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Antiurolithiatic and Diuretic Investigation of Nausadar with Extracts from *Piper nigrum, Morus alba, Vitis vinifera* in Sodium Oxalate-Induced Urolithiasis in Wistar Rats

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Abstract

The present study deals with the synergistic effect of ethnomedicinal plants such as Piper nigrum, Morus alba, and Vitis viniferain preventing kidney stones and enhancing diuresis in sodium oxalate-induced Wistar rats, a model for urolithiasis. The design of the experiment included the administration of these extracts to sodium oxalate-induced rats to test their efficacy in reducing the formation of stones and facilitating urinary excretion. Results showed that the toxicity of survival of the rats even up to 2000 mg/kg did not produce any significant ill effect. In addition, biochemical analyses of treated groups revealed a statistically significant reduction and enhanced, biphasic response in groups T4, T5, T9, and T10 as compared to disease control (T3), which may be dependent upon the source (kidney, urine, and serum) and on treatment with ethnomedicine. Catalase activity in kidney tissues had significantly increased in treatment groups, which is indicative of an enhanced antioxidant defense mechanism leading to a decrease in oxidative stress, which protects renal tissues from further damage. Histopathological assessment of renal structure and function demonstrated obvious improvements in treatment groups, with a high degree of effect elicited by a combination of extracts with Nausadar. The combination of Piper nigrum, Morus alba, and Vitis vinifera with Nausadar was highly effective, and from this, it could be instituted that these herbal extracts act in synergy to enhance their therapeutic action. These plant extracts showed synergistic interactions, hence ethnomedicine may emerge as an alternative/complementary therapy to conventional ones against kidney stones and warrants further study in possible clinical practice.

Keywords: Urolithiasis, Ethnomedicine, Sodium oxalate, Antiurolithiatic

1. Introduction

Ethnomedicine, being part of the cultural and spiritual heritage of indigenous and tribal peoples, is an important repertoire of traditional knowledge about healing that has been passed down orally from generation to generation(Jacob *et al.*, 2023; Gupta and Sindhu, 2024). While Ayurveda and Traditional Chinese Medicine are documented and follow well-established principles like other regular and organized systems of medicine, ethnomedicine is traditionally based on knowledge regarding nature and the medicinal properties of plants, animals, and minerals(Busia, 2016; Najmi *et al.*, 2022). Thus, such knowledge contributes valuably to solving common health problems in many rural and tribal communities(Kumar *et al.*, 2021). One of the diverse uses of

ethnomedicine is in the treatment of a rather common malady known as urolithiasis, which involves the formation of urinary stones and is said to afflict a significant percentage of the world's population(Sorokin *et al.*, 2017).Urolithiasis, or the formation of kidney stones, involving crystallization of calcium, oxalate, phosphate, and uric acid in the urinary tract, is a painful and often recurrent condition(Arya, 2017). Conventional treatments, such as pharmacotherapy and surgery, though often effective, are not accessible, especially in resource-limited settings(Sun *et al.*, 2024). It is in this context that the contribution of ethnomedicine proves to be a natural alternative to remedies that are better integrated into the daily lives of the concerned communities by providing a low-cost, sustainable option(Keshamma and Kumar, 2022). This system of medication largely draws on the therapeutic effects of various plants known for their efficiency in preventing the formation of urinary stones or in dissolving them(Sorokin *et al.*, 2017).

Some of these plants, like *Berberis asiatica*, *Apium graveolens*, and *Annona species*, have been traditionally used in the management of urolithiasis(Kumar, 2023). Such plants reportedly possess antiurolithiatic and diuretic properties due to rich contents of bioactive compounds like flavonoids, saponins, alkaloids, and other phytochemicals(Pullaiah, 2021). Antiurolithiatic research into ethnomedicinal plants focuses on the balance of stone promoters (such as calcium and oxalate) and inhibitors-like citrate and magnesium-within the body(Makbul, Jahan and Kalam, 2019). Kidney stone pathogenesis is a highly complex process that involves supersaturation of urine with stone-forming minerals, nucleation, growth, aggregation, and retention of crystals in the kidneys(Alelign and Petros, 2018). Ethnomedicinal antiurolithiatic plants may act on any aspect of the processes involved in preventing stone formation or promoting their dissolution(Arya, 2017). Another critical component of the role of ethnomedicine in managing urolithiasis is its diuretic effect, which helps in flushing out excess salts and minerals through the kidneys, thereby reducing the risk of stone formation(Makbul, Jahan and Kalam, 2019).

The efficacy of various ethnomedicinal plants in the treatment of ailments through preclinical studies has been found in recent year(Khan, Bashir and Khan, 2021; Allam and Sabra, 2024). Experimental models, such as sodium oxalate-induced urolithiasis in animals, are commonly used to mimic the pathophysiology of kidney stone formation in humans(Khan, 2013; Alford *et al.*, 2020). This model has now become very reliable in screening for antiurolithiatic potential since the stone-forming agent induces crystal formation in the kidneys(Kumar and Sindhu, 2024b; Ponugoti, Guntupalli and Malothu, 2024). Moreover, preclinical evaluation using these plants against sodium oxalate-induced models gives vital information on the mode of action that includes reduction of crystal aggregation, facilitating urinary excretion, and antioxidant effects(Sun *et al.*, 2024).

