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Actividad antibacteriana y sobre nematodos gastrointestinales de metabolitos secundarios vegetales: enfoque en Medicina Veterinaria

Antibacterial and antihelmintic activity of plant secondary metabolites: approach in Veterinary Medicine

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RESUMEN

En la actualidad el uso de plantas medicinales se ha convertido en una alternativa para el tratamiento y control de enfermedades tanto en medicina veterinaria como en medicina humana. En estudios recientes se ha reportado que los metabolitos secundarios presentes en la mayoría de las plantas ejercen efectos a nivel productivo y de salud; ya que poseen efectos bactericidas o bacteriostáticos, antihelmíntico (taninos y saponinas), anticancerígeno, antioxidante e inmunoestimulante (compuestos fenólicos, saponinas alcaloides y terpenos); e incluso gracias a su contenido de metabolitos secundarios se han propuesto como parte de la alimentación en animales debido a que pueden mejorar parámetros productivos y reproductivos. La presencia o ausencia de estos efectos dependerá del tipo de planta, tipo de metabolito secundario y la cantidad y frecuencia con la que se consuman. El objetivo de la presente revisión fue realizar una búsqueda bibliográfica de los principales metabolitos secundarios de plantas con actividades antimicrobianas y sobre nematodos gastrointestinales, reportadas en Medicina Veterinaria.

Palabras clave: metabolitos secundarios, antibacteriano, antihelmíntico, Medicina Veterinaria.

ABSTRACT

Currently, the use of medicinal plants has become an alternative for treatment and control of diseases in both veterinary and human medicine. Recent studies have reported that secondary metabolites present in all plants have effects on production and animal health as they have bactericidal or bacteriostatic, anthelmintic (tannins and saponins), anticancer, antioxidant and immunostimulant (phenolic compounds, alkaloid saponins, and terpenes) effects; and for their content of secondary metabolites they have been proposed as an alternative in animal feed because can increase productive and reproductive parameters. The presence or absence of these effects depends on the kind of plant, the content of secondary metabolites, the kind of secondary metabolite and the quantity and the frequency in which they are consumed. The aim of the present review was to carry out a bibliography search of the main secondary metabolites of plants with antimicrobial and over gastrointestinal nematodes activity, reported in Veterinary Medicine

Keyword: secondary metabolites, antimicrobial, antihelmintic, Veterinary Medicine.

INTRODUCTION

Many of the diseases that occur in the practice of Veterinary Medicine are associated with the presence of bacteria and parasites, which have developed some resistance to commercial drugs (McKellar and Jackson, 2004, Cabrera *et al*., 2007, Epe and Kaminsky, 2013). Therefore, the use of secondary metabolites of plants as an alternative for the control and treatment of them has been chosen.

Secondary metabolites are compounds derived from the primary metabolism of plants (Augustin *et al*., 2011) these compounds play an important ecological role as they serve as a defense mechanism (Pérez and Jiménez, 2011). The majority of plant species have secondary metabolites, such as terpenes, phenolic compounds, glycosides and alkaloids (Ávalos and Pérez-Urria, 2009), of which, about 8000 polyphenols, 270 non-protein amino acids, 32 cyanogens, 10,000 alkaloids , several saponins and steroids (Domingo and López Brea, 2003; Duraipandiyan *et al*., 2006; Carmona, 2007).

Secondary metabolites are a source of active ingredients of drugs and valuable chemicals, whose pharmaceutical applications are due to their function as analgesics, antibacterials, antihepatotoxics, antioxidants, antiviral, antitumorals, fungicides, immunostimulants, among others (Isaza, 2007, Pérez and Jiménez, 2011, Agustín *et al*., 2011).

It has been proposed that the active components of the extracts (secondary metabolites) can inhibit microbial growth by the same mechanisms as antibiotics: inhibition of cell wall synthesis and activation of enzymes that destroy this wall, the permeability of the cell membrane, interference with protein synthesis and alteration of nucleic acid metabolism among others (Ordaz *et al*., 2010).

