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Pharmacological and clinical approach to plant based complementary health products in lower urinary system diseases in cats and dogs

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ABSTRACT

Medicinal plants, which are widely used in the treatment of many diseases in folk medicine, are alternative treatment approaches that allow to overcome the limitations of modern treatments such as high treatment costs and difficulty in accessing health services. In addition to their traditional uses, the World Health Organization (WHO) also recommends the use of medicinal plants as alternative applications, especially in countries where have limited access to modern medical facilities. Limitations on the methods used in the treatment of lower urinary tract diseases such as urinary tract infection and urolithiasis in both human and veterinary practice (high treatment cost, low tolerability, development of antibacterial resistance, etc.) have brought the use of natural products of herbal origin within the scope of supportive/complementary treatment approaches. Although the mechanism of action of medicinal plants in the treatment of lower urinary tract diseases is not clearly known, studies have shown that they increase the glomerular filtration rate; and they can be complementary alternatives to conventional treatment due to their anti-lithogenic, antibacterial, antioxidant and anti-inflammatory activities. Patients that referred to with one or more of the symptoms of urinary system diseases such as polyuria, pollakiuria, dysuria, stranguria, anuria, hematuria, urinary incontinence constitute the case group of one of the first three systemic diseases most frequently brought to the clinic. Failure to intervene in the diseases shaped in the lower urinary system in a timely manner causes negative consequences such as the disease becoming chronic, the progression of the disease to the upper urinary system in progressive cases, and a decrease in the quality of life. Complementary products used in addition to medical treatment are sometimes used for prophylactic purposes. In this context, many supplements have been prescribed for different diseases in small animal practice in recent years. In this review, it is aimed to convey current developments about medicinal plants, which are used effectively within the scope of supportive treatment practices in lower urinary system diseases of cats and dogs, to veterinary clinical practice.

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Introduction

Plants and herbal materials (phytopharmaceuticals) are increasingly being used by veterinarians and animal owners to prevent and treat animal diseases (Altınok Yipel and Yipel, 2014). Since the development of chemistry, plants and plant-derived materials have largely been replaced by synthetic and semi-synthetic substances in the treatment of human and animal diseases. However with the emergence of side effects associated with conventional drugs, the use of plants and herbal substances has become increasingly popular at human and animal medicine in recent years (Karaoğlan and Özgen, 2011; Raditic, 2015).

It is estimated that more than 80% of drug substances are derived from natural products or are developed from natural compounds, such as antibiotics, cardiovascular drugs, immunosuppressive

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antibiotics, cardiovascular drugs, immunosuppressive drugs, and anticancer agents (Raditic, 2015). Plant-based therapy has a number of advantages, including low cost, fewer side effects, easy accessibility, environmental friendliness. In addition, they also have disadvantages, such as inaccuracies in plant identification, difficulties in dosing, inadequate written records, insufficient scientific studies, and low hygiene standards (Altınok Yipel and Yipel, 2014). Research on plants examines the chemical composition, the clinical and therapeutic effects, but little is known about their toxicological properties. The use of herbal products outside of physician control has been associated with side effects such as direct toxicity, contamination, and drug interactions, which may induce death (Peixoto et al., 2010). Biological activities of medicinal plants should be evaluated in scientific studies in order to determine the effects and toxicities of these plants (Peixoto et al., 2010).

As a result of their antimicrobial, anti-inflammatory and diuretic effects, medicinal plants play an important role in the treatment and/or prevention of diseases such as lower urinary tract infections (UTIs), recurrent lower urinary tract infections (RUTIs), and urolithiasis. Currently, the World Health Organization (WHO) reports that natural products are increasingly used in developed countries to prevent and treat diseases in humans and animals (Bag et al., 2008; Bernal et al., 2011).

Turkey has the richest flora in the Middle East in terms of species rate and diversity of all the countries in Europe with 2891 endemic plants. The Mediterranean (South) region of Turkey has the highest number of endemic species and varieties, with 497 subspecies and 390 varieties (Kendir and Güvenç, 2010). Despite the fact that Turkey has a very diverse flora, studies concerning the use of medicinal plants in lower urinary tract diseases in cats and dogs are relatively limited. The purpose of this article is to provide information about medicinal plants that are effective in supporting treatment protocols for lower urinary system diseases in cats and dogs.

