

Review Article

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES

[ISSN: 0975-4725; CODEN(USA): IJPS00] Journal Homepage: https://www.ijpsjournal.com



Emerging Nanotechnology-Based Approaches for Kidney Stone Treatment: A Review

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ARTICLE INFO

Published: 18 Jul. 2025 Keywords: nanoparticles, kidney stones, calcium oxalate, lithotripsy, probiotics, urolithiasis DOI: 10.5281/zenodo.16089819

ABSTRACT

Kidney stones are hard deposits that form due to supersaturation of minerals like calcium, oxalate, and phosphate in the urine. They are often linked to dehydration, highsodium diets, obesity, and metabolic disorders. Symptoms typically include severe lower back or abdominal pain, hematuria, and painful urination. Conventional treatment includes hydration, dietary changes, medications, and surgical interventions like lithotripsy or percutaneous nephrolithotomy. However, these approaches have limitations, including recurrence and side effects. Recent advances in nanotechnology offer promising alternatives for both treatment and prevention. Nanoparticles can be engineered to target stone components, enhance drug delivery, and improve the precision of lithotripsy, thereby minimizing damage to surrounding tissues. Additionally, their potential roles in biosensing, anti-inflammatory therapy, and crystal inhibition make them attractive candidates for future therapeutic use. This review explores the current landscape of kidney stone disease, outlines conventional therapies, and highlights emerging nanotechnology-based interventions. It also discusses future directions and challenges, including safety, efficacy, and translation from bench to bedside.

INTRODUCTION

Kidney stones, also known as renal calculi, are solid crystalline structures formed by the aggregation of mineral salts in the urinary tract. They may be found attached to the renal papillae or freely moving in the calyces and pelvis. Stone formation, also termed nephrolithiasis or urolithiasis, is initiated by supersaturation of urine with minerals, leading to crystal nucleation, growth, aggregation, and retention. The majority of stones are composed of calcium oxalate and calcium phosphate, with less common types including uric acid, struvite, and cystine. Certain medications, such as protease inhibitors

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

like indinavir and atazanavir used in HIV treatment, can also induce iatrogenic stones due to their low solubility in urine. The recurrence rate of kidney stones is high—up to 50% within five years. Risk factors include obesity, diabetes, hypertension, metabolic syndrome, and lifestylerelated dietary changes. Patients with recurrent stones are at increased risk of developing chronic kidney disease (CKD) and end-stage renal disease (ESRD).

EPIDEMIOLOGY: -

Kidney stone disease (KSD) demonstrates a growing global burden, with notable geographic, gender-based, and metabolic associations.

Global and Regional Prevalence:

A recent evaluation across seven countries revealed that the prevalence of kidney stones ranges from 1.7% to 14.8%, and incidence varies from 114 to 720 cases per 100,000 people. The United States has seen a tripling in self-reported prevalence, from 3.2% (1976–1980) to 8.8% (2007–2010)^{12,28}. In the United Kingdom, lifetime prevalence rose by 63%, from 7.14% to 11.62% between 2000 and 2010²⁹.

Gender and Ethnic Disparities:

Historically, men were 2–3 times more likely to develop stones. However, recent trends show narrowing gender gaps:

- In the US, the male-to-female ratio of hospital discharges for stones fell from 1.7 (1997) to 1.3 (2002)³⁰.
- In Rochester, Minnesota, USA, the same ratio decreased from 3.1 to 1.3 between 1970 and 2000³¹.
- A study in Florida (1998–2004) showed higher rise in KSD procedures among women than men³².

• In Canada, a 48% rise in stone treatments (1991–2010) was largely attributed to procedures in women³³.

This increase among females may be due to lifestyle and dietary changes contributing to obesity, a known risk factor for stones.

Racial and Ethnic Patterns:

In the US:

- Prevalence among non-Hispanic Whites: 10.3%
- Hispanics: 6.4%
- Non-Hispanic African Americans: 4.3%¹²[1]

Prevalence increases between

NHANES II (1988–1994) and NHANES III (2007–2010) were twice as high in Hispanics and African Americans compared to Whites^{12, 28}.

