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To Formulate And Evaluate The Microemulsion To Treat Kidney Stone Using The : Tridax Procumbens , Pedalium Murex , Kalanchoe Pinnate , Sour Orange

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Abstract

The prevalence of kidney stones (*Urolithiasis*) is affecting 12% of world population at the age of 20-30 years and it happens more frequently in men than women, but now a day's kidney stones are found in young children's at the age of 5 years also and their main cause is not drinking enough fluids and high intake of ultra-processed foods. To highlight the properties of Kalanchoe pinnata as herbal remedy for kidney stones. Tridax procumbens is a typical medicinal herb that is generally found in India as a weed and pest plant. It is classified as part of the Asteraceae family and is commonly referred to as Coat Button, Kansari (Hindi), or Ghamara (local language). The most valuable medicament utilized for the manufacturing of compounds described in Ayurvedic literature is Tridax procumbens. Kalanchoe pinnata has significant ability to dissolve (calcium oxalate) that is most common element in forming stones in urinary tract and also carry lots of phytochemicals such as flavonoids, quercitrin, glycosides, carotenoids, saponin, kamferol and alkaloids. These flavonoids prevent forming of CaOx crystal and calcium oxalate deposition in renal tubules. Kalanchoe pinnata plant extract also reduces the size of calcium oxalate stone and has treatment and preventive action in urolithiasis. Pedalium murex (L.) is a traditional herb, commonly used for the treatment of kidney stone related problems. Struvite stone can swiftly grow and become 'staghorn calculi' in kidney and its associated areas, which is the most aching urological disorder. The present study investigated the anti-urolithiasis activities of ethyl acetate extract of P. murex L. (EAEP) against struvite crystaOrange juice, researchers found, boosted the levels of citrate in the urine and reduced the crystallization of uric acid and calcium oxalate, but lemonade did not increase the levels of citrate.

A)Introduction

Kidney stone is a disease contain crystal concretion formed usually within the kidneys. It is an increasing urological disorder of human health, it affects about 12% of the total world population. It has been associated with an increased risk of end-stage renal failure Kidney stones affect up to 5% of the population, with a lifetime risk of passing a kidney stone of about 8-10% Increased incidence of kidney stones in the industrialused world is associated with increase standards of living and is strongly associated with race or ethnicity and region of recidenceKidney stones are mainly lodged in the kidney(s) . Mankind has been afflicted by urinary stones since centuries dating back to 4000 B.C. , and it is the most common disease of the urinary tract. The prevention of renal stone recurrence remains to be a serious problem in human health . The prevention of stone recurrence requires better understanding of the mechanisms involved in stone formation . Kidney stones have been associated with an increased risk of chronic kidney diseases , end-stage been suggested that kidney stone may be a systemic disorder linked to the metabolic syndrome. Nephrolithiasis is responsible for 2 to 3% of end-stage renal cases if it is associated with nephrocalcinosis renal failure , cardiovascular diseases , diabetes, and hypertension . The symptoms of kidney stone are related to their location whether it is in the kidney, ureter, or urinary bladder . Initially, stone formation does not cause any symptom. Later, signs and symptoms of the stone disease consist of renal colic (intense cramping pain), flank pain (pain in the back side), hematuria (bloody urine), obstructive uropathy (urinary tract disease), urinary tract infections, blockage of urine flow, and hydronephrosis (dilation of the kidney). These conditions may result in nausea and vomiting with associated suffering from the stone event . Thus, the treatment and time lost from work involves substantial cost imposing an impact on the quality of life and nation's economy.

