A SYSTEMATIC REVIEW OF HERBAL EXTRACTS IN TREATING UROLITHIASIS IN CATS AND DOGS

RISHIKESAN A/L VIVEKANANTH

(D17A0033)

A RESEARCH PAPER SUBMITTED TO THE FACULTY OF VETERINARY MEDICINE, UNIVERSITI MALAYSIA KELANTAN
IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR
THE DEGREE OF
DOCTOR OF VETERINARY MEDICINE

MAY 2022

UNIVERSITI MALAYSIA KELANTAN

CERTIFICATION

This is to certify that we have read this research paper entitled **'A Systematic Review of Herbal Extracts in Treating Urolithiasis in Cats and Dogs'** by Rishikesan A/L Vivekananth, and in our opinion it is satisfactory in terms of scope, quality and presentation as partial fulfillment of the requirement for the course DVT 5436 – Research Project.

Dr. Sujey Kumar Rajendran
DVM (UPM), Master of Veterinary Science (UPM)
Senior Lecturer,
Faculty of Veterinary Medicine
Universiti Malaysia Kelantan
(Supervisor)

Dr. Erkihun Aklilu Woldegiorgis
DVM (UPM), Master of Science (UPM)
Senior Lecturer,
Faculty of Veterinary Medicine
Universiti Malaysia Kelantan
(Co-supervisor)

ACKNOWLEDGEMENT

Special thanks for those who have given their support, guidance, advice, and aid for the completion of this project paper:

Dr. Sujey Kumar Rajendran

Dr. Erkihun Aklilu Woldegiorgis

Parents

Brothers

DVM 5 class of 2017/2022

Thank You

DEDICATIONS

I dedicate my work wholeheartedly to my family and many friends. My deepest sense of gratitude to my loving parents, who continually provide their moral, spiritual, emotional, and financial support for me at all times. My three brothers who have shared their support and valuable prayers to complete this thesis.

I also dedicate this dissertation to many of my lecturers and seniors who have supported me throughout the process. I will always appreciate all of the things they have done, especially Dr. Sujey Kumar and Dr. Erkihun Aklilu Woldegiorgis, for providing me invaluable guidance throughout the study.

I dedicate this work and give special thanks to my wonderful friends, Raghinhy, Aruut, Thiva and Kanmani for always being there for me throughout the entire program of Doctor of Veterinary Medicine. I am extremely grateful for their words of advice and encouragement.

Above all, to the Great Almighty, the author of knowledge and wisdom, for his countless love.

Table of Contents

List of tables

List of diagrams

List of appendices

ABSTRACT

An abstract of the research paper presented to the Faculty of Veterinary Medicine, Universiti Malaysia Kelantan, in partial requirement for the course DVT 5436 – Research Project

Urolithiasis is the concretion of stone development known as uroliths in the urinary system. It is a severe condition that causes clinical pain in animals and requires early treatment to avoid complications such as urinary infections and obstructions. Although various conventional therapies are available for the urothialisis, recurrence and the side effects of the drugs are the major drawbacks of those treatments. With the increasing prevalence of urolith formation accompanied with inflammation and severe discomfort, the demand for medicinal plants in avoiding lithiasis has increased. This is a systematic review to thoroughly review the evidence on the use of common medicinal plants, particularly their herbal extract efficacy in treating urolithiasis in small animals, especially cats and dogs between the years 2000 to 2021, as there is lack of analysed data on their use in those patients. A total of 2,356 publications from 2000 to 2021 were extracted from two databases, Science Direct and PubMed and 35 studies were selected based on defined eligibility criteria. The mechanism of action of the herbal plants with their possible toxicological effects were reviewed. The main underlying mechanisms of these dietary plants and their isolated phytonutrients in the management of urolithiasis include diuretic, antispasmodic, and antioxidant activity, as well as an inhibitory effect on crystallization, nucleation, and aggregation of crystals. All proposed and reported herbal extracts appeared to be beneficial and efficient in managing urolithiasis in canine and feline species.

Keywords: *Urolithiasis, herbal extracts, canine, feline, diuretic*

ABSTRAK

Abstrak daripada kertas penyelidikan yang dikemukakan kepada Fakulti Perubatan Veterinar, Universiti Malaysia Kelantan, untuk memenuhi keperluan kursus DVT 5436 – Projek Penyelidikan

Penyakit batu karang ialah pertumbuhan konkrit yang dikenali sebagai urolit atau batu karang dalam sistem saluran kencing. Ia adalah keadaan serius yang menyebabkan tanda-tanda klinikal pada haiwan dan memerlukan rawatan awal untuk mengelakkan komplikasi seperti jangkitan sistem saluran kencing dan pembentukan batu karang yang menghalang sistem saluran kencing. Walaupun pelbagai terapi konvensional telah tersedia untuk merawat penyakit batu karang, pembentukan batu karang akan berulang dan kesan sampingan ubat tidak dapat dielakkan. Dengan peningkatan kelaziman pembentukan batu karang yang disertai dengan keradangan dan ketidakselesaan, permintaan untuk herba dalam mengelakkan batu karang telah meningkat. Kajian ini adalah tinjauan sistematik untuk mengkaji secara menyeluruh berkenaan bukti penggunaan herba, keberkesanan ekstrak herba dalam merawat penyakit batu karang pada haiwan peliharaan, terutamanya kucing dan anjing antara tahun 2000 hingga 2021 disebabkan kekurangan data yang dianalisis tentang penggunaannya dalam bidang veterinar. Sebanyak 2,356 penerbitan dari tahun 2000 hingga 2021 telah diekstrak daripada dua pangkalan data, Science Direct dan PubMed dan 35 kajian telah dipilih berdasarkan kriteria kelayakan. Mekanisme dengan kelaziman kesan toksikologi ekstrak herba telah dikaji dalam kertas ini. Mekanisme asas herba dan fitonutrien spesifik dalam pengurusan penyakit batu karang termasuk aktiviti diuretik, antispasmodik dan antioksidan, serta pencegahan pembentukan kristal, nukleasi, dan pengagregatan kristal. Semua ekstrak herba yang dicadangkan

dan dilaporkan bermanfaat dan efisien dalam mengurus penyakit batu karang pada spesies anjing dan kucing.

Kata kunci: *Urolithiasis, ekstrak herba, anjing, kucing, diuretik*

1.0 Introduction

Urolithiasis is the concretion of stone development known as uroliths in the urinary tract (Bartges & Callens, 2015). Uroliths can be found everywhere in the urinary system, from the kidneys to the urethra. Urolith development is not a disease, but rather a consequence of several disorders (Osborne, 2009). It is caused by a series of physicochemical phenomena such as supersaturation, nucleation, growth, aggregation, and retention inside the urinary system (Butterweck & Khan, 2009).

