Journal of Animal & Plant Sciences, 33(4): 2023, Page: 786-793
ISSN (print): 1018-7081; ISSN (online): 2309-8694
https://doi.org/10.36899/JAPS.2023.4.0672

FIRST REPORT ON THE ANTI-UROLITHIATIC ACTIVITY OF *VIBURNUM OPULUS* ON UROLITHIASIS/CRYSTALLURIA IN DOGS AND CATS

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ABSTRACT

Lower urinary tract problems were increasingly encountered in small animal practice. Urinary stones and crystals are common problems in these cases and are still a problem in cats and dogs. Dilution of urine or restriction of mineral intake is a way to reduce urolithiasis/crystalluria. *Viburnum Opulus* was prescribed as anti-urolitiatic in human medicine. The objective of this study was to evaluate the efficacy of *Viburnum Opulus* in urolithiasis or crystalluria in companion animals. For this purpose, 42 animals were presented with urinary system problems and diagnosed with urolithiasis or crystalluria, which were included in the study and divided into two main groups (21 calcium oxalate, 21 struvite) and two subgroups (Control and Study). The urinary score was noted as the presence of pollakiuria, crystals in the microscopic examination, hematuria, stranguria, proteinuria, leucocytes, and blood in the urine. The mean ages were 3.81 and 3.95 for the calcium oxalate and struvite groups, respectively. It was determined that the clinical urinary score of the calcium oxalate control group was 11.39 before the treatment and increased to 14.06 at the end of 2 weeks. However, it was observed that this score decreased from 10.71 to 8.71 in the calcium oxalate study group. In calcium oxalate-diagnosed animals, a decrease in clinical scores was significant in the *Viburnum opulus* group than in controls. The urinary scores decreased in both struvite subgroups, but no statistical differences were determined. All animals except the calcium oxalate control group were clinically healthy at the second visit. Using *Viburnum opulus* as an integrative medical approach will provide safe and effective treatment for urolithiasis/crystalluria.

Keywords: *viburnum opulus*, urolithiasis, crystalluria, small animal, supplement

Published first online April 15, 2023 Published final August 04, 2023

INTRODUCTION

Urolithiasis and crystalluria are common disorders in small animal practice (Okafor *et al.*, 2019). The origin of word urolith comes from the Greek word meaning urine and lithos, which means urinary stones (Osborne *et al.,* 1999). Thus, urolithiasis can be defined as inflammation along the urinary tract due to urine crystals or stones. In non-optimal conditions, wastes of the body, mostly minerals, precipitate out of the solution to form crystals (Dvorska and Saganuwan, 2015). If these minerals are kept in the urinary system, they grow and consolidate into stones (Lulich *et al*., 2010).

Urinary crystals can be a specific marker of some disorders (e.g., cystinuria, adenine phosphoribosyltransferase deficiency, metabolic disorders) and drug use in cats and dogs (Daudon and Frochot, 2015; Okafor *et al.*, 2019). Crystalluria is also used to predict urolith recurrence in humans (Okafor *et al*., 2019).

Urolithiasis has a remarkably high incidence of being responsible for lower urinary tract diseases, up to 23% in cats and up to 20.61% in dogs (Lekcharoensuk *et al*., 2001; Dorsch *et al*., 2014; Kopecny *et al*., 2021). There are four main mineral types in cats and dogs; urate, cystine, magnesium ammonium phosphate (struvite), and calcium (Daudon and Frochot, 2015). In cats, 68.8% and 24.2% of all uroliths are composed of calcium oxalate and struvite, respectively, while 43.6% and 47% of uroliths are struvite or calcium oxalate in dogs (Burggraaf *et al*., 2021; Kopecny *et al*., 2021). Urolithiasis in cats and dogs is a common problem still being studied today (Hesse *et al*., 2016; Burggraaf *et al*., 2021; Tefft *et al.*, 2021).