A)Type of Kidney Stones and Their Risk Factors

1.Calcium stone

Generally, kidney stones are classified based on their main crystalline composition . Several studies from different regions have consistently reported that the most common inorganic composition among all kidney stones is calcium . Calcium stone is most frequently made of calcium oxalate (CaOx), either homogeneously or mixed with others, such as calcium phosphate (CaP) . CaOx has 3 crystalline forms based on its hydration status. These include CaOx monohydrate (COM; $CaC_2O_4 \cdot H_2O$), CaOx dihydrate (COD; $CaC_2O_4 \cdot 2H_2O$), and CaOx trihydrate ($CaC_2O_4 \cdot 3H_2O$). Among them, COM (also called whewellite) is the most common hydrate form found in clinical stones followed by COD (also called weddellite) . Hypercalciuria, hyperoxaluria, hypocitraturia, and hypomagnesuria have been recognized as the major risks of calcium stones. In particular, hyperoxaluria favors urinary COM crystallization, whereas hypercalciuria favors urinary COD crystallization . CaP in the form of apatite, either hydroxyapatite [$Ca_5(PO_4)_3OH$] or carbapatite (carbonated apatite) [$Ca_{10}(PO_4)_6CO_3$], is more common than brushite ($CaHPO_4 \cdot 2H_2O$) . Pure CaP stone is rarely seen because it usually mixes with other crystals, especially

CaOx. Both CaOx and CaP have some common metabolic risk factors, such as hypercalciuria and hypocitraturia. However, CaP crystal is more susceptible to the urine pH .

2.Struvite stone

Struvite stone comprises magnesium ammonium phosphate ($MgNH_4PO_4 \cdot 6H_2O$) and is commonly referred to as infection stone. Struvite commonly combines with CaOx and CaP, especially carbapatite, in the stone matrix . This type of the stone is associated with urinary tract infection (UTI) by urease-producing bacteria, such as Proteus spp. and Klebsiella spp. . Such infection leads to increased production of ammonium that causes urinary alkalinization, thereby facilitating the formation of struvite crystals . As expected, a recent study has demonstrated that the stone formers with high-struvite composition in kidney stone matrix are associated with positive urine culture for *Proteus* spp. . In addition to urease-producing bacteria, others (that is, *Escherichia coli* and Enterococcus spp.) are also found to be associated with struvite stone . Interestingly, this stone type is more common in females than in males in some regions .

3.Uric acid stone

Uric acid stone comprises uric acid crystals that are normally crystallized in acidic urine, and most of the uric acid crystals are in the dihydrate form . This stone type is particularly common in patients with type 2 diabetes and obesity. The prevalence of uric acid stone seems to be increasing in males over recent years . However, uric acid crystals mostly mix with other types of crystals . Hyperuricosuria and persistent or overly low urinary pH (acidic urine) are the major risk factors for uric acid stone formation.

4.Cystine stone

Cystine stone is a rare kidney stone type associated with cystinuria, a genetic disorder. It is caused by autosomal recessive gene, such as *SLC3A1*, which regulates renal cystine transporter . This genetic disorder results in defective cystine transport, leading to a decrease in urinary cystine reabsorption and subsequently increased urinary cystine concentration or cystinuria . Under the normal urine pH (below 6.5), cystine is relatively insoluble in the urine, leading to its precipitation, crystallization, and formation of cystine stone

B) Mechanism of kidney stone formation :-

Mechanisms of CaOx stone formation. The first mechanism takes place within tubular lumens involving supersaturation of crystalline salts, crystallization, growth, self-aggregation, and adherence on tubular epithelial cells. Bacteria (both urease-producing and non–urease-producing groups) also play roles in this intratubular mechanism. The second mechanism initially takes place at renal interstitium by forming the so-called Randall

plaque, which is a result of interstitial hydroxyapatite CaP crystal deposition and tissue inflammation. Some of the Randall plaques at and adjacent to the papillary tip can erode into the pelvicalyceal system, where CaOx is commonly supersaturated and crystallized. CaOx crystals subsequently deposit on the eroded Randall plaque, which then serves as the stone nidus, and the stone starts to form. CaOx, calcium oxalate; CaP, calcium phosphate; COM, calcium oxalate monohydrate; ECM, extracellular matrix.

a)Microemulsion:-

A microemulsion is a thermodynamically stable, transparent, and isotropic mixture of two immiscible liquids (typically water and oil) that are stabilized by surfactants. These mixtures are often nanosized and can form spontaneous, without the need for external energy input.

