

## ***Centella asiatica* (TAKIP-KUHOL) AS A POTENTIAL AGENT FOR REDUCING CALCIUM OXALATE FORMATION IN URINE**

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### **ABSTRACT**

Kidney stones, particularly those composed of Calcium Oxalate (CaOx), pose a growing health concern in the Philippines and worldwide. The continuous rise in urolithiasis cases and the limitations of the existing therapeutic interventions underscore the need for alternative, natural remedies. This study determined the potential of *Centella asiatica*, locally known as *takip-kuhol*, as an agent for reducing calcium oxalate crystal formations in human urine. A descriptive experimental design was used, involving the collection of *takip-kuhol* leaves, preparation of varying extract concentrations, and administration of CaOx to human urine samples. Test tube phytochemical analysis confirmed the presence of flavonoids and triterpenoids. These compounds are responsible for the anti-urolithiatic property of *C. asiatica*. Microscopic examination shows that there is a significant reduction of CaOx crystal count in all the *takip-kuhol* ethanolic extract (TKEE) concentrations, such as 50%, 75%, and 100%, respectively. The 100% TKEE concentration showed the greatest reduction, comparable to that of the positive control. Morphological assessments also showed dissolution and fragmentation, and eventual disappearance of Calcium Oxalate Monohydrate (COM) and Calcium Oxalate Dihydrate (COD) crystals after administration of TKEE extract. The TKEE shows a significant reduction in CaOx crystal formation and changes the crystal shape, indicating its potential as a natural reducing agent for CaOx crystals, which could be relevant for conditions such as kidney stones. Further research is essential to confirm these benefits in larger, more diverse populations and across different dietary and health conditions. This ensures safe and effective use of *takip-kuhol* as a natural reducing agent for calcium oxalate crystals.

*Keywords:* Anti-urolithiasis, calcium oxalate dihydrate, calcium oxalate monohydrate, cystone, morphological characterization

### **INTRODUCTION**

#### **Background of the Study**

In the Philippines, the number of Filipinos with kidney problems is quite alarming. The most recent World Health Organization (WHO) data available indicates that 39,380 fatalities in the Philippines were from kidney disease in 2020, accounting for 5.84% of all deaths. The Philippines' age-adjusted death rate of 51.96 per 100,000 people ranks it in the top 10 worldwide. In addition, according to the Philippine Society of Nephrologists, 1.5 million Filipinos are suffering from kidney problems. Kidney stones or *renal calculi* is one of them, with increasing prevalence in men over forty (40) and women over seventy (70) years old (Aragones, 2022).

Medical City (2017) found that the most common type of kidney stone contains calcium combined with either oxalate or phosphate. This crystal contributes to pain, urinary tract obstruction, and other complications. The occurrence of kidney stones remains high despite the treatments available, and these too have interventions that may lead to side effects. Urolithiasis is a condition in which crystals in urine supersaturate, leading to the formation of renal calculi in the kidney parenchyma. These stones can then exit the renal pelvis and migrate through the

urinary collecting system, which includes the ureters, bladder, urethra, and kidneys. If the stone obstructs the ureter and prevents the passage of urine, hydronephrosis can occur secondary to upstream dilation of the ureter and renal pelvis (Tharoke & Liang, 2024). Globally, the incidence and prevalence of urolithiasis have been on the rise. It increased by 48.57%, from 77.78 million incident cases in 1990 to 115.55 million in 2019. Because of the large number of new and recurrent cases, the high rate of surgical intervention, and the advent of novel technology, global healthcare costs related to the management of stones are relatively high (Qian, et. al., 2022).

*Centella asiatica* (*takip-kuhol*) has been investigated for its various medicinal properties, including its effects on inflammation, wound healing, and numerous health benefits. However, there is limited documentation in mainstream scientific literature specifically focused on its clinical role in reducing calcium oxalate crystals. Most existing research on urolithiasis tends to emphasize more widely recognized herbs and dietary components. While *takip-kuhol* has been used for various traditional medical purposes for a long time, its potential as a reducing agent for the formation of calcium oxalate crystals in urine remains unknown. Hence, further laboratory and clinical trials are necessary to confirm any specific CaOx-reducing effects. Given the limitations of conventional approaches, there is an urgent need to explore alternative and complementary remedies that can effectively reduce the risk of calcium oxalate crystallization in urine.

