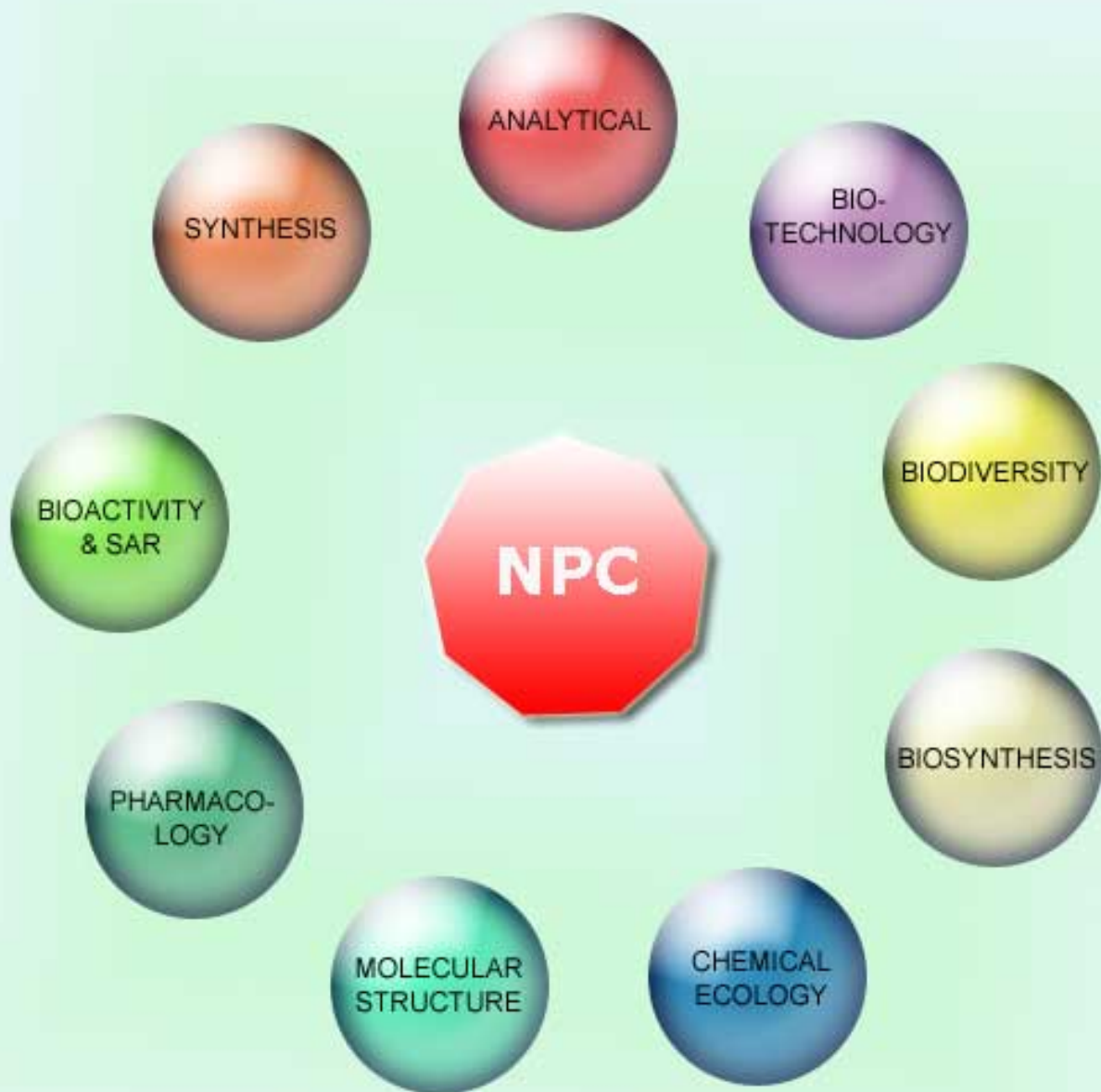


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Professor Francesco De Simone
on the Occasion of his 72nd Birthday**

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Pharmaco-Toxicological Aspects of Herbal Drugs Used in Domestic Animals