I)Types of Microemulsions:

a) **Oil-in-Water (O/W):** Oil is dispersed in a continuous aqueous phase.

b) **Water-in-Oil (W/O):** Water is dispersed in a continuous oil phase.

c) **Bicontinuous:** Both oil and water phases form a continuous and interconnected network,

II) **Characteristics of Microemulsions:-**

1. **Immiscible Liquids:**

   Microemulsions are typically formed from water and oil, which would normally not mix together.

2. **Surfactants:**

   Amphiphilic surfactants (molecules with both hydrophilic and hydrophobic parts) act as an interface between the oil and water phases, stabilizing the mixture.

3. **Thermodynamic Stability:**

   Microemulsions are stable over time and don't require constant agitation or energy input to maintain their structure.

4. **Isotropic:**

   They are uniform in all directions, meaning they have the same properties regardless of the direction you view them from.

5. **Nanosized:**

   While the name "microemulsion" might imply larger droplets, they are actually often in the nanometer range (10-200 nm).

6. **Formation:**

   They are typically formed by simple mixing of the oil, water, and surfactant components.

7. **Applications:**
    a. Microemulsions are used in various fields, including:
    b. **Drug delivery:** They can carry drugs through the body.
    c. **Cosmetics:** They can be used in topical applications.
    d. **Cleaning agents:** They are effective in cleaning due to their ability to solubilize oil.
    e. **Enhanced Oil Recovery:** They can be used to improve oil extraction from wells.
    f. **Other Industrial Applications:** They are used in various industrial processes, such as hydrogen production.

b)Water in Oil Microemulsion

A microemulsion where water is the dispersed phase and oil is the continuous phase is called a water-in-oil (W/O) microemulsion. In this type of microemulsion, tiny water droplets (typically 1-50 nm in diameter) are surrounded by a monolayer of surfactant molecules and dispersed within the oil. These droplets are stabilized by the surfactant, which helps to reduce the interfacial tension between the water and oil.

I)Characteristics of W/O Microemulsions:

1. **Thermodynamically Stable:**

W/O microemulsions are thermodynamically stable, meaning they remain dispersed without requiring continuous external energy input.

2. **Optically Transparent:**

They are generally transparent, allowing light to pass through.

3. **Nanosized Droplets:**

The dispersed water droplets are typically in the nanoscale range, providing a large surface area for interactions.

4. **Surfactant Stabilization:**

Surfactant molecules are crucial for stabilizing the microemulsion and preventing the water droplets from coalescing and separating.

5. **Applications:**

W/O microemulsions have various applications, including:

a. **Nanoparticle Synthesis:** They can be used to synthesize nanoparticles with controlled size and shape.
b. **Drug Delivery:** They can enhance the delivery of drugs, especially poorly water-soluble ones.
c. **Cosmetics and Personal Care:** They are used in various cosmetic and personal care products.
d. **Enhanced Oil Recovery:** They can be used to mobilize oil trapped in porous rock formations.

e. **Other Industrial Applications:** They find applications in dry cleaning, floor polishes, pesticides, and cutting oils.

b)Need And Objective of kidney stone:-

a)Need:

1. Pain:
   Kidney stones can cause excruciating pain in the side, back, or abdomen as the stones move through the urinary tract.
2. Complications:

Stones can lead to infections, kidney damage, and even the need for surgery.

3. Reduced Quality of Life:

Kidney stone episodes can disrupt daily life, causing pain, anxiety, and the need for medical attention.

b)Objective:

1. Prevent Stone Formation:

The primary objective is to reduce the concentration of substances in the urine that can form stones, such as calcium, oxalate, or uric acid.