Investigating the potential of *takip-kuhol* as a reducing agent for calcium oxalate could greatly benefit the public, given that calcium oxalate is the primary cause of kidney stone disease. The result will significantly impact vulnerable populations, particularly those with limited access to medical care. This study addresses the key priorities of the National Unified Health Research Agenda (NUHRA) and Department of Health (DOH), disease management and health innovation. It also addresses several Sustainable Development Goals (SDGs), such as SDG 3- Good Health and Well-being. Reducing calcium oxalate excretion in urine may improve health outcomes by preventing kidney stones and promoting overall urinary health. This aligns with the target of reducing the global burden of disease; SDG 9- Industry, Innovation, and Infrastructure, this research could contribute to innovative medical solutions and alternative therapeutic approaches, fostering sustainable industrialization in healthcare and pharmaceutical research; SDG 12- Responsible Consumption and Production, utilizing natural remedies like *takip kuhol* as a potential treatment implies a focus on sustainable practices in healthcare and medicine, promoting the idea of using natural resources responsibly; SDG 15- Life on Land, this research highlights the use of a plant-based remedy, which supports the conservation and sustainable use of terrestrial ecosystems. Because many people are unaware they have calcium oxalate in their urine, which often remains asymptomatic until it forms larger, painful kidney stones, the prevalence of urolithiasis remains high, underscoring the need for alternative, natural treatments to manage and prevent CaOx crystallization. The findings may benefit medical professionals, researchers, and the general public by raising awareness of early CaOx detection and supporting accessible, cost-effective herbal remedies.

### Statement of the Objectives

This study determined the potential of *takip-kuhol* (*C. asiatica*) as a reducing agent for calcium oxalate formation. It was conducted from January to March 2025.

Specifically, it sought to:

1. Determine the presence of flavonoids and triterpenes that may reduce calcium oxalate formation in urine.
2. Evaluate the reduction of CaOx crystals in human urine samples treated with varying concentrations of *takip-kuhol* ethanolic extract based on the quantity per field under high power Objective.

3. Assess the morphology of the CaOx before and after treatment of the *takip-kuhol* ethanolic extract.

## METHODOLOGY

### Research Design

The study employed a descriptive experimental design. The morphology of the CaOx crystals was described using microscopic examination. The reduction of CaOx was determined by counting crystals per field under a high-power objective. The study followed laboratory protocols and tests to assess the plant's potential to reduce CaOx formation in human urine.

### Study Site and Sample Collection

The leaves of the plant samples were collected from the riversides in Barangay Cutar, Aritao, Nueva Vizcaya. The laboratory processes, such as drying, extraction, and urinalysis, were conducted at the SMU-Center for Natural Sciences Research Laboratory. The laboratory had the equipment, reagents, setups, and facilities needed for this study.

### Specimen Identification

The plant specimen in this study was submitted to the Research Extension and Training (RET) Division of Nueva Vizcaya State University, Bayombong, Nueva Vizcaya, for certification of its taxonomic identity.

#### *Urine Samples and Donors*

Urine samples were collected from random, willing donors aged 18 years and above. Ten (10) persons were included as urine donors. The urine samples collected were first-morning urine. At least three (3) urine samples with the most turbid appearance were used in the experiment.

### Data Gathering Procedure

#### *Collection of Takip-kuhol Leaves*

Five kilograms of *takip-kuhol* leaves were collected, stored in a clean, ventilated container, and brought to the laboratory. They were washed with distilled water and air-dried.

#### *Oven-Drying and Crude Extraction*

The leaves were oven-dried at 50–55°C for 48 hours, then ground into a fine powder. One kilogram of the powder was macerated in 1000 mL of ethanol for 48 hours. The mixture was filtered using cheesecloth to obtain the crude extract.