Urolithiasis is a severe condition that causes clinical pain in animals and need early treatment to avoid complications such as urinary infections and obstructions (Rocha & Granato, 2021). To recognise the kind of urolith caused by various etiologies, a precise diagnosis is necessary for efficient therapy. As a result, therapy must be tailored to the main factors that contribute to the creation of each specific urolith (*Cruces et al*., 2014). The approved treatment for stone disease spans from medicinal dissolution to surgical stone removal. The size and location of the calculi, the degree of obstruction, the severity of clinical manifestation, renal function and the presence or absence of concurrent infection all influence the decision of management (*Sathoshi et al.,* 2020).

Uroliths more than 5 mm of diameter or stones that fail to pass through should be removed via surgical interventional approach, which is an invasive method (*Nirumand et al.,* 2018). Unfortunately, urolith removal utilising those surgical procedures has little effect on the tendency for recurrence, and stone recurrence remains about 50%. Calcium oxalate or struvite type are the commonly occurring stones are in most cases (*Tion et al.,* 2015). In addition, these techniques can cause adverse effects, including

tubular necrosis, hypertension, hemorrhage, mucosal damage and subsequent fibrosis of the surgical site which will cause cellular injury and stone recurrence.

Many treatments have been suggested to cure urinary stones. Most remedies in ancient systems of medicine were derived from plants and were proven to be effective, despite the fact that the rationale for their usage has not been clearly established via a thorough pharmacological and clinical trials. Medicinal plants have been used worldwide in human medicine, proving efficiency in preventing reoccurrence. They include a variety of phytoconstituents that combat urolithiasis through various mechanism (Rahul, 2010). However, although there is evidence that these medicinal herbs have benefits in therapy, their use in veterinary medicine is currently limited. (Rocha & Granato, 2021).

The focus of this review is to comprehensively analyse the evidence on the use of such medicinal plants, particularly their herbal extract efficacy in treating urolithiasis in cats and dogs. A systematic review is a summary of the literature that use replicable procedures to systematically seek, critically evaluate, and integrate the findings of many primary studies that are related to one another, all while minimising bias and random errors (Gopalakrishnan, 2013).

2.0 Research problem

Some medicinal herbs have been employed as substitutes for current invasive surgical therapies because of their therapeutic and preventative capabilities properties against urinary stones. However, sufficient evidence has not been properly published to identify the common herbal medicines that can be used in veterinary treatment approach. Therefore, it is essential to review the studies on available common herbal extracts that can be used to treat urolithiasis in small animal practice in association with the pharmacokinetics behind the extracts along with the clinical effectiveness in treating the condition.

3.0 Research questions

3.1 What are the common types of herbal extracts that can be used to treat urolithiasis in cats and dogs?

3.2 What are the main mechanisms of actions and possible toxicological effects of the herbal extracts used in treating urolithiasis in cats and dogs?

4.0 Research hypothesis

4.1 Herbal extracts are effective and safe alternatives for treatment and management of urolithiasis in small animals

5.0 Objectives

5.1 To summarise and compile the common herbal extracts that can be used for treatment of urolithiasis in cats and dogs.

5.2 To elaborate the mechanisms of actions and possible toxicological effects of the herbal extracts.

6.0 Literature review

6.1 Urolithiasis

Uroliths are microscopic sediments and precipitates that occur when stones form in the urinary system. They can form under pathological or physiological settings. It's a frequent disease in dogs and cats, and it may happen anywhere along the urinary tract, though it's most prevalent in the urinary bladder (*Prasad et al.*, 2007). the fundamental aetiology is the relation between the alterations in urine pH resulting an acid-base imbalance that allows crystal precipitation in accordance with each urolith specification (Rodrigues, 2015). Other reasons might include hereditary, congenital, or acquired diseases that lead to a rise in mineral excretion in the urine.

Urolithiasis affects around 3% of dogs and cats examined in veterinary clinics (Osborne, 2009). Uroliths in cats, dogs, and humans are classified as urate (which includes ammonium urate, sodium urate, and uric acid), magnesium ammonium phosphate (struvite), cystine and calcium ammonium phosphate (calcium oxalate and calcium phosphate). Uroliths largely composed of urate or cystine are rare in cats and dogs, accounting for fewer than 10% of uroliths examined at the Minnesota Urolith Center in the United States, but struvite and calcium-containing uroliths are the most common mineral types discovered in both cats and dogs (*Gomes et al.*, 2018).

Males are more likely than females to develop urethral obstruction due to their anatomical variations such as a long narrowed urethra with penile bone (Gomes *et al.*, 2018). Females, on the other hand, are more predisposed to develop urinary infections due to the urethra's location near to the anus and the ground during micturition. Furthermore, the four-feet stance during micturition might interfere with full bladder

emptying, resulting in residual urine that might concentrate wastes, create aggregation of crystals and possibly develop a nidus.

6.2 Treatment options for urolithiasis

A number of factors influence the strategy and reasonable method of treating urolithiasis, including the size, shape and location of the stone, with the chemical composition, the renal functioning status, the degree of urinary tract dysfunction with complications and concurrent diseases (*Khokhlenkova et al.*, 2019). Several treatment options have been described in managing urolithiasis which include: 1) surgical stone removal or nephrolithotomy for kidney stones; 2) symptomatic treatment; 3) therapy with conservative approaches; 4) medical management of litholysis; 5) instrumental stone removal; 6) percutaneous removal of kidney stones by extracting or litholopaxy; 7) distant shock-wave lithotripsy (*Lulich et al.*, 2016).

Surgically removing urinary stones does not ensure that the body's proclivity for urolithiasis will be eliminated or at least weakened. Because the primary source of salt precipitation is not addressed, stones might develop quickly if the proper treatment regimen is not followed after surgery. Since the emergence of extracorporeal shock wave lithotripsy (ESWL), which has nearly become the standard method of delaying kidney stones, the modern treatment of urolithiasis with open renal surgery is not unusual and is used on a regular basis. ESWL, on the other hand, might cause significant renal damage, a decrease in kidney function, and an increase in stone recurrence in addition to the irritating impact of shockwaves, continual leftover stone particles, and the likelihood of contamination. (*Waqas et al.*, 2017).

6.3 Phytotherapy

Medicinal herbs have been utilised to treat urolithiasis all throughout the world. The development of clinical studies to determine its utility has proved the efficiency of this treatment for disease control, with the objective of extending research in this field (*Kant et al.*, 2020). Herbal extracts are derived from plant raw materials or active chemicals known as the phytochemical compounds that function in disease healing or reduction of clinical manifestations, and their safety and effectiveness are proven by clinical trials. Examples of phytoconstituents include tannins, terpenes, flavonoids, alkaloids, mineral salts and many more. These phytoconstituents work against urolithiasis through a variety of mechanism, including (*Pareta et al.*, 2011):

- Increasing urine volume, pH, and anti-calcifying action to promote diuretic activity through the spontaneous passage of calculi.
- Stabilizes the crystallisation inhibitor and promoter in urine, affecting crystal nucleation, aggregation, and development.
- Possessing lithotriptic action by relieving calculi's binding mucin.
- Improving renal function, oxalate metabolism regulation, regulation of crystalloid colloid imbalance.
- Shows substantial anti-microbial efficacy against the main pathogens
- Giving analgesia and anti-inflammatory activity by showing a significant improvement in urinary calculi symptoms such as discomfort, burning micturition, and haematuria.

