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Clinical Evidence and Molecular Mechanisms of Ficus Species Plants for Preventing and Managing Kidney Stones

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After prostate pathology and urinary tract infections, kidney stones rank third in the frequency of urinary tract issues. Urine flow obstruction and severe pain are two possible side effects of kidney stones. Typically, they are treated with drugs that have a lot of potential negative effects. In many cultures, medicinal herbs provide a dependable source of natural cures. This study aimed to determine native medicinal plants used by traditional healers of Shiraz to treat kidney stones. The findings reported in the published research confirm that dietary plants and phytosterols have a confirmed function in kidney stone control and prevention. More research is needed to ensure that these ingredients are safe and effective. In terms of safety and effectiveness, they can be processed and developed to create natural remedies. One of the urinary tract system's most prevalent and ancient illnesses is kidney stones. Numerous researches on humans have indicated that diets that include more plant-based foods may help reduce kidney stones. These dietary plant-based ingredients their essential chemical constituents and their potential modes of action have all been briefly discussed in this review.
Keywords: Nephrolithiasis; Urolithiasis; Dietary Supplement; Phytochemicals.

1. Introduction

One of the most prevalent health issues affecting the urinary tract is kidney stones, which happen 50% of the time within five to ten years [1]. Nephrolithiasis, urolithiasis, or renal calculi are hard deposits that resemble pebbles and are caused by high concentrations of specific minerals and salts. It can range in size and form from micrometers to several centimeters in diameter. With rates as high as 14.8% and rising, stone formation is very

common. Within the first five years following the initial stone episode, recurrence rates can reach 50% [2]. The kidneys, ureters, and bladder can all develop urinary tract stones. Approximately 80% of kidney stones are calcium stones, with calcium oxalate and calcium phosphate making up 80% of the total. Uric acid (UA) makes up 9%, and struvite (magnesium ammonium phosphate hexahydrate, which is caused by bacterial infections that have the enzyme urease) makes up 10%. The remaining 1% is made up of cysteine, drug stones, and ammonium acid urate [3]. Among urinary diseases, it is the third most prevalent condition [4]. According to reports, 10–12% of persons in developed nations will experience a urinary stone at some point in their lives (10% of males and 3% of women) [5]. According to reports, this disease impacted over 40% of the global population in 2000 in high-risk regions (Asian countries specially India and Saudi Arabia), and by 2050, this number is predicted to rise to 50% [6]. Southern China, India, and Pakistan are the nations that make up Asia's "stone belt." There are reports that this condition affects about 15% of the Indian population [7].

2. Literature Search Methodology

From 2005 to December 2017, herbal plants and their bioactive substances utilized for urolithiasis management and prevention were found utilizing online resources like Scopus, Science Direct, and PubMed. The keywords were dietary plant, dietary herb, phytochemical, fruits, or vegetables, kidney stone, urolithiasis, nephrolithiasis, renal calculi, renal stone, or antilithiatic. The publications that were retrieved were divided into three categories: clinical, in vitro, and in vivo. The included studies were assessed in terms of the plant's phytochemical content, potential for usage as a dietary agent, the type of kidney stone that the dietary agent effectively treats, and underlying mechanisms of action.

Dietary approaches to kidney stone prevention

Recent human studies indicate that diets rich in fruits and vegetables may help prevent urolithiasis [8]. Diet may be one of the primary risk factors for renal illnesses, based on epidemiological research [9]. Increased water and liquid intake is the most straightforward and crucial lifestyle modification to prevent stone disease. A sufficient amount of fluid lowers urine saturation and dilutes calcium oxalate crystallization promoters. Consuming a lot of protein improves urinary calcium excretion through bone reabsorption while lowering urine pH and citrate levels. The primary phosphate found in natural sources is phytotate, and eating it is linked to the creation of insoluble compounds with calcium in the stomach. These complexes can reduce the risk of urolithiasis and inhibit the production of crystals in the urine [10]. A natural diet that increases alkali load can increase urine citrate, which significantly reduces the risk of kidney stones.[11].