#### *Test Tube Phytochemical Test*

Following Ghaeni et al. (2022), 200 mg of the extract was tested for flavonoids and triterpenes. Flavonoids were identified by a yellow-to-colorless change after adding HCl to a NaOH solution. Triterpenes were confirmed by a reddish-brown layer after mixing with chloroform and sulfuric acid.

#### *Preparation of Takip-Kuhol Concentrations*

Using the mass/volume percent formula by Petrucci et al. (2001), the crude extract was diluted with distilled water to prepare 50%, 75%, and 100% concentrations.

$$\frac{\text{Mass}}{\text{Volume}} \text{Percent} = \frac{\text{mass of solute}(g)}{\text{volume of solution}(mL)} \times 100\%$$

#### *Human Urine Collection*

Following Magharbeh et al. (2020), urine samples were collected from ten healthy individuals using polypropylene bottles and refrigerated immediately. Three turbid samples containing calcium oxalate (CaOx) were selected for the study.

#### *Takip-kuhol Ethanolic Extract Test on the Collected Human Urine*

Each urine sample was divided into five 4 mL portions: one negative control (no treatment), one positive control (treated with cystone), and three treated with 50%, 75%, and 100% concentrations of *takip-kuhol* ethanolic extract (TKEE). Two milliliters of each extract concentration were added accordingly, and all samples were refrigerated at 1–4°C for 48 hours. The pH was regularly monitored and adjusted using HCl, NaOH, or KOH.

#### *Evaluation on the Reduction of Human Urine CaOx*

Initial pH checks were conducted at 2, 6, and 18 hours post-treatment, with further examinations every 24 hours for two days. To evaluate CaOx reduction, samples were centrifuged at 400 RCF for 5 minutes and observed under a high-power microscope to assess crystal morphology and count.

#### *Characterization of Human Urine CaOx Morphology*

Using the same observation intervals, the morphology of CaOx crystals was analyzed. Calcium Oxalate Monohydrate (COM) appeared dumbbell-shaped or bipyramidal and denser, while Calcium Oxalate Dihydrate (COD) was octahedral or prism-like with pyramid ends. Observations were done using a high-power objective under a light microscope.

#### **Treatment of the Data**

In clinical settings, microscopic examination of urine sediments had to be read on a minimum of ten (10) fields consistently under both (10x) and (40x) power (Strasinger, 2021). To evaluate the reduction of calcium oxalate (CaOx) crystals, the researchers examined urine samples under a microscope. They counted the number of crystals present in ten (10) high-power fields. After quantifying the CaOx in these fields, the researchers calculated the average number of crystals per field to determine the overall crystal count. The average count after TKEE treatment was then compared with the initial count recorded before treatment to assess TKEE's effectiveness in reducing CaOx crystal formation.

To analyze the effects of the treatment on calcium oxalate (CaOx) crystal formation, the researchers performed a morphological characterization of the two primary types of CaOx crystals: monohydrate (COM) and dihydrate (COD), both typically colorless or white (Khan et al, 2016). COM, the more stable form, is commonly found in kidney stones and has a dumbbell-shaped morphology. However, it can also appear prismatic or octahedral (Lieske et al., 2020). On the other hand, COD has an octahedral crystal structure and typically forms large, smooth, colorless prisms or needles with a twinned or flattened appearance. Understanding these forms and structures of calcium oxalate is important for studying its biological roles in

plant tissues and kidney stones. Below is the basis for the morphological characterization of calcium oxalate dihydrate and calcium oxalate monohydrate.

### Ethical Section

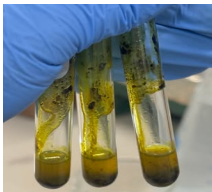
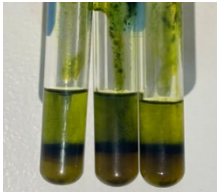
The study was approved by Saint Mary's University Research Ethics Board (SMUREB), located at the 2nd Floor, Rev. John Van Bauwel Hall, SMU Main Campus, Ponce Street, Don Mariano Marcos, Bayombong, 3700 Nueva Vizcaya, Philippines (email: reb@smu.edu.ph; cellphone: 09177053041).