The etiology of urolithiasis is multifactorial, including genetic predisposition, acquired or congenital alterations in metabolism, environmental factors, and diet

(Daudon and Frochot, 2015). The degree of supersaturation (Relative supersaturation, RSS) of urine with lithogenic substances determines the potential of a crystal to dissolve, form, or grow in size (Robertson *et al.*, 2002). Limiting the amount of stone precursors excreted in the urine (Queau *et al.*, 2020) and promoting urine dilution to reduce their concentration is therefore recommended to reduce the risk of crystallization. In addition, larger urine volumes increase the frequency of micturition and reduce the residency time of crystals in the bladder (Queau *et al*., 2020). Identifying the mineral composition of crystals or uroliths is necessary for optimal treatment strategies. Especially, dietary treatment strategies aim to decrease the degree of RSS with precursors of crystals and uroliths (Queau *et al.*, 2020).

Some studies show that medical herbal extracts could contribute to the treatment of urinary stones (Bouanani *et al.*, 2010); therefore, World Health Organization has also paid importance to the use of herbal drugs and traditional medicines due to their low cost and low side effects (Rathod *et al*., 2012).

The species *Viburnum opulus L*. belongs to the *Caprifoliaceae* plant family. The genus *Viburnum* includes more than 230 species from South America to Southeast Asia, most of them endemic (Altun *et al*., 2009). In Anatolia, Viburnum species are used for several purposes in folk medicine (Altun and Yilmaz, 2007; Altun *et al*., 2008). Viburnum species contains diterpenoid, sesquiterpenes, coumarin, phenolic acid, and organic acid, a rich chlorogenic acid source (Altun *et al*., 2009). Antinociceptive (Altun *et al.*, 2009), relaxant and spasmolytic (Cometa *et al*., 2009), hepatoprotective and hypoglycemic (Yilmaz *et al*., 2006), antioxidant (Erdogan-Orhan *et al.*, 2011; Kraujalytė *et al.*, 2013), anticholinesterase (Erdogan-Orhan *et al.,* 2011), and anticarcinogenic (Ulger *et al*., 2013) potential are related to these components. In addition, various studies have proven the anti-urolithiatic effects of *Viburnum Opulus* extract, and the extract has taken its place as an alternative curative and protective protocol for urolithiasis in human medicine (Ashok *et al*., 2010; Patel *et al.*, 2012; Najeeb *et al*., 2013; Ilhan *et al*., 2014).

This study aims to determine the effect of *Viburnum opulus* in both canine and feline crystalluria and urolithiasis. To our knowledge, it is the first study that evaluates the *Viburnum opulus* extract effect for struvite and calcium oxalate urolithiasis in cats and dogs.

MATERIALS AND METHODS

Client-owned cats and dogs were included for the study between May 2018 and February 2020. Examinations of all animals were done at academic teaching hospital (Ondokuz Mayis University, Veterinary Faculty, Veterinary Teaching Hospital, Samsun, Turkiye). The study was approved by The Ethics Committee of Ondokuz Mayıs University (ID: 68489742-604-e.6861).

Fifty animals applied to the veterinary hospital with any of these complaints, such as stranguria, pollakiuria, dysuria, hematuria, lower abdominal pain, anorexia, and not paying attention to the environment. Still, the study was completed with 14 dogs, and 28 cats due to eight animals with total obstruction in the urinary system were excluded from the study.

All animals underwent urinary system examinations as well as clinical examinations. Ultrasonography was performed to determine the presence or absence of stones in the urinary bladder (MyLabFive-Vet, E-Saote) (Figure 1). Acoustic shadowing and twinkling artifact findings were evaluated as positive for the presence of stones in the urinary bladder. A five ml urine sample was taken with ultrasound-guided cystocentesis (Figure 2). One urine sample was dropped on each reagent area of the urine strip (Cybow 11M), and the results were evaluated with a urine strip reader (Cybow Reader).