Phytoconstituents that prevent kidney stones

The use of traditional medicine and herbal therapies to prevent and treat a large range of disorders has grown significantly in recent years [12]. Since ancient times, people have recognized medicinal plants as a rich source of therapeutic chemicals that can help avoid a wide range of illnesses. These plants are highly respected worldwide [13]. The potential of several medicinal plants and phytochemical ingredients to prevent and treat kidney stones has been assessed [14]. Most of the remedies used in traditional medicinal systems, such as

Ayurveda, were plant-based. According to reports, these plant products effectively and without causing any negative side effects reduce the recurrence rate of renal calculi [15].

Ficus species provide urolithiasis defense

The Moraceae family, which includes the genus Ficus has about 850 species of trees, shrubs, vines, and epiphytes [16].Throughout the world, a number of Ficus species are traditionally employed in a broad range of ethnomedical treatments. Research on Ficus has mostly concentrated on its edible components (fruits), with aerial roots and bark coming in second and third, respectively. Seldom are the leaves examined in comparison to other sections. The genus Ficus's therapeutic qualities have been thoroughly examined through pharmacological research as well as ethnobotanical field surveys [17] such as research on antibacterial [18], antidiabetic activity [19], hepatoprotective, antipyreti, anti-inflammatory, antispasmodic, antiplatelet, antihelmintic, anticancer, antiurolithiasis, anti-HIV activity and anti-diarrheal [20 & 21].

Pharmacological applications of Ficus species.

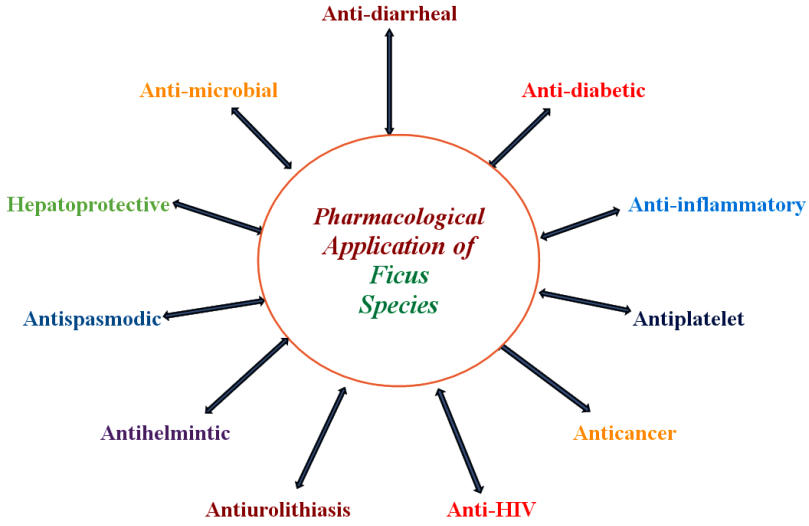

Table 1: Distribution and traditional uses of some Ficus species in Uttarakhand.

Species	Distribution	Uses as diet	Ethno- medicine
Ficus benghalensis	*Kumaon, Chakrata, Chamoli, Tons Valley:*	Fruits edible, Wood used to make tentpoles, boats,	latex used in diabetes
Ficus carica	Garhwal regions, mostly grown in garden Or homeyard.	Fruits eaten fresh or dried, making jams, pickles, Cookies	latex used in anthelmintic and used to destroy warts.
Ficus drupacea	Garhwal and Kumaon	Shade tree	
Ficus hispida	Garhwal and Kumaon regions, mostly Found in moist and Shady places, old walls.	Unripe fruits use in Curries. Ripe fruits edible and also making in jam, pickles, bark strong fibres.	
Ficus palmata	Garhwal and Kumaon Regions	Fruits edible,	digestive disorder
Ficus pumila	Garhwal and Kumaon Regions, sub-Himalayan tract,	Non-edible,	fruits and leaves, used bleeding, swelling, haemorrhoids, intestinal disorders,

			fevers, etc.
Ficus religiosa	Garhwal and Kumaon Region.	Wood used for making charcoal.	Bark and figs used in treat bronchitis and skin Diseases [59].