## RESULTS AND DISCUSSIONS

### Section 1. Presence of Flavonoids and Triterpenoids

**Table 1**

*Results of Test Tube Phytochemical Analysis*

| Secondary Metabolites | Results |  |
|-----------------------|---------|--|
| Flavonoids            | ++      |  |
| Triterpenoids         | +       |  |

The phytochemical analysis of the ethanolic extract of *takip-kuhol*, conducted in test tubes, showed the presence of flavonoids and triterpenoids based on specific color reactions. Flavonoids turned yellow while triterpenoids turned brown, confirming the presence of metabolites that are responsible for reducing the formation of calcium oxalate.

Research by Wang et al. (2021) shows that flavonoids help prevent kidney stones by lowering urine calcium and oxalate levels and protecting kidney tissue from damage. They inhibit the formation and growth of calcium oxalate crystals, which are responsible for stone formation. Similarly, Lobine et al. (2020) found that triterpenes also play a significant role in preventing kidney stones. These compounds reduce oxidative stress in kidney tissues by boosting antioxidant activity, protecting cells from damage caused by calcium oxalate crystals. They also prevent these crystals from clumping together and sticking to kidney tissues. Additionally, studies, including one by Zeng et al. (2019), suggest that flavonoids and triterpenes may work together to reduce calcium oxalate stone formation. Flavonoids increase urine production and act as antioxidants, while triterpenes enhance the body's defenses against oxidative stress. Together, they help modify urine composition and lower the levels of minerals that can form stones.

The presence of these active compounds in *takip-kuhol* suggests its potential as a natural agent for reducing calcium oxalate, which may help prevent kidney stone formation. These findings underscore the necessity for further research to assess its clinical applications and enhance its efficacy in kidney stone prevention.

**Section 2. Reduction of Calcium Oxalate Crystals**

**Table 2**

*Calcium Oxalate Count Before and After Administration of Takip-Kuhol Ethanolic Extract*

| Groups           | D1            |       |       | D2            |       |       | D3            |       |       |
|------------------|---------------|-------|-------|---------------|-------|-------|---------------|-------|-------|
|                  | Initial count | Day 1 | Day 2 | Initial count | Day 1 | Day 2 | Initial count | Day 1 | Day 2 |
| Positive Control |               | 0.05  | 0     |               | 0.1   | 0     |               | 0.1   | 0     |
| Negative Control |               | 1.5   | 1.75  |               | 5     | 5.1   |               | 5.35  | 5.9   |
| 50%              | 1.05          | 0.55  | 0.15  | 4.9           | 0.8   | 0.25  | 5.30          | 1.1   | 0.3   |
| 75%              |               | 0.2   | 0.05  |               | 0.3   | 0.15  |               | 0.5   | 0.15  |
| 100%             |               | 0.1   | 0     |               | 0.2   | 0.1   |               | 0.15  | 0.05  |

\*Counts were based on the quantity of CaOx per field (count ÷ 10)

\*D1 stands for donor 1, D2 for donor 2, and D3 for donor 3

Table 2 showed a reduction in calcium oxalate count in the fer field after administration of takip-kuhol ethanolic extract in three donors. The positive control group displayed a significant reduction in calcium oxalate count. In contrast, the negative control group consistently showed the highest CaOx count, indicating continued crystal formation despite the lack of intervention. In comparison, urine samples treated with takip-kuhol ethanolic extract at concentrations of 50%, 75%, and 100% showed a significant reduction in CaOx crystal count after 2 days. The 100% concentration showed the greatest decrease, with final counts approaching zero across all donors. The 75% concentration also led to a considerable reduction, with final counts ranging from 0.05-0.15 calcium oxalate per field, while the 50% concentration showed moderate effects, with final counts ranging from 0.15-0.3 calcium oxalate per field.

