

## Herbal Drugs Used for Domestic Animals

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### Introduction

Ethnoveterinary medicine (EVM) comprises a complex system of beliefs, skills, knowledge and practices relating to animal husbandry and general animal care (McCorkle 1986). The practice of EVM includes the use of diagnostic procedures, animal husbandry practices, surgical methods and traditional veterinary theory in addition to the use of ethnoveterinary plants to prevent and control disease (Schillhorn van Veen 1997, Van der Merwe et al. 2001). Ethnoveterinary medicine, the scientific term for traditional animal health care, provides low-cost alternatives to allopathic drugs. Research into ethnoveterinary medicine is often undertaken as part of a community-based approach that serves to improve animal health and provide basic veterinary services in rural areas (Mathius-Mundy and McCorkle 1989). In many poor rural areas, ethnoveterinary medicine can play an important role in animal production and often becomes the only available means for farmers to treat sick animals (Maine et al. 1996, Tamboura et al. 2000, Jabbar et al. 2005).

In animal health, as in human health, the market in traditional medicines is expanding. The number of both doctors and veterinarians using non-conventional medicines is increasing all over the world; moreover, the number of people who request such practices for either themselves or their pets is higher and higher.

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The recent return to “natural medicine” in Italy has emphasized the importance of gathering information about medicinal plants traditionally used to treat animals. Phytotherapy represents one of the most used non-conventional medicines in both human and veterinary medicine. It utilizes plants, parts of them such as flowers, leaves, roots, and seeds, and substances extracted from them to treat many different minor diseases. Phytotherapy is also often utilized to support traditional treatment with synthetic drugs. Many plants were used in traditional medicine to treat cows, sheep, poultry, horses and pigs, and these traditions have survived in some areas of the world (Anon 1994, 1996, Bizimana 1994, Viegli et al. 2003).

Phytotherapy is a very ancient practice; medicinal plants or extracts of vegetable origin have been utilized by Asian populations for many centuries as natural remedies for the treatment of several illnesses, while native Americans used *Echinacea* spp. to treat cold and flu symptoms, wounds and snake bites, and to reduce inflammation because of its anti-inflammatory, antibiotic and healing properties (Foster 1995).

Medicinal properties of the plants used in phytotherapy are due to the large amount of active compounds that can be found in the vegetable kingdom. Often, active principles extracted from plants are equivalent to synthetic drugs according to their therapeutic efficacy; for this reason they are utilized in veterinary medicine, mainly as antibacterial, antimycotic, antiparasitic, disinfectants and immunostimulants.

Regarding large animals, phytotherapy is mainly utilized in organic farms to reduce the use of allopathic drugs more and more. For the animal market many of the currently used antimicrobial, feed additive antibacterial, endectocide and anticoccidial drugs are either natural products or synthetics based on natural products (Ruddock 2000). The majority of these natural products are produced from the fermentation broth of microorganisms, though plants have also been an important source of bioactives. There is an increasing public concern regarding the use of pharmaceuticals in the animal industry. Much of this has been as a result of the emergence of drug resistance. A particular area of criticism has been in the use of antibiotics as growth promoters and the associated risk of developing antibiotic resistance in human pathogens (Barton 2000).

In organic farms, not only herbal drugs such as plant extracts and essential oils, but also homeopathic products, nutraceuticals and oligoelements, such as sodium, calcium, phosphorus, magnesium, and sulfur, are considered the main drugs to administer to animals for the treatment of different diseases. Nevertheless, it is possible to use synthetic allopathic drugs only when the previous products are ineffective; in such an eventuality, it is preferable to choose drugs that are metabolized rapidly, with a low environmental impact and less adverse effects on the animals.

Herbal drugs used in human practice are often utilized in pets, in particular by owners who use such remedies for themselves. They are given to companion animals to treat respiratory, skin, urinary, digestive, and cardiovascular affections, and to reduce stress; moreover, they are also used to treat some chronic diseases instead of conventional drugs in order to avoid adverse effects that sometimes could occur as a consequence of a prolonged administration of synthetic drugs. Finally, phytotherapy could represent a useful support to conventional therapies in the case of severe illness (Severino et al. 2008).

It is therefore important to keep in mind that lack of activity in a laboratory-based *in vitro* screening system does not automatically correspond to lack of efficacy of a traditional medication. Many aspects of EVM need to be taken into account, for example methods of preparation and administration of the remedy, as well as management practices to limit the impact of the disease. Orthodox treatments are certainly indispensable in cases such as epidemics of contagious diseases, but for common ailments, for example mild diarrhea, skin diseases, intestinal worms and wounds, ethnoveterinary medicine may function effectively (Martin et al. 2001). Shortcomings of ethnomedicine include seasonal unavailability of plant material, inefficacy or harmfulness of treatments, as well as lack of dosage certainty and standardization of remedies (Martin et al. 2001). Means of overcoming these disadvantages need to be formulated and should be communicated to the users of EVM. The benefits of understanding, evaluating and ultimately integrating EVM into primary animal healthcare are evident.

