Pharmacological activities of Laurus Nobilis linn Leaves for Nephrolithiasis - Review article

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Abstract: Urinary tract stone disease is a medical challenge due to its multifactor etiology and high recurrence rate. As a result, there is a strong need to prevent this condition from recurring. The review focuses on all about the nephrolithiasis, formation of stone and its mechanism and pharmacological results for one of the easily available herb (Laurus Nobilis) for its treatment. Renal stones are a frequent condition that causes significant morbidity and financial expenditures around the world. The terms phyto therapy of kidney stones, and lithotriptic action of plants were used to search for in vitro and in vivo studies on alternative treatment of kidney stones. The goal of this study was to investigate and expand on the efficacy and availability of treatments for kidney stones using herb in order to provide safe, cost-efficient, and effective management choices while also reducing disease burden. Improvements in treatment efficiency that are cost-effective may benefit both patients and the healthcare system. To assess the safety and efficacy of medicinal plants, more randomised clinical trials should be done.

Keywords: *Nephrolithiasis, Kidney stone, Lithiasis, Calcium oxalate crystals, Renal Calculi, Laurus Nobilis*

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Introduction

The term "nephrolithiasis" is derived from the Latin name "nephro," that refers to the kidneys, and the clinical terminology "lithiasis," which refers to stones. Hence, the existence of crystalline stones (calculi) in the urinary system usually in kidneys and

ureter is known as nephrolithiasis (fig.1). These renal stones are made up of a mixture of crystalloid and organic matrix. Ureteric stones are generally quite often formed in the kidney and then transit into the ureter [1, 2].

Whenever there's an overabundance of crystal-forming chemicals in the urine that can't be disintegrated, stones form. High urine evacuation of some chemicals, such as calcium, oxalate, uric acid, and cysteine, might stimulate stone development, however high urinary secretion of alternatives, such as citrate, could safeguard against stone production [2]. Stone development may be facilitated by changes in urinary pH, a low urine volumes, and a deficiency of preventive chemicals that keep the stones from binding together [3]. Ecological variables like lower water consumption, harsh climates, and nutritional issues also have a contribution in the progression of nephrolithiasis [4]. Hence, this review covers the mechanism of stone formation and its treatment from a specific natural material i.e., leaves of Laurus Nobilis linn plant.

Historical data show that individuals probably suffered kidney and bladder stones for millennia. People in the western hemisphere tend to be at an increased potential of getting urolithiasis (1–5%), however the greatest implications have been observed in several Asian nations (20.1%), with long lasting recurring percentages of up to 50%. The time between recurrences varies, with 10% occurring throughout a year, 35% around five years, and 50% throughout ten years [5]. Moreover, 75 percent of stones are calcium oxalate, with up to 50 percent including calcium hydroxyl phosphate (brushite or calcium hydroxyapatite) in marginal or higher levels; 10–20 percent are magnesium ammonium phosphate (struvite or triple phosphate); 5% are urate; and 1-2 percent are cysteine [6].

Before demonstrated diversely, each constituent of matrix is a possible functional participant in stone pathology [4]. *Doyle et al.* theorised that studying crystals allowed them to investigate urine proteins specifically implicated in the essential crystal nucleation stage of stone formation, devoid of any macromolecular impurities that could be introduced into a stone by cellular damage [7]. Morse and Resnick discovered that, despite the large number of proteins present in urine, the crystals precipitated from it included only a small number of proteins. While the existence of such proteins might suggest that they play a

role in stone synthesis, it's also probable that their appearance in the stone building was either coincidental or caused by the stone's harmful consequences [8]. Various proteins have been documented to be found in the renal stone matrix, but only a handful have been studied in terms of performance. The prevalence of urine supersaturation and crystalluria has encouraged research into oscillators of mechanisms other than supersaturation [9].

Methodology of Stone development

Increased urine supersaturation leads to the development of crystalline fragments as it act as catalyst for crystallization, which leads to the accumulation of renal stones and supersaturation [10]. Nephrolithiasis is the end effect if crystallization inhibitors fail to work. Inhibitors allow for a larger concentration of calcium salts in solution than unadulterated solvents. Urine is thus calcium salts metastable. Stone cohorts do, in fact, discharge more supersaturated urine than non-stone constituents [11]. It has been proposed that a passage period of 5 to 10 minutes throughout the kidney is extremely short for crystals to nucleate and develop massive enough to be stuck in a healthy person [9].

