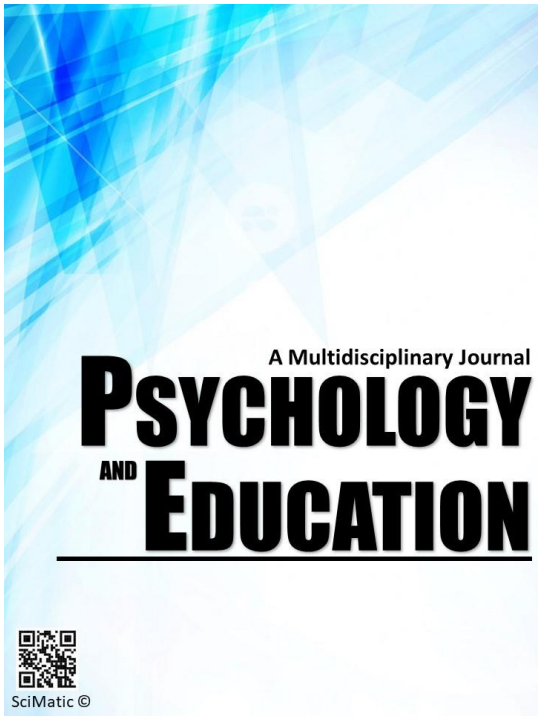
A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE IN VITRO ANTIUROLIATHIC STUDIES UTILIZING MEDICINAL AND HERBAL PLANTS



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Research Article

A Systematic Review and Meta-Analysis on the in Vitro Antiuroliathic Studies Utilizing Medicinal and Herbal Plants

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Abstract

Urolithiasis is one of the conditions that has found its medicine in nature. This research was conducted using a systematic review and meta-analysis of published journals from a number of reputable research sources. The goal of this meta-analysis is to find out whether medicinal and herbal plants have antiurolithiatic properties in in-vitro research. The heterogeneity between the studies was minimized by summarizing the various types of plant extracts used and evaluating the capacity of various solvents to prevent calcium oxalate formation, and the data were analyzed according to the percentage dissolution. The results revealed that the aqueous extracts of Kalanchoe pinnata, Chloris barbata , Gossypium Herbaceum Linn, Vigna radiata, and Euphorbia thymifolia Linn; methanolic extracts of Mentha piperita, and Vigna Mungo Linn; ethanolic extracts of Chloris barbata, Gossypium Herbaceum Linn, Euphorbia thymifolia Linn, Piper nigrum, and Syzygium cumini; hydroalcoholic extract of Euphorbia thymifolia Linn and butanolic extract of Digitaria sanguanalis exhibited antiurolithiatic effects since they significantly reduced calcium oxalate accumulation based on high percentage dissolution of the experimental kidney stone by the plant extracts as compared to the standard drugs used. The findings of this study can be used as a guideline for future researchers studying medicinal and herbal plants native to the Philippines.

Keywords: *medicinal plants, education, meta-analysis, herbal plants, antiurolithiasis*

Introduction

Urolithiasis is the presence of one or more calculi in any location within the urinary tract, and it is one of the oldest and most common diseases known to man (Manasa et al., 2018). Over the years, the occurrence and prevalence of urolithiasis have increased (Qian et al., 2022). According to the World Health Organization (WHO), approximately 12 percent of men and 55 percent of women will experience at least one episode of kidney stone during their lifetime (Naharika et al. 2018). In the Philippines, a study that shows 2.3 percent of the entire population has, kidney stones and out of 90 million Filipinos, it is possible that 2 million have kidney stones without knowing it (Villar, 2017).

Because of the rising number of cases and recurrences of urolithiasis, a global research, and development, is relatively high. Medical practitioners have used synthetic drugs and procedures to treat urolithiasis, such as endoscopic stone removal and extracorporeal shock wave lithotripsy, but the procedures are expensive and recurrence is common (Manasa et al., 2018). Moreover, Aryal et al. (2019) state that technological progress in the treatment of kidney stones has been remarkable, but it has resulted in several complications such as a high recurrence rate, hemorrhage, hypertension, and tubular nephrosis. With the effects of synthetic drugs and procedures mentioned above, humans have been motivated to return to nature for safe remedies (Naharika et al., 2018). According to Sharma et al. (2016), there is a growing public interest in urolithiasis herbal medicine in both developed and developing countries due to their broad biological and medicinal values, low toxicity, and lower costs.

Natural plant extracts have been used for medicinal purposes since ancient times. A medicinal plant is one whose therapeutic capabilities and contents have been scientifically verified and which includes substances that can be utilized for therapeutic reasons or that are precursors for the manufacture of valuable pharmaceuticals in one or more of its organs (Sofowora et al., 2013). Moreover, herbal plants are defined as plants that are commonly used for disease treatment and prevention (Firenzuoli & Gori, 2007). On a 5000-year-old Sumerian clay slab from Nagpur, the oldest written evidence of medicinal plant use for drug preparation was discovered. It included 12 recipes for drug preparation based on over 250 different plants. (Petrovska, 2012). According to the WHO, herbal medicines are used by 80% of the world's population, and over 21,000 plant species have the potential to be used as medicinal plants (Khan, 2016).

There have been studies that show positive results when medicinal and herbal plants are used as a natural remedy for urolithiasis. Naharika et al., (2018) found that the plant Chloris barbata has antiurolithiatic properties in an in vitro study titled "Evaluation of In

Vitro Antiurolithiatic Activity of Chloris barbata." Manasa et al., (2018) reported the same conclusion in their work ―Evaluation of In Vitro Antiurolithiatic Activity of Mentha piperita.‖ The plant also has antiurolithic properties. With the current research on medicinal and herbal plants with antiurolithiatic properties. Most studies are conducted to investigate the various medicinal and herbal plants that have antiurolithiatic properties; however, in this study, the researcher intended to conduct a systematic review and meta-analysis to look into the various medicinal and herbal plants that are positive with antiurolithiatic properties.

The researcher would share the findings with the faculty members and students in the related field, through a symposium. It will also be presented through a national or international research forum, and to widely disseminate, this study will be submitted to an online refereed journal for publication.

Review Question

This study aimed to conduct a systematic review and meta-analysis on the in vitro antiurolithiatic study utilizing medicinal and herbal plants. Specifically, It sought answers to the following questions:

1. What is the percentage dissolution of CaOx in each plant extract as compared to the standard drug used?
2. What are the known medicinal and herbal plants that exhibit antiurolithiatic properties?
3. In testing the antiurolithiatic property of medicinal and herbal plants, what is the effect of using medicinal and herbal plants on experimental kidney stones compared with standard drugs?

Literature Review

Medicinal and Herbal Plants

Ancient medical knowledge has been introduced to us through the use of various plants found in nature, and this knowledge has been passed down from generation to generation. Medicinal plants are plants that are used in herbalism, which is the use of plants for medicinal purposes as well as the study of such uses (Khan, 2016). Medicinal plants have the ability to cure certain diseases and may be a source of potential drugs (Boy et al., 2018). According to the record, humans have been using plants as medicines for at least 60,000 years (Yuan et al., 2016). Plants have been subjected to extensive scientific research to confirm their efficacy over the years, and such plants should be classified as medicinal plants (Sofowora et al., 2013). "Crude drugs" or drugs of natural or biological origin are terms used by pharmacists and pharmacologists to describe whole plants or parts of plants that have medicinal properties.

Furthermore, herbs are medicinal plants (also known as phytomedicines) that can be administered as the whole plant or plant parts, or by extracting one or more ingredients with solvents to produce tinctures, tea, or other extracts, according to Albers (2012). In addition, Firenzuoli and Gori (2007) defined herbs as natural products whose chemical composition varies depending on several factors and thus varies from person to person, ranging from energetic decoctions to the use of herbal extracts in accordance with Western methodologies of mainstream medicine.