These findings support earlier research showing that herbal extracts containing bioactive compounds, such as flavonoids and triterpenes, can reduce calcium oxalate (CaOx) crystallization. In the study of Zeng et al. (2018), it is revealed that the mechanisms of flavonoids or flavonoid-rich plant extracts are endowed with anti-urolithiasis activity, in correlation with their antioxidant, anti-inflammatory, antibacterial, and diuretic properties. Furthermore, Lobine et al. (2020) mentioned that pentacyclic triterpenes can also effectively treat calcium oxalate urolithiasis through various mechanisms such as antioxidant, anti-inflammatory, diuretic, and angiotensin-converting enzyme inhibition.

The findings showed a clear reduction in calcium oxalate count for all donors after TKEE administration. Further studies are necessary to confirm these findings across larger populations and under varying conditions.

**Section 3. Morphology of Calcium Oxalate Crystals Before and After Treatment**

**Table 3**

*Morphology of Calcium Oxalate Crystals Before and After Administration*

| Morphology of CaOx Before Administration of TKEE | CONCENTRATION | Morphology of CaOx After Administration of TKEE |
|--|---------------|---|
|--|---------------|---|


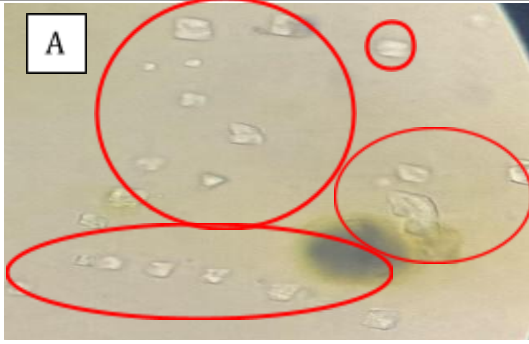

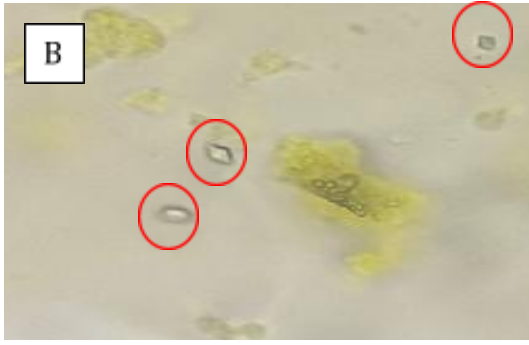
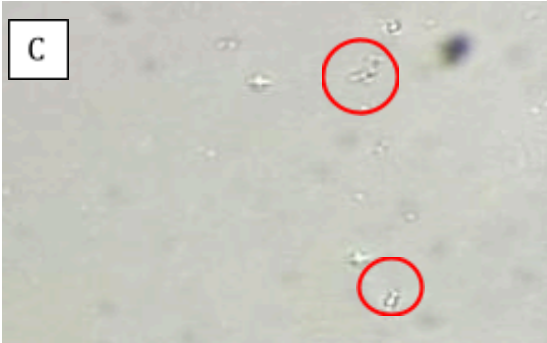
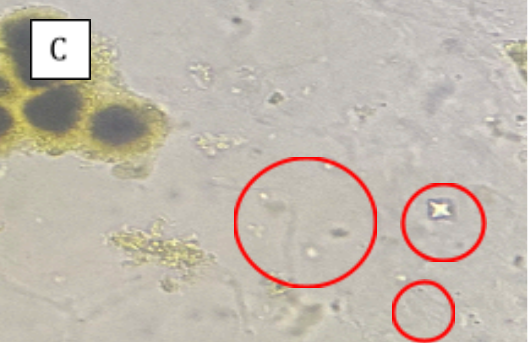
|  |                      |  |
|--|----------------------|--|
|   | <p>50%</p>           |    |
|   | <p>75%</p>           |    |
| <p><b>Morphology of CaOx Before Administration of TKEE</b></p>   | <p>CONCENTRATION</p> | <p><b>Morphology of CaOx After Administration of TKEE</b></p>  |
|   | <p>100%</p>          |    |
| <p><i>Images A and B are examples of Calcium Oxalate Dihydrate. It appears as an enveloped shape, with overlapping crystals or curved surfaces. Image C is an example of a calcium oxide monohydrate that appears dumbbell-shaped. However, prismatic or octahedral forms are also possible.</i></p> |                      | <p><i>Similar to the morphology of CaOx at the 75% concentration, the crystals also appear more translucent, with a noticeable loss of sharp edges, and the previously well-defined structures also seem rounded and eroded.</i></p> |