Figure 1. Longitudinal ultrasound image o the urinary bladder with abnormal content.

The urine samples were centrifuged at 2000 RPM for 5 min. The supernatant and precipitate of the urine were separated, and a microscopic examination was performed from the precipitate. The type of uroliths/crystals was determined (Figure 3). Only the dogs and cats were diagnosed with struvite and calcium oxalate urolithiasis/crystalluria, which were not totally obstructed, included in the study.

Animal Material and Grouping: The animals were divided into two groups as, struvite and calcium oxalate, according to the character of the detected stone. Afterward, they were randomly divided into two subgroups according to the date of arrival: the study group and the control group. In both groups (struvite and calcium oxalate group), there were 21 animals (12 in the study and 9 in the control group) Fig. 2. In total, there

were thirteen cats and five dogs in the control and fifteen cats and nine dogs in study groups.

Conventional treatment was applied to all animals (dissolution therapy, urine acidifiers, long-term Hills urinary prescription diet food use, urinary tract antiseptics, antibiotic protocol in infection complication, and supportive therapy). The second group of animals was considered the study group, which was applied at a dose of 285 mg/10 kg *Viburnum Opulus* extracts (Gilaburine-Arbis) 3 times a day for two weeks in addition to the conventional therapy. The dose was calculated according to Ilhan *et al*. (2014).

Tracking parameters: Following the diagnosis of urolithiasis for each patient, urine examination and microscopy, ultrasonographic study, and clinical scoring were recorded. Clinical scoring was determined regarding the modification of the scoring presented by Meyer and Bečvářová (2016) as follows; during the clinical examinations, the pH value of the urine and the presence of protein, leukocytes, and blood in the urine and the clinical findings of pollakiuria, hematuria and stranguria were evaluated. Clinical scoring was performed by giving "0 "or "1" points according to the absence or presence of each existing parameter.

Urine examination and microscopy, ultrasonographic examination, and clinical scoring were repeated in the 1st(V_1) and 2nd-week (V_2) controls (Table 1).

Statistical Analysis: Statistical analyzes were performed in the SPSS v21 program. The distribution was evaluated with the Shapiro-Wilk test. For the parameters that did not show normal distribution (clinical score at week 0, clinical score at week 1, and clinical score at week 2), statistical analyzes between the groups were done with the Mann-Whitney U test. The statistical analyzes of the values at different times within the group were made with the Friedman analysis.

Figure 2. Ultrasound-guided cystocentesis.