The use of herbal medicine is more affordable, more closely aligns with the patient's ideology, alleviates concerns about the adverse effects of chemical (synthetic) medicines, satisfies a desire for more personalized health care, and allows greater public access to health information, among the most common reasons for using it (Galor & Benzie 2011).

Recorded Medicinal Plants Used for Antiurolithiatic Study

According to Deering (2019), 11 % of the 252 medications classified "basic and essential" by the World Health Organization at the start of the twenty-first century were "exclusively of flowering plant origin."In this regard, Nagal & Singla (2013) published a list of medicinal and herbal plants that have been utilized in vitro studies for the treatment of urolithiasis. The following are some of the plants mentioned in the study:

Herniaria hirsute. The common name of *Herniaria hirsuta* is hairy rupturewort. Southern Europe and southwest Asia are the origins of hairy rupturewort. It has long been used in Morocco as a traditional herbal cure for kidney stones (Botany, 2021). In addition, according to Ammor et al., (2018) in Moroccan folk medicine, *Herniaria hirsuta* has been used to treat biliary dyskinesia, urolithiasis, and as a diuretic.

Tribulus terrestris. Also known as the puncture vine is a spine-covered Mediterranean fruit-producing shrub (Stuart & Mikstas, 2021). Furthermore, puncture vine is a natural herb that is used to treat a variety of disorders and can be found in a variety of tropical and temperate climates around the world, including the United States and Mexico, the Mediterranean region,

and Asia. T. terrestris has properties that are aphrodisiac, antihypertensive, diuretic, and antiurolithiatic. (Kamboj et al., 2011)

Bergenia ligulata. *Bergenia ligulata* Wall is a highly appreciated medicinal herb and one of the most well-known examples of contentious medications (Gurav & Gurav, 2014). Antiurolithic, antiviral, free radical scavenging, antidiabetic, hepatoprotective, diuretic, antipyretic, anti oxaluria, antitumor, antibacterial, antifungal, anti-inflammatory, anti-implantation, and cardioprotective activities are all demonstrated by crude extracts and isolated compounds from B. ligulata. (Gurav & Gurav, 2014)

Dolichos biflorus. Muthira is a branching, suberect, and downing herb that is native to most of India (Mathew et al., 2014). Kidney problems, dysuria, rashes, and tumors are the most common uses for the young plant. The plant's seeds are used to treat urinary problems, kidney stones, piles, discomfort, constipation, wounds, urinary calculi, cough, edema, and asthma with diuretic and spasmolytic properties (Kaushik et al., 2021).

In addition, the medicinal and herbal plants used in the in vitro antiurolithiatic investigation are listed below as mentioned in other studies.

***Moringa oleifera* Root Bark.** Certain research in India used the root bark of *Moringa oleifera* Lam. (Moringaceae) which is reported to be useful in the treatment of urinary stones. *Moringa oleifera* is commonly known as drumstick or horseradish. The root bark is used as an aphrodisiac, alexiteric, anthelmintic, analgesic, and for heart complaints, eye diseases, inflammation, dyspepsia, etc. Root juice mixed with milk is used as an antilithic. Though the purpose for using this plant has not been proven scientifically. The study's findings support M. oleifera's historic use in the treatment of kidney stone sufferers. The mechanism behind this action is uncertain, however it appears to be linked to diuresis and decreased urine concentrations of stone-forming components (Karadi, et al., 2009)

Punica granatum. In this study, the researcher used *Punica granatum* or pomegranate seeds for the evaluation of antiurolithiatic activity. *Punica granatum* (Family: Punicaceae) is a tree that grows best in well-drained ordinary soil. The edible fruit is a berry that is between a lemon and a grapefruit in size, with thick reddish skin with a diameter of 5-12 cm and a rounded hexagonal shape. The edible rail is a water-laden pulp that surrounds each seed and ranges in color from white to deep crimson or purple. Pomegranate seeds are embedded in a white, spongy, astringent pulp with 85.4 percent water, 10.6 percent total sugars, 1.4 percent pectins, and 0.2-1.0 percent polyphenols (Sindu et al., 2012).

Allium sativum. *C*ommonly known as garlic. In this study, *Allium sativum* was cultivated well-drained moderately clay loamy soil. It was used for the evaluation of antiurolithiatic activity and in this study garlic and pomegranate were both evaluated. Garlic bulbs contain 29% of carbohydrates, about 56% of proteins (albumin), 0.1% of fat, mucilage, and 0.06 to 0.1% of volatile oil. It also contains phosphorus, iron, and copper. The volatile oil of the drug is the chief active constituent, and contains allyl propyl disulphide, diallyl disulphide alliin and allicin. Garlic boosts the creation of nitric oxide and hydrogen sulphide, which relax blood vessels and improve kidney circulation, preventing the formation of infectious stones, according to the findings of the study. Finally, the researcher discovered that garlic produced superior results than pomegranate (Sindu et al., 2012).

Calcium Oxalate. Calcium oxalate(CaOx) is an oxalate mineral that occurs naturally in humans, plants, and various industrial processes (Hegnauer, 2019). In humans, calcium oxalate can precipitate and cause kidney stones (urolithiasis) in the urogenital tract. Many in vitro and in vivo models have been designed to effectively understand the mechanisms underlying the urinary stone formation and to test the effects of various therapeutic agents and protocols on disease development and progression. The most common type of stone used was calcium oxalate (Khan, 1995)

Urolithiasis

The calculi or stones that form the urinary tract are referred to as urolithiasis. Calcium makes up around 85% of calculi, mostly calcium oxalate; uric acid makes up 10%; cystine makes up 2%, and magnesium ammonium phosphate makes up the rest (struvite). Urolithiasis is a condition in which calcifications occur in the urinary system, most commonly in the kidneys or ureters but also in the bladder or urethra. Approximately 10% of people will get kidney stones at some point in their lives. Furthermore, one person in every 1000 people was admitted to the hospital due to urolithiasis, according to the data. This disorder appears to be more common in men than in women, with a 3:1 risk ratio, and those between the ages of 20 and 40 are more likely to acquire kidney stones (Yolanda, 2018).

Although various variables may raise your risk of developing urolithiasis, there is no specific cause. Renal calculi, on the other hand, occur when the urine is too salty and contains minerals such as calcium oxalate, struvite (ammonium magnesium phosphate), uric acid, and cystine. Calcium is found in 60-80% of stones (Worcester & Coe, 2010). The creation of Randall's plaque is another element that contributes to the formation of stone. In the basement membrane of the thin loops of Henle, calcium oxalate precipitates develop; these gradually build up in the renal papillae's subepithelial region, forming Randall's plaque and eventually a calculus (Evan et al., 2006). Furthermore, urine may lack chemicals that prevent crystals from sticking together, resulting in an ideal environment for the formation of stones.

There are a number of identified risk factors for developing urolithiasis. One of them has a connection to the family. If you have a family history of kidney stones, you are more likely to have them as well. Second, dehydration, which occurs when you don't drink enough water during the day, can raise your risk of kidney stones. Third, dietary factors, such as a high-protein, sodium (salt), and sugar diet, may raise the risk of kidney stones in some cases. This is particularly true if you eat a high-sodium diet. Obesity has been related to an increased incidence of kidney stones, as has a high body mass index (BMI), a large waist circumference, and weight growth (Mayo, 2020).

Treatments have been created to address the health hazard caused by a rise in the number of persons who got urolithiasis, which resulted in a variety of health issues. In general, good diet and medication use are required to prevent the first and second bouts of urolithiasis. The best way to avoid kidney stones is to follow a healthy diet (Alelign & Petros, 2018). Furthermore, patients are encouraged to drink more water because appropriate fluid intake reduces urine saturation and finally dilutes calcium oxalate crystallization promoters. In addition, high-oxalate foods such as spinach, almonds, potato chips, fries, and beets are discouraged or limited in consumption. It's also critical to cut back on sodium consumption. By decreasing renal tubular calcium reabsorption and increasing urine calcium, sodium raises the risk of stones (Saljoughian, 2020).