2. Minimize Recurrence:
   For individuals who have experienced kidney stones, the objective is to prevent them from recurring.
3. Maintain Kidney Health:

Preventing kidney stones helps to ensure the long-term health and function of the kidneys.

c)Strategies for Prevention:

1. Hydration:

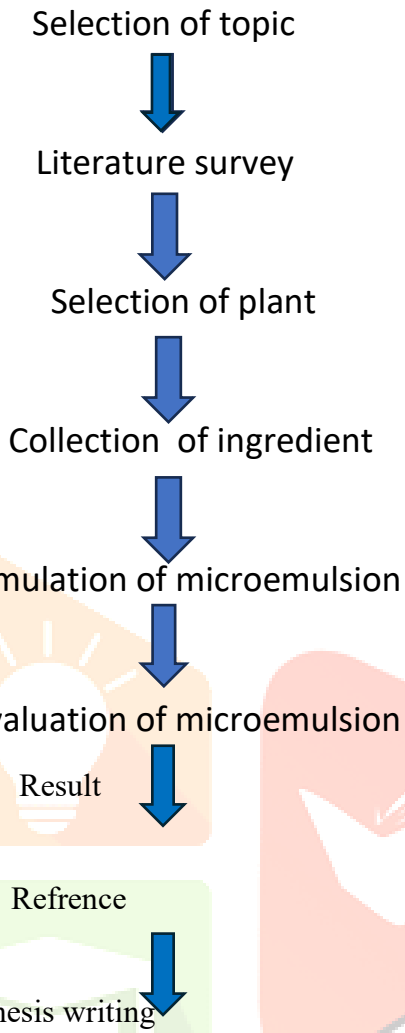
Drinking plenty of water dilutes urine, making it less likely for stones to form.

2. Dietary Modifications:
   Limiting salt, animal protein, and oxalate-rich foods can help prevent certain types of stones.
3. Medical Interventions: In some cases, medications may be prescribed to prevent stone formation or to help pass existing stones.

C)Literature survey

Authors	Title	Source	findings
Sneha Mundada, et al,	Pharmacology of Tridax procumbens a Weed: Review	Int J Pharmtech Res.	The studies on plant Tridax procumbens Linn. also desired development of novel therapeutic agents isolated from it, as isolation of oleanolic acid a single triterpenoids is reported from this plant
Samantha Beck et al.	A Review of Medicinal Uses and Pharmacological Activities of Tridax Procumbens (L.)	J Plant Stud.	Tridax procumbens has a long history of traditional use but isolation and evaluation of each phytochemical has not been properly related toits pharmacological properties and could show difficulty in reproducibility after isolation and evaluation.
P. Ghosh, et al	Morphological, Ethno biological and Phytopharmacological Attributes of Tridax procumbensLinn. (Asteraceae)	Int. j. sci. res. biol. sci	This study may be helpful for identification and preparation of a clear profile of the plant which may open new avenues in the medical field in the treatment of various diseases.
Laroubi A, Touhami M, Farouk L	Prophylaxis effect of Trigonella foenum graecum L. seeds on renal stone formation in rats	Phytother Res	The inhibitory effect of the aqueous extract of Tfg seeds was examined on the formation of calcium oxalate renal stones induced by ethylene glycol (EG) with ammonium chloride.

D)Plan of Work:-



E)Material and Methodology:-

I)Ingredients:-

1. Surfactant
2. Oils
3. Water
4. Flavonoids

1.Surfactant:-

Non-ionic surfactant are often preferred beause they can improve the stability of flavonoids in emulsion by reducing their degradation under various condition.

Non-ionic Surfactant:- Tween 80,

Tween 40

Tween 80- 2-3 gram

gram→ml

Density of tween 80 is -1.06g/ml

Then 2g→1.89ml

2.Oils:- Sunflower oil,almomd oil,coconut oil,palm oil,avocado and Essential oils, (lemon oil).

A)Tridax procumbens:-

The effect leaf of tridex procumben extract on crystal growth has reduced. The final effect of crystal aggregation reiterates the fact that the plant extract of tridex procumben could readily hold back crystal formation, which clearly shows the antilithiatic activity of the plant Tridax procumbens. Stone formation is a multiplex process containing the crystal nucleation, and the secondary nucleation, fixation within the kidney, and more aggregation and secondary nucleation.