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Herbal drugs are more and more used both in human and veterinary medicine to mitigate and prevent minor diseases and to support conventional medicine using allopathic drugs. Nevertheless, 'natural product' does not mean lack of adverse effects, and many people and veterinarians do not know enough about the adverse reactions that can occur following the administration of such drugs in domestic animals. Moreover, herbal products can interact with each other when administered concomitantly or can agonize or antagonize the effects of synthetic drugs administered as primary therapy. The use of non-conventional medicines (NCM) should be considered as a veterinary practise. In this paper, the herbal drugs most utilized in domestic animals, both pets and large animals, are reviewed, as their use is increasing, despite the prejudices of the academic world and some of the adverse effects and interactions that can occur in domestic animals.

Keywords: phytotherapy, adverse reactions, domestic animals, dog, cat.

Introduction

In recent years, the use of non-conventional medicines (NCMs) in humans has been increasing all over Europe, particularly in the United Kingdom, France, Germany and Switzerland. It is estimated that from 70 to 80 per cent of the world's population uses NCM, such as phytotherapy, homeopathy, acupuncture and homotoxicology, to treat several diseases [1]. The number of both doctors and veterinarians using NCM is increasing in Italy too; moreover, the number of people who request for either themselves or their pets such practices is higher and higher.

Phytotherapy represents one of the most used NCMs 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.

Phytotherapy is a very ancient practice; medical 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 [2].

Medicinal plants used in veterinary practice

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 (Table 1).

According to Viegi *et al.* [3], who carried out a veterinary ethno-botanical study in Italy, large animals (cattle, horses, sheep, goats and pigs) represent 70.5% of domestic animals treated with herbal remedies in Italy, followed by poultry (9.1%), dogs (5.3%) and rabbits (4.3%).

Table 1: Main plants used in veterinary phytotherapy.

Scientific name	Used parts	Use	Species	Reference
<i>Allium sativum</i>	Cloves	Endoparasites	P; LA	6
<i>Aloe vera</i>	Latex	Skin diseases; Gastrointestinal diseases	LA	43
<i>Arctostaphylos uva-ursi</i>	Leaves	Urinary diseases	P	44
<i>Artemisia spp.</i>	Aerial parts	Gastrointestinal diseases; Endoparasites	P; LA	6 ; 23
<i>Avena sativa</i>	Aerial parts	Mastitis	LA	3
<i>Calendula officinalis</i>	Leaves; Flowers	Wounds; Gingivitis	P; LA	45
<i>Capsella bursa pastoris</i>	Aerial parts	Hemorrhages, Reproductive disorders	LA	3
<i>Carica papaya</i>	Seeds; Latex	Endoparasites	P; LA	25; 46
<i>Cichorium intybus</i>	Aerial parts	Endoparasites	LA	26
<i>Crataegus oxyacantha</i>	Leaves; Flowers	Cardiotonic	P; LA	47
<i>Cucurbita pepo</i>	Seeds	Endoparasites	P	6
<i>Cynara scolymus</i>	Leaves	Hepatic diseases; Gastrointestinal spasms	P	48
<i>Dorycnium spp.</i>	Aerial parts	Endoparasites	LA	20
<i>Echinacea spp.</i>	Root; Aerial parts	Immunostimulant; Wounds	P; LA	9
<i>Eucalyptus globulus</i>	Leaves; Essential oil	Ectoparasites; Respiratory diseases	P	49
<i>Euphrasia officinalis</i>	Aerial parts	Eye affection	P	6
<i>Genziana lutea</i>	Root	Gastrointestinal diseases	P	6
<i>Glycyrrhiza glabra</i>	Root	Gastrointestinal diseases; Otitis	P	10
<i>Gossypium spp.</i>	Leaves	Endoparasites	P	46
<i>Hedera helix</i>	Leaves	Placental retention	LA	3
<i>Hypericum perforatum</i>	Flowers	Wounds	LA	3
<i>Juniperus communis</i>	Aerial parts; Oil	Skin diseases; Ectoparasites	P	10
<i>Lavandula officinalis</i>	Essential oil; Stems	Ectoparasites; Wounds	LA	10
<i>Lotus corniculatus</i>	Aerial parts	Endoparasites	LA	26
<i>Malva sylvestris</i>	Aerial parts	Immunomodulation; Respiratory diseases	P; LA	50
<i>Matricaria chamomilla</i>	Flowers	Eye Inflammation; Ear problems	P	12
<i>Melissa officinalis</i>	Leaves	Anxiety; Stress	P; LA	14
<i>Mentha piperita</i> and <i>M. cardifolia</i>	Leaves; Essential oil	Ectoparasites and Endoparasites	P; LA	51
<i>Onobrychis viciifolia</i>	Aerial parts	Endoparasites	LA	19
<i>Passiflora incarnata</i>	Aerial parts	Anxiety; Hormonal imbalance	P ; LA	52
<i>Plantago major</i>	Leaves	Gastrointestinal diseases; Wounds	P; LA	53
<i>Rosa canina</i>	Hip	Inflammation	P	54
<i>Ruta graveolens</i>	Leaves	Ectoparasites	LA	43
<i>Salvia officinalis</i>	Leaves; Flowers	Endoparasites; Dehydration	P; LA	6
<i>Silybum marianum</i>	Fruits	Hepatic diseases	P	55
<i>Taraxacum officinalis</i>	Root; Leaves	Gastrointestinal diseases	P; LA	6
<i>Thymus vulgaris</i>	Flowers	Respiratory and gastrointestinal diseases	P	46
<i>Tilia cordata</i>	Flowers	Respiratory diseases	P	46
<i>Urtica dioica</i>	Seeds	Endoparasites; Diarrhea	LA	43
<i>Valeriana officinalis</i>	Root	Analgesic; Stress	P; LA	14
<i>Zingiber officinale</i>	Rhizomes	Vomiting	P	7