Recorded Antiruolithiatic Studies

The major goal of this first recorded study is to look into the antiurolithiatic properties of Pavonia lasiopetala leaves extract using several in-vitro models. The results revealed that the extract of Pavonia lasiopetala has a higher ability to dissolve calcium oxalate in dissolution models, whereas the Cystone standard has better demineralization for calcium phosphate than the extract of Pavonia lasiopetala. Cystone was found to have a considerable inhibitory effect in the nucleation experiment but not in the aggregation assay. In both nucleation and aggregation studies, the extract of Pavonia lasiopetala showed a strong inhibitory effect. As a result, the researchers concluded that Pavonia lasiopetala extract has considerable antiurolithiasis action in vitro (Ramprasad et al., 2019). Further, the main objective of this second recorded study is to apply in vitro methodologies in order to examine the antelithic potential of D. carota radical extract (DCRE). The results of the experiment showed that DCRE significantly inhibited the nucleation, growth, and aggregation of CaOx crystals. CaOx crystals from calcium monohydrate oxalate to calcium oxalate dihydrate have been transformed in a favorable morphological manner. The study by FT-IR validated the development of monohydrate calcium oxalate crystals utilized for growth and aggregation tests. In conclusion, DCRE has significant antiurolithiatic activity in vitro against CaOx urolithiasis, which could be attributed to its saponins, tannins, flavonoids, and polyphenolic content (Bawari et al.,2018). Futhermore, the purpose of this third recorded study is to perform fluorescence analysis, phytochemical extraction, preliminary phytochemical screening, estimation of total flavonoids, tannins, alkaloids, steroids saponins, and in vitro antiurolithiatic studies on Bauhinia variegata leaf aqueous and ethanolic extracts. The fluorescence analysis results show that the powder after treatment with 50% H2SO4 has a dark brown color under UV. The presence of saponin glycosides, tropane alkaloids, and acidic compounds was detected in preliminary phytochemical screening. The quantitative results showed that the aqueous extract has the highest number of flavonoids expressed as 54.6 mg/gm equivalents of quercetin, the highest number of tannins in ethanolic extract as 56.30 mg/gm equivalents of quercetin, equal amounts of alkaloids in both extracts as 25mg/gm equivalents of atropine sulfate, and the lowest amount of steroids and saponins. In conclusion, the plant is said to have antiurolithiatic activity, but more in vivo research and isolation of individual compounds responsible for the activity are needed (Mamillapalli, et al., 2016).

Synthetic Drugs and Procedures for Urolithiasis

Urolithiasis is a global problem that affects people from all walks of life, with an annual incidence of 1%, a prevalence of 3–5%, and a lifetime risk of 15–25% (

Moe et al., 2011). A significant amount of research is being conducted in order to find a cure for this disease condition, which has resulted in various procedures and treatments being used to treat urolithiasis at the present time. Presented in the study of Bawari et al., (2016) are the procedures and treatments for urolithiasis.

Neeri. Neeri is a poly-herbal formulation that helps with urinary issues. Neeri's potent herbal extracts provide corrective and preventive management for a variety of urinary problems, including burning micturition, chaotic or turbid urine with occult blood, and painful urination (Goyal et al., 2017). Neeri is a well-known traditional Indian Ayurvedic polyherbal sugar-free formulation that is manufactured under license by Aimil Pharmaceuticals India Ltd. *Amaranthus spinosus*, *Boerhaavia diffusa*, *Butea monosperma*, *Crataeva nurvala*, *Carica papaya*, *Moringa oleifera*, *Nelumbo nucifera*, *Tinospora cordifolia*, *Solenum nigrum*, *Tribulus terrestris*, *Veteveria zizanioides*, and other herbs are included in the formulation(Gautam et al., 2021).

Cystone. Cystone is a polyherbal tablet that has been approved by the FDA for the treatment of urolithiasis (Azarfar et al. 2020). According to Erickson et al., 2011 cystone causes stone and crystal disintegration. Cystone also has antimicrobial, antispasmodic, and anti-inflammatory properties that aid in the prevention of urolithiasis-related urinary tract infections. In the United States, Cystone is known as Uricare. Himalaya Health Care manufactures it all over the world.

Procedures (Bawari et al. 2016)

Kidney-Ureter-Bladder (KUB) Radiography is one of the preliminary imaging studies, which is essentially an X-ray of the abdomen. It helps with stone placement as well as visualizing their number, shape, and size. It is better suited to detecting calcium-rich radiopaque stones than uric acid, struvite, and cystine stones, which are less radio-dense.

Ultrasound is a type of imaging that employs high-frequency sound waves that echo or bounce back in the presence of solid structures such as stones, resulting in an image of the same.

Intravenous Pyelography (IVP) is a technique in which iodinated contrast media is administered intravenously to the patient, travels in the blood, and is eventually filtered from the kidneys and cleared from the ureters and bladder during micturition.

Helical Computed Tomography (CT) is a popular procedure due to its speed, accuracy, and efficiency in detecting all types of stones at any location, with no need for contrast media administration.

Dual Energy CT (DECT) has been introduced recently. DECT has two X-ray sources and two detector units, and it uses differences in X-ray attenuation properties of stone constituents to determine the mineral composition

Treatment (Bawari et al., (2016)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Non-opioids are the most commonly prescribed medications for urolithiasis pain relief, and both classes of drugs have been shown to be equally effective.

Medical expulsive therapy (MET) is used to allow the urinary tract to expel moderately sized distal ureteral calculi spontaneously. MET is treated with alpha-adrenergic blockers or calcium channel blockers, either alone or in combination with corticosteroids.

Thiazide and related diuretics are used to treat renal stone disease that is accompanied by idiopathic hypercalciuria. They are known to produce hypocalciuric action by increasing calcium reabsorption in the proximal and distal convoluted tubules.

Allopurinol is a medication used to treat calcium oxalate and uric acid stones. As a xanthine oxidase inhibitor, it inhibits uric acid production from hypoxanthine and xanthine, lowering urine urate levels (Spernat & Kourambas , 2011; Heilberg & Schor, 2006).

Potassium citrate essentially raises urinary citrate levels. Citrate converts urinary calcium to a soluble form, inhibiting the formation of calcium phosphate and calcium oxalate crystals. Because of its alkalinizing effect on urine, potassium citrate also helps to prevent the formation of uric acid stones.

Sodium cellulose phosphate is known to bind to intestinal calcium and thus inhibit calcium absorption, resulting in lower calcium excretion and thus less calcium stone formation.

D-penicillamine is used to treat cystinuria caused by cystine stones. It promotes the dissolution of cystine stones and lowers cystine levels in urine by forming penicillamine-cysteine heterodimers, which are more

soluble than cysteine-cysteine homodimers.

Acetohydroxamic acid is used to treat struvite stones, which are commonly caused by or associated with UTI caused by urease producing organisms.

Hemolytic dissolution therapy is a dissolving technique that uses pH changes, chelation, and disulphide rearrangement to dissolve and remove urinary stones (Korets , et al., 2012)

Extracorporeal shock wave lithotripsy (ESWL) is a common and least invasive treatment for active stone removal. Shock waves from a lithotripter are used for fluoroscopically guided stone fragmentation in a patient lying in a water-filled or gel-filled cushion that acts as a transition medium for transmitting shock waves into the patient's body.