B)Pedalium Murex:-

Pedalium murex is believed to help prevent kidney stones, particularly calcium oxalate stones, by inhibiting calcium oxalate crystal formation and promoting diuresis. It may achieve this by reducing calcium and uric acid levels, improving kidney function, and acting as an antioxidant, potent.

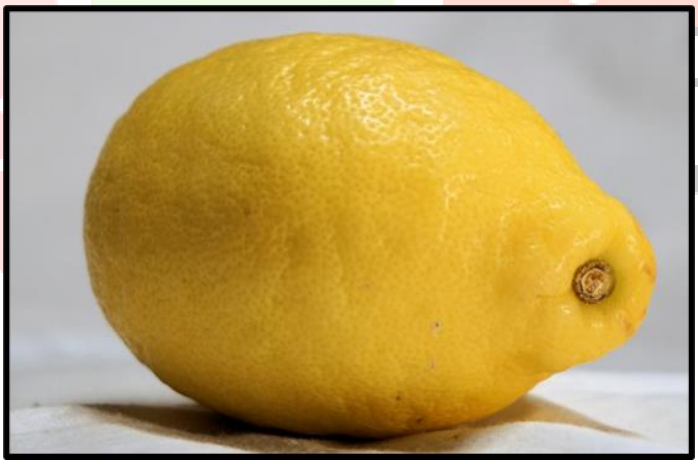
Other Potential Mechanism:

i) Some studies suggest that Pedalium murex may help regulate calcium and uric acid levels, which are important factors in stone formation.
ii) It may also improve renal function, which can further contribute to the prevention of kidney stones.
iii) The exact mechanism of action is still being investigated, but the plant's ability to inhibit crystal formation, promote diuresis, and act as an antioxidant all contribute to its potential anti-urolithiatic effects.

C)Kalanchoe pinnate:-

The study investigates the antiurolithiatic potential of the leaves of *Kalanchoe pinnata*, a plant recognized in traditional medicine for its use in treating urinary stones. Phytochemical screening of the plant's extract revealed the presence of bioactive compounds like flavonoids, phenolic compounds, and saponins, which are believed to play a role in inhibiting crystal formation. The research employed in vitro methods to assess the effects of the alcoholic extract on the formation of calcium oxalate crystals utilizing two critical assays: nucleation and aggregation tests.

D)Sour Orange:-



Sour oranges, like other citrus fruits, may help prevent kidney stones by increasing urinary citrate levels, which can inhibit alkalinizing effect on urine, which can help dissolve uric acid stones. However, some citrus juices, like orange juice, can also increase urinary oxalate, which may not be ideal for individuals prone to calcium oxalate stones. the formation of calcium oxalate stones

E) Active ingredients:-

a)Flavonoids:-

Flavonoids are a type of plant polyphenol that has been linked to several health benefits. Recent research has revealed that plant flavonoids can significantly reduce the formation of kidney stones *in vitro* and *in vivo*,

which correlates with their anti-inflammatory, antioxidant, diuretic, antibacterial, and other beneficial actions. Thus, the flavonoids or extracts of flavonoid-rich plants associated with anti-urolithiasis activity were evaluated.

plant flavonoids can significantly reduce the formation of kidney stones in vitro and in vivo, which correlates with their anti-inflammatory, antioxidant, diuretic, antibacterial, and other beneficial actions.

b)Extraction Method of flavonoids:-

I)Traditional Methods:

1.Maceration:

A simple infusion method where the plant material is soaked in a solvent at room temperature for a period of time.

2.Percolation:

A continuous extraction process where the solvent is passed through the plant material until all flavonoids are extracted.

3.Soxhlet Extraction:

An improved maceration method using a continuous extraction cycle, where the solvent is repeatedly heated and evaporated to extract the flavonoids.