On the other hand in the control of the gastrointestinal nematodes has been proposed the herbal as alternative, according to the analysis of the compounds in different plants, the tannins are those that take part in vital functions of the nematodes affecting the mobility, the nutrition and, possibly (Durmic and Blache, 2012, Hernandez *et al*., 2014). In the present study, the results obtained in this study are similar to those reported in the present study. Tannin plants may have direct antiparasitic activity but may also have an indirect effect through enhancing the animals' immune responses against gastrointestinal nematodes (Hoste *et al*., 2005).

There are reports that tannins can improve resilience (fewer clinical signs, better growth and wool production) and resistance (fewer nematode eggs in feces, lower parasite load and lower fertility of parasitic females) of infected goats and sheep with gastrointestinal nematodes (Torres-Acosta *et al*., 2008).

According to the aforementioned, the present review was proposed with the objective of carrying out a bibliographic search in the Scopus, SciELO and Redalyc databases of the main secondary metabolites of plants with antimicrobial activities and on gastrointestinal nematodes reported in Veterinary Medicine. The aim is to favor the use of these alternative sources in the treatment and control of some diseases associated with the presence of bacteria and parasites of importance in the Veterinary Medicine practice.

Secondary metabolites

Secondary metabolites (MS) are compounds derived from the biosynthesis routes of primary carbon metabolism in plants, which appear in the cytoplasm of most plant cells (Augustin *et al*., 2011).

These compounds do not have an apparent importance however; they play an important ecological role since many of the compounds serve as defense mechanism against herbivores, viruses, bacteria and fungi (Pérez and Jiménez, 2011).

Other MSs have physiological functions, such as alkaloids and pectins, which can serve to transport toxic nitrogen and other storage compounds, while phenolic compounds such as flavonoids play a role as ultraviolet ray protectors (Pérez and Jiménez, 2011). MSs as opposed to primary metabolites have a restricted distribution in the plant kingdom as they are synthesized in small quantities and in a specific way determined to the genus, family or plant species (Ávalos and Pérez-Urria, 2009).

Up to 2007, about 8000 polyphenols, 270 non-protein amino acids, 32 cyanogens, 10,000 alkaloids, various saponins and steroids had been reported (Domingo and López Brea, 2003; Duramandiyan *et al*., 2006; Carmona, 2007).

MSs are grouped into four main groups: Terpenes, phenolic compounds, glycosides and alkaloids, all with different pharmacological properties as shown in Table 1.

Use of secondary metabolites as antibacterials

Plants have been considered as a sustainable option against pathogens and an important source of natural diversity due to the large number of compounds they synthesize; (Aedes aegypti, L., *et al*., 2005). In addition, the use of antibiotics has been shown to have an anti-bacterial effect (Montes-Belmont, 2009; Cruz-Carrillo *et al*., 2012, Soto Vázquez *et al*., 2014)

Table 1. Classification of secondary metabolites and their pharmacological properties

Group	Compounds present	Main Features	Pharmaceutical properties
Alkaloids	Hormones, carotenoid pigments, sterols, latex and essential oils	Group of major importance with more than 40,000 molecules, they are considered of importance for the survival of plants. They are insoluble in water and are derived from the union of isoprene units	Anticarcinogenic, antiulcerous, antimalarial, antimicrobial, etc.
Phenolic compounds	Coumarins, flavonoids, lignin and tannins.	They are derived from a phenol group	Antidiarrheals, antitumorals, antibacterials, antivirals and enzyme inhibitors (Isaza, 2007)
Glycosides	Saponins, cardiac glycosides, cyanogenic glycosides and glucosinolates.	They arise from the condensation of a sugar molecule with another containing a hydroxyl group, thus forming a glycosidic bond	Antimicrobials, fungicides, insecticides, anticancer, anti-inflammatory and allelopathic (Agustín *et al*., 2011)
Terpenes	Quinoline, isoquinoline, indole, tropane, quinolizidine, piperidine, purine, pyrrolizidene.	Group with about 15000 secondary metabolites. They are soluble in water, contain at least one nitrogen atom and exhibit biological activity. Most are heterocyclic and some are aliphatic compounds.	At high doses, most are very toxic, however, at low doses they work as muscle relaxants, tranquillizers, antitussives or analgesics.