Ureteroscopy is a minimally invasive procedure that involves passing a flexible fiberoptic ureteroscope through the urethra, through the bladder, and into the ureter to view the complete renal collecting system (K, 2008; Gayer et al.,2006; Papatsoris et al.,2012; Morton et al.,2002)

Percutaneous nephrolithotomy (PCNL) is a method for fragmenting and extracting stones that require a back incision and dilatation of the tract to allow for the insertion of a nephroscope to access stones in the renal pyelocalyceal system and proximal ureters (Purpurowicz, 2010; Celik et al., 2014; Ritter, et at., 2011)

Percentage Dissolution

Percentage dissolution determination is the successor to the disintegration test, which was designed for quality control of solid dosage forms such as tablets and capsules (Lau, 2001). It is widely used as an analytical technique for evaluating a pharmaceutical product's drug release characteristics and consistency (Chen et al., 2017). In addition, according to Bateman (2005), When comparing different formulations, dissolution percentage may provide useful information. It will adequately provide the difference between the data from the control group and the rest of the comparator in an experiment. As a result, whether the drug is efficient or not.

Systematic Review and Meta-Analysis

Systematic reviews and meta-analyses present findings by combining and analyzing data from various studies on similar research topics (Ahn & Kang, 2018).

According to Kang (2015), a systematic review gathers all possible studies on a specific topic and design, and then reviews and analyzes their findings. Further, a meta-analysis is a legitimate, objective, and scientific method of analyzing and combining various results. A meta-analysis is typically performed on randomized controlled trials (RCTs) with a high level of evidence in order to obtain more reliable results (Uetani et al., 2019). Furthermore, meta-analysis is a subset of systematic reviews that is highly specialized. It is not found in all systematic reviews, but all systematic reviews have meta-analysis. Simply put, a systematic review is an entire process of selecting, evaluating, and synthesizing all available evidence, whereas meta-analysis is the statistical approach to combining data from a systematic review (Northcentral University Library, 2022)

A well-defined research question is required for the systematic review and meta-analysis. PICO and SPIDER are two commonly used tools in systematic review and meta-analysis. In quantitative evidence synthesis, the acronym PICO (Population, Intervention, Comparison, Outcome) is commonly used. PICO is more sensitive than the more specific SPIDER method (Methley et al., 2014). As a method for conducting qualitative and mixed methods research, SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, and Research Type) was proposed.

According to the data, despite known high-technological solutions to the global problem of urolithiasis, humans have returned to nature. This study was inspired by the fact that it focused on using medicinal and herbal plants with antiurolithiatic properties, which, if further investigated, could potentially be a viable treatment for urolithiasis. Every study involving medicinal and herbal plants is significant because it teaches us more about nature's hidden gifts. The effectiveness of the plant extracts used in all studies will be determined by the percentage dissolution.

Methodology

Participants

This study is a systematic review and meta-analysis of medicinal and herbal plants. Thus, no person is involved in this research.

Instruments of the Study

A systematic review is a complete method of selecting, assessing, and synthesizing all available evidence (Impellizzeri & Bizzini, 2012). In addition, a systematic review is a method for identifying all studies for a specific focused question (from research and other sources), evaluating the studies' methods, summarizing the findings, presenting key findings, identifying reasons for different results across studies, and citing current knowledge limitations (Garg et al., 2008). Furthermore, according to Jorgensen, Hilden, and Gotzsche (2006), all decisions used to compile material in a systematic review are supposed to be explicit, allowing the reader to judge the quality of the review process and the potential for bias themselves.

A meta-analysis is when data from numerous separate primary studies addressing the same question are combined to provide a single estimate, such as the effect of a treatment or a risk factor. It is the statistical analysis of a large number of analyses and outcomes from individual studies with the goal of combining the results (Gopalakrishnan & Ganeshkumar, 2013). Meta-analysis is the act of mathematically combining results (a procedure frequently referred to as pooling). The pooled result is frequently represented graphically as a diamond at the bottom of the plot (Garg et al., 2008). In addition, according to Mikolajewics & Komarova (2019) reviewers can then use meta-analytic approaches to objectively appraise and synthesize outcomes across studies to determine statistical significance and relevance.

Systematic review and meta-analysis are methods for synthesizing research findings considered to be the best type of evidence and thus placed at the top of the evidence hierarchy. Because their study design reduces bias and produces more reliable findings, systematic reviews and meta-analyses are regarded as the highest-quality evidence on a research topic. This is because high-quality systematic reviews and meta-analyses take great care to find all relevant studies, critically evaluate each study, unbiasedly synthesize the findings from individual studies, and present a balanced important summary of findings while taking into account any flaws in the evidence.

Procedure

Date Sources and Selection

Education Resources Information Center (ERIC), Google Scholar, Proquest Research Journal, PubMed, and other University Library research databases were searched for studies from 2010 to May 2021 using key terms such as medicinal plants, herbal plants, in vitro antiurolithiatic, and urolithiasis, which were modified according to each database. More papers were discovered by scanning the reference lists of studies discovered during the initial search, as well as conducting direct searches in the following journals: Asian Journal of Pharmaceutics (AJP), European Journal of Biomedical and Pharmaceutical Sciences, International Brazilian Journal of Urology: Official Journal of the Brazilian Society of Urology, International Journal of Current Pharmaceutical Research, International Journal of Pharmaceutical Sciences and Medicine (IJPSM), Journal of Medicinal Plants Research, Journal of Pharmaceutical Sciences and Research, and Pharmacognosy Journal. Furthermore, all articles were uploaded to Mendeley referencing software, which was used to identify and remove duplicate articles using the remove duplicate function. To ensure that the studies met the criteria for inclusion, the titles, abstracts, and method section were thoroughly reviewed.

Inclusion and Exclusion Criteria

The following were used to determine the inclusion of the study: problem, intervention, control, and outcome. Experimental studies of antiurolithiasis in vitro studies were used to identify the problems. As a result, studies on antiurolithiasis in vitro from 2010 to January 2022 with positive antiurolithiatic agent results were considered for inclusion in the selection. The exposure was medicinal and herbal plants with antiurolithiatic properties; studies using medicinal and herbal plants with antiurolithiatic properties in vitro and recorded in English were considered. Studies comparing the effects of plant extracts and standard drugs on the experimental kidney (calcium oxalate) were included. The percentage of dissolution of the experimental kidney stone will be the outcome; therefore, studies that show a high percentage of dissolution of the artificial kidney stone indicate the plant's antiurolithiatic property were included in the study.

In vivo studies, non-experimental studies, negative in vitro antiurolithiatic investigations employing medicinal and herbal plants, unpublished papers and research relevant to urolithiasis, and studies conducted in other languages were discarded from the review.

Data Extraction

Data extraction is the process of retrieving data from a variety of sources (Alley, 2018). The PRISMA guidelines, developed by Moher et al., and The PRISMA Group (2009) are followed in this study. The PRISMA Statement: Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (see Appendix F) is a set of guidelines for reporting systematic reviews and meta-analyses. The checklist covers key elements in each section of the systematic review, such as the title, abstract, methods, results, discussion, and finding (Brooks & McNeely, 2013). Furthermore, a data extraction form was created particularly for this review (see Appendix E). The following data were extracted: the year of publication, the first author, the name of the herbal or medicinal plant, the type of extract, the part of the plant utilized for extraction, the standard medication employed, the exposure time to the experimental kidney, and the percentage dissolution as a result. Two reviewers independently evaluated and determined study eligibility for papers that had been identified for inclusion.

Quality Assessment

It is just as important to evaluate the quality of evidence contained within a systematic review as it is to analyze the data contained within. Joanna Briggs Institute (JBI) appraisal tools were used to assess the research's quality (see Appendix G). The purpose of this appraisal, according to Lilleheie et al., (2019), is to evaluate a study's methodological quality and to determine how well a study addressed the possibility of bias in its design, conduct, and analysis. Furthermore, the JBI approach to systematic reviews is pragmatic, with the goal of including a summary of the best available evidence rather than just randomized controlled trials (Hannes & Lockwood, 2011; Jordan et al., 2019; Munn, 2015).