The bioactive compounds are frequently extracted from plant materials using various extraction processes that take their chemistry and uneven distribution in the plant matrix into account (*Sulthana et al.*, 2009). Solvent extraction is the most often utilised

approach for isolating phytochemical components depending on the site of extraction from that plant. Extraction is carried out by using aqueous mixes comprising ethanol, methanol, acetone, and ethyl acetate as solvents. (*Sulthana et al.*, 2009).

There are a number of literatures that studies the use of medicinal plants to treat urolithiasis before the year 2000. *Anand et al.* (1994) conducted an extensive investigation in albino rats on the antiurolithiatic action of *Tribulus terrestris* and *Crateva nurvala*. They concluded that a phytoconstituent called lupeol from those herbs that have an antiurolithiatic effect by inhibiting the formation of vesicle calculi and reducing the size of existing stones. Poonguzhali (1994) had researched on the effect of banana stem extract on urinary risk factors for stones by comparing between normal to hyperoxaluric rats. The banana stem extract lowers urinary oxalate excretion and may be effective in the treatment of hyperoxaluria. Varalakhsmi (1990) had researched on *Crataeva nurvalu* bark decoction where it resulted as urine excretion of the crystalline components increased whereas magnesium excretion decreased in stone-forming rats. *Grases et al*. (1995) did a research on the influence of *Herniaria hirsuta* and *Agropyron repens* on the risk of calcium oxalate urolithiasis in rats by comparing on the effectiveness of antilithiatic action of both plants based on dietary. *Araujo Viel et al*., (1999) conducted a study on the antiurolithiatic action of *Costus spiralis* Roscoe extract in rats and found out that the plant inhibited the development of urinary stones, validating folklore about the plant's antiurolithiatic action, however the mechanisms behind this effect are yet unclear.

7.0 Methods

Systematic review was chosen because it aims to discover and synthesise related studies in a systematic, transparent, and repeatable manner at each stage of the process (*Shaffril et al.*, 2021). The systematic review in this research is done using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

7.1 Literature search

The search database used for literature and articles searching in this review were PubMed and Science Direct. The keyword used for the search were “dog” OR “canine” OR “cat” OR “feline” AND “urolithiasis” OR “urinary stones” OR “urinary calculi” AND “veterinary herbal medicine” OR “herbal extracts” OR “medicinal plants” OR “phytotherapy". All the search results were recorded and summarized in Table 7.1 and 7.2.

7.2 Screening, inclusion, and exclusion criteria

Screening of the retrieved total literature were conducted based on the inclusion and exclusion criteria that are relevant to the scope of this review. The first screening was conducted by removing all the duplicated articles based on the same citations. EndNote website was used to perform this removal.

Second screening was conducted according to the inclusion and exclusion criteria that were set for this review. The inclusion criteria of this review included the studies about the common herbal plants used in treating for canine and feline urolithiasis that were published within the year 2000 to 2021. The time of the published articles were selected as such to ensure that the evidence was recent. Studies about the pharmacodynamics behind the herbal plant treatment and their possible toxicological effects were also included.

The exclusion criteria in this review include studies of herbal plants used in treating urolithiasis in species other than cats and dogs, literature about in-vitro studies, general herbal medicine treatment, and scope irrelevant or beyond treating urolithiasis based on titles were excluded. Literature in form of the books, discussion, articles not available in English, and unavailability of full text were all excluded as well. Studies that describe unspecific and multiple therapeutic approaches were also discounted. The literature that met the exclusion criteria will be discounted and proceeded to the third screening.

Third screening was performed manually based on the evaluation of title, abstract, and methodology of publications to select studies about the treatment of urolithiasis using herbal medicine for eligibility process. The reference lists of each study were then searched to identify additional research and works mentioned in those publications in order to identify any following studies that had not been detected in the current literature to guarantee that all relevant studies and significant research were not overlooked. The finalized total literature will be obtained according to the inclusion and exclusion criteria after the third screening. The process and result of the screening were illustrated in Diagram 7.1.

7.3 Result synthesis

The retrieved final literature after the third screening were systematically reviewed, and the results were tabulated based on the type of herbal medicine used for treating urolithiasis.

Table 7.1: Search words for canine species, herbal treatment and literature retrieved

Search words	Databases		Total
	PubMed	*Science direct*	
Dog urolithiasis, herbal medicine treatment	2	22	24
Dog urinary stones, herbal medicine treatment	3	158	161
Canine urolithiasis, herbal medicine treatment	2	33	35
Canine urinary stones, herbal medicine treatment	1	129	130
Dog urolithiasis, medicinal plant treatment	1	38	39
Dog urinary stones, medicinal plant treatment	1	227	228
Canine urolithiasis, medicinal plant treatment	1	29	30
Canine urinary stone, medicinal plant treatment	1	104	105
Dog urolithiasis, herbal extract therapy	1	25	26
Dog urinary stones, herbal extract therapy	1	132	133
Canine urolithiasis, herbal extract therapy	1	28	29
Canine urinary stones, herbal extract therapy	1	58	59
Dog urolithiasis, phytotherapy	3	1	4
Dog urinary stones, phytotherapy	3	21	24