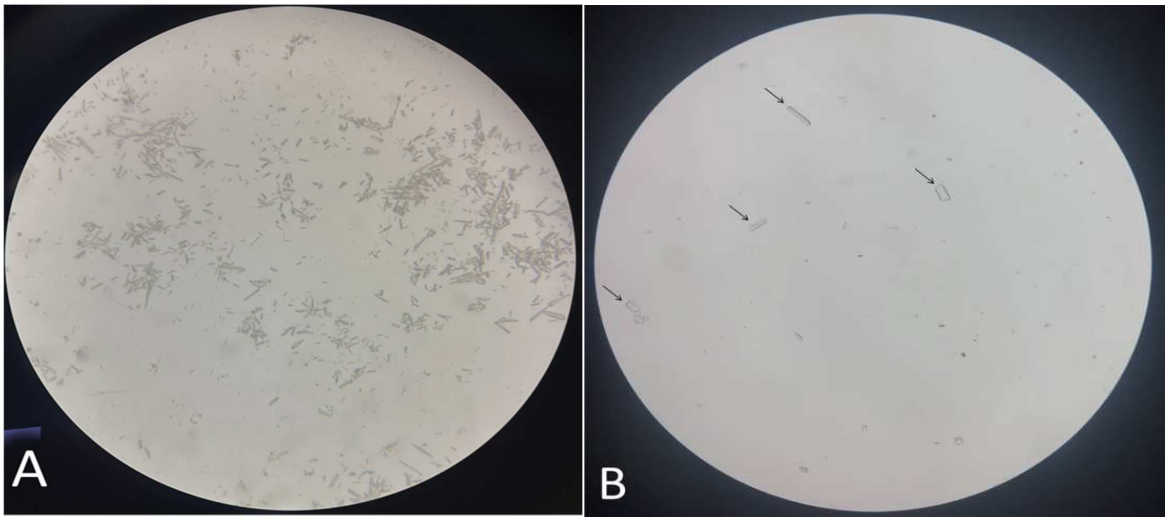

Figure 3. Microscopic image of calcium oxalate monohydrate (A) and Struvite (Arrows) (B) crystals in a urine sample.

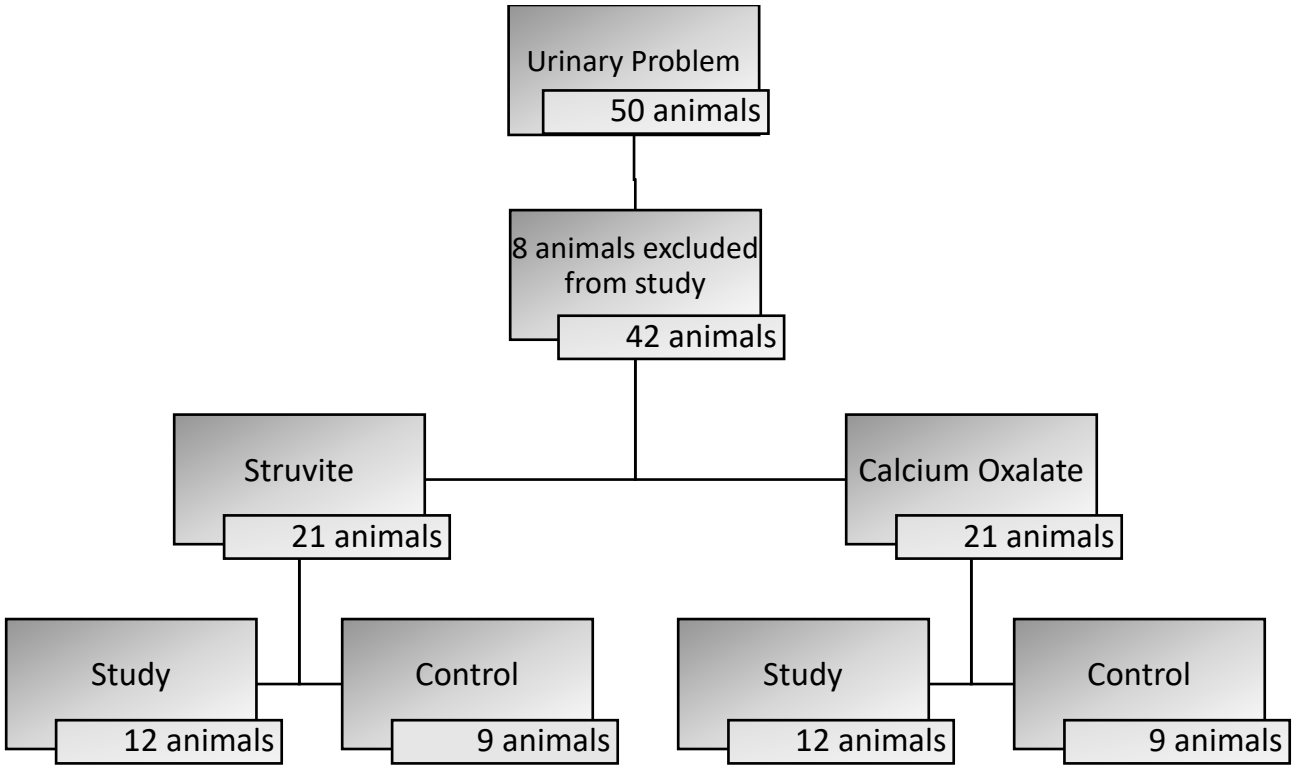

Figure 2. Animal grouping and subgroups

RESULTS AND DISCUSSION

Fifty animals were applied to our hospital with distal urinary system problems, but the study was completed with 14 dogs and 28 cats. The mean ages were 3.81 years for the calcium oxalate group and 3.95 years for the struvite group.