Geographical Influence:

Stone disease is more common in hot, arid climates:

- Southern and Southeastern US have the highest prevalence.
- Western US has the lowest^{28, 34–37}. ³⁷. ³⁷

Metabolic and Systemic Associations:

Large cohort studies associate KSD with:

- Obesity, BMI, and weight gain^{15, 38, 39}
- Diabetes^{18, 40}

NHANES data reveals:



- Obesity increases KSD risk by 55% (95% CI: 1.25–1.94; P < 0.001)
- Diabetes increases risk by 59% (95% CI: 1.22-2.07; P < 0.001)

Metabolic syndrome also elevates risk, with a 25% higher rate of radiographic stones in affected individuals (95% CI: 1.03–1.50; P < 0.001)⁴².

Cardiovascular Link:

Several studies have noted an association between KSD and cardiovascular risk:

- In 3 prospective cohorts, women with a history of stones had a 30% increased risk of cardiovascular disease (HR: 1.30; 95% CI: 1.04–1.62)⁴³.
- In Canada, KSD was linked to a 63% higher myocardial infarction risk (95% CI: 1.51– 1.76), particularly in women⁴⁴.
- In Olmstead County, Minnesota, a matchedpair analysis showed a 31% increased MI risk in stone formers (95% CI: 1.02–1.69)⁴⁵.

PATHOPHYSIOLOGY: -

Initiation of Stone Formation:

The initial stage of stone formation is when crystals precipitate out of urine that is too concentrated and adhere to the urothelium, creating the nucleus for future stone development. The means by which crystals adhere to the urothelium are still unknown. Calcium oxalate stones can develop on Randall's plaques, which are of calcium phosphate composed (= hydroxyapatite) crystals, but not all of them. These get bigger and eventually kill the urothelium, forming a nucleus for the accumulation of calcium oxalate.

Crystal Adhesion and Recurrent Stone Formation:

More recent theories place more emphasis on the function of cell surface molecules in promoting or preventing crystal adhesion.^{4,5} Following a stone episode, urothelial damage and repair may increase surface expression of these molecules, which may favour additional crystal adhesion.⁶ As a result, stones beget stones⁷ because there may be a residual nucleus on which further stones may form and/or upregulation of molecules favouring crystal adhesion. The main objective of stone prevention is to identify and treat the risk factors that promote crystal development.

Key Factors in Kidney Stone Pathophysiology:

Urine Supersaturation:

A high concentration of specific solutes in the urine (such as calcium, oxalate, uric acid, etc.) is the primary factor in the formation of stones.

Crystal Formation and Development:

When urine gets supersaturated, crystals start to develop. Consequently, these crystals grow as they attract more solutes, resulting in the formation of larger stones.

Tissue Adhesion in the Kidneys:

Crystals attaching to the kidney lining (urothelium) or other surfaces might cause a nidus, or starting place, for more stone formation.

Stone Makeup:

Different types of kidney stones (calcium oxalate, calcium phosphate, uric acid, struvite, cystine) have different underlying causes and risk factors.

Personal Tendency:

Numerous variables, such as genetics, food, hydration, and specific medical diseases, affect a person's risk of developing stones.



SYMPTOMS

Kidney stones might be as little as a grain of sand. A few are the size of a pebble. The size of some of the stones is comparable to that of a golf ball. The symptoms are usually more evident the larger the stone.

Typical Symptoms

The following could be symptoms:

- agonizing discomfort on either side of your lower back
- a persistent, less specific pain or discomfort in the stomach
- urine containing blood
- nausea or vomiting
- fever and chills
- urine that is turbid or smells bad

Pain Characteristics:

The kidney stone begins to hurt when it starts to irritate or block. This quickly escalates into unbearable agony. Although kidney stones typically pass without causing harm, they often induce severe pain. Pain relievers can be the only treatment needed for tiny stones.

Severity and Need for Treatment:

Additional treatment may be required, especially for stones that cause ongoing symptoms or other problems. However, surgery may be required in severe cases.