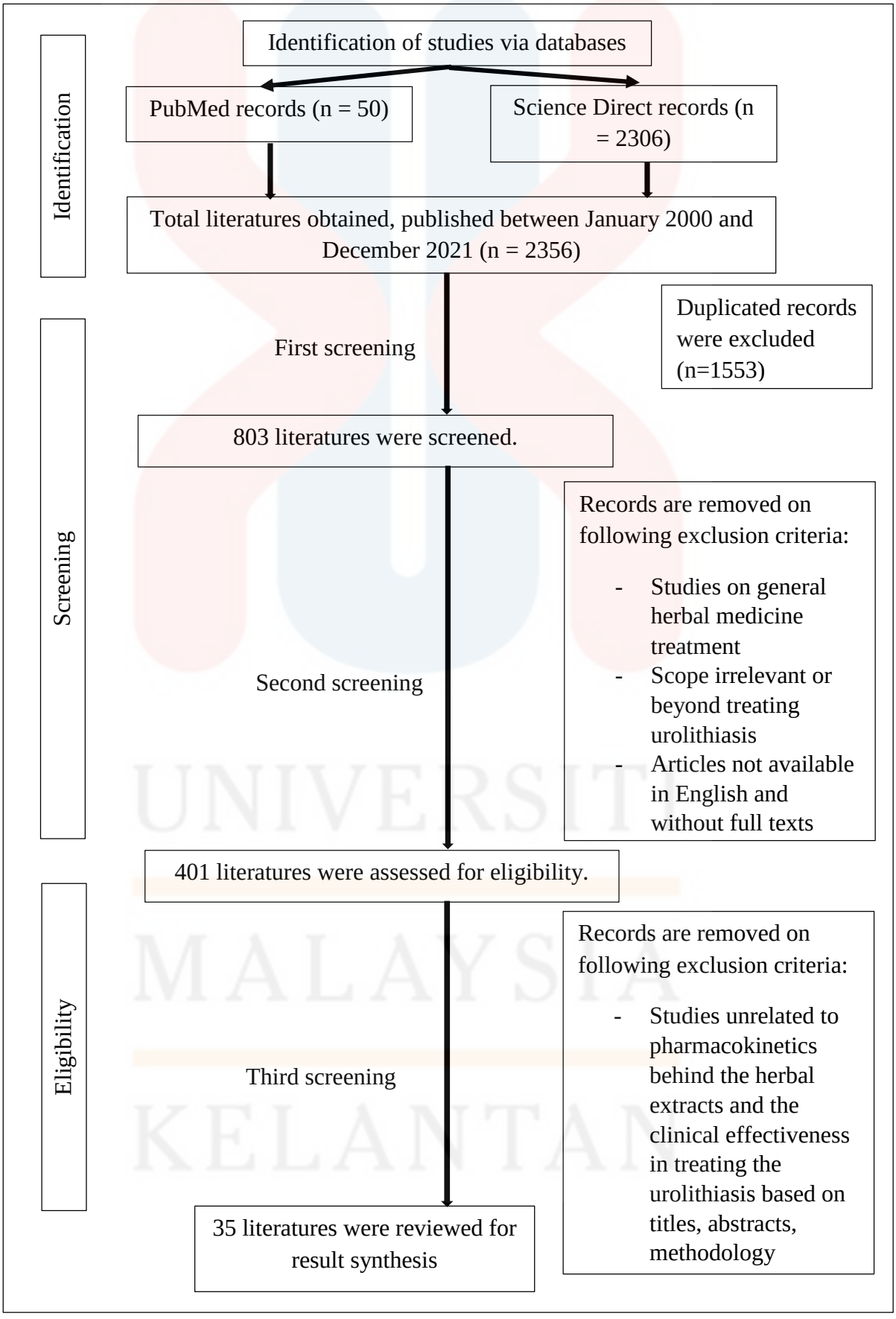
Canine urolithiasis, phytotherapy	4	10	14
Canine urinary stones, phytotherapy	2	16	18
Total	**28**	**1031**	**1059**

Table 7.2: Search words for feline species, herbal treatment and literature retrieved

Search words	**Databases**		**Total**
	PubMed	*Science direct*	
Cat urolithiasis, herbal medicine treatment	10	64	74
Cat urinary stones, herbal medicine treatment	3	291	294
Feline urolithiasis, herbal medicine treatment	2	5	7
Feline urinary stones, herbal medicine treatment	2	22	24
Cat urolithiasis, medicinal plant treatment	1	69	70
Cat urinary stones, medicinal plant treatment	0	417	417
Feline urolithiasis, medicinal plant treatment	1	4	5
Feline urinary stones, medicinal plant treatment	1	28	29
Cat urolithiasis, herbal extract therapy	2	61	63
Cat urinary stones, herbal extract therapy	2	246	248

Feline urolithiasis, herbal extract therapy	0	4	4
Feline urinary stones, herbal extract therapy	0	19	19
Cat urolithiasis, phytotherapy	1	9	10
Cat urinary stones, phytotherapy	1	36	37
Feline urolithiasis, phytotherapy	0	0	0
Feline urinary stones, phytotherapy	0	0	0
Total	**22**	**1275**	**1297**

Diagram 7.1: Flow chart illustrating the PRISMA flow diagram and result of screening for systematic review



8.0 Results

The result of the screening for this review has been illustrated in Diagram 7.1. A total of 2356 literatures were obtained from the keyword search. 50 literatures were obtained from PubMed while 2306 literatures were obtained from Science Direct. After the first screening, a total of 1553 were identified as duplicates in citation using EndNote website and was removed resulting in 803 literatures. The second screening excluded 402 items of literature as they general herbal medicine studies and scope irrelevant or beyond treating urolithiasis. The final 401 literatures were screened manually according to the review's inclusion and exclusion criteria.

Therefore, a total of 35 literatures were selected for this systematic review, where most of the studies reported were in-vivo studies in animals especially rats, cats and dogs. 11 herbal medicines were identified and reviewed, with the common ones named *Phyllanthus niuru*, *Arctostaphylos uva-ursi*, *Vaccinum macrocarpon*, *Tribulus terrestris* and so on.

Table 8.1 shows the number of studies published according to the type of herbal plants used to treat urolithiasis in cats and dogs reported from year 2000 to 2021. Each table contains information on the cited study, the year of study, the common and scientific names of the plant with the part of the plant that was employed and antiurolithic activity/mechanism with the possible toxicological effects. The table only shows 21 references because some of the plants were actually studied on their efficacy before the timeframe of this review.

Table 8.1: Summarized data of the common species of herbal plants used to treat urolithiasis with their specifications

Scientific name	Family	Common Name	Part Used	Antiurolithic activity	Toxicity (Prolonged use/High dose)	Reference
Apium graveolens	*Apiaceae*	Celery	Flower, seeds	Urinary tract infection	Nephritis, abortion	Rocha & Granato (2021) *Stiani et al.* (2019) Sumalatha (2017)
Arctostaphylos uva-ursi	*Ericaceae*	Bearberry	Fruit	Urinary tract infection, Diuresis	Hepatotoxicity	Rocha & Granato (2021) Tahseen (2013) Butterweck & Khan (2009) Gürocak & Kupeli (2006)
Crataeva nurvala	*Crataeva*	Three leaved caper	Bark	Urolithiasis, Diuresis	Reddening and blistering upon topical application	*Prasad et al.* (2007) Aggarwal (2014)
Echinodorus macrophyllus	*Alismataceae*	Aquatic plant	Leaves	Diuresis	Risk of degenerative diseases	Rocha & Granato (2021) *Pereira et al.* (2020)
Equisetum arvense	*Equisetaceae*	Field horsetail	Seeds	Urinary tract infection, Diuresis	Heart or kidney disease, Abortion Lactation	Rocha & Granato (2021) *Smyslova et al.* (2017)
Moringa oliefera	*Moringaceae*	Drumstick tree	Rootbark	Diuresis	-	*Jordan et al.* (2015) *Karadi et al.* (2006)