In this chapter, the current status of information on the ethnoveterinary usage of plants as antibacterial and anthelmintic will be reviewed. Moreover, known adverse effects of some medicinal plants frequently used in veterinary medicine are described.

### **Medicinal Plants Used in Veterinary Practice as Antibacterial**

Many hundreds of plants worldwide are used in traditional medicine as treatments for bacterial infections. Some of these have also been subjected to *in vitro* screening but the efficacy of such herbal medicines has seldom been rigorously tested in controlled clinical trials. Conventional drugs usually provide effective antibiotic therapy for bacterial infections but there is an increasing problem of antibiotic resistance and a continuing need for new solutions. Although natural products are not necessarily safer than synthetic antibiotics, many people prefer to use herbal medicines. For these reasons, many researchers have attempted to find natural materials to replace antibiotics to treat bacterial infections.

While few studies have been carried out to evaluate the therapeutic efficacy of herbal remedies in companion animals, many studies have been found in the literature relating to the use of plants and plant materials in farm animals.

Recently, Kalemba and Kunicka (2003) reviewed the classical methods commonly used for the evaluation of the antibacterial and antifungal activities of essential oils, including the agar diffusion method, the dilution method and the turbidimetric and impedimetric monitoring of microorganism growth in the presence of tested essential oils to draw conclusions about the factors that influence the *in vitro* antimicrobial activity of essential oils and their mechanisms of action. Moreover, they include an overview of the susceptibility of human and food borne bacteria and fungi towards different essential oils and their constituents. The most relevant ones, which include the essential oils of thyme, origanum, mint, cinnamon, salvia and clove, have antimicrobial properties.

Several research articles focus on the potential antibacterial activity of medicinal plants used in ethnoveterinary medicine.

Luseba and co-workers (2007) tested dichloromethane extracts for antibacterial and anti-inflammatory activity in a study appraising the efficacy of South African medicinal plants used in the treatment of wounds and retained placenta in livestock. *Cissus quadrangularis* L. (Vitaceae) stem and *Jatropha zeyheri* Sond. (Euphorbiaceae) root extracts were selectively inhibitory in the anti-inflammatory assay against cyclooxygenase-2 enzyme. The extracts tested were not mutagenic in the Ames test against *Salmonella typhimurium* strain TA98.

In an interesting discussion, Luseba et al. (2007) claimed that although water is traditionally a commonly available solvent to prepare medicinal extracts, the activity of organic extracts do not need to be disregarded. The whole plant is often processed and applied locally for the treatment of wounds in livestock, while mixtures of medicinal plants are given orally making the active compounds more available in other cases such as retained placenta.

The antibacterial activity of essential oils derived from plants such as *Salvia* spp. (Lamiaceae) and clove has been demonstrated against many microorganisms such as *Brucella*, *Salmonella typhimurium*, *E. coli*, *Bacillus cereus* and *Staphylococcus aureus* in several *in vitro* studies (Burt 2004, Horiuchi et al. 2007, Lans et al. 2007, Bouaziz et al. 2009, Motamedi et al. 2010). The antibacterial components in these oils have been identified as phenolic compounds such as carvacrol, eugenol and thymol, perillaldehyde, cinnamaldehyde and cinnamic acid, camphor, alpha-pinene, b-pinene, 1,8-cineole and alpha-tujone (Burt 2004). The oils and their compounds are hydrophobic, which allows them to disturb the structures and membrane of bacterial cells rendering them more permeable and vulnerable (Burt 2004).

Antraquinones are also hydrophobic (Alves et al. 2004). *Mentha piperita* L. (Lamiaceae) oil was more effective against a multiresistant strain of *Shigella sonnei* and *Micrococcus flavus* than oils from other *Mentha* species (McKay and Blumberg 2006).

Emodin, an anthraquinone, is the virucidal agent in *Aloe vera* (L.) Burm. F. (Xanthorrhoeaceae) and *Frangula purshiana* (DC.) Cooper (Rhamnaceae) and also possesses antibacterial properties (Alves et al. 2004).

The antibacterial activity of different extracts of *Eugenia caryophyllata* Thunb. (Myrtaceae) was demonstrated against pathogenic bacteria (Larhsini et al. 2001, Burt and Reinders 2003). Benzoic acid and its derivatives may contribute to antibacterial activity of *Gentiana lutea* L. (Gentianaceae) and *Gentiana punctata* L. (Gentianaceae). Isoorientin was isolated from the EtOAc extract of *Gentiana olivieri* Griseb. (Gentianaceae) and has antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *P. aeruginosa* (Georgieva et al. 2005, Wynn and Fougère 2007).