Data Synthesis and Analysis

In order to assess the pooled mean of medicinal and herbal extract effect on Calcium oxalate, the mean of percentage dissolution was calculated for each individual study in this meta-analysis. Percentage dissolution showed the efficacy of plant extracts on calcium oxalate (Aykul & Hackert, 2016).

A random-effects model with a 95% confidence interval was used to report the findings (CI). A random-effects meta-analysis combines the findings of multiple independent studies to summarize a specific measure of interest, such as a treatment effect (Partlett & Riley, 2016). Estimating the overall mean (summary or pooled) effect and its confidence interval, quantifying heterogeneity, or deriving predictive inferences about the treatment effect in the future, such as a 95% prediction interval or the probability the treatment will be effective, may be of interest (Higgins et al., 2009)

The Cochran'Q test (p0.1 indicates heterogeneity) and the I-square statistic [low (25 percent -49 percent), moderate (50 percent -74 percent), and high (75 percent)] were used to assess study heterogeneity. Under the statistical hypothesis, the Cochran Q test uses a test statistic Q with a chi-squared distribution on k-1 degrees of freedom (k represents the number of studies) (Sutton et al., 2000). Because of the small number of studies, the statistical power of the test is relatively low; heterogeneity may exist even if the Q statistic is not statistically significant at conventional levels of significance such as 0.05. Instead of the standard 0.05, a cut-off significance level of 0.10 has been proposed (Sutton et al., 2000).

Moreover, the I-square test describes the proportion of variation across studies caused by heterogeneity rather than chance (Higgins & Thompson, 2002). The I^2 index can be defined as the percentage of the total variability in a set of effect sizes caused by true heterogeneity (between-studies variability) (Huedo-Medina et at., 2006). If I^2 is equal to zero, this means that all variation in effect size estimates is due to sampling error within studies. If I^2 = 50%, it means that true heterogeneity between studies accounts for half of the total variability in effect sizes, rather than sampling error (Huedo-Medina et at., 2006).

Subgroup analysis was used to identify potential sources of heterogeneity. Subgroup analyses entail dividing all participant data into subgroups, often in order to compare them. Subgroup analyses can be performed on subsets of participants (for example, males and females) or subsets of studies (such as different geographical locations). In addition, subgroup analyses can be used to investigate heterogeneous results or to answer specific questions about specific patient groups, intervention types, or study types (Higgins & Green, 2011).

To assess the risk of publication bias in this study, the Funnel plot test was used. According to Lee & Hotopf (2021), a funnel plot is a tool for determining the impact of publication bias. A funnel plot is a simple scatter plot of intervention effect estimates from individual studies versus some measure of the size or precision of each study. As with forest plots, the effect estimates are typically plotted on the horizontal scale, with the study size measured on the vertical axis (Higgins & Green, 2011). As a result, effect estimates from small studies were more widely spread at the bottom of the graph, whereas the spread among larger studies will be narrower. The plot should resemble an

inverted symmetrical funnel in the absence of bias (Higgins & Green, 2011).

Ethical Considerations

While ethical considerations in research are important, systematic reviews and meta-analysis, unlike primary research, do not acquire highly personal, sensitive, or confidential information from individuals (Suri, 2019). As proof, systematic reviews and meta-analysis utilize publicly available papers. Therefore, no human participants are involved in this research; however, ethical considerations for no human participants have been considered. These are the social value of the study, potential benefits to society, use of publicly available data or secondary data, adequacy of facilities, and qualifications of the researcher.

Social Value. The researcher hoped that this study would aid in the search for a potential treatment for urolithiasis that would involve the use of medicinal and herbal plants. The study's findings revealed the disadvantages of using synthetic drugs and procedures to treat urolithiasis. This study presents a variety of herbal and medicinal plants that have been shown to be effective in the treatment of urolithiasis. The findings of this study can be used by other researchers to develop more effective medicines with fewer side effects.

The researcher will publish this research on a university research portal and other research platforms and databases so that future researchers can access the information about medicinal and herbal plants that can be used as antiurolithiasis, which treatment is more effective, has less recurrence, and has fewer side effects

Potential Benefit to the Society. A systematic review and meta-analysis of medicinal and herbal plants with antiurolithiatic properties were conducted in this study. The goal of this study would be to find a natural alternative treatment for urolithiasis. The researcher hopes that this type of study will pave the way for the discovery of more effective treatments with fewer side effects.

Use of Publicly Available Data or Secondary Data. Republic Act No. 8293 also known as the “Intellectual Property Code of the Philippines” is a law that protects a person's intellectual property as well as his or her work. One of the terms that comprise the term "intellectual property rights" is "copyright and related rights," as stated in section 4 of RA No.8293. According to Bailey (2014), without the author's permission, no one else can legally post it on a website, share it in a journal, or use lengthy passages of it for their own research. The researcher guarantees the fair use of all data presented in this study. According to Hibbler (2021), fair use allows certain uses of copyrighted material without the permission of the copyright holder.

This study is reliable because the researcher followed the extensive research and used all of the necessary parameters and approaches to achieve the study's objectives. A statistician was also hired to ensure that the data is correctly calculated resulting in the researcher’s correct interpretation. Lastly, the Panel in this study also participated in the review of this paper, ensuring its dependability.

Adequacy of Facilities. The researcher self-financed this study hence the use of the computer, internet connection, and all necessary resources for this research are personally owned by the researcher. Furthermore, the school facilities are an important factor in the success of any research. The University library research databases include Education Resources Information Center (ERIC), Proquest, e-Learning Management System (eLMS), and PH eJournal, all of which were used to search for relevant literatures included in this review.

Qualification of the Researcher. Conducting research is never easy; thus, the researcher ensures that before beginning the research, the researcher is fully equipped with the necessary skills and abilities.

The researcher holds a Bachelor of Science in Secondary Education with a major in Biological Science from the University of the Immaculate Conception. With four years of experience teaching in a private school and a current affiliation with the Department of Education, the researcher has honed the necessary skills in computer manipulation, using Microsoft Office and other software, and internet searching, which are vital in this study.

The researcher's adviser is a registered chemist, a professor, and a statistician in the College of Pharmacy and Chemistry of the University of the Immaculate Conception, Father Selga Street., Davao City. The adviser has experience conducting various types of research and has contributed to a number of scientific studies, so he is very qualified to guide the researcher in conducting this study.

The University of the Immaculate Conception's graduate school also has competent and experienced

consultants. From the dean of the graduate school to the program coordinator, who have handled various studies in the past therefore they ensured the quality of the research they evaluate and provided the researcher with complete guidance for the success of this endeavor.

Results

Study Selection

Google Scholar and University library research databases yielded a total of 2186 papers (Google Scholar=1760, ProQuest=254, PubMed=84, and ERIC=90). After removing duplicates (n=1236), the titles and/or abstracts of 950 publications were screened; 895 studies were dropped at this stage for a variety of reasons; 425 papers are In Vivo studies, 214 are studies published in 2009 or earlier, and 256 are studies with irrelevant study design. For further eligibility assessment, full-text papers were collected for 55 research, and 45 of them failed to meet the inclusion criteria; 19 studies showed negative antiurolithiatic activities, and 26 studies did not employ medicinal and herbal plants. In the final step, 10 papers were appraised using the Joanna Briggs Institute (JBI) appraisal tool. This review included all ten studies.