Phyllanthus niuru	*Phyllanthaceae*	Gale of wind	Whole plant	Urolithiasis	Abortion	Rocha & Granato (2021) *Pucci et al.* (2018) *Smyslova et al.* (2017) *Cruces et al.* (2013) *Moran et al.* (2013) Marques (2013) *Asare et al.* (2012) Butterweck & Khan (2009) Gürocak & Kupeli (2006) Atmani (2003)
Tribulus terrestris	*Zygophyllaceae*	Puncturevine	Fruit, leaves	Diuresis	Increase estrogen secretion	Aggarwal (2014) *Cruces et al.* (2013) Tahseen (2013) *Joshi et al.* (2005)
Trigonella foenum-graecum	*Fabaceae*	Fenugreek Seeds	Seeds	Solute balance	-	Chinmay et al. (2013)
Vaccinum macrocarpon	*Ericaceae*	Cranberry	Fruit juice	Urinary tract infection	Concurrent use with warfarin	Rocha & Granato (2021) *Olszewski et al* (2020) Butterweck & Khan (2009) *Moran et al.* (2013)
Zea mays L.	*Poaceae*	Corn silk	Seed oil	Urinary tract infection, Diuresis	Heart or kidney failures, Abortion, Lactation	Rocha & Granato (2021) Gürocak & Kupeli (2006)

9.0 Discussion

Apium graveolens, also known as celery from the *Apiaceae* family has a therapeutic purpose in treating urolithiasis derived from the seeds found in the flowers. The flavonoid compound derived from the seeds have an antimicrobial activity reducing the bacterial load in the surface of urinary tract mucosa (Sumalatha, 2017). The plant's roots have a stronger diuretic effect, which is useful in the treatment of UTIs. Prolonged use of this celery medication make the uterus to contract resulting in abortion (*Stiani et al.*, 2019).

Arctostaphylos uva-ursi or bearberry contains hydroquinone heterosides as its main compound that serve as an antimicrobial activity against UTI. The hydroquinone heteroside will undergo hydrolysis by the intestinal flora and transported to the liver for conjugation releasing hydroquinone derivates that acts as an antimicrobial and antiseptic when they are excreted via urine (Tahseen, 2013). Bearberry leaves contain tannins and flavonoids, which have anti-inflammatory and diuretic actions. The anti-inflammatory and diuretic properties of this plant complement its antibacterial properties in the prevention and treatment of urinary tract infections. (Gürocak & Kupeli, 2006).

Crataeva nurvala, or the three leaved caper plant, from *Crataeva* family is very useful in treating calcium oxalate type of uroliths. The plant contains a triterpene compound, called Lupeol that reduce oxalate level and promote supersaturation in renal tissues by diuretic activity (*Prasad et al.*, 2007). The stem bark decoction from *C.nurvala* has the tendency to lower urinary and renal oxalate levels, as well as hepatic glycolate oxidase activity, which is responsible for renal oxalate crystallisation (Aggarwal,

2014). Topical treatment of *C. nurvala* leaves has been found to produce reddening and blistering in rodents.

Echinodorus macrophyllus, from *Alismataceae* family is an aquatic plant which is often used to treat rheumatism and syphilis. This plant can also be used as a diuretic and to reduce uric acid buildup (Rocha & Granato, 2021). A number of chemical compounds contribute to this mechanism of actions which are polyphenols, terpenes, tannins, and flavonoids which are derived from the leaves. Long-term and uncontrolled use of this extract may raise the risk of developing degenerative disease (*Pereira et al.*, 2020). *Equisetum arvense*, on the other hand, is diuretic due to its high amount of flavonoids, phenolic compounds, and minerals. *E.arvense* has compounds that serve to strengthen both bladder and kidney tissue, as these activities contribute in the reduction of inflammation in diseases such as nephrolithiasis, bladder and renal infections. (*Smyslova et al.*, 2015).

The rootbark of *Moringa oliefera* from *Moringaceae* family, play a regulatory function in the synthesis of oxalate. The stem bark contains two alkaloids, namely Moringine and moringinine. They decrease oxalate levels in the urinary tract by increasing calcium excretion through diuresis and hastening the process of dissolving preformed stones, hence reducing new stone formation in the urinary system. The root-wood extract also restores phosphate level (*Karadi et al.*, 2006).

The most common herbal extract retrieved from most literature that was used to treat urolithiasis for dogs and cats in this review was the *Phyllanthus niuru* species known as the gale of wind from *Phyllanthaceae* family. It is a small herb with an erect, slender, and branchy stem that grows 10 to 30 cm tall, with oval leaves, yellow-green flowers, and dry fruits. (*Cruces et al.*, 2013). Marques, 2013 has proposed that several

functioning mechanisms were postulated by the *P.niuru.* The plant extract inhibits calcium oxalate endocytosis by renal tubular cells, preventing the production of urinary stones and slowing the growth and aggregation of calcium oxalate crystals, thereby easing their removal. The effect may be due to higher levels of glycosaminoglycans (GAG) incorporated into calculi where the GAG compete with calcium for binding sites on the crystal surface. *P. niuru* can also modify the form and texture of urinary stones, making them easier to remove. It improves glomerular filtration and urine excretion of uric acid, indicating its effectiveness in removing urinary stones. The herb has analgesic effect, acting as a powerful and long-lasting anti-nociceptive activity in numerous pain models tested in rats. It exhibits antispasmodic properties owing to the inhibition of smooth muscle contraction in the ureter, which aids in the removal of urinary stones. Many phytochemicals and pharmacological studies have been conducted on this plant, resulting in the identification of many groups of chemicals such as alkaloids, flavonoids, lactones, steroids, triterpenes, lignans, and tannins (Atmani, 2003). Each of these compounds serve a different mechanism in treating urolithiaisisThe alkaloids in this plant, for example, is the one having antispasmodic actions that facilitate smooth muscle relaxation in the ureter. Triterpenes reduce renal crystal formation while also inhibiting calcium oxalate-induced cytotoxicity. The triterpenes also inhibit calculi formation by diluting promoters and preserving tissues (*Moran et al.*,2013). In-vivo studies have revealed that lignans from the plant compound has the ability to lower uric acid levels in hyperuricemic rats (Rocha & Granato, 2021). The *P. niuri* plant is abortive when used in excessive doses, so it is not suitable to be used in treating pregnant animals (*Asare et al.*, 2012).

The fruit of *Tribulus terrestris* has a potential diuretic activity after studies were conducted on anesthetized dogs. The studies revealed that the ether extract from the fruit is shown to enhance glomerular filtration accompanied with a considerable improvement in creatinine clearance. These effects were demonstrated to be comparable to responses obtained with a furosemide dosage of 120 mg/kg. (Aggarwal, 2014). Fenugreek seeds, or *Trigonella foenum-graecum* have been studied to enhance urine excretion of oxalate, citrate, and chloride but not sodium and potassium. This prevents a hypokalemic environment in the urine, which has the potential to reduce citrate excretion and encourage stone formation (*Chinmay et al.*, 2013).