Adapted of Ávalos and Pérez-Urria, 2009

It is clear that in veterinary practice there are a large number of pathologies associated with the presence of bacterial pathogens which cause significant economic losses in livestock production (Pugh, 2002), however, resistance to conventional antimicrobials is a factor that has limited the treatment and control of the infections caused by these pathogens (Pellegrino *et al*., 2011), that is why antimicrobial alternatives extracted from plants have been used.

The bacterial resistance generated is due to the increase in the use of antibiotics and the respective selective pressure exerted, has caused bacteria with multiple mechanisms such as biochemical, genetic and cellular, to develop strategies to evade the action of these compounds (Cabrera *et al*. 2007), for this reason antimicrobial alternatives extracted from plants have been used, some examples are described in Table 2.

Table 2. Activity of plant extracts on different bacterial genera

Used plants	Bacteria	Reference
Metanolic of *Acacia modesta*	*S. aureus, E. coli, P. aeruginosa, S. epidermis* and *B. subtilis.*	(Bashir *et al.*, 2012)
Thymus serphylum	*S. aureus, E. coli, P. aeruginosa, S. epidermis* and *B. subtilis.*	(Bashir *et al.*, 2012)
Syzygium comuni L.	*S. aureus, E. coli, P. aeruginosa, S. epidermis* and *B. subtilis.*	(Bashir *et al.*, 2012)
Olea ferruginea	*S. aureus, E. coli, P. aeruginosa, S. epidermis* and *B. subtilis.*	(Bashir *et al.*, 2012)
Family *Lauraceae*	*Fusarium oxysporum, E. coli, B. subtilis, P. aeruginosa and S. aureus.*	(Avello Lorca *et al.*, 2012)
Family *Atherospermateceae*	*Fusarium oxysporum, E. coli, B. subtilis, P. aeruginosa and S. aureus.*	(Avello Lorca *et al.*, 2012)
Allium sativum	*E. coli, B. subtilis, P.aeruginosa, S. aureus, S. tiphy.*	(Srinivasan *et al.*, 2001)
Curcuma longa	*E. coli, P. aeruginosa, B. subtilis, S. aureus, S. tiphy.*	(Srinivasan *et al.*, 2001)
Eucalyptus globulus	*E. coli, P. aeruginosa, B. subtilis, S. aureus, S. tiphy*	(Srinivasan *et al.*, 2001)
Jatropha glandulifera	*E. coli, P. aeruginosa, B. subtilis, S. tiphy*	(Srinivasan *et al.*, 2001)
Leucas aspera	*E. coli, P. aeruginosa, B. subtilis, S. aureus.*	(Srinivasan *et al.*, 2001)
Tamarindus indica	*E. coli, P. aeruginosa, B. subtilis, S. aureus, S. tiphy*	(Srinivasan *et al.*, 2001)
Sonneratia alba	*E. coli and P. aeruginosa*	(Kaewpiboon *et al.*, 2012)
C. albicans	*S. aureus, E. coli and P. aeruginosa.*	(Kaewpiboon *et al.*, 2012)
Albizia adianthifolia	*E. coli, Klebsiella pneumoniae, P. aeruginosa*	(Tchinda *et al.*, 2017)
Laportea ovalifolia	*E. coli, Klebsiella pneumoniae*	(Tchinda *et al.*, 2017)

Antibiotics have been used in veterinary medicine for three purposes: therapeutic, prophylactic and as growth promoters, the latter being a practice known since 1950, to discover that small doses of tetracycline improved the development of animals and shortly after this discovery were used other drugs such as penicillin and chloramphenicol (Puig *et al*., 2011), it is also known that veterinary hospitals play a role in the transmission of multiresistant organisms and not only by the continuous administration of antibiotics but also by the exchange of bacteria between people and animals (Ríos *et al*., 2015).