MEDICATIONS:

Medicine may be necessary for those who are at a high risk of experiencing new or recurring KSD. Some of the most widely prescribed and used drugs for preventing the recurrence of stones include potassium citrate, potassium bicarbonate, sodium bicarbonate, diuretics. allopurinol, tiopronin, acetohydroxamic acid, and sodium thiosulfate. To reduce urinary calcium excretion and avoid the formation of stones in the future, it is recommended that diuretics like thiazides be used to induce diuresis caused by medications. The use of thiazides in patients with hypercalciuria or recurrent calcium stone formation has been agreed upon by several guidelines. The thiazides' kind and dose vary somewhat. Hydrochlorothiazide is administered at 25 mg twice daily (AUA, EAU, and CUA) or 50 mg once daily (AUA, EAU, CUA, and UAA); chlorthalidone is administered at 25 mg once daily (AUA, EAU, CUA, and UAA) or 50 mg once daily (CUA); and indapamide is given at 1.25 mg once daily (CUA) or 2.5 mg once daily (AUA, EAU, and UAA). According to a retrospective cohort analysis of older individuals, thiazides had similar protective effects against KSD at both low and high dosages. Thiazides are not recommended for long-term use in the treatment of recurrent KSD because of the potential for negative side effects. If prolonged use unavoidable, potassium supplementation is (potassium citrate or chloride) should be considered since thiazides commonly cause hypokalemia.

Potassium citrate, an alkaline citrate, is another popular treatment for preventing the recurrence of kidney stones. According to the AUA, EAU, CUA, and UAA, people with recurrent calcium stones, hypocitraturia, uric acid stones, and cystine stones should have their urine alkalinized. In vivo research on genetically hypercalciuric stoneforming rats has shown that potassium citrate treatment not only causes urine alkalinization but also increases urine citrate levels and decreases urine calcium levels. By chelating calcium in the gastrointestinal tract, citrate may reduce the amount of calcium absorbed by the intestines. Citrate can also bind calcium in urine, which



would lower the degree of calcium supersaturation in urine. In people with hypercalciuria who have CaOx stones, daily oral intake of potassium citrate, according to recent research, reduces urine calcium excretion. According to a recent study, thiazides (particularly chlorthalidone) were more successful at decreasing CaP stones than citrate. combination potassium The of chlorthalidone and potassium citrate was found to be more effective than either medication used alone in preventing CaOx stones in hypercalciuric Additionally, sodium and potassium rats. bicarbonates are often used to address metabolic acidosis, one of the causes of hypocitraturia. Abdominal pain and other gastrointestinal symptoms are potential adverse effects of extended potassium citrate use. Due to the high cost and these adverse effects, additional alkalinizing drugs may be used to avoid kidney stones. The over-the-counter, nonprescription oral alkalinizing agents are less effective than their citrate and alkali counterparts, despite the fact that they provide a notable cost advantage. In comparison to potassium citrate, further study is required to determine their cost-effectiveness. According to the EAU, the recommended daily dose of potassium citrate is 3 to 10 mmol twice or thrice daily, whereas the CUA advises 30 to 60 mEq in two or three divided doses. More significantly, the goals for urinary pH are higher than 6.0-6.5 (AUA, CUA, and UUA) for uric acid stone producers and higher than 7.0-7.5 (AUA, EAU, CUA, and UUA) for cystine stone producers.

To prevent stone recurrence, the AUA recommends that people who get CaOx stones and hyperuricosuria (regardless of serum uric acid level) and normocalciuria be treated with allopurinol as an additional therapy. However, to prevent the stone from reappearing, the CUA recommends using allopurinol only in people with

hyperuricemia and calcium stones, and not in those with normouricemia. The aforementioned drugs may also be used to prevent uric acid stones. Their negative impacts, however, must be regularly monitored.

REMOVAL OF BACTERIA

Urinary tract infections brought on by ureaseproducing bacteria result in the formation of struvite stones. However, the causal role of UTIs in several types of kidney stones has also been established. According to bacterial cultures of urine samples from stone formers and stone matrices (both nidus and periphery), Escherichia coli is the most common organism in all of these clinical sample types, indicating that E. coli may be the cause of kidney stone formation. Strangely, live, healthy bacteria promote the development and aggregation of CaOx crystals, but dead, whole, and fractured E. coli do not. A subsequent study revealed that the outer membrane vesicles (OMVs) produced by E. coli in the urine of stone formers promote CaOx crystallization, crystal formation, and aggregation. The surface of the OMVs contains the elongation factor (EF)-Tu, which mediates the stimulating effects of E. coli OMVs, and neutralization with a specific antibody against EF-Tu significantly reduces these effects. Interestingly, the urine of stone formers with UTIs contains a greater concentration of EF-Tu in E. coli than does the urine of non-stone formers with UTIs. According to a recent study, flagella originating from live E. coli also promote the crystallization, development, and aggregation of CaOx in addition to OMVs. Urine from stone formers, as well as the cortex and stone nidus, also contains other bacteria such as Klebsiella pneumoniae, Pseudomonas aeruginosa, and Staphylococcus aureus. Additionally, these bacteria promote the development and aggregation of CaOx.