Crude extracts of leaves of *Rumex nervosus* Vahl. (Polygonaceae) and the root of *Rumex abyssinicus* Jacq. (Polygonaceae) have antibacterial activity against *Streptococcus pyogenes* and *S. aureus*. *Rumex abyssinicus* contains oxalic acid, chrysophanic acid, chrysophanol, emodine and physcion. An acetone:water (7:3) extract obtained from the leaves of *Rumex obtusifolius* L. (Polygonaceae) contains epicatechin (Getie et al. 2003, Spencer et al. 2007).

Members of the Combretaceae family are widely traded in the traditional medicine market in southern Africa. The Combretaceae contains a diversity of known antibacterial compounds (Eloff et al. 2008).

Different extracts of *Aloe barberae* Dyer (Xanthorrhoeaceae) were evaluated for antibacterial activity. All the extracts showed activity against four bacterial strains: *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* (Ndhala et al. 2009).

*Micromeria graeca* (L.) Benth. ex Reichenb. (Lamiaceae) is well known in phytotherapy for its antibacterial activity due to monoterpenes in its essential oil, but the specific anti-inflammatory effect emerging from folk veterinary uses requires further investigations, in view of the fact that flavones (acacetin glycosides)—known for a wide range of pharmacological properties—have recently been isolated from the genus *Micromeria* (Marin et al. 2001).

*Psidium guajava* L. (Myrtaceae) contains three flavonoids with strong antibacterial action: quercetin, its 3-L-4- rabinofuranoside (avicularin) and its 3-L-4- pyranoside (Oliver-Bever 1986). The trunk sap of various *Musa* spp. (Musaceae) is used for burns in different countries such as eastern Nicaragua and India. The plant contains 5-kaempferol with antibacterial properties (Duke 2000).

Bizimenyera et al. (2006) used a serial microplate dilution technique to identify antibacterial activity against *Staphylococcus aureus* (Gram-positive) and *Pseudomonas aeruginosa* (Gram-negative) in organic solvent extracts of *Peltophorum africanum* Sond. (Fabaceae). Pastoralists use extracts of the root and bark to treat stomach ailments such as diarrhea and dysentery in cattle (Bizimenyera et al. 2006), and the detected antibacterial activity, as well as antioxidant efficacy, provides some support to the traditional EVM use against bacterial infections. Masika and Afolayan (2002) tested extracts of three plant species used for livestock disease treatment, namely *Combretum caffrum* (Eckl. & Zeyh.) Kuntz (Combretaceae), *Salix capensis* Thunb. (Salicaceae) and *Schotia latifolia* Jacq. (Caesalpiniaceae), for antibacterial and antifungal activity. They reported some activity against Gram-positive bacteria. Most extracts were not active against Gram-negative bacteria but generally all of them were active against the five test fungi (Masika and Afolayan 2002).

*Gunnera perpensa* L. (Gunneraceae) is a widely used herb for endometritis and retained placenta in cattle, and extracts of the rhizomes were investigated for antibacterial efficacy (McGaw et al. 2005). The relatively weak antibacterial activity of *Gunnera perpensa* extracts against four bacterial species did not appear to be a major factor in the reputed activity of the plant, but its known uterotonic activity was probably largely responsible for such an effect. In a screening procedure of 17 plant species used to treat infectious diseases in cattle, McGaw et al. (2007) used the bacteria recommended for antibacterial testing by the NCCLS (1990), namely *Escherichia coli*, *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Hexane, methanol and water extracts were generally more active against the Gram-positive bacteria, confirming earlier reports of increased susceptibility of these organisms. They reported that a third of the plant extracts screened exhibited MIC values less than 1mg/ml, rationalizing to an extent the use of these plants in EVM. The same plant extracts were also screened for anthelmintic activity.

Following the preliminary screening study showing high levels of antibacterial efficacy in extracts of *Ziziphus mucronata* Willd. (Rhamnaceae) (McGaw et al. 2007), further work was conducted on this plant. Compounds, isolated from leaves of the plant, are 2,3- dihydroxyl-up-20-en-28-oic acid and zizyberanalic acid (Moloto 2004). The first compound demonstrated excellent activity against *Staphylococcus aureus*, promoting claims of the efficacy of a *Ziziphus mucronata* leaf paste in treating bacterial infections in animals and humans.

Medicinal plants used the most in veterinary phytotherapy as antibacterial are listed in Table 12.1.

Table 12.1. Main plants used in veterinary phytotherapy as antibacterial.