Resistance is a natural property of an organism (intrinsic) or achieved by mutation or acquisition of plasmids (self-replication, extrachromosomal DNA) or transposons (chromosome integrated into plasmids, transmissible DNA cassettes) (Cabrera *et al*., 2007). Plasmids and transposons are mobile genetic elements where resistance genes are transported (Pérez and Robles, 2013).

Antibiotic resistance may be the result of chromosomal mutations or the interaction of genetic material through the transport of resistance genes by means of transduction, conjugation or transposition mechanisms. There are 5 mechanisms of acquired resistance, of which the bacteria can use more than two: enzymatic modification or destruction of the antibiotic, impermeability to the antibiotic, alteration or production of new target sites, the presence of efflux pumps that expel the antibiotic and over expression of the target site (Cabrera *et al*., 2007), although there may also be alterations in the composition and content of bacterial wall glycoproteins (Puig *et al*., 2011).

Bacteria that are resistant to more than one antibiotic are called multiresistant bacteria, which present an even more serious problem because they have developed different resistance mechanisms (Pérez and Robles, 2013).

Similarly the mechanisms by which the active components of the extracts can inhibit microbial growth are known and already mentioned: inhibition of cell wall synthesis and activation of enzymes that destroy that wall, increased permeability of the cell membrane, interference with protein synthesis and alteration of nucleic acid metabolism among others (Ordaz *et al*., 2010).

In the case of *Staphylococcus aureus*, the antimicrobial effect of phenols has been associated with the ability of these compounds to produce alterations in the cytoplasmic membrane of the bacterium (Domingo and López Brea, 2003).

Within the genus of importance in Veterinary Medicine are *Staphylococcus*, *Escherichia*, *Salmonella*, *Pseudomona* and *Bacillus* among others. Within the genus *Staphylococcus* the species of veterinary importance are *aureus*, which produces great variety of suppurative infections in wounds, mastitis, endometritis, cystitis, osteomyelitis, pyoderma in most domestic species as well as companion animals; epidermidis, which generates mastitis in ruminants; *hyicus*, species associated with exudative epidermis in pigs, and intermedius, which causes pyoderma, otitis, conjunctivitis, osteomyelitis in dogs (Velasco and Yamasaki, 2002). In addition, this genus presents high morbidity and mortality in domestic and companion animals (Ríos *et al*., 2015).

Some pathogenic *Escherichia* serotypes are associated with diarrhea in pigs, cattle, sheep, goats and horses. This genus is considered an opportunistic pathogen in urinary and respiratory tract infections, mastitis, omphalitis and different infectious processes (Velasco and Yamasaki, 2002). The subspecies *coli* is a pathogen associated with the presence of diarrhea in small ruminants of less than 2 weeks of age, which present fever and diarrhea linked to severe damage in the intestinal epithelium altering the transport of electrolytes and water, causing a rapid dehydration to cause of hypersecretion of liquids, the morbidity rate is between 20 and 25 % and the mortality is usually greater than 50 %. On the other hand, *E. coli* has also been reported as a causal agent of clinical mastitis in cattle, sheep and goats producing milk, causing considerable losses due to the decrease in milk production, causing anorexia, fever, and even loss of the fourth or middle affected in extreme cases (Pugh, 2002).

For its part, *Bacillus anthracis*, belonging to the genus *Bacillus*, causes sudden deaths with haemorrhages in natural holes in cattle and sheep. Some other species cause enteritis in pigs and dogs, mastitis, abortions, food poisoning, corneal ulcers, among others (Velasco and Yamasaki, 2002).

Bacteria belonging to the genus *Pseudomonas* generate abscesses and purulent infections in different species, bovine mastitis, enteritis, pneumonia and myeloidosis in pigs as wel as in different animal species (Velasco and Yamasaki, 2002).