Nucleation

The process of combining free ions into tiny particulates in a medium is known as nucleation. This is the initial step in the formation of stone [12]. Crystallization can happen in solution microenvironments, such as those seen in the nephron, as well as on surfaces like cells and extracellular matrix. The significance of free solution crystallization vs. crystallization in different regions, such as renal tubules or bladder borders, regular or shattered cells, sections depleted by specific forms of injury, or interstitial spots, is a point of contention [13].

Crystal formation

The production of microscopic crystals is achieved by transmitting ions from solutions to the emerging crystal [14]. Although the migration of ions from solution must contribute to the formation of nuclear crystals, this would be certainly a constrained mechanism, as enormous solitary crystals of stone components are rarely seen. Aggregation of pre-existing crystals or secondary crystal nucleation on the other matrix-coated layer are increasingly inclined to result in stone formation [15]. This has been claimed that the formation of these minuscule crystals requires consolidation or adherence to

various intra renal elements to the point where they can be sustained in the kidney solely on the rationale of size [11].

Clustering

Clustering is the phenomenon by which crystals in a pure solution clump together to create bigger multicomponent aggregates. It could also refer to the formation of new crystals on the base of previously created crystallites [16]. Stones are made up of crystals and an organic matrix that serves as a connecting element. Proteins, lipids, polysaccharides, and other cell-derived components make up the organic matrix [17].

Cell-Crystal Relationship

Crystal adhesion or interface between crystal cells refers to the adherence of growing crystals to the epithelial wall of the renal tubular membrane. Access to excessive amounts of oxalates or sharp crystals of calcium oxalate monohydrate (COM) harmed renal tubular epithelial cells in people with hyperoxaluria [17].

Crystals from the basolateral edge of the cells move through the crystal cell interface to the underlying barrier. The interaction of a COM crystal with the surfaces of a renal epithelial cell could be a key beginning event in nephrolithiasis [18].

CaOx crystallisation is facilitated by the elevated retention pressure between the crystal's epithelial cells and the weaker renal tubule. Certain crystals linked to epithelial cells are thought to be degraded in the cells by macrophages and/or lysosomes before being excreted in urine [19].

CaOx crystals are endocytosed

The primary mechanism in the production of kidney stones is endocytosis, or crystal ingestion by renal tubular cells. COM crystals readily cling to microvilli on the cell's interface and then assimilate it, as per the observations on crystal-cell tissue culture relationships [20]. Glycosaminoglycans, glycoproteins, and citrate, which are found in tubular fluid and urine, might encapsulate crystals and prevent them from adhering to the cell membrane [16].

Apoptosis and cell damage

Proximity to higher levels of oxalate or CaOx crystals damages epithelial cells, which is a risk determinant for the production of stone. CaOx crystal accumulations in the kidneys could perhaps enhance inflammation by up regulating

macromolecule articulation and synthesis [21].

Cells can transfer crystals to the interstitium or endocytize them. It's now been theorized that injured cells form a nidus that enhances material accumulation on the renal papillary membrane [11].

Randall's slabs

Randall's slabs seems to be a significant predictor for stone development, it's unclear if they're essential in any growing stone, given both intra tubular crystals and significant crystalluria are hallmarks of stone disorder [22].

Although urine is not usually supersaturated in calcium phosphate, Henle's loop may have such circumstances. Calcium phosphate deposition at interstitial places in the internal medulla may arise as a consequence of this. Randall's slabs are typically huge enough to be observed macroscopically as a result of such sediments. It has been proposed that certain aggregates act as a nidus for the formation of the most frequent calcium oxalate stones [23]. According to various investigations stones have been found to be closely linked to the Randall's slabs, which has disintegrated on the base of a renal papilla via the underlying uroepithelium [24].