Vaccinium macropan, also known as cranberry from the *Ericaceae* family features little green leaves, dark pink blossoms, and white berries that become red as they grow (Rocha & Granato, 2021). The main compounds found to be having the greatest therapeutic relevance in the plant is the proanthocyanidins (PAC) for the prevention and treatment of urinary tract infections (UTI) (*Moran et al.*, 2013). The PAC in the fruit has an antimicrobial activity that inhibits the binding of bacteria possessing fimbriae such uropathogenic *Escherichia coli* to the urinary tract mucosa, thus preventing them from reproducing and proliferating (*Olszewski, V.R. et al.*, 2020) The large amount of vitamin C in the fruit allows bacteriostasis through acidification of the urine by lowering the urine pH and increasing diuresis (Butterweck & Khan, 2009). Cranberries are contraindicated when the patient is undergoing warfarin therapy as the juice destabilizes the warfarin and increases the risk of bleeding (Rocha & Granato, 2021).

Zea mays, or also known as corn silk from *Poaceae* family is used for its diuretic potential, due to potassium salts and flavonoids present in their chemical composition. According to research, the diuretic action is achieved by reducing sodium tubular

reabsorption, which results in sodium excretion accompanied by a larger urine volume. (Gürocak & Kupeli, 2006). However, the plant is not recommended giving to animals having heart or renal disease, pregnancy, or lactation as it causes uterine stimulation due to sterol activity. It is not suggested for long-term or excessive usage since it might cause vomiting, cramping, and diarrhoea (Rocha & Granato, 2021).

There are several herbs that were identified in the literature were studied before the timeframe of this review which is before the year 2000. Those herbs were also identified in the recent literature, however those extracts usually possessing diuretic activity cannot be acknowledged in this review for treatment of urolithiasis as the entire mode of action for cure is not completely elucidated scientifically. An example of extract is *Randia echinocarpa* in which has the mechanism of action is assumed to be due to the extract's binding to the crystal surface, which increases crystal growth and the crystal aggregation rate. However, studies conducted by *Vargas Solis et al*., 1999 suggested that this extract should be avoided in treating urolithiasis as the plant itself can also work as a urolithogenic agent.

Costus spiralis or also known as spiral ginger is another popular herbal remedy that was studied to reduce the growth of urinary stones conducted by *Araujo Viel et al*., 1998 but concluded that the mechanisms behind this action are yet unclear and appear to be unrelated to increased diuresis and excretion of urinary salts that form stones.

Agropyron repens is another popular extract used to treat urinary tract infections and calculi (*Grases et.al.*,1995). The principal effects of this medicine have been proven to be decreased citruria, increased calciuria, and decreased magnesium, implying that its usage is even contraindicated. has been reported to lower urinary oxalate excretion

and may be effective in the treatment of hyperoxaluria, although the actual mechanism of action of banana stem extract on urinary oxalate excretion is unknown. (Poonguzhali, 1994).

10.0 Conclusion

Based on the findings of this review, it is possible to conclude that the phytotherapeutic substances could be used as alternative or complement therapies to existing antilitholytic therapies. The reviewed research suggests that a few mechanisms of action of plants related to diuretic, increasing urinary oxalate excretion, antioxidant, antimicrobial, and inhibitory characteristics contribute the effectiveness of these plants in treating urolithiasis. The efficacy of herbal plants in treating urolithiasis before the timeframe of this review were also compared to the modern day herbal plants in this study. As a result, the modern herbal plants are safer to be used compared to the traditional ones as the mechanism of action with the side effects are well studied.

11.0 Recommendations and future work

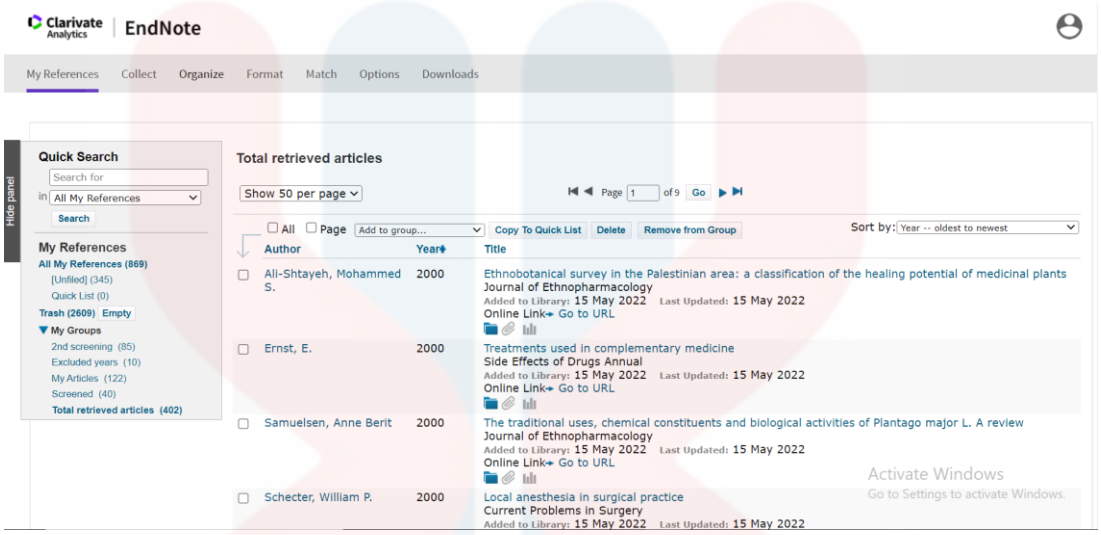
Most herbal medicine reviewed in this research were evaluated in experimental studies on conducted on animals, especially rats. The plants were tested on the experimentally induced urolithiasis, mainly against calcium oxalate type of urolith formation. There is lack of data on the use of herbal extracts against other urolith types which result in questionable therapy outcomes. Experimental studies such as randomized clinical trials on evaluation of those plants against urolith types should be included and done in the future to provide a more regulated and accurate result.

Apart from that, there are no reports in those literatures on their adverse effects of these herbs after long term consumption. More databases or search keywords on the side effects of herbs should also be explored particularly regarding the quality and safety aspects using herbs in treating urolithiasis.

Last but not least, bias assessment should be conducted to study the potential biases of each article to evaluate the degree of validity of the evidence offered in those articles.

Appendix

Appendix 1: Printscreen from Endnote Web after second screening.



References

Anand, R., Patnaik, G. K., Srivastava, S., Kulshreshtha, D. K., & Dhawan, B. N. (1994). Evaluation of Antiurolithiatic Activity of Tribulus Terrestris. International Journal of Pharmacognosy, 32(3), 217-224.

Antonio, R. L., Souza, R. M., Furlan, M. R., Pedro, C. R., Cassas, F., Honda, S., & Rodrigues, E. (2015). Investigation of urban ethnoveterinary in three veterinary clinics at east zone of São Paulo city, Brazil. J Ethnopharmacol, 173, 183-190.

Aggarwal, A., Singla, S. K., & Tandon, C. (2014). Urolithiasis: phytotherapy as an adjunct therapy. *Indian J Exp Biol*, *52*(2), 103-111.