An overview of lower urinary system infections in veterinary medicine

Veterinary practitioners often treat simple lower urinary tract disorders (LUTDs) such as bacterial urinary tract infections (UTIs) using conventional methods with good results. Most simple infections will resolve after two weeks of oral antibiotic treatment, however persistent or recurrent UTIs caused by resistant bacteria may be difficult to treat. These infections are caused by a breach in the host's defense mechanisms, which allows virulent microbes to adhere, multiply, and remain in the urinary tract for a prolonged period of time. An estimated 14% of all dogs in their lifetime are affected by bacterial urinary tract infections, which are more prevalent in female dogs. It is more common in cats over 10 years old, and the incidence increases with age. It is usually ineffective to repeat courses of antibiotics in these patients to maintain long-term urinary bladder sterility, and it is therefore necessary to develop an antibiotic-free treatment strategy to prevent urinary bladder infection. Dogs and cats are susceptible to the same bacteria that cause UTIs; *E. coli* accounts for more than half of all positive urine cultures (Litster et al., 2011; Thompson et al., 2011). Based on a literature review, evidence was developed for the usefulness of non-antimicrobial therapies of urinary tract infections in veterinary medicine using canine/feline cells in vitro, human cells *in vivo*, and *in vitro* cell lines (Raditic, 2015). In this study, its aimed to evaluate the plants for low urinary tract disorders in cats and dogs and to give information about the use of herbal complementary products to veterinary practitioners.

Cranberry (*Vaccinium macrocarpon*)

In vitro and *in vivo* studies have demonstrated the effectiveness of cranberry products in treating/ preventing urinary tract infections and kidney stones (Kingwatanakul, 1996; Terris, 2001; McHarg, 2003). Initially, it was believed that cranberry juice inhibited bacteria growth through acidification of the urine. However, recent studies have begun to focus on the effects of cranberry juice on the inhibition of bacterial adhesion. An important step in the development of urinary tract infections is the adhesion of bacteria to mucosal surfaces (Reid, 1987). A fimbriae in the bacterial cell wall facilitates the attachment of adhesins produced by bacteria to specific receptors on host uroepithelial cells (Beachey, 1981). Cranberry inhibits the adhesion of uropathogens of type I and P fimbriae (e.g., uropathogenic *E. coli*) to the uroepithelium. In addition, it prevents the spread of infections by preventing colonization. Various components in cranberry can also alter the adhesion ability of P-derived uropathogenic bacteria. As well, cranberry can affect bacterial adhesion by changing the cell surface properties of bacteria and causing a positive shift in the distribution of zeta potentials (electric potentials across the interface of solids and liquids). Cranberry juice alters the conformation of P-fimbriae *E. coli* surface macromolecules, particularly reducing their length and density. The cranberry is also believed to reduce fimbrial activity at the genetic level. It has been demonstrated in a study that proanthocyanidins extracted from cranberries inhibit the adhesion of *E. coli* with P-fimbriae to uroepithelial

cell surfaces, suggesting that proanthocyanidins might contribute to the prevention of urinary tract infections (Howell, 1998). Additionally, cranberry juice cocktail has been shown to provide anti-adherence activity against gram-negative rods, including *Klebsiella,* E*nterobacter*, *Pseudomonas* and *Proteus* species (Schmidt, 1988).

The anti-adherence activity of a cranberry product was examined both *in vitro* and *ex vivo* using mannose -resistant hemagglutination urinalysis in six Beagles. In an in vitro assay, collected urine samples were tested for the ability of P-fimbriated *E. coli* to agglutinate human red blood cells after a daily administration of a cranberry product tablet for three weeks. Hemagglutination activity was observed in control urine. Anti-adhesive activity appeared 3 hours after administration of the cranberry tablet, peaked on day 7, and remained high until day 21. Consequently, the researchers hypothesized that the metabolites found in the urine of 6 healthy dogs were sufficient to reduce the adhesion of Pf E coli and may be useful in preventing E coli-associated UTIs in dogs. It has been reported that a clinical trial on affected dogs indicated the need for further study of this extract (Howell et al., 2010).