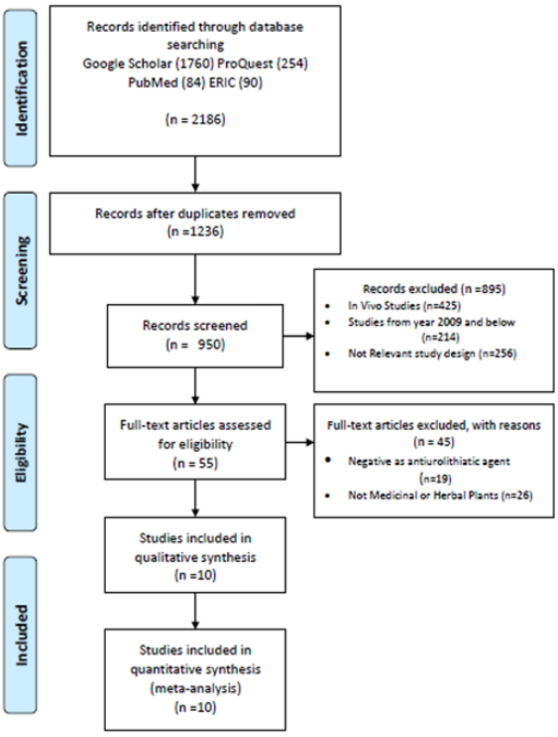

Figure 1. *PRISMA Flowchart Diagram*

Features of Included Studies

Table 1 summarizes the features of ten studies, including the year of publication, the first author, the name of the herbal or medicinal plant, the type of extract, the part of the plant used for extraction, and the percentage dissolution. All ten studies were carried out in India. Around 70% of India's rural population relies on the ancient Ayurvedic medical system. Plants have long been used as a source of medicine in India, and they form an essential part of the country's healthcare system (Pandey et al.2013).

In an in-vitro study of *Kalanchoe pinnata* the inhibition of the plant was lower at 47.65%, as compared to the positive control. However, the results indicated that the plant extract is suitable to be utilized as an inhibitory agent for the formation of CaOx. In *Mentha piperita* methanolic extract, the plant showed the highest inhibition of 98%, as compared to the positive control Neeri (81.0 %) indicating the plant material is more potent antiurolithiatic agent.

The *Chloris Barbata* etahanolic extract revealed the highest inhibition of 87% as compared with the positive control (Neeri), 81%, and aqueous extract (76%). Similarly, the *Gossypium Herbaceum* extract in ethanol showed the highest inhibition of 87% as compared with the positive control (81%) and aqueous extract (64%). This could be due to the extract of both hydrophilic and hydrophobic metabolites in plant that has the pharmacological property to inhibit CaOx formation. Meanwhile, Vigna radiata in an aqueous medium showed the highest inhibition of 98.1 percent as compared with the positive control, Neeri (81%). While the *Euphorbia thymifolia l.* revealed a decreases in calcium oxalate formation of 52 percent in the positive control, 48.0%, in aqueous, 55 % in hydroalcoholic and alcoholic solvent.

All of the studies used various medicinal and herbal plants native to India. All medicinal and herbal plants have been certified and identified by different organizations. Based on the findings of the studies, the medicinal and herbal plants *Kalanchoe pinnata*, *Mentha piperita* , *Chloris barbata*, *Gossypium Herbaceum Linn*, *Vigna radiata*, *Euphorbia thymifolia Linn*, *Piper nigrum*, *Vigna mungo Linn*, *Digitaria sanguanalis*, and *Syzygium cumini* all have positive antiurolithiatic properties.

Table 1. *Features of the Included Studies*

	Publication Year	Author	Name of Herbal or Medicinal Plants	Type of Extract	Parts of Plants Used	Percentage Dissolution of Calcium Oxalate
1	2015	Rohan Sharadanand Phatak Anup Subhash Hendre	*Kalanchoe pinnata*	Aqueous extract	Leaves	47.65%
2	2018	Manasa Reddy.J Prathyusha.K Himabindhu.J Ramanjaneyulu.K	*Mentha piperita*	Methanolic extract	Leaves	98.1%
3	2018	Niharika M. Harshitha V. Ashwini P. Srivinya B. Himabindhu J. Ramanjaneyulu K.	*Chloris barbata*	Ethanolic extract Aqueous extract	Leaves	87% 76%
4	2018	Niharika.M. Suchitha.N, Akhila.S. Himabindhu.J, Dr. Ramanjaneyulu.K	*Gossypium Herbaceum L*	Ethanolic Extract Aqueous extracts	Leaves	87% 64%
5	2018	Spandana. K, Shivani. M. Himabindhu. J. Ramanjaneyulu. K	*Vigna radiata*	Aqueous extracts	Seeds	98.1%
6	2018	Asheesh Kumar Gupta Rishabh Dobriyal T. Dougnon Victorian	*Euphorbia thymifolia Linn*	Aqueous extract Ethanoic extract Hydroalcoholic extract	Whole plant	48% 52% 55%
7	2018	Shivani.M Spandana.K, Himabindhu.J, Ramanjaneyulu.K	*Piper nigrum*	Ethanolic extract	Seeds	96.3%
8	2018	Sridivya Goud.K Rani.M, Himabindhu.J, Ramanjaneyulu.K	*Vigna mungo Linn.*	Methanolic extract	Seeds	98%
9	2018	Krishna Priyanka.B Sai Sruthi.G, Umema Naaz T	*Digitaria sanguanalis*	Butanolic Extract	Stems and Leaves	98%
10	2019	Chiluveri Sanjuna Mittapalli Anjali Naravanolla sandhya Mukkera Prasad Boppana Rohini J. Himabindhu Dr. K. Ramanjaneyulu	*Syzygium cumini*	Ethanolic extracts	Leaves	98%

Study Characteristics

Types of Extraction Solvents

Result of the studies revealed that the medicinal and herbal plants *Kalanchoe pinnata, Chloris barbata, Gossypium Herbaceum Linn, Vigna radiate,* and *Euphorbia thymifolia Linn* used water as a solvent. Methanol was used on the research of the medicinal and herbal plants *Mentha piperita* and *Vigna mungo Linn.* Furthermore, ethanol was used in the studies of *Chloris barbata, Gossypium Herbaceum Linn, Euphorbia thymifolia Linn, Piper nigrum,* and *Syzygium cumini*. The hydroalcoholic solvent was used by the plant *Euphorbia thymifolia Linn,* while the butanol solvent was used for the plant *Digitaria sanguanalis*.

Parts of Plant Material Utilized

The leaves of *Kalanchoe pinnata, Mentha piperita, Chloris barbata, Gossypium Herbaceum Linn, Digitaria sanguanalis,* and *Syzygium cumini* were used in the studies, while the stems of *Vigna radiate, Piper nigrum, Vigna mungo Linn,* and *Digitaria sanguanalis* were while the entire plant was used in the study of *Euphorbia thymifolia Linn.*

All of the plant parts used in the included studies have been shown to inhibit the formation of calcium oxalate Solomon et al .,(2019) study of *Maerua angolensis* leaf extracts revealed that the leaf extract inhibited crystal formation and promoted crystal dissolution in aqueous, ethanol, and chloroform solvents. Furthermore, Yyas et al., (2011) found that using the whole plant of *Pergularia daemia* in a hydroalcoholic solvent reduced urinary concentrations of stone-forming constituents. Lastly, Zarin et al. (2020) found that using *Musa pseudo* stem in methanol reduced the formation of calcium oxalate (CaOx) crystals significantly.

Standard Medications

Cystone medicine was used as the standard drug in studies of plants *Kalanchoe pinnata* and *Euphorbia thymifolia Linn*, while Neeri Medicine was used as the standard drug in studies of *Mentha piperita, Chloris barbata, Gossypium Herbaceum Linn, Vigna radiata, Piper nigrum, Vigna mungo Linn, Digitaria sanguanalis, and Syzygium cumini.*

Neeri, is a well-established polyherbal formulation prescribed for renal stones by the physicians but has not been experimentally evaluated for its antiurolithiatic potential (Goyalet al.. 2017) while cystone tablets are an Ayurvedic treatment for stones, traditionally practiced in India. Many studies and long experience attest to the safety of this compound. It is also claimed that Cystone decreases urinary supersaturatiomicro pulverizers and expels kidney stones, but existing studies have been limited by small patient numbers, weak methodology, and poor study design including lack of proper controls (Erickson et al., 2011)

All studies included in this research revealed that both controls can significantly inhibit calcium oxalate formation indicative of its antiurolithiatic property.