Table legend: P, pets; LA, large animals.

Table 2: Adverse reactions of some medicinal plants and plant products in domestic animals.

Scientific name	Adverse effects	Reference
<i>Allium sativum</i>	Antiplatelet effect; Hematologic disorders	35; 36
<i>Artemisia absinthum</i>	Convulsions	38
<i>Echinacea spp.</i>	Hepatotoxicity	29
<i>Ephedra spp.</i>	Hyperactivity, tremors, seizures, behaviour changes, vomiting, tachycardia, hyperthermia	41
<i>Juniperus sabina</i>	Gastrointestinal and respiratory disorders; haemorrhages	11
<i>Mentha piperita</i>	Hepatotoxicity	39
<i>Rubus idaeus</i>	Reproductive disorders	42

Regarding the large animals, phytotherapy is mainly utilized in the organic farms to reduce more and more the use of allopathic drugs. In the organic farms, in fact, 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 sulphur 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 eventuality, it is necessary to prefer drugs that are

metabolized rapidly, with a low environmental impact and less adverse effects in the animal organism [4].

Herbal drugs usually used in human practice are often utilized in pets, in particular by owners that used such remedies for themselves. They are given to companion animals to treat respiratory, skin, urinary, digestive, and cardiovascular affections, and to reduce stress (Table 1); 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 [5].

Although the utilizing of phytotherapeutic products is increasing in companion animals, there are few studies and clinical trials reported in the literature regarding the therapeutic use of phytomedicine in pets. We collected some information by local veterinarians and reported some examples of plants and plant products used in the clinical practice for the treatment of different minor diseases (unpublished data). Mother tincture obtained from *Calendula officinalis*, *Centella asiatica* and *Commiphora myrrha* can be useful in the case of gingivitis; *Euphrasia officinalis* is commonly used in the treatment of conjunctivitis. Camomile infusion, carrot juice and a 10% rice decoction are often used to treat diarrhea in pets, while thyme (*Thymus vulgaris*) essential oil (3 drops body weight until remission) or syrup (2 teaspoons 3 times per day until remission) are prescribed for the treatment of cough in both dogs and cats. Finally, lemon-balm (*Melissa officinalis*), valeriana (*Valeriana officinalis*) and hawthorn (*Crataegus oxyacantha*) mother tincture (1 drop/kg body weight 2-3 times per day) are often utilized for the treatment of anxiety, to reduce stress and control behavioral or psychological problems in pets.