Parsley (*Petroselinum crispum*)

Parsley is a potent diuretic that works by inhibiting the activity of Na+/K+/ATPases both in the renal cortex and medulla. This inhibition reduces apical cellular N+ reabsorption, decreases K+ secretion, increases intercellular K+ concentration, and consequently passively inhibits passive K+ across tight junctions. Parsley inhibits the Na+ and K+ pumps, thereby decreasing Na+ and K+ reabsorption, which results in osmotic fluid passage into the lumen and diuresis (Kreydiyyeh, 2002). In an experiment with rats, it was found that after ingestion of parsley seed extract, a greater amount of urine volume was eliminated in 24 hours compared to the control group that drank only water. This provides evidence for the diuretic effect of parsley seed extract (Wynn and Fougère, 2007).

Valerian (*Valeriana officinalis*): Valerian (valerian extract) has soothing and calming properties which are beneficial to cats suffering from FLUTD and feline idiopathic cystitis. Despite the fact that there is little research on pets, one study found that Valerian reduced aggression in cats (Wynn and Fougère, 2007). Another study concluded that approximately 50% of cats responded positively to Valerian (Bol et al., 2017). For maximum therapeutic efficacy, valerian may need to be administered for a period of time ranging from a few days to a few weeks in pets (Wheatley 2005; Wynn and Fougère, 2007). It has been reported that some pets respond to Valerian with hyperactivity, the opposite of the intended sedative and calming effects (Kidd, 2000; Wulff-Tilford and Tilford, 1999; Wynn and Marsden, 2003).

Corn silk (*Zea mays*)

This plant is believed to have diuretic and stone-reducing properties. It has been used to treat cystitis, urethritis, nocturnal enuresis, prostatitis, and especially acute or chronic inflammation of the urinary system (Wren, 1988). A high potassium concentration (2,7%) is thought to be responsible for the diuretic effect observed in animals (Bradley, 1992). Maizenic acid has also been suggested to be active ingredient; it acts as a heart tonic and stimulates diuretic activity (Willard, 1991).

Buchu (*Agathosma betulina*)

It has been reported that it can be used to treat acute cystitis, urethritis, nephritis, prostatitis and inflammation of the urinary bladder (Wren, 1988). The essential oils of the bukko bush are thought to be responsible for the antiseptic properties of the plant in the urinary tract. Monoterpene disophenol is the primary component of essential oils believed to have antibacterial properties. In contrast, Didry et al. (1982) found no significant antibacterial activity of buchu oil. There was very minor activity observed against *E coli*, *Saccharomyces cerevisiae*, and Staphylococcus aureus, suggesting little potential for use as an antimicrobial agent (Lis-Balchin, 2001).

Couch grass (*Agropyron repens*)

Diuretic properties are claimed to be associated with this plant. It has been used for cystitis, urethritis, prostatitis, benign prostatic hypertrophy, renal calculus, lituria, and specifically cystitis with urinary tract irritation or inflammation (Wren, 1988). It contains the ingredient mannitol, an osmotic diuretic that can produce a mild diuretic effect when taken in small amounts. A study conducted in rats with calcium oxalate urolithiasis showed that it had no effect on the main risk factors for the development of this disease (Grases, 1995). Triticum 3% to 8%, which is a polysaccharide related to inulin, and 8% to 10% mucilage are both present in this plant. The antibiotic properties of agropyrene and its oxidation products have been documented by Leung and Foster (1996).

Lavender (*Lavandula officinalis*)

Aqueous extracts of lavender were compared with acetazolamide in order to determine their diuretic properties. A significant decrease in urinary osmolarity and moderate sodium excretion was observed during the peak of the diuretic response when compared to acetazolamide, a synthetic diuretic. With the stability of aldosterone and the absence of correlation with

plasma sodium concentrations, together with the observed clearance of free water, it appears that the increase in diuresis is due to tubular activity (Elhajili, 2001).

Dandelion (*Taraxacum officinalis*)

Dandelion extracts have been shown to induce diuresis in rats and mice after oral administration (Rácz -Kotilla, 1974). Extracts from plants have been found to produce more diuretic effects than root extracts; this effect is comparable to that of furosemide. The administration of leaf or root extracts or purified fractions to mice did not significantly increase urine volume or sodium excretion (Hook, 1993). As well, oral and intravenous administration of dandelion root ethanolic extract did not produce diuretic effects in laboratory animals (Tita, 1993).