Plant	Family	Used parts	Reference
<i>Aloe barbarae</i> Dyer	Xanthorrhoeaceae	Aerial parts	Ndhiala et al. 2009
<i>Aloe vera</i> (L.) Burm. F.	Xanthorrhoeaceae	Aerial parts	Alves et al. 2004
<i>Cissus quadrangularis</i> L.	Vitaceae	Stem	Luseba et al. 2007
<i>Combretum caffrum</i> (Eckl. & Zeyh.) Kuntze	Combretaceae	Aerial parts	Masika and Afolayan 2002
<i>Eugenia caryophyllata</i> Thunb.	Myrtaceae	Aerial parts	Lans et al. 2007, Burt 2004
<i>Frangula purshiana</i> (DC.) Cooper	Rhamnaceae	Aerial parts	Alves et al. 2004
<i>Gentiana lutea</i> L.	Gentianaceae	Root	Georgieva et al. 2005, Wynn and Fougère 2007
<i>Gentiana olivieri</i> Griseb.	Gentianaceae	Root	Georgieva et al. 2005, Wynn and Fougère 2007
<i>Gentiana punctata</i> L.	Gentianaceae	Root	Georgieva et al. 2005, Wynn and Fougère 2007
<i>Gunnera perpensa</i> L.	Gunneraceae	Rhizomes	McGaw et al. 2005
<i>Jatropha zeyheri</i> Sond.	Euphorbiaceae	Root	Luseba et al. 2007
<i>Mentha piperita</i> L.	Lamiaceae	Aerial parts	Alves et al. 2004
<i>Micromeria greca</i> (L.) Bentham ex Reichenb.	Lamiaceae	Aerial parts	Martin et al. 2001
<i>Musa</i> spp.	Musaceae	Trunk	Duke 2000
<i>Peltophorum africanum</i> Sond.	Fabaceae	Root and barks	Bizimenyera et al. 2006
<i>Psidium guajava</i> L.	Myrtaceae	Leaves	Oliver-Bever 1986
<i>Rumex abyssinicus</i> Jacq.	Polygonaceae	Leaves	Spencer et al. 2007, Getie et al. 2003
<i>Rumex nervosus</i> Vahl.	Polygonaceae	Leaves	Spencer et al. 2007, Getie et al. 2003
<i>Rumex obtusifolius</i> L.	Polygonaceae	Leaves	Spencer et al. 2007, Getie et al. 2003
<i>Salix capensis</i> Thunb.	Salicaceae	Aerial parts	Masika and Afolayan 2002
<i>Salvia</i> spp.	Lamiaceae	Aerial parts	Lans et al. 2007, Burt 2004
<i>Schotia latifolia</i> Jacq.	Caesalpinaceae	Aerial parts	Masika and Afolayan 2002
<i>Ziziphus mucronata</i> Willd.	Rhamnaceae	Leaves	McGaw et al. 2007

### Medicinal Plants Used in Veterinary Practice as Anthelmintics

Intestinal nematodes are extremely important pathogens of domestic livestock, especially sheep, goats and cattle. Collectively, they are responsible for severe losses to livestock agriculture throughout the world. It has been calculated that, in the U.K., intestinal worms constitute the most important disease-related cost of farming sheep, being responsible for an estimated annual loss to the industry of £83 millions (Nieuwhof and Bishop 2005). In developing countries, intestinal worm infestations are perceived to be the single most important threat to economic success, as was made dramatically clear in a recent review of the attitudes and concerns of small hold farmers in Africa (Perry et al. 2002).

Intestinal nematodes are also important pathogens of humans, with a range of pathologies and consequences for human health (Bethony et al. 2006). Four species dominate: *Ascaris lumbricoides*, *Trichuris trichiura* and two hookworms *Ancylostoma duodenale* and *Necator americanus* (Horton 2003, Bethony et al. 2006).

The treatment of intestinal nematode infestations in the 21st century is largely through the use of modern synthetic anthelmintics. Three classes of these anthelmintics dominate the market, each mediating its effect through a different mode of action on the target nematodes. Group 1 anthelmintics include the benzimidazoles and these were introduced in the early 1960s for use in livestock but resistance (in this case to thiabendazole) was detected after only 4 yr of usage in the U.S.A. Group 2 anthelmintics, the nicotinic acetylcholine agonists such as pyrantel, levamisole, morantel etc., were introduced in the early 1970s and resistance was detected for the first time in 1977 in Australia. The macrocyclic lactones (e.g., ivermectin), which form group 3 anthelmintics, were first licensed for use in the early 1980s and resistance became apparent again within 7 yr and was first reported in South Africa (Kaplan 2004, Behnke et al. 2008).

Since then, resistance has spread around the world, particularly in species affecting sheep, it is however also a significant problem in the husbandry of horses, especially with respect to the cyathostomins (Little et al. 2003, Kaplan 2004, Kaplan et al. 2004), and is an increasing problem in cattle and pigs (Gerwent et al. 2002, Suarez and Cristel 2007). Of particular concern is the discovery of triple resistant nematodes which cannot be easily controlled by any of the three classes of drugs. This was first detected in South Africa in sheep, and then in Scotland among Angora goat flocks (Coles et al. 1996), but is now known to be more widely distributed (Wrigley et al. 2006).