Table 2: Plant's which have antiurolithiasis activity

Plant/Family	**Common name**	**Phytochemical**	**Part of plant**	**Study type**	**Assay**	**Activity**	**References**
Ficus palmata/ Moraceae	Bedu	carbohydrates, steroids, saponins, flavonoids, tannins and phenols	Fruits/Aerial parts	in vitro/vitro	hydroethanolic extract,aggregation assays, DPPH	Antiurolithiasis, Antimicrobial, Antidiabetic, Thrombolytic, anticancer Activities,	[22, 23]
Ficus carica/ Moraceae	Fig	Flavonoids,Vitamin C, Saponins, tannins, steroids and flavonoids.	Leaves, Fruits	In vivo	By using equine extract in mate-wister rats, serum analysis, and serum parameter evaluation, freeradical scavenging activity.	Anti-urolithiasis, Anti-inflammatory, Antioxidant.	[24,25, 26]
Ficus pseudopalmata/Moraceae	Philippine fig.	lupeol and ethyl acetate,	leaves	Invivo/ In - vitro	Screening for Triterpenes, Free radical scavenging activity, Animalstudy, Urine analysis	Anti-urolithiasis, anti-oxidant Antibacterial	[27,28]
Ficus religiosa/ Moraceae	Weeping fig, Peepal		*Leaves*	in vitro	growth of CHPD crystals, Fourier transform infrared spectroscopy, thermogravimetric analysis etc	Anti-urolithiasis	[29]
Ficus religiosa/ Moraceae			Seeds, Root, Bark, fruit, leaves	In vitro/ In vivo	In vitro free radical scavenging activity, GC–MS analysis, Statistical analysis	Anti-urolithiasis, stomatitis, ulcers, and other inflammatory conditions like, gout anticancer. Antidiabetic. Analgesic. Anticonvulsant. Antimicrobial.	[30, 31,32,33 ,34, 35,36]
Ficus tikoua Bur. Moraceae	Wild mellon		Whole plant	In vivo	Microscopic analysis of urine,	Anti-urolithiasis	[37]
Sonchus arvensis Asteraceae	Perennial sowthistle, Field sowthistle.		Leaves	In vivo/in vitro		Anti-urolithiasis, Antimalarial, Plasmodium falciparum	[38,39]
Artocarpus altilis (PARK) Moraceae	Breadfruits		Leaves	in vitro	Atomic absorption spectrophotometry.	Anti-urolithiasis	[40]

Amaranthus viridis Amaranthaceae	Blood Amaranthus		Root	In vivo	Collection and Analysis of Urine, Serum Analysis, Statistical Analysis.	Anti-urolithiasis	[41]
Raphanus sativus\ *Brassicaceae*	Radish	Tannins, flavonoids and Saponins.	Leaves	In vivo	aggregation assays, hydroethanolic extract, FT-IR, HPLC Chromatography.	Anti-urolithiasis	[22]
Nyctanthes arbor-tristis\ *Oleaceae*	Night - flowering jasmine, coral jasmine or parijaat.	saponins, tannins, flavonoids and polyphenolic compounds	Leaves	In vivo	hydroethanolic extract, aggregation assays, FT-IR, HPLC Chromatography	Anti-urolithiasis	[22]
Solanum virginianum\ *Solanaceae*	Thorny nightshade, wild tomato etc.		whole plants	In vivo	Pharmacological screening for anti urolithiatic activity,	Anti-urolithiasis	[42]
Andrographis paniculata\ *Acanthaceae*	Kalmegh, king of bitters, bhui-neem etc.	Alkaloid, saponin, tannin, and flavonoid	Whole plant	In vitro	(FTIR) spectroscopy,	Anti-urolithiasis	[43]
Dolichos biflorus\ *Fabaceae*	Horsegram, kulthi.	carbohydrate, steroid, tannins, phenol, protein, amino acid, alkaloids, glycosides, flavonoids and saponins	Seeds	In vitro	LC-MS analysis, Molecular docking, Statistical analysis.	Anti-urolithiasis	[44]
Solanum nigrum Solanaceae	Black nightshade, Blackberry.		Fruits	In vivo	Estimation of biochemical parameters, Statistical analysis	Anti-urolithiasis	[45]
Coriandrum sativum L.\ *Umbelliferae*	Coriander	glycosides, alkaloids flavonoids, saponins, phenols, steroids, tannins, and triterpenoids	Seeds	*in vitro*	nucleation, aggregation, and inhibition. Spectrophotometry and microscopic inspection	Anti-urolithiasis	[46]
Phyllanthus amarus\ *phyllanthaceae*	Stonebeaker, bhuiavla.etc	Alkaloids	Leaves	In vivo	use of the turbidity method and the calcium oxalate dissolution method,	Anti-urolithiasis	[47]
Citrus limon\ *Rutaceace*	Citrus	Alakaloids, saponin, flavonoids, phenolic acid.	Fruit's peel	In vivo	(GC–MS) analysis, Urinary investigations, Serum investigations, Tissue investigations,	Anti-urolithiasis	[48]