Juniper (*Juniperus communis*)

Juniper is estimated to increase urine volume without causing electrolyte losses, such as potassium (Blumenthal, 2000). As a diuretic, juniper berries contain the essential oil terpinen-4-ol and hydrophilic compounds that are reported to increase glomerular filtration rate (Foster, 1999). It has also been stated that terpenin-4-ol may cause irritation to the kidneys, but a later review by the same author made no such claim and concluded that there was no danger associated with the oil (Wynn and Fougère, 2007; Tisserand and Young, 2013).

Bearberry (*Arctostaphylos uva ursi*)

Several properties of uva ursi have been described as being diuretic, antiseptic, and astringent. Cystitis, urethritis, dysuria, pyelitis, lituria, and especially acute catarrhal cystitis with dysuria and highly acidic urine have traditionally been treated with this herb (British Herbal Pharmacopoeia, 1983; Wren, 1988). Hydroquinone derivatives, particularly arbutin, are responsible for the antiseptic and diuretic properties of uva ursi. The active compound in arbutin, hydroquinone, is absorbed intact from the gastrointestinal tract and hydrolyzed during renal elimination to produce astringent and anti-septic effects on urinary mucous membranes (Matsuda, 1992).

It should be noted that arbutin is not effective unless the urine is alkaline. The presence of urinary acidifiers prevents arbutin from converting into an active hydroquinone, which reduces the effectiveness of uva ursi (De Smet, 1993). In a pharmacological evaluation, the aqueous extract caused increased urine flow in rats when tested for diuretic activity (Beaux, 1999).

Tribulus (*Tribulus terrestris*)

The ethanolic extract of *Tribulus* berries showed significant dose-dependent protection against uroliths induced in rats. It prevented the deposition of calculogenic material around a glass bead, as well as preventing leukocytosis and serum urea elevation. Additionally, *T. terrestris* has been reported to increase the contractility of the ileum of guinea pigs in addition to its diuretic properties. Based on its diuretic and contractile effects, *T.terrestris* may be able to dissolve urinary stones (Al Ali, 2003).

Kava (*Piper methysticum*)

Kava rhizomes are traditionally used to treat cystitis, urethritis, infections and inflammations of the genitourinary tract, and rheumatism (British Herbal Medicine Association, 2003).

Gravelroot (*Eupatorium purpureum*)

According to the literature, this plant is anti-lytic, diuretic, anti-inflammatory, and antirheumatic. The herb has traditionally been used to treat urinary stones, cystitis, dysuria, urethritis, prostatitis, rheumatism, gout, and especially renal or vesicular stones (British Herbal Pharmacopoeia, 1983; Wren, 1988, Habtemariam, 2001).

Hydrangea (*Hydrangea arborescens*)

It is reported to have diuretic and antilytic properties. The herb has traditionally been used to treat cystitis, urethritis, urinary stones, prostatitis, and enlarged prostate glands, especially pebbles and cystitis stones (British Herbal Pharmacopoeia, 1983; Wren, 1988).

Crataeva (*Crataeva nurvala*)

This herb significantly inhibited the formation of urinary bladder stones in an experimental model using rats, In comparison with the controls, the bladders of the treated animals showed less edema, ulceration, and cellular infiltration (Deshpande, 1982).

It has been reported that the extract administered orally to rats significantly reduces stone formation (Prabhakar, 1997). The extract from the trunk bark of *Crataeva nurvala* has been reported to improve smooth muscle (intestines and ureters) and skeletal muscle tone in guinea pigs, dogs, and humans in vitro (Das, 1974). In dogs treated with Crataeva for 40 days, there was a significant increase in bladder tone (Deshpande, 1982).

Saw palmetto (*Serenoa repens*)

This plant is reported to possess diuretic, urinary antiseptic, endocrinological, and anabolic properties. A traditional use of this herb is in the treatment of chronic or subacute cystitis, catarrh of the genitourinary tract, atrophia of the testicles, sex hormone disorders, and in particular enlargement of the prostate (British Herbal Pharmacopoeia, 1983; Wren, 1988).

