible standardisation of the tannin containing resources and **v**) the possibility to export and commercialise the resource.

- *Exploiting the biodiversity of plant resources in rangelands by browsing*

In many areas of the world under temperate, mediterranean or (sub)tropical conditions, the natural ecosystems present a wide botanical diversity. Several plant species composing these browse include tannin containing potential nutraceuticals which can be exploited as natural forage. For many of those plant species, there is no information on the agronomic conditions needed to cultivate them or on possible propagation methods. However, in many situations of such silvo pastoral systems, farmers are relying on the natural availability of these nutraceuticals, either by direct browsing or by collecting and cut carrying them from the field.

- *Exploring the value of agro industrial by-products*

As previously mentioned, the concept of nutraceuticals also corresponds to plant-based products that contain nutrients and bioactive compounds either used directly as part of the plant diet or added in a concentrated form to another diet after extraction from the bioactive plants.Based on the secondpart of this definition, recent interest has been growing, in different areas of the world, aiming atexploring the use of tannin-containing by-products from agro-industries for their potential AH effects.

These agro industrial by-products represent an alternative option to natural nutraceuticals because the bioactive PSMs can be extracted from the by-products and then added to an existing feed. Some examples are listed in the table 1.

In regard to the concept of nutraceuticals, the use of such agro-industrial by-products has several advantages: **i)** it transformssome ‘waste’ materials into valuablenutraceutical feeds with antiparasitic properties;**ii)** it can help to address the question of the inherent variability of PSM content in nutraceutical plants, by allowing to adjust the bioactive PSM concentration(s) in feeds (Girard et al., 2013); **iii)** consequently, it may also help to avoid any negative consequences by avoiding an excess of PSM in the feed.

Conclusions

Several consistent *in vitro* and *in vivo* results have been obtained worldwide to support the “proof of concept” for using tannin-containingnutraceuticals against GINs. Because of the widespread resistance to synthetic chemical anthelmintic drugs, it is now imperative to further explore this novel approach.

Because of the intrinsic definition of nutraceutical, these further researches will require a multidisciplinary approach based on a network of scientists with variousexpertise in parasitology, phytochemistry, animal production, ruminant digestive physiology, ethology, etc. However, two main axes of researches can yet be defined. One is related to more basic objectives in order to better understand the mode of action of various polyphenolic compounds against the different GIN stages in order to address the question of the variability in AH effects. The second axis is linked with applied objectives by holistic studies aiming at better defining the conditions of use of different tanniniferous resources in a range of breeding systems and epidemiological condition for GIN infections.

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Table 1: Some examples of different mode of use of tannin-containing resources against GIN in small ruminants

Mode of exploitation	Tannin-containingresources	References
TANNIN-CONTAINING LEGUMES		
Direct grazing	Birdfoot trefoil (*Lotus corniculatus*) Big trefoil (*Lotus pedunculatus*) Sulla (*Hedysarumcoronarium*)	Niezen et al., 1998a Niezen et al., 1998 a,b Niezen et al., 1995
Hay	Sainfoin(*Onobrychisviciifoliae*) Sericea lespedeza (*Lespedeza cuneata*)	Paolini et al.,2003, 2005, Heckendorn et al., 2006, Werne et al., 2013 Shaik et al., 2006, Lange et al., 2006
Silage	Sainfoin	Heckendorn et al., 2006
Dehydrated pellets	Sainfoin Sericea lespedeza	Girard et al., 2013, Gaudin et al., 2015 Terrill et al., 2007 ; Gujja et al., 2013, Kommuru et al., 2014.
TANNIN-CONTAINING AGRO INDUSTRIAL BY-PRODUCT		
Use of by-products	Hazel nut peels Caroob pods Bark of *Acacia sp*	Desrues et al., 2012 Manolaraki et al., 2010, Arroyo-Lopez et al., 2014. Minho et al., 2008, Xhomfulana et al., 2009, Murare et al., 2012