II)Modern Methods:

1.Ultrasound-Assisted Extraction (UAE):

Uses ultrasonic waves to disrupt plant cell walls and enhance solvent penetration, leading to faster and more efficient extraction.

2.Microwave-Assisted Extraction (MAE):

Employs microwave energy to heat the solvent, accelerating the extraction process and reducing extraction time.

3.Supercritical Fluid Extraction (SFE):

Uses a supercritical fluid, like carbon dioxide, as a solvent, allowing for efficient extraction with minimal environmental impact.

c)Extraction method of flavonoids:-

1)Maceration Method:-

1.Course or powdered plant material is soaked in a solvent like water ,oil or alcohol.

↓

2.The material is soaked for a long time which rupture the cell walls and released the bioactive compounds into the solvents.

↓

3.filter the solvent

↓

4.Collect the filterate

i)Identification test of flavonoids:-

Test	Procedure	Obsevation	Result
1.Alkaline reagent test	Test solution+few drop of NaOH solution	Intense yellow colour from which turns to colourless on the addition of few drop of dilute acid.	positive
2.sulphuric acid test	Test solution +sulphuric acid (66%or 80%)	Flavones and flavones- Deep yellow colour	positive
3.Lead acetate test	Test solution +lead acetate solution	Yellow precipitate	positive

F)Formulation Table :- (10ml)

Sr no.	Ingredients	Excipients	Quantity
1	Surfactant	Tween-80 Tween-40	1.89ml 1.89ml
2	oil	Lemon Oil	2.5ml
3	Flavonoids	i)Tridax procumbens extract, ii)Pedalium murex etract, iii)Kalanchoe pinnate extract, iv)Sour orange extract	1ml 1ml 1ml 1ml
4	Water	-	Required quantity

G) Procedure of Microemulsion:-

Mix the surfactant and oil in a hot bath

↓

Dissovle the flavonoid powder in the surfactant and Oil mixture.

↓

Add distilled water to the mixture

↓

Mix the mixture gently

↓

Measure the particle size

H)Formulation:-

Fig no 1

I) Result

A) Organoleptic characterization of drug :-

Identification test	Observed result
Appearance	Transparent or translucent,single phase liquid
colour	Pale yellow
odour	Lemonene,citral
solubility	Methanol,ethanol,ethyl acetate,chloroform
Particle Size	18.3nm

B) Test of microemulsion:-

Sr no	Test	observation	Result
1	A) Dilution test		
	i)adding in water	Water separate out as a layer	Positive
	ii)adding in oil	Emulsion gets mixed with oil phases	Positive

fig no 2. Test of microemulsion

j)Discussion:-

Tridax procumbens , Pedalium murex , kalanchoe pinnate and sour orange has significant ability to dissolve (calcium oxalate) that is most common element in forming stones in urinary tract and also carry lots of flavonoids, quercitrin, glycosides, carotenoids, saponin, kamferol and alkaloids. These flavonoids prevent forming of CaOx crystal and calcium oxalate deposition in renal tubules. also reduces the size of calcium oxalate stone and has treatment and preventive action in urolithiasis. And also cure Properties such as Diuretic and Antiurolithic,

anti-diabetic, anti-microbial, anti-inflammatory, anticancer, anti-ulcer, wound healing,Antileishmanial, Anticonvulsant, Antiproliferative , Hepatoprotective, Immunosuppressive and Immunomodulatory by leaf extract of tridax procumbens ,Pedalium murex, Kalanchoe pinnata , and sour orange which contain phenolics compound, tannins, titerpenses, steroids, lipids, cardienolides

K)Conclusion

The rich flavonoid content of Tridax procumbens, Pedalium murex, Kalanchoe pinnata, and Citrus aurantium supports their potential use in microemulsion drug delivery systems. While Citrus aurantium has been moderately studied in this context, the other three remain largely untapped. Further research is recommended to formulate and evaluate microemulsions incorporating these plant-derived flavonoids for enhanced therapeutic efficacy.

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