					Histopathological examinations, mmunohistochemical analyses.		
Bergenia ciliata\ *Saxifragaceae*	Hairy Bergenia, Pakhanabhed, Pashanbheda	alkaloids, flavonoids saponins, terpenoids, and tannins	Rhizomes	In vivo	Nucleation assay, Aggregation assay,	Anti-urolithiasis	[49]
Bergenia ligulate\ *saxifragaceae*	Paashaanbhed, prashanbheda		Rhizomes	In vitro\In vivo	EG+ aluminium chloride-induced	Anti-urolithiasis	[50]
Anacardium occidentale\ *anacardiaceae*	Cashew nut	phenol, alkaloid, saponin, tannin, and terpenoid	leaves extracts	In vitro	Nucleation assay, Staytisticalanalysis, phytochemical screening.	Anti-urolithiasis	[51]
Costusarabicus L.\ *Costaceae*	Spiral ginger		Whole plant	In-vitro	*Calcium oxalate monohydrate, crystals induced in MDCK cells*	Anti-urolithiasis	[52]
Hypericum perforatum L.\ *Hypericaceae*	Goat weed, klamathweed		leaves	In vivo	Ethylene glycol and ammonium chloride-induced stone in rats	Anti-urolithiasis	[53]
Cinnamomum zeylanicum Blume\ *Lauraceae*	Cinnamon,	flavonoid, alkaloids, triterpenes, magnesium, saponins, phenolics, tannin, resin, citrate and citric acid,	Bark	In vitro	Phytochemical analysis and HPTLC	Anti-urolithiasis	[54]
Carica papaya\ *Caricaceae*	Papaya,		ripen fruits	In vivo	Ethylene glycol induced urolithiatic rats, Serum analysis, Statistical analysis	Anti-urolithiasis	[55]
Lepidagathisprostrata\ Acanthaceae	Pashanbhed	Flavonoids and polyphenols	whole plant	In vitro	Nucleation assay, Aggregation assay, DPPH radical scavenging assay, Statistical analysis	Anti-urolithiasis	[56]
Hylocereus undatus Linn.\ *Cactaceae*	Dragon fruit,	flavonoids,Terpenoid,alkaloids, saponins, tannins and phenols	Fruit	In vitro	Phytochemical Analysis, Synthesis of Zinc Nanoparticles, Struvite Crystal Growth, FT-IR spectroscopy.	Anti-urolithiasis	[57]

Ficus palmata

The antiurolithiatic potential of the hydroethanolic extract of Ficus palmata fruit was investigated by an in vitro method using nucleation, growth, and aggregation assays along with microscopic analysis of calcium oxalate crystals. The calcium oxalate crystals' number and size were reduced, and their nucleation, growth, and aggregation were inhibited by the plant extract. The study showed that the extract had a noteworthy anti-crystallization effect on calcium oxalate crystals, which might be translated into excellent antiurolithiatic activity. The extracts also influence different stages of the urinary stone production process. Cystone and the extract both showed a concentration-dependent increase in the decrease in calcium oxalate crystallization [22].