Investigating Laurus Nobilis Linn. Leaves

The bay laurel tree, a thickly foliage green perennial tree that flourishes extensively near the Mediterranean Sea, is harvested and dried for bay leaves [25]. The bay leaf has a strong, woodsy scent. When boiled in water, it has a little eucalyptus flavour. The foliage are aromatic and have a strong, bitter flavour on their own. Freshly, dried, pulverized, and oil forms are all consumed [26]. The oil derived from bay leaves offers a wide range of therapeutic benefits. The dried form of bay leaf is preferable because it has a greater distinctive scent and is slightly astringent. Although dried foliage impart more flavour into food, it's seldom marketed raw for cooking usage [27].

Dry Bay leaves and their preparations have predominantly been prescribed to alleviate digestive issues such as epigastric discomfort, diarrhea, bloating, and eructation [28]. Bay plant leaves and fruits have been utilised as astringents, diaphoretics, stimulants, emetic, emmenagogues, abortifacient, and insect repellents. Furthermore, because it is a flavorful species, its essential oil is used in

cosmetics such as soaps, lotions, and perfumes [29].

Description

Bay Leaf or Laurel Leaf refers to the dried foliage of a perennial shrub or, less commonly, a tree that grows to a height of 15 to 20 metres [30]. The leaf's top portion is glabrous and bright, and the lower portion is dreary olive to brown with an eminent rib and veins. The pulverized leaves have a subtle and pleasant perfume, as well as an astringent and sharp flavour [31]. The leaves are 2.5 to 7.5 cm long and 1.6 to 2.5 cm wide, with a length of 2.5 to 7.5 cm and a width of 1.6 to 2.5 cm. The leaves are elliptical in shape, curving to a juncture at the foundation and tip [29].

Chemistry

- Bay leaf contains remnants of fats (that is, only a small amount), it has a minimal caloric significance [32].
- It's also a strong source of vitamin A and a variety of minerals [33].
- One ounce of bay leaf has 54 calories, 1–1.2 grammes of protein, 12–13 grammes of carbs, a trace of fat, 1–1.5 milligrammes of iron (Fe), 51–53 milligrammes of calcium (Ca), 2000–3000 international units (IU) of vitamin A, 14–15 milligrammes of vitamin C, and a traces of potassium [34].
- Dietary fibres abound in bay seeds [33].
- Substances like eugenol (11 percent–12 percent), methyl eugenol (9 percent–12 percent), and elemicin (1 percent–12 percent) are important for the spicy aroma of bay leaves, and these are used as considerable tastemakers in identifying the impactful reliability of bay leaves [31].

Pharmacological Activities of Laurus Nobilis

Chiluveri Sanjuna et, al. (2019) determined the antiurolithiatic activity of the medicinal plant Laurus nobilis leaves in vitro by taking Neeri as a standard medication. In the disintegration of calcium oxalate crystals, ethanolic extracts demonstrated their highest efficiency. The L. nobilis leaves are rich in acylated favonol glycosides, quercetin, myricitin, myricetin 3-O-4-acetyl-L-rhamnopyranoside, triterpenoids, esterase, galloyl carboxylase and tannin, hence are used in various other ailments associated

with inflammation. The soxhlet extraction of the plant leaves upto 6 cycles were done and was stopped when colorless solvent is obtained. Artificial kidney stones of calcium oxalate had been prepared in lab by reaction of equimolar solution of calcium chloride dehydrate in distilled water and sodium oxalate in 10 ml of 2N H_2SO_4. The antiurolithiatic action of an aqueous extract of L. nobilis is investigated in this work along with the conventional medication called Neeri as a standard, and results showed the highest rate of CaOx dissolution, say 98 percent than that of conventional drug. This study established L. nobilis as a plant with lithotriptic properties as the key evidence. The findings clearly showed that the aqueous leaf extract of L. nobilis is a potential solvent for further research in this area [32].

Mahmood Biglar et al, (2014) conducted a study by taking Laurus nobilis and 19 other herbs for the treatment of H.Pylori. All the 20 plants were extracted with 20:80 water methanol ratio at room temperature for 24 hrs. As the extracts has been obtained, they has been tested for their urease activity from 1- 125 µg/ml, by using advanced spectrophotometric procedure against jack bean urease by Berthelot reaction [2]. For standard inhibitor, hydroxyurea has been used. All the herbs were extracted with 80% of aqueous methanol and then its IC_{50} had been tested. For the determination of urease activity a solution assay mixture has been prepared that consists of 850 µl urea, 135 µl crude extract and volume make upto 985µl. In a phosphate buffer solution, 15µl urease enzyme solution has been added for the initiation of reaction. After 60min of enzyme reaction, urease activity has been evaluated by measuring the concentration of ammonia at 37^{o}C and the absorbance has been calculated at 625nm. By using Graphad software prism and with the help of dose-response curves by linear regression method the IC_{50} of Laurus nobilis was found to be the most i.e., 48.69 µg/ml [33].