Table 3 shows the effects of *TKEE* on calcium oxalate crystals before and after administration, highlighting significant changes in shape and a reduction in count. The dissolution of calcium oxalate dihydrate suggests that *takip-kuhol* ethanolic extract contains bioactive compounds that interact with calcium oxalate dihydrate, leading to partial breakdown and dissolution.

The result is consistent with studies reporting that flavonoids, polyphenols, and organic acids in plant extracts can inhibit calcium oxalate crystallization, weaken crystal integrity, and promote dissolution (Patel et al., 2022). This suggests that *TKEE* weakens the calcium oxalate dihydrate, allowing it to degrade into smaller fragments before eventually dissolving.

The complete disappearance of calcium oxalate monohydrate in the samples suggests that *TKEE* has a pronounced effect on Calcium Oxalate Monohydrate dissolution. Calcium Oxalate Monohydrate is generally denser and more resistant to dissolution due to its monoclinic structure (Sun et al., 2015). Still, its disappearance after treatment suggests that *TKEE* may contain compounds capable of targeting Calcium Oxalate Monohydrate surfaces, disrupting its stability and promoting dissolution. The absence of Calcium Oxalate Monohydrate in samples 1, 2, and 3 further reinforces this potential.

All in all, this study showed that calcium oxalate dihydrate crystals were much more common than calcium oxalate monohydrate crystals in normal urine before treatment. After treatment with *TKEE*, many dihydrate crystals broke into smaller pieces, and calcium oxalate monohydrate was completely gone from the three samples tested. These results suggest that the *takip-kuhol* extract has the potential to dissolve calcium oxalate crystals.

## CONCLUSIONS AND RECOMMENDATIONS

### Conclusion

This study determined the potential of *takip-kuhol* (*C. asiatica*) as a reducing agent for calcium oxalate formation. The ethanolic extract of *takip-kuhol* contains bioactive flavonoids and triterpenoids, which may help to reduce calcium oxalate (CaOx) crystal formation in human urine. The quantitative study demonstrated that increasing concentrations of the extract, particularly at 100%, significantly reduced CaOx crystal counts, with results comparable to those of the positive control. Furthermore, morphological assessments revealed that both calcium oxalate dihydrate (COD) and calcium oxalate monohydrate (COM) crystals changed significantly after treatment, including fragmentation, reduced density, and a loss of defined edges, indicating partial to complete crystal dissolution. The *takip-kuhol* ethanolic extract shows a significant reduction in CaOx crystal formation and changes crystal shape, indicating its potential as a natural reducing agent of calcium oxalate crystals, which could be relevant for conditions like kidney stones.

### Recommendations

1. Evaluate the optimal dosage and cytotoxicity of the extract in relevant animal models to establish its safety for long-term use.
2. Initiate pre-clinical trials to evaluate the efficacy and safety of *takip-kuhol* extract in human subjects at risk for kidney stones, or other types of kidney stones, such as uric acid or struvite stones, to determine its broader therapeutic potential.
3. Develop health education programs to raise awareness about the benefits of natural extracts like *takip-kuhol* in managing urinary health and preventing kidney stones.
4. Assess the impact of the extract on additional urinary parameters, such as pH and citrate levels, which are critical in stone formation and dissolution.
5. Further research is essential to confirm these benefits in larger and diverse populations and under different dietary and health conditions. This ensures safe and effective use of *takip-kuhol* as a natural reducing agent for calcium oxalate crystals.

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