Recovery was followed by urinary system scoring in the study. In animals with calcium oxalate urolithiasis, an increase in the clinical scoring between weeks was observed in the control group, while a significant decrease in the scores at visits 0, 1, and 2 was found in the study group.

Although there was a decrease in clinical scores in the control and study groups in animals with struvite urolithiasis, no significant difference was found between the groups at each visit. This decrease in clinical scoring in the control and study groups was not significant after the second week Table 1.

At the end of the second week, all animals except in the calcium oxalate control group were clinically healthy.

Crystalluria is a result of excessive supersaturation of electrolytes mostly ingested by diet. Crystalluria can be observed in the normal urinary tract, which is clinically harmless and unimportant (Lulich *et al.*, 2010). Although crystal identification in urinalysis is the primary method for predicting the composition of uroliths, it is not a consistent feature in cats and dogs (Lulich *et al*., 2011). However, crystalluria was essential in predicting urolith reoccurrence in humans (Okafor *et al.*, 2019).

Table 1. Change in daily clinical urinary scores. There is a statistically significant difference between letters (A, B) containing different letters in the same column (P<0.05). There is a statistically significant difference between letters (a, b) containing different letters on the same line (P<0.05).

Groups		Visits		
	V0	V1	V2	
Calcium	Control	$11,39_{a}$	$12,6_{a}$	14.06_{Aa}
Oxalate	Study	$10,71_{a}$	$10,21_{b}$	8.71_{Bc}
Struvite	Control	$9,67_{a}$	$6,88_{b}$	$6,13_{b}$
	Study	$11,18_{a}$	$8,33_{b}$	8.40_{b}

Previous studies revealed that calcium oxalate is mainly seen in male animals, while struvite oxalate is more dominant in female animals (Houston *et al*., 2003; Ling *et al*., 2003; Cannon *et al*., 2007). Our findings showed that male animals were predominant in both groups, but those findings may be attributed to the limited study group number. The literature demonstrates that younger animals (<4 years of age) are more likely to produce struvite uroliths, and animals which are older

than seven years are more likely to have oxalate uroliths (Ling *et al*., 1998; Cannon *et al.*, 2007; Kopecny *et al*., 2021). We found that young animals were predominant in both struvite and oxalate groups. The mean ages were 3.8 years for oxalate groups and 3.95 years for struvite groups. Neutered dogs and cats are more susceptible to urolithiasis, especially calcium oxalate uroliths (Lekcharoensuk *et al*., 2000; Kopecny *et al*., 2021). Otherwise, Okafor *et al*. (2019) noticed that un-neutered cats were significantly higher odds for hemorrhagic struvite crystalluria than neutered cats. In this study, consistent with previous studies, the proportion of neutered animals with oxalate crystalluria was higher, but struvite crystalluria was predominant in the sexually intact animals.

Urolith composition and degree of supersaturation are important guiding tools for the patient's management and treatment protocol (Gomes *et al.*, 2018). Precipitation of crystals depends on many factors, including water intake, diet, the degree of urine saturation, presence or lack of promoters and inhibitors of precipitation, pH of urine, and urine volume. All these factors contribute to the increasing occurrence of urolithiasis; the most likely seems to be a change in dietary composition. Diets containing 0.15 to 1.0% magnesium on a dry matter basis have been associated with the formation of struvite uroliths (Buffington *et al.*, 1994; Queau *et al*., 2020). Dietary interventions for preventing and treating struvite uroliths include increasing water intake, restricting phosphorus and magnesium intake, and moderate urinary acidification (Tefft *et al.*, 2021). Treatment and preventional options for calcium oxalate uroliths are; changing dietary moisture, changing dry food to canned, and increasing dietary sodium to induce oral water intake (Stevenson *et al*., 2003).