Drinking more water is one of the typical ways to prevent UTIs. Consequently, increasing water intake and promoting diuresis may lower the risk of KSD in a number of different ways. Especially in those who get recurrent UTIs, bacterial eradication may necessitate eliminating the infection sources, such as stones. Additionally, using antibiotics depending on bacterial culture from the urine and/or stone matrices can help prevent the return of stones. However, the use of antibiotics to eradicate bacteria should be given careful consideration because multidrug resistance has already been discovered in bacteria obtained from urine and stone matrices. Specific antibiotic classes are associated with an increased chance of developing crystal-induced nephropathy or KSD. Furthermore, a longer period of antibiotic use during young adulthood and middle age is linked to a higher chance of getting KSD later in life. Additionally, a recent study found that antibiotic use may prevent the development of Oxalobacter formigenes in the gut microbiome. Consequently, it is possible to kill bacteria with antibiotics, but only under stringent supervision and with extreme caution.

PROBIOTICS:

Contrary to uropathogenic bacteria, increasing studies have shown that specific probiotics, particularly those that degrade oxalate (such as Oxalobacter spp., Lactobacillus and spp., Bifidobacterium spp.), offer defense against KSD. Oxalobacter formigenes is an oxalate-degrading, anaerobic bacteria. These probiotics frequently reside in the digestive system. Recent research found that stone formers have fewer O. formigenes in their gut tracts than healthy individuals. Curiously, the concentration of oxalate in the urine is inversely proportional to the quantity of O. formigenes. Bear in mind that the maintenance of oxalate homeostasis in the digestive tract is

brought about by the cooperative interaction between O. formigenes and several other microbiotas, not by O. formigenes alone. In addition to O. formigenes, additional probiotics like Bifidobacterium spp. and Lactobacillus spp. are also capable of breaking down intestinal oxalate and reducing urine oxalate excretion. In another recent study, which used a Drosophila melanogaster model of urolithiasis, Bacillus subtilis was found to be able to reduce the formation of CaOx stones. In addition, a more recent study has revealed that dietary patterns and styles have a considerable influence on the variety and quantity of gut flora. As a result, diets may have an impact on how well gut probiotics work to prevent KSD.

NANOTECHNOLOGY-BASED APPROACHES FOR KIDNEY STONE TREATMENT:

Introduction to Nanoparticles in Biomedicine:

In modern science, nanoparticles are essential, particularly in the field of biomedicine. The majority of nanomaterials have at least one dimension in the nanoscale range (1-100 nm), which gives them special thermal, biological, and electromagnetic properties that set them apart from regular materials. These include surface effects, quantum size effects, and macroscopic quantum tunneling effects.

Classification of Nanoparticles:

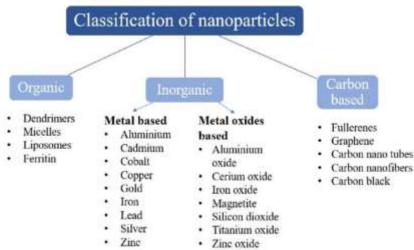
Nanoparticles are usually divided into two main categories, **organic** and **inorganic**, based on their chemical makeup. Lipid nanoparticles, liposomes, nanohydrogels, nanospheres, polymeric micelles, dendrimers, and polymeric vesicles are examples of organic nanoparticles. These organic nanoparticles are frequently employed in vaccine development, gene therapy, and medication delivery due to their great biocompatibility and adjustable physicochemical characteristics. Nonmetallic and metallic nanomaterials make up inorganic nanoparticles. Due to their special electrical and optical characteristics, metallic nanoparticles like gold, silver, and iron oxides are widely employed in biological imaging, targeted medication delivery, and cancer therapy. Superb mechanical qualities of non-metallic nanomaterials, such as graphene and carbon nanotubes, can promote cell growth and tissue regeneration.