The serotypes *abortus*, of the genus Salmonella, cause abortions in bovines, horses and sheep, besides generating diarreas and septicemias in different species of animals; and in the case of *S. cholerasuis* it generates enteritis, septicemia and pneumonia in pigs (Velasco and Yamasaki, 2002).

Extracts of different species of plants with different solvents have been analyzed, while the identification of the compounds or compound groups present in these plants has been carried out, it has even been reported that these compounds tend to have a greater effect on bacterial genera which present multidrug resistance.

As a result, phenols exert an antimicrobial action against *S. aureus*, *Salmonella thyphimurium*, tannins on various bacterial genera and some viruses, flavones on *Shigella and Vibrio*, alkaloids against Gram positive cocci, **Lactobacillus** and fungi, the saponins obtained from *Panax ginsen* have an important effect inhibiting the growth of *E. coli* and *S. aureus* (Domingo and López Brea, 2003, Moreno *et al.*, 2010, Pereira *et al.*, 2013).

Saponins have an antibacterial activity and can modify ruminal fermentation by suppressing protozoa and selectively inhibiting ruminal and intestinal bacteria (*Lactobacillus plantarum* and *Enterococcus faecium* in lambs) (Salem *et al*., 2010).

In an experiment carried out in 2013 with hexanic extract of cedar, it was observed that this extract had a potent antimicrobial activity against *Staphylococcus aureus*; with inhibition halos of 12 mm that were responsible for this activity were the alkaloids, triterpenes or sterols, and quinones present in this extract (Pereira *et al*., 2013).

MS anthelmintic activity

The parasitic diseases caused by gastrointestinal nematodes in ruminants represent a serious problem worldwide as they affect host productivity causing reductions in growth rates in young animals, low body conditions, reduced fertility, increased susceptibility to diseases of different origins (Moreno *et al*., 2010, Felice, 2015), and increased mortality, leading to significant economic losses in livestock production (Moreno *et al*., 2010, Felice, 2015)

Drug-based anthelmintic treatment is limited due to the development of resistance of some gastrointestinal nematode populations to most commercial anthelmintics (McKellar and Jackson, 2004, Epe and Kaminsky, 2013).

This problem is common in gastrointestinal nematodes of sheep, goats, horses (Gonzalez *et al*., 2012) and cattle (Encalada *et al*., 2008), however this situation has been studied extensively in sheep because of the low effectiveness of the main chemicals such as benzimidazoles, imidazothiazoles and macrocyclic lactones, a study carried out in 2011 confirmed anthelmintic resistance to the main anthelmintics (Closantel, Albendazole, Ivermectin and Nitroxinil) used in the Sierra de Tabasco and North Chiapas region in sheep (González *et al*., 2012).

One of the alternatives proposed for the control of gastrointestinal nematodes is the use of plants used in traditional herbal medicine with anthelmintic effect. The main compounds of these plants are terpenes, alkaloids, saponins, anthraquinones and tannins. Although, according to the analysis of the compounds in different plants, tannins are involved in vital functions of nematodes affecting mobility, nutrition and possibly reproduction (Medina *et al*., 2014).

The use of plants rich in bioactive secondary metabolites and especially those containing tannins have received great attention and have been proposed as a method of control of gastrointestinal nematodes in sheep and goats, some examples are shown in Table 3 (Durmic and Blache, 2012, Hernández *et al*., 2014).

On the other hand, plants rich in tannins have attracted the greatest attention for their effect on the gastrointestinal nematodes of ruminants. Tannin plants may have direct antiparasitic activity but may also have an indirect effect through enhancing the animals' immune responses against gastrointestinal nematodes (Hoste et al., 2005). There are reports that tannins can improve resilience (fewer clinical signs, better growth and wool production) and resistance (fewer nematode eggs in feces, lower parasite load and lower fertility of parasitic females) of infected goats and sheep with gastrointestinal nematodes (Torres-Acosta *et al*., 2008). The antiparasitic property of the secondary metabolites depends on the structure of the secondary compound, the level of ingestion and their availability in the gastrointestinal tract of the animals (Athanasiadou and Kyriazakis, 2004).