Ficus carica

In Asian cultures, Ficus carica has long been used as a medicine. The present work aimed to investigate how Ficus carica fruit affects ethylene glycol urolithiasis in albino Wistar rats. The preliminary phytochemical investigation was carried out with an aqueous extract of Ficus carica (FCAE) for BHAH identification. This study proved that F. carica has a regulating effect on Calculi formation, thereby indicating its positive role in treating Urolithiasis. Wister rats weighing between 200 and 300 grams were chosen for this investigation, and they were acclimated to the animal house for seven days. There were five groups of male Wistar rats, each with six rats. To induce urolithiasis, 0.75% v/v of ethylene glycol is added to drinking water and fed to all groups except the control group until day 28. The test groups were given FCAE (once daily by oral route) from day 15 to day 28. Cysteine was administered as a standard medication (750 mg/kg body weight) to group III. After the drug and fruit extract therapy ended, serum and urine samples were collected and analyzed to identify several parameters. Serum biochemical parameters like creatinine, urea, uric acid, and calcium were significantly reduced in animals treated with FCAE at a dose of 400 mg/kg. Reduction of these parameters indicates that FCAE has a potential anti-urolithiatic effect. This study investigates the anti-urolithiasis effect of F. carica extract, which showed promising results in improving renal functions by reducing elevated levels of creatinine, uric acid, and calcium. The extract also showed potential protective action against renal calculi and inflammatory infiltration, with more potent anti-urolithiatic activity in ethylene glycol-induced urolithiasis rat models [24].

Ficus psedopalmata

This study investigates the antiurolithiatic and antioxidant potential of Ficus pseudopalma Blanco. The crude dichloromethane (DCM) leaf extract was fractioned by silica gel column chromatography. Ethyl acetate fraction showed an IC50 of 0.2586 mg/mL against OH radical and 5.289 mg/mL against H202. 42 rats were used for this experiment and six rats were randomized and assigned per experimental group. Induction of urolithiasis was done by daily oral administration of 0.75% ethylene glycol and 1% ammonium chloride from Day 1-5, followed by daily oral administration of 0.75% ethylene glycol alone from Day 6-28. All experimental groups received urolithiatic induction for 28 days except for the vehicle control. The effect of Ficus pseudopalmata crude DCM extract was evaluated in two treatment designs: preventive and therapeutic regimens. Preventive groups received stone induction with simultaneous treatment with extract on Days 1-28. Therapeutic groups received stone induction on Day 1, and the administration of extract started on Day 15. The experimental

groups for the antiurolithiatic study were as follows: Group 1 – Vehicle control, Group 2 – Induction control, Group 3 – 1000 mg/kg dose of F. pseudopalma crude DCM extract (Preventive), Group 4 – 500 mg/kg dose of F. pseudopalma crude DCM extract (Preventive), Group 5 – 1000 mg/kg dose of F. pseudopalma crude DCM extract (Therapeutic), Group 6 – 500 mg/kg dose of F. pseudopalma crude DCM extract and lastly Group 7 – 10 mg/kg dose of Lupeol (Therapeutic- Positive control) [27].

Ficus religiosa L has been shown to have numerous biological activities such as wound healing, antibacterial, anticonvulsant, antidiabetic, and anti-inflammatory. The present study investigated the inhibitory action of an aqueous extract of Ficus religiosa leaves on the method: of growth of CHPD crystals. This technique provides a much-simplified method to understand the growth of urinary crystals in vitro. The putative activity of plant extracts as inhibitors of CHPD crystal formation was investigated. The various concentrations (50, 75, and 100 g) of the plant extract were dissolved in respective 50, 75, and 100 ml of distilled water to give 50, 75, and 100 % solution at the time of the experiment. The first Liesegang ring was observed within 12 min of pouring the solution. In total, 18 Liesegang rings were observed over time. Elongated platelet-shaped CHPD crystals grew within the rings. The crystals were characterized by Fourier transform infrared spectroscopy, thermogravimetric analysis, scanning electron microscope,y and powder x-ray diffraction methods, and confirmed to be CHPD. The results of the decreased optical density with the increase in concentration of the extract of F. religiosa indicate decreased nucleation of CHPD crystals [29].