Although there are signs that novel synthetic drugs are being developed (e.g., nitazoxanide, cyclic depsipeptides, octadepsipeptides such as emodepside, tribendimidine, diketopiperazines such as paraherquamides,



amino-acetonitrile derivatives), no new anthelmintic drugs that operate through a different mode of action to the Class 1, 2 and 3 have become available on the market for the treatment of either livestock or human parasitosis (Geary et al. 1999, Harder et al. 2005, Xiao et al. 2005, Cappello et al. 2006).

Studies from various parts of the world have shown that certain plant species effectively reduce the degree of parasite infestation in sheep and are promising alternatives to conventional anthelmintics (Githiori et al. 2006).

An alternative to synthetic drugs is to exploit naturally-occurring compounds that exist in plants and trees and in their seeds and fruits. Medicinal plants and fruits have been used by indigenous people for centuries as sources of extracts used in the treatment of a variety of disorders, including infectious diseases and those caused by parasites, in livestock and humans (Hammond et al. 1997, Waller et al. 2001, Mueller and Mechler 2005). These are often referred to as ethno-veterinary or ethno-medical remedies, and, in general, they are shunned by traditional, conventional western medicine (Behnke et al. 2008).

The use of ethnoveterinary plant preparations has been documented in different parts of the world (Anon 1994, 1996, Bizimana 1994, Wanyama 1997a, b, Waller et al. 2001). In many developing countries, farmers, herders, pastoralists and occasionally veterinary surgeons use plant or plant products to treat cases of parasitism. The related available evidence mainly concerns gastrointestinal helminths, but there is also evidence for effects on blood parasites and external parasites. In traditional societies a number of plant remedies are described as suitable for each parasitic disease (Githiori et al. 2006). Some of the earliest known medicinal anthelmintic plants include *Carica papaya* L. (Caricaceae), *Ficus* spp. (Moraceae) and *Ananas comosus* (L.) Merr. (Bromeliaceae). Anecdotal reports of their usage for the treatment of worm infestations by the native inhabitants of Panama and South America stretch back to over a century ago (Robbins 1930). Their extracts were shown to be highly effective in clearing the most obstinate of human intestinal worms, *Trichuris trichiura*, in the 1920s (Caldwell and Caldwell 1929) and more effectively than any of the current synthetic drugs (Keiser and Utzinger 2008). Indeed, European doctors used papain and papaya latex for the treatment of worms in the 19th century (Jonxis and Bekins 1953, Stransky and Reyes 1955) but, it was not until the 1930s that they were shown to be actually capable of digesting nematodes (Robbins 1930) and their enzymic basis was discovered (Walti 1938). The active principles are now known to be cysteine proteinases (CP) that occur naturally in various parts of the plant. For example, in pineapple, different combinations of enzymes occur in the stem, and in the fruit (Behnke et al. 2008). The latex of both papaya and figs contains CPs. These plant-derived CPs probably evolved primarily

to defend plants against insect pests (Konno et al. 2004) but possibly also against plant parasitic nematodes, against which they are likewise highly effective (Miller and Sands 1977, Stepek et al. 2007a).

Githiori et al. (2006) and Jackson and Miller (2006) claim that plants with anthelmintic properties typically contain saponins, alkaloids, non-protein amino acids, tannins and other polyphenols, lignins, glycosidesalkaloids, terpenes, lactones, glycosides and phenolic compounds (Table 12.2). Other active anthelmintic compounds include cysteine proteinases which digest the protective cuticle of the rodent gastrointestinal nematode *Heligmosomoides polygyrus* (Stepek et al. 2007b), and anthraquinones which are active against *Schistosoma mansoni* (Dhananjeyan et al. 2005). Rogerio et al. (2003) claim that some flavonoids exert an antiproliferative action on T cells which could modulate lymphocyte activation and IL-5 production during a *Toxocara canis* infestation. The plant evaluation section includes research on those plants that have shown repellency against mosquito species since Jaenson et al. (2005) claim this is an indication that they may also repel *Ixodes ricinus* nymphs; these plants may have potential for study as novel anthelmintics.

*Artemisia absinthium* L. (Asteraceae) is commonly called wormwood and is locally known as "Tethwen" in the Kashmir valley, India. It is used in indigenous systems of medicine as a vermifuge in the treatment of chronic fevers and for inflammation of the liver, as an antispasmodic and antiseptic (Koul 1997). Its essential oil has antimicrobial (Juteau et al. 2003) and antifungal activity (Saban et al. 2005). Chemical analysis of *A. absinthium* has shown that its volatile oil is rich in thujone ( $\alpha$  and  $\beta$ ), which has been earlier reported as an anthelmintic (Meschler and Howlett 1999). In Turkish folk medicine, *A. absinthium* has been used as an antipyretic, antiseptic, anthelmintic, tonic, and diuretic and for the treatment of stomach aches (Baytop 1984). A study was designed to evaluate the *in vitro* and *in vivo* anthelmintic efficacy of crude aqueous and ethanolic extracts of the aerial parts of *A. absinthium* (Tethwen) when compared to a reference drug albendazole against the gastrointestinal (GI) nematodes of sheep (Tariq et al. 2009).