Lans and colleagues [6] claim that an infusion of peppermint (*Mentha piperita*) and lemon-balm (*Melissa officinalis*) administered orally to dogs for 2 days is useful to treat stomach and intestinal illness; while *Aloe vera* juice (3 mL orally), made by pulverizing the leaf gel in water, represents an effective remedy for vomiting and irritation. An *in vivo* study revealed that the acetone and ethanolic extracts of ginger (*Zingiber officinale*) exerted a significant antiemetic effect in dogs treated with doses of 100 and 200 mg/kg orally, respectively [7]. These results have been recently confirmed by Lans *et al.* [8], who showed that ginger infusion can be administered to pregnant dogs to treat nausea and vomiting.

Significant reductions in the severity and resolution of clinical symptoms, such as clear nasal secretions, enlargement of lymph nodes, dry cough, dyspnea and dry lung sounds, are evident after 4 weeks of treatment with *Echinacea* powder, suggesting this preparation as an alternative remedy for canine upper respiratory tract infections [9].

Many plants are used in domestic animals for their anti-parasitic activity. A spray made with one to five drops (0.25 mL) of essential oil of juniper (*Juniperus communis*) and water represents an effective flea repellent to be used for topical treatment of these parasites in dogs and cats [10], although this plant could be dangerous for domestic animals, if ingested [11]. An *in vitro* study revealed that a 10% decoction of dried flower heads of *Matricaria chamomilla* showed 100% acaricidal activity when tested against the mite *Psoroptes cuniculi*, one of the agents responsible for otoacariasis in domestic animals. For this reason, chamomile is suggested for ear problems in pets [12].

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. A lot of plants, such as *Brassica oleracea*, *Avena sativa*, *Anagallis arvensis*, *Linum usitatissimum*, *Scrophularia canina* and *Buxus sempervirens* are often used by farmers in many regions of Italy to either treat or prevent mastitis in cattle because of their anti-inflammatory and emollient properties [3]. An *in vivo* study showed that *Echinacea* extracts administered to horses for 42 days not only enhanced the immune system (increased phagocytic ability of isolated neutrophils, boosted peripheral lymphocyte counts and stimulated neutrophil migration from peripheral circulation into the tissues), but also improved the quality of blood by increasing hemoglobin levels and the number of erythrocytes. Therefore, considering the following effects on oxygen transport cells, *Echinacea* spp. could be considered to improve parameters of exercise physiology and performance [13].

Peeters *et al.* [14] suggested sedative and antianxiety effects of a commercial herbal product containing *Valeriana officinalis* and *Passiflora incarnata* in pigs during transport stimulation. In particular, it was found that the administration of 2.5 g/L drinking water of the herbal product for two days resulted in significantly smaller increases in some heart parameters (minimum heart rate; ventricular ectopic beats; ST elevation) during and after stress evocation compared with the control group.

Many plants are used to alleviate anxiety in domestic animals, especially in horses, such as leaves of magnolia (*Magnolia acuminata*) and flowers of passion flower (*Passiflora incarnata*). Alternatively,

lavender (*Lavandula officinalis*) infusion or tincture was given in water or placed on the feed. For nervousness and restlessness, flowers of chamomile (*Matricaria recutita*, *M. chamomilla*) were added to the feedstuffs. One or two teaspoons of valerian (*Valeriana officinalis*) ground root was given to horses that froze in stressful situations. In addition, one teaspoon of powdered valerian, hops (*Humulus lupulus*) and skullcap (*Scutellaria lateriflora*) was put into the feed, twice a day [15].

Most of the studies found in the literature focus on the anti-parasitic effects of different plants, such as *Allium sativum*, *Anethum graveolens*, *Eucalyptus globulus*, *Mentha piperita*, *Lavandula officinalis* and forages in livestock, especially in ruminants [16-21]. Such effects seem to be due to essential oil, secondary metabolites and other active substances such as terpenes, alkaloids, glycosides and tannins contained in the medicinal plants [22].