Ficus religiosa seeds. F. religiosa seeds were extracted by Soxhlet extraction using a variety of solvents in ascending order of polarity. Antioxidant potential was assessed for each extract. The most powerful antioxidant, F. religiosa seed extract, was analyzed using GC–MS profiling to assess the phytoconstituents. In silico ADMET analysis was performed to assess these compounds' pharmacokinetics and drug-likeness characteristics. Using the Autodock Vina tool, multitarget-based virtual screening tests were conducted to understand the binding potential of the best ADMET-evaluated phytochemicals found in the F. religiosa seed extract against the various protein targets (matrix metalloproteinases (MMP-2, MMP-9), and human calcium-sensing receptor and antioxidant enzymes (glutathione S-transferase (GST), glutathione-disulfide reductase (GR), glutathione peroxidase (GPX), and superoxide dismutase (SOD)) involved in urolithiasis [30].

Phytochemicals that Prevent Urolithiasis

Several current researches have demonstrated the potential of dietary treatments as a means of protection of the kidney, either in conjunction with or independently of genetic or hereditary variables. It is possible to treat urolithiasis, reduce the chance of kidney stones coming back, and influence the growth and creation of crystals by incorporating nutritional plants and their phytochemicals into the regular diet or as dietary supplements. There are very few clinical trials for S. crispus and O. stamineus. The majority of research on these plants was done either in vitro (in a lab) or in vivo (in experimental animal models). It might not accurately depict the mechanisms and effects of O. stamineus and S. crispus on kidney stones in humans. Plant extracts have been the primary focus of most studies. This study's shortcomings include the fact that it treats kidney stones by rising

3. Discussion

Dietary plant-based ingredients such as fruits, vegetables, and food additives are significant for maintaining human health and prohibiting diseases like kidney stones. This review shows several dietary plants' effectiveness, pharmacological mechanisms, and phytochemicals in managing or preventing kidney stones. According to the most recent research, extensive in vitro and animal studies have been conducted to assess the potential of dietary plants and their phytochemicals as nutritional supplements to avoid the development of urolithiasis. These studies have shown that dietary plants have the potential to prevent and treat kidney stones, and further research is needed to determine their efficacy in humans. However, there are many clinical investigations into the effectiveness of dietary and herbal remedies in kidney stone treatment. Among the plants whose effectiveness has been verified by clinical trials are Ficus benghalensis, Ficus carica, Ficus drupacea, Ficus hispida, Ficus palmata, and Ficus religiosa. Catechin, epicatechin, EGCG, diosmin, rutin, quercetin, hyperoside, and curcumin are among the nutraceuticals (mostly dietary polyphenols) that may be suggested as effective dietary supplements for urolithiasis prevention. However, Fig. 1 describes the various medicinal applications of Ficus species in our investigation. Research studies have been performed both in vitro and in vivo to investigate the effects of Ficus species, a plant used in traditional medicine to treat urolithiasis. Still to be determined, these plants might be useful in preventing recurrence.

4. Conclusion

The review attempts to highlight the Ficus species of different plants and how their phytonutrients can assist in preventing and curing urolithiasis. Since patients frequently ask for instructions for a beneficial dietary regimen and natural dietary recommendations for patients at risk of kidney stones are inadequate, doctors must possess evidence-based knowledge about the effectiveness, pharmacological mechanisms, and adverse effects of administering a protective dietary regimen. More research utilizing clinical trials is required to verify these dietary treatments' safety and effectiveness in kidney stone patients. Additional preclinical and human research is required to identify the bioactive phytonutrients of these dietary plants in urolithiasis and the molecular and cellular mechanisms.

Conflicts of interest:

The authors declare no conflicts of interest.

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Author Contributions:

Swati, KK, and SC designed the structure of the paper and drafted the manuscript. Swati performed a literature search and contributed to writing the manuscript. KS and SC reviewed and revised the manuscript. All authors had full access to the final version of the manuscript

and gave their approval before publishing.

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