*Artemisia herba-alba* Asso (Asteraceae) contains santonin which has a selective toxic action on the ganglion located in the nerve ring of *Ascaris* spp., but its narrow range of activity does not include *Oxyuris* spp., and cestodes (Waller et al. 2001).

The sulfuric compound in garlic contributes to its anthelmintic effect, and walnut's active compound is naphthoquinone (Githiori et al. 2006). Many polyphenols (hydrolysable tannins, proanthocyanidins, caffeic acid derivatives) reduced the survival of the intracellular, amastigote parasite form of *Leishmania donovani* or *Leishmania major* strains *in vitro*.

Table 12.2. *In vivo* evaluation of plant preparations against mixed GI nematode infestations in ruminants.

Plant	Family	Used parts	Active principles <sup>a</sup>	Host <sup>c</sup>
<i>Adhatoda vesica</i> L.	Acanthaceae	Root	Alkaloids, glycosides	S
<i>Albizia anthelmintica</i> Brong.	Fabaceae	Root, barks	Sesquiterpene, kosotoxins	S
<i>Ananas comosus</i> L. (Merr.)	Bromeliaceae	Leaves	Bromelain	S, B
<i>Annona squamosa</i> L.	Annonaceae	Leaves	Anthraquinone terpenoids	G, B
<i>Azadirachta indica</i> A. Juss	Meliaceae	Seeds	Azadirachtin	S, B
<i>Chenopodium ambrosioides</i> L.	Amaranthaceae	Leaves, seeds	Ascaridole	S
<i>Chrysanthemum cinerariaefolium</i> (Trev.) Vis.	Asteraceae	Flowers	Pyrethrins <sup>b</sup>	S
<i>Caesalpinia crista</i> L.	Fabaceae	Seeds		S
<i>Embelia ribes</i> Burm. f.	Myrsinaceae	Fruits		S
<i>Fumaria parviflora</i> Lam.	Fumariaceae	Whole plant		S
<i>Hagenia abyssinica</i> Willd.	Rosaceae	Fruits	Kosotoxin	G
<i>Hildebrandtia sepulosa</i> Rendle	Convolvulaceae	Root, barks		S
<i>Khaya anthotheca</i> (Walt.) C. DC.	Meliaceae	Barks		B
<i>Khaya senegalensis</i> (Destr.) A. Juss.	Meliaceae	Barks		S
<i>Maerua edulis</i> (Gilg. & Ben.) De Wolf	Capparaceae	Tuber		S
<i>Myrsine africana</i> L.	Myrsinaceae	Fruits	Benzoquinone	S
<i>Naucllea latifolia</i> Sm.	Rubiaceae	Barks	Resin, tannins, alkaloids	S
<i>Solanum aculeastrum</i> Dunal	Solanaceae	Root		B
<i>Terminalia glaucescens</i> Planch. ex Benth.	Combretaceae	Barks	Anthraquinone	B
<i>Vernonia anthelmintica</i> Willd.	Asteraceae	Seeds		S
<i>Vernonia amygdalina</i> Delile	Asteraceae	Leaves		B

<sup>a</sup>Where specified.<sup>b</sup>Active principle(s) evaluated.<sup>c</sup>Host (if specified): B, bovines, G, goats, S, sheep.

Ethyl alcohol fruit extracts of *Juniperus drupacea* Labill. (Cupressaceae) and *Juniperus oxycedrus* L. (Cupressaceae) have anthelmintic activity but aqueous fruit and leaf extracts are not very effective (Kozan et al. 2006). Egualé et al. (2007) speculated that the better activity of hydroalcoholic versus aqueous extracts in his study of the anthelmintic activity of *Coriandrum sativum* L. (Apiaceae) against *Haemonchus contortus* in sheep is due to easier transcuticular absorption of the hydroalcoholic extracts into the body of the parasite. He cites as an example the study by Iqbal et al. (2004) in which the methanol extract of *Artemisia brevifolia* Wall. ex DC. (Asteraceae) at a concentration of 25 mg/ml had a significant *in vitro* anthelmintic activity on adult *Haemonchus contortus*, but the aqueous extract did not.

Pumpkin seeds have mid-level validity as an anthelmintic and this use is widespread. The French Cevenol shepherds used herbs during transhumance including dosing *Cucurbita maxima* Duchesne (Cucurbitaceae) seeds to purge their herd dogs of coenurosis (Martin et al. 2001). *Gentiana lutea* has mid-level validity as an anthelmintic and is used as such in the Ubaye Valley of France's Alpes de Haute Provence (Martin et al. 2001). *Ruta graveolens* L. (Rutaceae) and *Salvia officinalis* L. (Lamiaceae) formed part of a multi-plant remedy used by 17th century blacksmiths in Luxemburg for internal inflammations in animals (Martin et al. 2001).