Synthesis and Design Strategies:

Scientists can precisely regulate the size, shape, and surface properties of inorganic nanoparticles using a variety of synthesis techniques, including top-down and bottom-up approaches, in order to maximize their application in biomedicine. Hybrid nanoparticles, such lipid-polymer hybrids, combine organic and inorganic materials to enhance medication bioavailability and targeting.

Applications in Kidney Stone Treatment:

Recent experimental studies have shown that gold nanoparticles can facilitate targeted photothermal lithotripsy by precisely absorbing laser energy and breaking down calcium oxalate stones with minimal tissue injury¹. Similarly, iron oxide nanoparticles have been used in magnetic hyperthermia approaches for stone dissolution. In another study, chitosan-based polymeric nanoparticles were loaded with citrate to inhibit crystal growth and reduce stone formation in animal models. These findings underline the potential of nanotechnology in achieving sitespecific treatment while reducing systemic side effects.



Hybrid Nanoparticles:

FUTURE CHALLENGES AND THEIR SOLUTIONS: -

Challenge: The small size and vast surface area of nanoparticles, which have great promise for targeted drug delivery or kidney stone disintegration, may lead to toxicity or unfavourable immunological reactions. Ensuring that nanoparticles are biocompatible and do not accumulate in large amounts in tissues or organs is a significant challenge. Researchers are creating nanoparticles with certain coatings or changes in order to improve their biocompatibility and biodegradability.



Challenge: Nanoparticle treatment may not be as effective for all varieties of kidney stones (calcium oxalate, uric acid, cystine, etc.) because there are so many different types. Understanding how nanoparticles interact with different stone materials is essential. Future research may concentrate on developing novel nanoparticles that are better at breaking down certain varieties of kidney stones.

DIAGNOSIS

Determining if you have kidney stones involves the steps taken by your healthcare practitioner to diagnose them. The diagnosis may also include testing to ascertain the origin and chemical composition of kidney stones. First, your healthcare professional will conduct a physical assessment. You might also need tests like the ones below:

- **Blood tests**: Blood tests can reveal an excess of uric acid or calcium in your bloodstream. A blood test can be used to track kidney health. These results may also prompt your healthcare provider to look for other potential health issues.
- Urine analysis: Over the course of 24 hours, your healthcare practitioner may ask you to collect urine specimens. If your body is generating an excessive amount of stoneforming minerals or not enough stonepreventing chemicals, a 24-hour urine collection test can help you determine. Follow your healthcare provider's instructions to the letter. In order to alter your course of therapy and prevent the formation of more stones, it is imperative that you properly collect your urine.
- **Imaging**: Images from tests like CT scans can reveal kidney stones in your urinary tract. Advanced scans called high-speed or dual energy CT scans can identify minute uric acid

stones. Simple X-rays of the stomach area, also known as the abdomen, are used less often since they may miss minute kidney stones.

- Ultrasound can also be utilized as an imaging technique to detect kidney stones.
- A review of any stones that have been passed. You may be asked to urinate through a filter to collect any stones that have been passed. The lab then examines the chemical makeup of your kidney stones. Your doctor uses this information to determine the cause of your kidney stones and create a plan to prevent them in the future.

TREATMENT

The treatment of kidney stones varies. The type of stone and its underlying cause are the deciding factors.

1. Tiny pebbles with few indicators

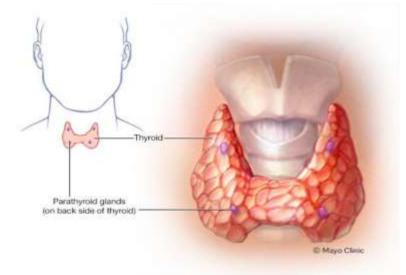
Minor kidney stones rarely require surgery. You could perhaps get over a small rock by:

- **Drinking water:** Drinking 2 to 3 quarts (1.8 to 3.6 litres) of water daily is likely to dilute the urine, which may help prevent the development of stones. Unless doctor advises otherwise, drink lots of fluids. The best way to have urine that is either clear or nearly clear is to mostly drink water.
- **Pain relievers:** A tiny stone might cause pain that ranges from moderate to excruciating. Doctor may recommend over-the-counter pain relievers, such ibuprofen (Advil, Motrin IB, etc.) or naproxen sodium (Aleve), to ease minor pain. More treatments may be required for severe pain in the emergency room.
- Additional drugs: Doctor may give medicine to help pass the kidney stone. This type of medication is known as an alpha blocker. It



relaxes the muscles in the ureter. With less pain, this makes it simpler forvto pass the kidney stone. Alpha blockers include tamsulosin (Flomax) and the drug combination dutasteride and tamsulosin (Jalyn).