Wermerson Assuncao Barroso et al. (2018) by following the methodology from the 5th edition of British Pharmacopeia, Pharmacognostic characteristics and histochemical reactions for evaluation of various chemical components in Laurus nobilis linn has been adopted [34]. Three different marketed brands of L. nobilis linn say, *Ricco Cheiro verde Mercado and Central Nitrogen* has been purchased and then tested for their internal and external morphological characteristics [35]. The histochemical reaction results showed presence of tannins in Laurus nobilis linn

and it is well known that substances rich in tannins have been used as a therapeutic material for kidney stones, wounds, burns and various other inflammatory diseases. They also stated that Laurus nobilis contains a number of polyphenolic chemicals, as well as monoterpenes and sesquiterpenes, which are interconnected by their anti-allergic and anti-inflammatory properties [36].

Aelius Promotus 2020 wrote a book named as Dynameron. He appreciates the work of three more physicians in his book by including few chapters of their work. These three physicians are Soranus, Menemachus and Hermogenes. The author has described 36 types of formulations for the treatment of Nephrolithiasis, along with the lists of excipients used, method of preparations, method of administration and storage conditions. Here, in this literature few of his 36 formulations has been discussed. In formulation 1 he proposed, by taking form bay laurel, wild carrot and cucumber and crushed them into fine powder and then with the help of water a small pea sized pill had been prepared, and this medication was given to on an empty stomach to the patients, with three cups of water at the bed time [37]. In formulation 2 he proposed, powdered leaves of bay laurel, seeds of black pepper along with a large spoonful honey and all are diluted in lukewarm water had been given to the patient with Nephrolithiasis disorder, and results evaluated was the stone gets dissolved and hence passes out from body through urine [38].

Ophrastus at al. (1998) Decoction of the dried roots and leaves has been prepared and was given to the patients with Nephrolithiasis disorder. The prepared decoction has been diluted with water each time prior giving to the patients on an empty stomach. This formulation not only gives relief from Nephrolithiasis disorder but also from a Strangury problem [39].

Proposed that Bay leaves helps in the treatment of kidney disorders. They performed the experiment for the treatment of kidney stone disorder by preparing a tea from basil and bay leaves. They collected 5-6 leaves of bay, and then washed it thoroughly and boiled them in 200ml water. During this, when the water reduced to 50mlstrained it and consumed by the patient. This preparation not only inhibits the formation of kidney stone but also reduces inflammation [40].

Salman Ahmad et, al., (2016) described the contribution of Greco- Arabic Muslim Scientist *Ibn Sina.* In his book Al Qanoon

Fit Tibb (2012) had described all about the Nephrolithiasis, starting from the physiology of disease till its treatment and herbal medicines. He formulated various herbal, mineral and animal obtained sources formulations along with the surgical procedures for management and cure of urolithiasis [41]. Sina shared a pharmacotherapeutic regimen that includes cure and treatment from the problem of nephrolithiasis like, calculus annihilating agents [42]. They break the stone inside the body into tiny pieces and hence passes throughout the body via urine. Natural agents to control and suppress the pain occur during nephrolithiasis [43].

Conclusion

Kidney stones have been one of the most common health problems worldwide over the last few decades, and they pose a significant meditative hazard due to a lack of effective medications and higher recurrence levels. There is detailed evidences of the potential of one particular medicinal plant called as Laurus Nobilis in the prevention and management of kidney stones in this review. A great range of in vitro and in vivo studies were undertaken to quantify the influence of medicinal plants on the progression of nephrolithiasis, according to the most recent literature. However, there have only been a few human investigations on the efficacy of medicines in the treatment of nephrolithiasis. A little more study and research are necessary in order to confirm the utility and tolerability of these ingredients in individuals with nephrolithiasis.

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