*Lippia sidoides* Cham (Verbenaceae) is used in Brazilian folk medicine to treat gastrointestinal disorders (Craveiro et al. 1977, Barraca 1999) and is very common in northeast Brazil (Matos 2002). *L. sidoides* essential oil (LsEO) have been investigated regarding their anthelmintic properties against *Haemonchus contortus* eggs and larvae (Camurça-Vasconcelos et al. 2007, 2008).

In the Waterman et al. (2010) study, the organic and aqueous extracts of 17 plant species used in sub-Saharan African traditional medicine were screened for anthelmintic activity. Twelve of these plants exhibited significant evidence of activity against a levamisole resistant strain of *Caenorhabditis elegans*, providing some validation for their traditional use; however, further studies are needed to determine activity against specific parasitic species (Geary and Thompson 2001). These studies may result in active compounds with different mechanisms of action. The use of these active compounds or the plant material itself could be used as a supplement to current clinical treatments in hopes of preventing resistance. Plants showing no evidence of activity may be further investigated because many crude extracts may show activity at high concentrations (Ibrahim 1992). Moreover, the concentration of compounds can vary depending on the plant part used. Certainly, several potential leads to new anthelmintics have been discovered (Waterman et al. 2010).

A number of plants with denoted anthelmintic properties have also been included in the British pharmacopoeia (British Veterinary Codex 1953, 1965). For example, oil of *Chenopodium* that derives from *Chenopodium ambrosioides* L. (Amaranthaceae), was used for many years in the UK to treat nematode parasite infestations (*Strongylus*, *Parascaris* and *Ascaris* spp.) in monogastric animals including humans (Gibson 1965). Also leaves and dried flowers have been used as an anthelmintic since the early 1900s (Guarrera 1999). *Chenopodium* is still used to treat worm infections in Latin America. In addition, male fern *Dryopteris filix-mas* (L.) Schott (Dryopteridaceae) and *Artemisia* spp. plants have been used against cestodes such as *Moniezia* spp., and nematodes, such as *Ascaridia* spp., in ruminants and poultry respectively (British Veterinary Codex 1965). Recent surveys in developing countries have identified many plants that are intended and have the potential to be used as anthelmintics *in vivo* (Githiori et al. 2006). However, the majority of evidence reported in ethnoveterinary sources is in the form of observations, rather than from controlled studies (Hammond et al. 1997).

Despite ample evidence of anti-parasitic properties of several plants or plant products, there is still a need to provide validated experimental data of biologically meaningful reductions in infestation levels to support the view that plants may play a direct role in the sustainable control of helminth infestations in farming situations. Plant products that have shown high activity against nematode parasites *in vitro* need to be evaluated and tested in ruminant hosts.

However, plants with moderate anthelmintic activity should still be considered; may be not as a unique alternative to anthelmintic drugs, but as part of an integrated approach specifically designed to achieve sustainable parasite control in ruminant production systems.

### **Toxicological Aspects of Medicinal Plants**

Adverse reactions, often completely unknown to people who use herbal drugs, have been reported for many medicinal plants, although these are well known for their efficacy (Abebe 2002, Means 2002). In fact, the opinion that medicinal plants are mostly harmless ("*natural = safe*") is widespread, not only in the normal population using phytotherapy, but also in practitioners working in this field. As a result, medicinal plants are often used in self-medication without consulting a doctor. Sometimes, many people who use herbal drugs for themselves also administer such products to their pets without the prescription of a veterinarian. These habits increase the risk of adverse reactions, such as allergy. Drug interactions, although infrequent, can also occur between herbal drugs and synthetic ones or with concomitantly used herbal therapies. Other specific contraindications could be represented by pre-existing pathologies (for example, peptic ulcer, kidney

and hepatic failure) or surgery that could increase the risk of adverse effects by modification of the kinetics of the active principles. Finally, quality is very important for the safety of herbal drugs; in fact, adverse effects could occur because of the presence of residues of environmental pollutants (heavy metals, mycotoxins, radionuclides) in the phytotherapeutic product (Severino 2005).

In 1997, the American Herbal Products Association (AHPA) proposed a classification of medicinal plants into four classes: the first class includes plants with a large margin of safety, such as calendula, hawthorn, euphrasy, lavender, taraxacum, nettle, valerian, chamomile, echinacea, peppermint, lemonbalm, and thistle; the second class, further subdivided into four subclasses, includes herbs for which some limitation exists, such as artemisia, St. John's wort, sage, liquorice; the third class includes herbs for which scientific evidence exists to make the supervision of a specialized practitioner necessary; finally, the fourth class includes all herbs not yet classified in the previous classes (Guffin et al. 1997).