2. Large stones and those that cause symptoms



[Parathyroid glands Enlarge image]

Kidney stones that are too large to pass on their own may need a more thorough course of treatment. The same holds true for stones that cause kidney injury, hemorrhage, or recurrent urinary tract infections.

Therapy could include the following:

• Using sound waves to break apart stones: Extracorporeal shock wave lithotripsy is a treatment option that the healthcare practitioner may advise for some kidney stones. This is also called ESWL, but its efficacy depends on the size and location of the stones.

Shock waves are the powerful vibrations generated by ESWL using sound waves; these waves break the stones into tiny pieces that may be expelled via urine. The process takes between 45 and 60 minutes. Because it can cause moderate pain, patient might get medicine to help relax or alleviate the discomfort. Possible side effects of ESWL include bruises on the back or stomach and blood in the urine. Furthermore, it might cause bleeding in the vicinity of the kidney and other nearby organs. The stone pieces' passage through the urinary system can also cause discomfort.

- The surgical removal of overly large kidney stones: Percutaneous nephrolithotomy (nefrow-lih-THOT-uh-me) is a surgical procedure that involves inserting minute telescopes and instruments through a small incision in the back or side in order to remove a kidney stone. A general anesthetic, which puts you in a sleep-like state during the procedure and numbs pain, is the term for the treatment you get. Patient should anticipate staying in the hospital for one to three days after that. Doctor may recommend this course of treatment if ESWL is not enough for patient's needs.
- Using a scope to remove stones: The surgeon may employ a ureteroscope, a small, illuminated tube, to extract a smaller stone from the ureter or kidney. With this gadget

comes the camera. The surgeon employs the uteroscope to enter the ureter through the urethra and bladder.

When the stone is found, it may be captured using special equipment or broken up into pieces that will pass in the urine. After that, the surgeon may place a small tube known as a stent into the ureter to help with healing and lessen inflammation. Depending on the procedure, patient may require local or general anesthesia.

• Parathyroid gland excision: Some calcium phosphate stones might be caused by an overactive parathyroid gland. These glands are positioned right below the Adam's apple, at each of the thyroid glands four corners. Hyperparathyroidism is the term for when these glands release an excessive amount of parathyroid hormone. Kidney stones may result from the disease's increased calcium levels.

The development of a small, non-cancerous tumor in one of the parathyroid glands can sometimes cause hyperparathyroidism. hyperparathyroidism might Additionally, develop if patient has another illness that leads these glands to produce more parathyroid hormone. Kidney stones are prevented from forming by removing the tumor from the gland. Alternatively, the healthcare professional may suggest treating the underlying disease that is causing parathyroid gland to produce an excessive amount of the hormone.

CONCLUSION AND FUTURE PERSPECTIVES

The rapid advancement of nanotechnology holds tremendous promise for transforming the management of kidney stones. Nanoparticles offer potential in targeted drug delivery, biosensing, minimally invasive therapies, and preventing recurrence by modulating urinary biochemistry. Despite these benefits, challenges such as toxicity, variable effectiveness across stone types, and biocompatibility remain. To translate these innovations into clinical practice, interdisciplinary collaboration and patient-specific customization are essential. Continued research is needed to address safety concerns and validate efficacy in human trials. With thoughtful optimization, nanotechnology may soon revolutionize kidney stone prevention, diagnosis, and treatment, offering more precise, effective, and patientfriendly solutions.

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HOW TO CITE: Yug Patel, Falaq Jujara, Emerging
Nanotechnology-Based Approaches for Kidney Stone
Treatment: A Review, Int. J. of Pharm. Sci., 2025, Vol 3,
IssueIssue7,2587-2597.
https://doi.org/10.5281/zenodo.16089819