Araújo Viel, T., Diogo Domingos, C., da Silva Monteiro, A. P., Riggio Lima-Landman, M. T., Lapa, A. J., & Souccar, C. (1999). Evaluation of the antiurolithiatic activity of the extract of Costus spiralis Roscoe in rats. J Ethnopharmacol, 66(2), 193-198.

Asare, G. A., Bugyei, K., Sittie, A., Yahaya, E. S., Gyan, B., Adjei, S., . . . Nyarko, A. K. (2012). Genotoxicity, cytotoxicity and toxicological evaluation of whole plant extracts of the medicinal plant Phyllanthus niruri (Phyllanthaceae). *Genet Mol Res*, *11*(1), 100-111.

Atmani, F. (2003). Medical management of urolithiasis, what opportunity for phytotherapy? *Front Biosci*, *8*, s507-514.

Atmani, F., Farell, G., & Lieske, J. C. (2004). Extract from Herniaria hirsuta coats calcium oxalate monohydrate crystals and blocks their adhesion to renal epithelial cells. *J Urol*, *172*(4 Pt 1), 1510-1514.

Atmani, F., Slimani, Y., Mimouni, M., Aziz, M., Hacht, B., & Ziyyat, A. (2004). Effect of aqueous extract from Herniaria hirsuta L. on experimentally nephrolithiasis rats. *Journal of ethnopharmacology*, *95*(1), 87-93.

Bahmani, M., Baharvand-Ahmadi, B., Tajeddini, P., Rafieian-Kopaei, M., & Naghdi, N. (2016). Identification of medicinal plants for the treatment of kidney and urinary stones. *J Renal Inj Prev*, *5*(3), 129-133.

Bartges, J. W., & Callens, A. J. (2015). Urolithiasis. *Vet Clin North Am Small Anim Pract*, *45*(4), 747-768.

Bousta, D., Grafov, A., & Houssaini, T. S. (2021). Phytomolecules investigated for the prevention and treatment of urinary stones. *Mediterranean journal of chemistry*.

Butterweck, V., & Khan, S. R. (2009). Herbal medicines in the management of urolithiasis: Alternative or complementary? [Review]. *Planta Medica*, *75*(10), 1095-1103.

Chen, Y., Tsai, F., & Chen, W. (2008). Phytotherapies for urolithiasis. *A phoenix rising from fire: new applications of old traditional herbs*, 17-38.

Cruces, I. L., Patelli, T. H. C., Tashima, C. M., & Mello-Peixoto, E. C. T. (2014). Using medicinal plants in the control of urolithiasis [Review]. *Revista Brasileira de Plantas Medicinais*, *15*(SUPPL. 1), 780-788.

Daniels, M., Bartges, J. W., Raditic, D. M., Marsden, S., Cox, S. K., & Callens, A. J. (2018). Evaluation of three herbal compounds used for the management of lower urinary tract disease in healthy cats: a pilot study. *J Feline Med Surg*, *20*(12), 1094-1099.

Deo, Rahul & Jain, S & Alok, Dr. Shashi & Mahor, Alok & Bharti, jay prakash & Jaiswal, Manoj & Yadav, Rahul. (2010). A review: Herbal plants used in the treatment of Urolithiasis. Int J Pharm Sci Res. 2.

Emiliani, E., Jara, A., & Kanashiro, A. K. (2021). Phytotherapy and Herbal Medicines for Kidney Stones. *Curr Drug Targets*, *22*(1), 22-30.

Grases, F., Prieto, R. M., Gomila, I., Sanchis, P., & Costa-Bauzá, A. (2009). Phytotherapy and renal stones: the role of antioxidants. A pilot study in Wistar rats. *Urol Res*, *37*(1), 35-40.

Grases, F., Ramis, M., Costa-Bauzá, A., & March, J. G. (1995). Effect of Herniaria hirsuta and Agropyron repens on calcium oxalate urolithiasis risk in rats [Article]. *Journal of Ethnopharmacology*, *45*(3), 211-214.

Gomes, Veridiane & Ariza, Paula & Borges, Naida & Schulz, Francisco & Fioravanti, Maria Clorinda. (2018). Risk factors associated with feline urolithiasis. Veterinary Research Communications. 42. 10.1007/s11259-018-9710-8.

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. *J Family Med Prim Care*, *2*(1), 9-14.

Gurocak, Serhat & Küpeli, Bora. (2006). Consumption of Historical and Current Phytotherapeutic Agents for Urolithiasis: A Critical Review. The Journal of urology. 176. 450-5.

Jordan, M. G., Disney, B., Amstrong, E. F., & Luther, L. J. Dissolution of canine uroliths by Moringa root extracts using various aqueous and organic solvents.

Joshi, V. S., Parekh, B. B., Joshi, M. J., & Vaidya, A. B. (2005). Herbal extracts of Tribulus Terrestris and Bergenia ligulata inhibit growth of calcium oxalate monohydrate crystals in vitro [Conference Paper]. *Journal of Crystal Growth*, *275*(1-2), e1403-e1408.

Kant, R., Singh, T. G., & Singh, S. (2020). Mechanistic approach to herbal formulations used for urolithiasis treatment [Review]. *Obesity Medicine*, *19*, Article 100266.

Kapase, Chinmay & Bodhankar, Subhash & Mohan, Viswanathan & Thakurdesai, Prasad. (2013). Therapeutic effects of standardized fenugreek seed extract on experimental urolithiasis in rats. Journal of Applied Pharmaceutical Science. 3. 29-35.

Karadi, R. V., Gadge, N. B., Alagawadi, K. R., & Savadi, R. V. (2006). Effect of Moringa oleifera Lam. root-wood on ethylene glycol induced urolithiasis in rats. J Ethnopharmacol, 105(1-2), 306-311.

Khan, A., Bashir, S., & Khan, S. R. (2021). Antiurolithic effects of medicinal plants: results of in vivo studies in rat models of calcium oxalate nephrolithiasis—a systematic review [Review]. *Urolithiasis*, *49*(2), 95-122.

Khokhlenkova, N. V., Buryak, M. V., Povrozina, O. V., & Kamina, T. V. (2019). Principles of the urolithiasis phytotherapy [Review]. *Research Journal of Pharmacy and Technology*, *12*(9), 4559-4564.

Lulich, J., Berent, A., Adams, L., Westropp, J. L., Bartges, J., & Osborne, C. (2016). ACVIM small animal consensus recommendations on the treatment and prevention of uroliths in dogs and cats. *Journal of veterinary internal medicine*, *30*(5), 1564-1574.

Lulich, J. P., & Osborne, C. A. (2009). Changing paradigms in the diagnosis of urolithiasis. *Veterinary Clinics of North America: Small Animal Practice*, *39*(1), 79-91.

Mansoor, M., Jamil, M., Latif, N., Muhammad, S., Gull, J., Shoab, M., & Khan, A. (2019). Review Importance of Herbal Plants in the Management of Urolithiasis. *Biological Sciences-PJSIR*, *62*(1), 61-66.