Many studies can be found in the literature regarding the possible interactions (in relation to botanical species, dose, treatment) between the active principles of a specific phytocomplex and synthetic drugs (Miller 1988, Abebe 2002). Garlic, reducing the production of thromboxane B<sub>2</sub>, could increase the fibrinolytic activity and induce an antiplatelet effect (Harenberg et al. 1988). For this reason, the contemporary administration of garlic and anticoagulants is discouraged. Oxidative damage in the erythrocytes with formation of Heinz bodies and eccentrocytes appeared in dogs after the administration of garlic extract (1.25 ml/kg body weight) for 7 d (Lee et al. 2000). Additionally, horses fed freeze dried garlic at 0.4 g/kg per day showed Heinz bodies anemia (Pearson et al. 2005). Liquorice induced an increase of serum levels of corticosteroids (Tamura 1979) and caused a reduction of circulating concentrations of salicylates. It has also been reported in the literature that the effects of immunosuppressant drugs could be antagonized by plants with immunostimulant activities, such as echinacea, astragalus and liquorice (Poppenga 2001). Some species of echinacea contain pyrrole alkaloids that increase the risk of hepatic toxicity inducing the depletion of glutathione, particularly in patients treated with paracetamol (Abebe 2002). Therefore, in cases of co-administration, it is necessary to monitor possible signs of hepatotoxicity in the patients (Miller 1988). The American Society for the Prevention of Cruelty to Animals (ASPCA) recorded 45 calls from 1992 to 2000 for accidental ingestion of drugs containing *Echinacea* spp. in pets: a few animals showed symptoms, including vomiting, sialorrhea, and erythema.

The oil obtained from *Mentha piperita* is currently used in veterinary medicine as a flea repellent. Peppermint oil is composed primarily of menthol and menthone; other minor constituents include pulegone,

menthofuran and limonene. *In vivo* studies showed that pulegone is hepatotoxic for rabbits and is able to induce lesions in the cerebellum of rats at a dose of 200 mg/kg body weight (Nair 2001). Moreover, Sudekun et al. (1992) found that pennyroyal, an oil derived from *Mentha pulegium* L. (Lamiaceae) and *Hedeoma pulegoides* (L.) Pers. (Lamiaceae) that contains pulegone, was associated with toxic effects (vomiting, diarrhea, hemoptysis and hepistaxis) in a dog treated for fleas. The dog died within 48 hr of treatment.

Ooms et al. (2001) described the clinical signs following the ingestion of an herbal supplement containing guarana and ma huang (*Ephedra* spp.) in 47 dogs. Most dogs (83%) developed signs of toxicosis (hyperactivity, tremors, seizures, behavior changes, vomiting, tachycardia, hyperthermia) and 17% of intoxicated dogs died. Estimated doses of guarana and ma huang ranged from 4.4 to 296.2 mg/kg body weight and 1.3 to 88.9 mg/kg body weight, respectively.

Wormwood (*Artemisia absinthium*) could be dangerous for domestic animals, particularly in ruminants where it is used for the treatment of gastrointestinal nematodes (Tariq et al. 2009). An *in vivo* study showed that the intravenous injection of thujone, a toxic compound found in wormwood, induces convulsion (40 mg/kg body weight) and death (120 mg/kg body weight) in rats (Poppenga 2001).

Infusion of *Rubus idaeus* L. (Rosaceae) leaf is sometimes used for pregnancy support, postpartum supplement and to tone uterine muscles in companion animals (Lans et al. 2009). An *in vivo* study carried out by Johnson et al. (2009) to evaluate the consequences of the administration of raspberry leaf to Wistar rats (10 mg/kg per day until parturition) revealed that this remedy was associated with altered reproductive development and functions (increased gestation length, accelerated reproductive development, time to vaginal opening and lower birth weight) in the offspring.

## Conclusions

In recent years, the use of herbal drugs in veterinary practice particularly as antibacterial and antihelmintic remedies is increasing all over the world, not only in developing countries where ethnoveterinary medicine plays an important role in animal production and often becomes the only available means for farmers to treat animal affections.

Many ethnobotanical studies have been carried out and there is evidence that some plants used in folk veterinary medicine contain active compounds that may explain their popular use. Nevertheless, despite many anecdotal reports of the efficacy of herbal remedies, most of them have never been proven effective in domestic animals. It is necessary to undertake scientific studies and clinical trials to achieve a validation and

standardization. People should be informed that the use of herbal drugs in domestic animals does not imply the absence of risks, particularly if they are administered simultaneously with synthetic drugs or when plants for which scientific evidence able to justify their therapeutic use does not exist or in the case of utilizing unsafe herbs. Also, the consumption of marked herbal products may represent either a risk or a lack of therapeutic efficacy because the content may be uncertain. Scientific validation of therapeutic effects and the evaluation of the possible side effects of plant products and drug interactions in domestic animals are necessary prior to the adoption of such remedies as alternative therapeutic methods in clinical practice.

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