Ilhan *et al.* (2014) reported that the lyophilized juice of *Viburnum opulus* has diuretic and anti-urolithiatic features due to the inhibitory effects on oxalate levels and free radical production in their experimental study in which they constituted artificial urolithiasis in rats. Akyol *et al*. (2016) showed that *Viburnum opulus* could be used effectively in calcium oxalate urolithiasis in humans. Similarly, the present study indicated that *Viburnum opulus* had a potential effect, especially on calcium oxalate urolithiasis in cats and dogs. There was a significant decrease in urinary system complaints within visits. This could be explained by the diuretic effect of the *Viburnum opulus*, which diluted the urine and decreased the relative supersaturation. The antispasmodic effect of *Viburnum opulus* had a crucial role in resolving urethral spasms to promote urination. Limiting the amount of stone precursors excreted in the urine and promoting urine dilution to reduce their concentrations is recommended to reduce the risk of crystallization. In summary, diuretic efficacy increases urination and shortens the residency time of crystals in the urinary bladder (Queau *et al.*, 2020).

Complementary protocols in veterinary medicine are increasingly preferred, and clinicians have to meet the demands of pet owners who want new methods with minimal side effects (Lana *et al*., 2006; Harris *et al*., 2012). There is no study up to date about the effects of *Viburnum spp.* in feline and canine urolithiasis, which is one of the most popular herbal remedies in treating urolithiasis in human medicine. A limited number of studies evaluated the effects of *Viburnum opulus* on urolithiasis. One study assessed the impact of *Viburnum opulus* on sodium oxalate urolithiasis and crystalluria in rats (Ilhan *et al*., 2014). Kızılay *et al*. (2019) have reported that *Viburnum opulus* can be used as an alternative effective treatment method in human medicine for distal ureteral stones less than 10 mm. The present study found that using *Viburnum opulus* with conventional treatment was superior to conventional treatment alone in calcium oxalate crystalluria in cats and dogs. We can also mention that there was a superiority in clinical complaints in struvite crystalluria, although there was no statistical difference between the groups.

It was observed that the first improvement among the clinical findings used in scoring was hematuria. The lower urinary tract inflammation (caused mainly by crystalluria) can result in hematuria. Human studies showed that *Viburnum opulus* has many beneficial effects, including antioxidant, anti-inflammatory, and antinociceptive efficiency (Altun *et al*., 2009; Ilhan *et al*., 2014).

Low-quality commercial foods, as opposed to veterinary-formulated pet foods, generally have high salt and mineral ingredient to increase edibility, resulting in a higher incidence of calculus formation. In the present study, 80% of the dogs and %85 of the cats were on low-quality commercial diets. *Viburnum opulus* to veterinary-formulated pet foods could benefit the dissolution of uroliths and excrete urinary crystals.

Osborne *et al.* (1996) found a mean dissolution time of 36 days for sterile struvite uroliths and 44 days for infection-induced struvite urolithiasis. Medical protocols that promote the dissolution of calcium oxalate uroliths in cats and dogs are not yet available (Osborne *et al.,* 2009). This study was designed for a short period (14 days). Dissolution of the uroliths and urine dilution was observed, and clinical improvement was monitored with clinical scoring. A limitation of the study is the lack of urine culture. Antibiotic was administered to all animals without urine culture. In addition, this study indicates further research using more extensive randomized controlled trials to validate the results obtained from the study.

Conclusion: Using *Viburnum opulus* in an integrative medical approach will provide a safe and effective alternative to surgery or the administration of lifelong antibiotics to control urolithiasis in dogs and cats with calcium oxalate uroliths.

Author's declaration of interest: The authors have no conflict of interest.

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