Marques, Luis C. (2013). Phyllanthus niruri (Quebra-Pedra) in the Treatment of Urolithiasis: Documentation Proposal for Simplified Registration as a Herbal Medicine. Fitos Magazine, [S.l.], v. 5, n. 03, p. 20-33.

Monti, E., Trinchieri, A., Magri, V., Cleves, A., & Perletti, G. (2016). Herbal medicines for urinary stone treatment. A systematic review. *Arch Ital Urol Androl*, *88*(1), 38-46.

Morán, E., Budía, A., Broseta, E., & Boronat, F. (2013). Phytotherapy in urology. Current scientific evidence of its application in urolithiasis, chronic pelvic pain, erectile dysfunction and urinary tract infections [Short Survey]. *Actas Urologicas Espanolas*, *37*(3), 174-180.

Nirumand, M. C., Hajialyani, M., Rahimi, R., Farzaei, M. H., Zingue, S., Nabavi, S. M., & Bishayee, A. (2018). Dietary Plants for the Prevention and Management of Kidney Stones: Preclinical and Clinical Evidence and Molecular Mechanisms. *Int J Mol Sci*, *19*(3).

Olszewski, V., Bastos, T., Komarcheuski, A., Oliveira, S., Warth, J., & Félix, A. (2020). Cranberries (Vacciniummacrocarpon aiton) in dog nutrition: influence on diet digestibility and palatability and in the course of urinary tract infections. Arquivo Brasileiro de Medicina Veterinária e Zootecnia, 72, 1971-1979.

Pareta, Surendra & Patra, Kartik & Mazumder, Papiya & Sasmal, Dinakar. (2011). Establishing the Principle of Herbal Therapy for Antiurolithiatic Activity: A Review. Journal of Pharmacology and Toxicology. 6. 321-332..

Patle, A., Hatware, K. V., Patil, K., Sharma, S., & Gupta, G. (2019). Role of Herbal Medicine in the Management of Urolithiasis- A Review for Future Perspectives. *J Environ Pathol Toxicol Oncol*, *38*(2), 97-118

Pedro, R. N., Aslam, A. U., Bello, J. O., Bhatti, K. H., Philipraj, J., Sissoko, I., . . . Buchholz, N. (2020). Nutrients, vitamins, probiotics and herbal products: an update of their role in urolithogenesis [Review]. *Urolithiasis*, *48*(4), 285-301

Pereira, Hebert & Reis, Fernando & Machado, Ana Maria & Marques, Andréa & Garcia, Cleverson & Gomes, Fátima & Nelson, David. (2020). Characterization of the volatile compounds and anatomical features in commercial samples of Echinodorus plant species. Research, Society and Development. 9. e8719109199.

Poonguzhali, P. K., & Chegu, H. (1994). The influence of banana stem extract on urinary risk factors for stones in normal and hyperoxaluric rats. Br J Urol, 74(1), 23-25.

Prasad, Koganti & Dodoala, Sujatha & Koganti, Bharathi. (2007). Herbal drugs in urolithiasis-A review. Pharmacognosy Rev. 1. 175-179.

Pucci, N. D., Marchini, G. S., Mazzucchi, E., Reis, S. T., Srougi, M., Evazian, D., & Nahas, W. C. (2018). Effect of Phyllanthus niruri on metabolic parameters of patients with kidney stone: A perspective for disease prevention [Article]. *International Braz J Urol*, *44*(4), 758-764

Raditic, D. M. (2015). Complementary and Integrative Therapies for Lower Urinary Tract Diseases. *Veterinary Clinics of North America: Small Animal Practice*, *45*(4), 857-878

Rocha, C. O., & Granato, A. C. (2021). Medicinal plants used in the phytotherapeutic treatment of urolithiasis in dogs – an integrative review. *Research, Society and Development*, *10*(12), e501101220876

Santhoshi, B., Chidrawar, V., Uma, V., & Rao, M. (2020). A Brief Review On The Potential Medicinal Plants And Screening Models Of Urolithiasis. International Journal of Advances In Pharmaceutical Research, 6, 37-45.

Shaffril, H., Samsuddin, S. F., & Abu Samah, A. (2021). The ABC of systematic literature review: the basic methodological guidance for beginners. Quality & Quantity, 55, 1-28.

Singh, A., & Chitra, V. (2019). A probe on the activity of herbal medicines in nephrolithiasis [Review]. Research Journal of Pharmacy and Technology, *12*(9), 4539-4544

Smyslova, O. A., Litvinova, T. M., Glazkova, I. U., Denisova, M. N., Ermakov, D. A., & Suvorova, I. I. (2017). Pharmacotherapeutic efficiency of the new complex urological herbal medicine in experimental urolithiasis [Article]. International Journal of Green Pharmacy, *11*(4), S730-S736.

Stiani, S. N., Syahidah, F. M., Fikriani, H., Subarnas, A., & Rusdiana, T. (2019). Anticalculi Activity of Apigenin and Celery (Apium graveolens L.) Extract in Rats Induced by Ethylene Glycol-Ammonium Chloride. J Pharm Bioallied Sci, 11(Suppl 4), S556-s561.

Sultana, Bushra & Anwar, Farooq & Ashraf, Muhammad. (2009). Effect of Extraction Solvent/Technique on the Antioxidant Activity of Selected Medicinal Plant Extracts. Molecules (Basel, Switzerland). 14. 2167-80.

Tahseen, Moh & Mishra, Garima. (2013). Ethnobotany and Diuretic Activity of Some Selected Indian Medicinal Plants: A Scientific Review. The Pharma Innovation. 2. 109-121.

Tion, Matthew & Dvorska, Julia & Alhaji Saganuwan, Saganuwan. (2015). A Review on urolithiasis in dogs and cats. Bulgarian Journal of Veterinary Medicine. 18. 1-18. 10.15547/bjvm.806.

Varalakshmi, P., Shamila, Y., & Latha, E. (1990). Effect of Crataeva nurvala in experimental urolithiasis. Journal of Ethnopharmacology, 28(3), 313-321.

Vargas Solis, R., & Perez Gutierrez, R. M. (2002). Diuretic and urolithiasis activities of the aqueous extract of the fruit of Randia echinocarpa on rats. J Ethnopharmacol, 83(1-2), 145-147.

Waqas, M., Saqib, I.-u.-d., Imran Jamil, M., Ayaz Khan, M., & Akhter, S. (2017). Evaluating the importance of different computed tomography scan-based factors in predicting the outcome of extracorporeal shock wave lithotripsy for renal stones. icu, 59(1), 25-31.

Wynn, S. G., & Fougère, B. J. (2007). CHAPTER 20 - Veterinary Herbal Medicine: A Systems-Based Approach. In S. G. Wynn & B. J. Fougère (Eds.), *Veterinary Herbal Medicine* (pp. 291-409). Mosby