Horsetail (*Equisetum arvense*)

The herb has traditionally been used to treat gravel ulcers of the urinary tract and kidney ailments in general. Irrigation therapy can be used to treat bacterial and inflammatory diseases of the lower urinary tract and kidney stones (American Botanical Council, 1998). The haemostyptic effect of the herb may be due to the presence of silicic acid or flavonoids.

Overview of studies on the effect of plants on lower urinary tract diseases

In traditional medicine, medicinal plants and herbal formulas have been used to treat lower urinary tract diseases in many cultures, but little research has been conducted on lower urinary tract diseases in dogs or cats. According to an in vivo study, twelve cats fed herbal formula showed improvements in symptoms related to struvite in the lower urinary tract. Three traditional herbal remedies are commonly recommended for use in cats suffering from lower urinary tract disease (LUTD), including two formulas, San Ren Tang (SRT) and Wei Ling Tang (WLT), and a single herb, Alisma (A). These three herbal preparations are hypothesized to increase urine volume and decrease urinary saturation for CaOx and struvite. According to the results of study conducted by Daniels et al. (2011) SRT, WLT, or A were not found to increase urine volume in cats or decrease urinary saturation for CaOx or struvite; however, no adverse effects were detected during the study; therefore, it was concluded that these herbal products are safe for cats (Daniels et al., 2011).

The traditional treatment for urolithiasis in veterinary medicine has been to modify the diet in order to affect volume, pH, and solute concentration. As part of the herbal treatment, CrystaClair was administered twice a day and abdominal radiographs were taken to assess urolith size and number on presentation and periodically until the uroliths dissolving or the treatment was discontinued. There were no adverse effects reported, and the overall duration of treatment and end point were determined as the resolution of uroliths or the discontinuation of herbal medicine. There was dissolution reported in 56.5% of patients (58% of dogs and 54% of cats) after taking CrystaClair over a period of 4 to 60 weeks. Despite the fact that the researchers reported this case series was not ideal due to the unknown uroliths, they noted this was similar to clinical practice where the composition of the uroliths is often unknown. This study is difficult to interpret due to problems with its design, definition of known priors (surgery and crystalluria), and the use of diet therapy (Wen and Johnston, 2012; Raditic, 2015).

Fourteen Kampo extracts (10 mg/mL) were tested in vitro to determine whether they inhibited the formation of CaOx stones in Madin-Darby canine kidney cells by inhibiting crystal aggregation and adhesion to the renal tubular epithelium. An ethylene glycol (EG) rat model was used to study the inhibitory effects of the extracts on stone formation. The herbs Sanshishi (Gardeniae Fructus) and Takusha (Alismatis Rhizoma) inhibit CaOx monohydrate crystal aggregation (84.5% and 64.2%, respectively) and crystal adhesion to Madin-Darby canine kidney cells (88.2% and 54.6%, respectively). The researchers concluded that Gorin-san, a Kampo formula containing these two herbs, could be used as a prophylactic against CaOx urolithiasis due to its significantly stronger inhibitory effects (Nishihata et al., 2013; Raditic, 2015).

Conclusion

A drug development process is a lengthy, costly, and potentially risky process. Approximately 5,000 to 10,000 molecules are studied before a drug is approved and released to the market. Drug development costs increase as molecules studied become more complex and the requirements for obtaining sales licenses for drugs become more rigorous (Ernst and Young, 2006). It is estimated that millions of people are still unable to access affordable and high quality essential medicines around the world. In this regard, traditional treatment options based on natural compounds may offer new possibilities. Facilitating access to healthcare and overcoming limitations of modern treatments, such as bacterial resistance or high treatment costs, is essential.

The use of herbal medicines in veterinary medicine is becoming more popular day by day. Extensive research data are available on the effect of herbs from the perspective of their therapeutic effects or active ingredients. Plants as antilithogenic, antibacterial, antioxidant and anti-inflammatory agents have been shown to be effective in the treatment of lower urinary tract diseases in cats and dogs. Furthermore, it is seen that information on the therapeutic efficacy of medicinal plants is obtained based on traditional methods rather than scientific research results. As a consequence, scientific validation of the therapeutic effects of medicinal plants, evaluation of toxicity profiles, in vitro studies to determine whether they are cytotoxic and genotoxic, and evaluation of possible side effects that may arise as a result of drug-drug interactions are critical in accepting such drugs as alternative methods in clinical practice.

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