Apparently the action mechanism of tannins on the infective larvae (L3) of *Haemonchus contortus* and *Trichostrongylus colubriformis* is to prevent these parasites from drawing, this prevents the gastrointestinal nematodes can be established in their site of action and can continue with their evolutionary cycle, while in adult parasites the tannins apparently attach to the mouth and possibly to the reproductive apparatus of the parasites, by the affinity of the tannins to the proline-rich proteins of the nematode cuticle (Torres-Acosta *et al*., 2008) .

Table 3. Effect of different plants on gastrointestinal nematodes of small ruminants

Used plant	Effect	Evaluated helminth	Reference
Casuarina cunninghamiana,	%IEH and %IDL	*H. contortus* and *T. colubriformis*	(Moreno *et al*., 2010).
Acacia farnesiana,	%IEH and %IDL	*H. contortus* and *T. colubriformis*	(Moreno *et al*., 2010).
Acacia holosericea	%IDL	*H. contortus* and *T. colubriformis*	(Moreno *et al*., 2010).
Acacia nilotica	%IDL	*H. contortus and T. colubriformis*	(Moreno *et al*., 2010).
Mentha piperita	%IEH and %IDL	*H. contortus*	(Carvalho *et al*., 2012)
Lippia sidoides	%IEH and %IDL	*H. contortus*	(Carvalho *et al*., 2012)
Piper tuberculatum	%IEH and %IDL	*H. contortus*	(Carvalho *et al*., 2012)
Azadirachta indica	%IEH and %IDL	*H. contortus*	(Costa *et al.,* 2008)
Leucas martinicensis	%IEH and %IDL	*H. contortus*	(Eguale *et al*., 2011)
Leonotis ocymifolia	%IEH and %IDL	*H. contortus*	(Eguale *et al*., 2011)
Senna occidentalis	%IEH and %IDL	*H. contortus*	(Eguale *et al*., 2011)
Hura crepitans	%IDL	*H. contortus*	(Carvalho *et al*., 2012)
Albizia schimperian	%IDL	*H. contortus*	(Eguale *et al*., 2011)
Melia azedarach	%IEH	*H. contortus* and *Trichostrongylus sp.*	(Cala *et al.,* 2012)
Trichilia clausseni	%IEH and %IDL	*H. contortus* and *Trichostrongylus sp.*	(Cala *et al.,* 2012)
Annona squamosa	%IEH and %IDL	*H. contortus*	(Kamaraj *et al.,* 2010)
Eclipta prostrata	%IEH and %IDL	*H. contortus*	(Kamaraj *et al.,* 2010)
Solanum torvum	%IEH and %IDL	*H. contortus*	(Kamaraj *et al.,* 2010)
Terminalia chebula	%IEH and %IDL	*H. contortus*	(Kamaraj *et al.,* 2010)
Catharantus roseus	%IEH and %IDL	*H. contortus*	(Kamaraj *et al.,* 2010)
Cymbopongon schoenanthus	%IEH and %IDL	*H. contortus* and *Trichostrongylus sp.*	(Katiki *et al.,* 2011)

%IEH: Egg hatching inhibition rate,% IDL: Percent inhibition of larval development

The nematode *Haemonchus contortus* has been considered the one with the highest prevalence in small ruminants (Encalada *et al*., 2008) and one of the main causes of economic losses in sheep production, which is why most of the *in vitro* studies already performed have been with *Haemonchus contortus* (López Ruvalcaba *et al*., 2013).

CONCLUSION

At present, the treatment of bacterial and parasitic diseases of importance in Veterinary Medicine has been complicated by the resistance to commercial drugs, so it is necessary to use alternatives for the control of these resistant or multiresistant pathogens, one of which may be the use of secondary metabolites of plants with antibacterial activity and/or gastrointestinal nematodes.

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