Participants, Intervention, Comparator, and Outcome (PICO)

The four components for the PICO analysis of the ten included studies are shown in Table 2. PICO is an acronym that stands for Problem, Intervention, Comparator, and Outcome. PICO is an essential component of a research question.

Participants

The letter "P" in PICO stands for the problem. In this research, medicinal and herbal plants are identified as the problem. This section of the PICO table identified medicinal and herbal plants with antiurolithiatic

properties.

Plant material from *Kalanchoe pinnata* was identified and authenticated at India's Yashwantrao Chavan College of Sciences' Department of Botany. Plant materials *Mentha piperita, Chloris barbata, Gossypium herbaceum, Vigna radiate, Piper nigrum, Vigna mungo,* and *Digitaria sanguanalis*, on the other hand, were authenticated by D.Venkateshwara Rao, Deputy Director, Telangana. Dullapally, Hyderabad, Rangareddy District, Forest Academy. In addition, plant material *Euphorbia thymifolia Linn.* was identified and authenticated by taxonomist Dr. S. K. Srivastava, of the Botanical Survey of India, Dehradun, Uttarakhand. Lastly,the plant material *Syzygium cumini* was authenticated by M. Malla Reddy a retired lecturer in Botany, Vikarabad, Telangana, India.

Table 2. *Participant, Intervention, Comparator, and Outcome (PICO) Profile of the Included Studies*

Problem (Medicinal or Herbal Plants)	*Intervention (Experimental Kidney)*	*Comparator (Standard Drug)*	*Outcome (Percentage dissolution of CaOx)*
Kalanchoe pinnata	Calcium oxalate	Cystone	Group % Dissolution I -- II 57.81 III 47.65
Mentha piperita	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Methanolic Extract 98.1
Chloris barbata	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Ethanolic Extract 87 Aqueous Extract 76
Gossypium Herbaceum	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Ethanolic Extract 87 Aqueous Extract 64
Vigna radiata	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Aqueous Extract 98.1
Euphorbia thymifolia l.	Calcium oxalate	Cystone	Group % Dissolution Positive control 52.0 T. 1 (aqueous extract) 48.0 T. 2 (hydro alcoholic) 55.0 T. 3 (alcoholic) 55.0
Piper nigrum	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Ethanolic Extract 96.3
Vigna mungo	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Methanolic Extract 98
Digitaria sanguanalis	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Butanolic Extract 98
Syzygium cumini	Calcium oxalate	Neeri	Group % Dissolution Blank 0 Positive Control 81 Methanolic Extract 98

Intervention

The “I” for PICO is intervention. It is used to assess the efficacy of the desired outcome. The intervention used in all studies was the experimental kidney Calcium oxalate (CaOx).

Calcium oxalate. Urnary calculi can be composed of calcium oxalate (monohydrate or dihydrate), struvite (magnesium ammonium phosphate), uric acid, calcium phosphate, and cysteine (Solomon et al., 2019). Calcium oxalate is the most common component of renal calculi, accounting for approximately 80% of all cases (Pannigrani et al., 2016).

The synthesis of experimental kidney stones of the studies of plants *Kalanchoe pinnata*, *Euphorbia thymifolia Linn* was done by homogenous precipitation. In 100 ml of distilled water, 1.47gm of calcium chloride dihydrate was dissolved, and 1.34gm of sodium oxalate was dissolved in 100 ml of 2N H_2SO_4.

Meanwhile, the experimental kidney stones of the studies on plants *Mentha piperita, Chloris barbata, Gossypium herbaceum, Vigna radiat, Piper nigrum, Vigna mungo, Digitaria sanguanalis, and* Syzygium cumini was synthesized by the equimolar solution of calcium chloride dehydrated in distilled water and sodium oxalate in 10 ml of 2N H_2SO_4. Both were allowed to react in a beaker with enough distilled water to produce calcium oxalate as a precipitate.

Comparator

PICO's "C" stands for the comparator. The comparator compares the efficacy of the intervention, which in this study was the experimental kidney or calcium oxalate, to that of the control group or plant extracts. The standard drugs Neeri and Cystone are used to test the efficacy of the plant extracts.

The studies of plants *Kalanchoe pinnata* and *Euphorbia thymifolia Linn*, used Cystone as the standard drugs to test the efficacy of the plant extracts against calcium oxalate. On the other hand, the studies of plants *Mentha piperita , Chloris barbata*, *Gossypium herbaceum Linn*, *Vigna radiata*, *Piper nigrum*, *Vigna mungo Linn*, *Digitaria sanguanalis*, and *Syzygium cumini* used the standard Neeri

In the study of Goyal et al. (2017), Neeri, the standard drug, was described as a polyherbal formulation, specifically prescribed for renal stones and restoring altered renal functions. Neeri is made up of herbal extracts, traditional Ayurvedic preparations, lixiviated herbal ash, exudates, and other ingredients. The result of the experiment revealed that Neeri is a highly effective antiurolithiatic formulation that inhibited

CaOx crystallization and prevented tubular retention of crystals.

Erickson et al,. (2011) described Cystone as an Ayurvedic treatment for stones, and recorded studies and long experience attest to the safety of this compound. Furthermore, as explained in their study, Cystones inhibits calculogenesis by reducing stone-forming substances such as oxalic acid, calcium hydroxyproline, and others and causing their expulsion via micropulverization.

Outcome

The expected outcome of the research is the antiurolithiatic activity of the plants.The percentage dissolution determined the efficacy of the standard drugs and plant extracts used in this study.

Kalanchoe pinnata. In an in-vitro study of *Kalanchoe pinnata* extract using cystone as positive control, the inhibition of the plant was lower at 47.65% as compared to the positive control. However, the results indicated that the plant extract is suitable to be utilized as inhibitory agent for the formation of calcium oxalate (the main component of kidney stones).

Mentha piperita. In the study where a researcher used *Mentha piperita* methanolic extract, the plant showed the highest inhibition of 98.1% as compared to the positive control Neeri (81.0%) indicating the plant material is more potent antiurolithiatic agent.

Chloris barbata. The *Chloris barbata* etahanolic extract revealed the highest inhibition of 87% as compared with positive control (Neeri), 81% and aqueous extract (76%). *Chloris barbata* has an antiurolithic property based on the percentage inhibition of both extracts.

Gossypium herbaceum. The extract of *Gossypium herbaceum* in ethanol showed the highest inhibition of 87% as compared with the positive control (81%) and aqueous extract (64%). This could be due to the extract containing both hydrophilic and hydrophobic metabolites that has the pharmacological property to inhibit calcium oxalate formation.

Vigna radiata. The aqueous extract of *Vigna radiata* showed the highest inhibition of 98.1% as compared with the positive control, Neeri (81%).

Euphorbia thymifolia Linn. The study of the antiurolithiatic property of *Euphorbia thymifolia Linn* revealed a decreased calcium oxalate formation with 48% percentage dissolution in aqueous and 55% in hydroalcoholic and alcoholic solvents. This is higher compared to the positive control with a percentage dissolution of 52%.

Piper nigrum. The study revealed that when compared to the positive control, the *Piper nigrum* extract had a maximum inhibition of 96.3%.

Vigna mungo, ***Digitaria sanguanalis***, *and* **Syzygium cumini.** The methanolic extract of *Vigna mungo, Digitaria sanguanalis* in butanol extract, and *Syzygium cumini* in methanol extract all demonstrated 98% inhibition when compared to the positive control Neeri (81 %).