A number of medicinal plants, plant extracts and other products of vegetable origin used for the treatment of parasitism in domestic animals have been studied and reviewed. *Artemisia absinthium* extracts (2 g/kg body weight orally) represent an effective natural anthelmintic agent for the treatment of gastrointestinal nematodes of sheep causing a significant reduction in fecal egg counts [23]. The active principle is santonin, a sesquiterpene lactone, which has a selective toxic action, particularly against nematodes [24]. The oral administration of 8 g/kg body weight of papaya latex (*Carica papaya*) to pigs naturally infested with *Ascaris suum* caused a reduction of parasitic burden by up to 100% seven days after the treatment [25]. Finally, some forages such as sulla (*Hedysarum coronarium*), chicory (*Chicorium intybus*), alfalfa (*Medicago sativa*), and lotus major (*Lotus pedunculatus*) exert anti-parasitic properties, which are likely to be related to the content of tannins and other active secondary metabolites [21, 22]. In particular, Marley *et al.* [26] showed that lambs naturally infected with helminth parasites had a lower parasitic burden after grazing birdsfoot trefoil (*Lotus corniculatus*) and chicory for 5 weeks than sheep grazing other forages (*Lolium perenne*/*Trifolium repens*).

Nevertheless, some studies showed no significant differences in parasite levels between animals fed with forages supposed to have anti-parasite properties and the control group [27; 28]. However, it is very important not to exceed a tolerable daily intake

because many of the active principles contained in some medicinal plants could be toxic to domestic animals, in particular for grazing herbivores that can ingest large amount of vegetables. Moreover, some substances contained in plants and forages can act as antinutritional factors and reduce the absorption of nutrients with consequent loss of body weight and reduction of food intake and performances [11].

Toxicological aspects of medicinal plants

Adverse reactions, often completely un-known to people that use herbal drugs, have been reported for many medicinal plants, although these are well known for their efficacy (Table 2) [29, 30]. 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 that 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, the 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 [31].

In 1997, the American Herbal Products Association (AHPA) proposed a classification of the medicinal plants into 4 classes: the first class includes plants with a large margin of safety, such as calendula, hawthorn, euphrasy, lavender, taraxacum, nettle, valerian, camomile, echinacea, peppermint, lemon-balm, 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 necessary the supervision of a specialized practitioner; finally, the fourth class includes all herbs not yet classified in the previous classes [32].

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 [29, 33]. Garlic, reducing the production of thromboxane B₂, could increase the fibrinolytic activity and induce an antiplatelet effect [34]. 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 days [35]. Additionally, horses fed freeze dried garlic at 0.4 g/kg per day showed Heinz bodies anemia [36]. Liquorice induced an increase of serum levels of corticosteroids [37] 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 [38]. 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 [29]. Therefore, in cases of co-administration, it is necessary to monitor possible signs of hepatotoxicity in the patients [33]. 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 [39]. Moreover, Sudekun *et al.* [40] found that pennyroyal, an oil derived from *Mentha pulegium* and *Hedeoma pulegoides* that contains pulegone, was associated with toxic effects (vomiting, diarrhea, hemoptysis and hepistaxis) in a dog treated for fleas. The dog died within 48 hours of treatment.

Ooms *et al.* [41] described the clinical signs following the ingestion of a 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 [23]. 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 [38].

Infusion of raspberry (*Rubus idaeus*) leaf is sometimes used for pregnancy support, postpartum supplement and to tone uterine muscles in companion animals [8]. An *in vivo* study carried out by Johnson *et al.* [42] 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, 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 case of utilizing unsafe herbs. Also, the consumption of marked herbal products could represent either a risk or a lack of therapeutic efficacy because the content could 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.

Herbal drugs like allopathic drugs should be prescribed by a specialized practitioner; the National

Federation of the Orders of Italian Veterinarians (F.N.O.V.I.) asserted in 2005 that the use of NCM has to be considered a veterinary practise.

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