With the given data on the percentage dissolution, it validated the claims that the plant extracts from *Kalanchoe pinnata, Mentha piperita , Chloris barbata, Gossypium Herbaceum Linn, Vigna radiata, Euphorbia thymifolia Linn, Piper nigrum, Vigna mungo Linn, Digitaria sanguanalis,* and *Syzygium cumini,* significantly reduced the formation of calcium oxalate as compared to the standard drugs Neeri and Cystone.

Meta-Analysis

This meta-analysis shows an overall statistically significant reduction of calcium oxalate formation when treated with plant extract using different solvents as compared with positive control ($p < 0.05$). These results affirmed the benefit of herbal plant in reducing the risk of calcium oxalate formation, and with the standard drugs Neerie and Cystone as positive control for in vitro analysis.

Sample size	Standard error	Variance	Lowe Limit	upper limit	p value
2	7.184205	51.6128	47.65	57.81	0.000
2	12.0915	146.2044	81	98.1	0.000
3	5.50757	30.33333	76	87	0.000
3	11.93035	142.3333	64	81	0.004
2	12.09153	146.2051	81	98.1	0.001
4	3.316625	11	48	55	0.000
2	10.81873	117.0449	81	96.3	0.000
2	12.02082	144.5001	81	98	0.000
2	12.02082	144.5001	81	98	0.001
2	12.0282	144.6776	81	98	0.000

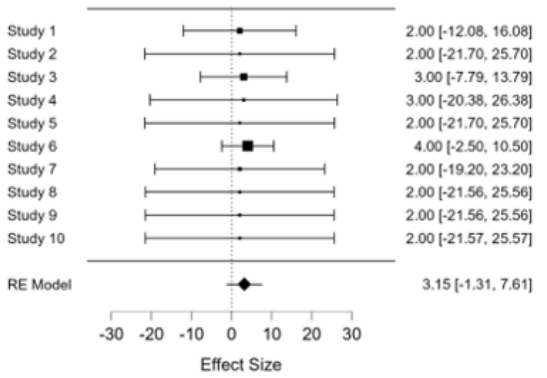

Figure 2. *Forest Plot*

Forest Plot. In the meta-analysis test, the forest plot presents data from numerous research on the same topic or question. This evaluate various study outcomes instead of analyzing each separately. It graphs meta-analysis findings. Figure 2 shows the forest plot for for the standardized mean differences (SMDs) in the measurement outcomes between the experimental and control of various studies that measure the anti-urolithiatic effect of plant materials.

Effect Size and the Null Effect Vertical Line. The effect of size can be interpreted that it has a significant effect. Shown in the forest plot is the line of no effect, which is the vertical line placed at the value of greater that 0.00 idicating that there is difference between the treatment and the control group. Apparently, it can be observe in most studies that the antiurolithiatic property of the positive control was significantly higher as compared with the experimental drug (plant extract).

Heterogeneity. The Cochran's Q test is a test for heterogeneity in meta-analyses. It generates a probability that, when large, indicates larger variation across studies rather than within-subjects within a study. The underlying null hypothesis assumes that the true treatment effect is the same across studies, and variations are caused by chance. Meanwhile, the I2 index is a more recent approach to quantify heterogeneity in meta-analyses. I2 provides an estimate of the percentage of variability in results across studies due to real differences and not due to chance (West, SL., Gartlehner, G., Mansfield AJ., et al., 2010).

Q-value. The Cochran's Q = 0.149 with p-value = 1.000 indicates that the individual studies' SMDs have statistically evaluated the same effect size regarding the overall SMD. It suggests that there may have differences underlying the results of the studies.

Table 3. *Heterogeneity Table*

Heterogeniety				*Tau-sqaured*		
Q value	*Df (Q)*	*P value*	*I-squared*	*Tau sqauared*	*Standard error*	*Tau*
0.149	9	1.000	0.000	0.000	2.275	0.000

I 2 -test. I 2 -test is another formal test for heterogeneity. The lower the I squared, the less heterogeneity there is, which means that's better and less variability between the studies. As demonstrated in the same table, this collection of studies has established an I2 = 0.000 thus, there is no observe heterogenity in the studies selected for testing. Based on results it can be shown that both control and experimental group have continuously provide almost similar inhibition in terms of its antiurlithiatic property.

Funnel Plot. A funnel plot is a scatterplot of treatment effect against a measure of study precision. It is used primarily as a visual aid for detecting bias or systematic heterogeneity. A symmetric inverted funnel shape arises from a 'well-behaved' data set, in which publication bias is unlikely.

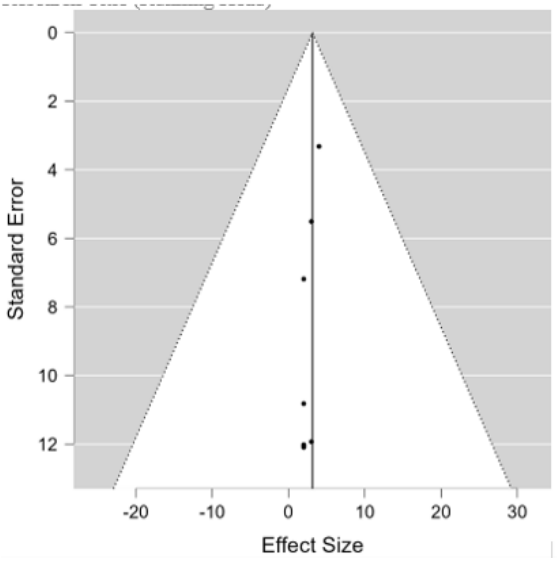

Figure 3. *Funnel Plot of the Study*

Discussion

This study demonstrated the efficacy of medicinal and herbal plants with antiurolithiatic properties. All ten studies included in this systematic review and meta-analysis showed high percentage dissolution of calcium oxalate by all plant extracts used. The positive outcomes of all ten medicinal and herbal plants with aniurolithiatic properties prompted the researcher to be forward-thinking and make the recommendation.

The findings of this study can serve as a baseline for our government agencies, specifically the Departments of Science and Technology (DOST) and the Department of Health (DOH). DOST has been funding various research projects in various fields across the country. DOST, in collaboration with DOH, the two government agencies may take the lead in encouraging researchers in this field to conduct studies on medicinal and herbal plants with known therapeutic properties. It is preferable to use medicinal and herbal plants native to the Philippines. Future research may focus on comparing the characteristics and phytochemicals of the medicinal and herbal plants included in this study to determine which medicinal and herbal plants have the same characteristics and phytochemicals, and future researchers can further study the identified plants for the possibility of discovering medicinal and herbal plants with antiurolithiuatic properties that are native to our country, the Philippines.

Conclusion

Based on a comprehensive systematic review and meta-analysis of all ten studies included in this review, it is concluded that the medicinal and herbal plants Kalanchoe pinnata, Mentha piperita , Chloris barbata, Gossypium Herbaceum Linn, Vigna radiata, Euphorbia thymifolia Linn, Piper nigrum, Vigna mungo Linn, Digitaria sanguanalis, and Syzygium cumini all have positive antiurolithiatic properties. This is based on the percentage dissolution of the experimental kidney, calcium oxalate (CaOx), which resulted in a higher percentage of inhibition than the percentage inhibition of the standard drugs Neeri and Cystone.

The percentage dissolution validated that the use of plant extracts has resulted in a significant reduction in the development of calcium oxalate as compared to standard drugs Neeri and Cystone. Since the plant extracts considerably reduced calcium oxalate deposition, this shows that they have antiurolithiatic properties.

As a result of these findings, herbal plants can be used to reduce the danger of calcium oxalate formation, and Neerie and Cystone can be used as positive controls for in vitro studies.

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