The present study was undertaken to investigate the role of ethnomedicine in the prevention of kidney stone and increased diuresis, focusing their action against sodium oxalate-induced urolithiasis. This study will validate the traditional knowledge of ethnomedicinal plants through biochemical and histopathological analysis and will bridge the gap between ancient healing practices and modern biomedical science. More importantly, this study identifies the phytochemical composition liable for such therapeutic action and thereby identifies such plants as candidates in the development of new plant-based treatments for urolithiasis.

2. Materials and Methods

2.1. Plant Materials

In this study, the air-dried fruits of *Vitis vinifera*, *Piper nigrum*, and *Morus alba* were procured from the market. These raw materials were visually inspected and confirmed free of any foreign particles or contaminants. Identification and authentication of herbs were further done through the ISO-certified Vedanta Testing and

Research Laboratory, Bhopal, Madhya Pradesh, India. Organoleptic tests were conducted on fresh and dried herbs, and the characteristics to be checked included color, odour, taste, size, shape, texture, and fracture, thus fully characterizing the properties of each herb.

2.2. Chemicals and Reagents

Sodium oxalate (SO), the major chemical for inducing urolithiasis in the animal models was procured from Merck Ltd., Mumbai, India. Other reagents/chemicals and solvents required for this study were obtained from approved companies; as a matter of fact, all reagents were analytical grade and of experimental purpose.

2.3. Instrumentation

The biochemical parameters were assessed using various analytical instruments. Haematological data was obtained by the Siemens ADVIA 2120i haematology analyzer, while biochemical analyses were performed with the Agappe Mispa Clinia system. Electrolyte measurements were obtained from the Nirmal Medical Nulyte Smart analyzer. These instruments were used in the study because they provided the accuracy and reliability needed to measure the biological parameters under consideration and, therefore, yielded accurate and reproducible results.

2.4. Study Design

The ethical clearance for the above experimental protocol was approved by the IAEC. Approval No: UH/IAEC/MS/21/03/2024/04. Healthy Wistar rats weighing between 150-200 grams were used for the present study. A total of 60 rats were randomly divided into 10 groups, each comprising six rats. The animals were housed under standard conditions of temperature and relative humidity, 25 ± 2°C and 45-55%, respectively, with a 12 h light/dark cycle. Food and water were provided ad libitum. The acclimatization period was one week, for normalizing the animals to the laboratory environment before the start of the experiment.

2.5. Acute Toxicity and Induction of Urolithiasis

Acute toxicity was performed according to the OECD 423 guidelines, calculating LD50 for the test substances. Urolithiasis was induced by administration of SO at a dose of 70 mg/kgIntraperitoneal. The model is highly quoted for mimicking the formation of kidney stones and related metabolic disturbances and hyperoxaluria in rats.

2.6. Experimental Group Details

The animals were further treated for 14 days post-induction of urolithiasis with various treatments. The overall duration of the experiment was 28 days. The study groups were organized as follows;Treatment 1 (T1): Normal control (Only vehicle treated), Treatment 2 (T2): Standard control diuretic (Furosemide 10 mg/kg), Treatment 3 (T3): Disease control Sodium oxalate 70 mg/kg IP, Treatment 4 (T4): Naox +Standard (Anti-urolithiatic) Cystone 500 mg/kg, Treatment 5 (T5): Naox + Ethnomedicine (*Piper nigrum* with Nausadar and water (1:2:4) 600 mg/kg, Treatment 6 (T6): Naox + Extracts of *P. nigrum*, *M. alba*&*V. vinifera* 300 mg/kg, Treatment 7 (T7): Naox+ *M. alba* Extract with Nausadar 300 mg/kg, Treatment 8 (T8): Naox +*V. vinifera* Extract with Nausadar300 mg/kg, Treatment 9 (T9): Naox +*P. Nigrum* Extract with Nausadar 300 mg/kg and Treatment 10 (T10): Naox +Extracts of *P. nigrum*, *M. alba*&*V. vinifera* withNausadar300 mg/kg.

2.7. Biochemical Analysis of Urine, Serum and Kidney Homogenate

2.7.1. Biochemical Analysis of Urine

The body weight of each animal was monitored at regular intervalson days 7, 14, 21, and 28throughout the study. Concurrently, clinical observations and biochemical assessments were conducted (Mammate *et al.*, 2024). To analyze urinary parameters, the animals were housed individually in metabolic cages for 24 hours on days 0, 14, and 28. Urine samples were collected during these periods, and various parameters such as pH, crystal urea, calcium, magnesium, uric acid, urea, phosphate, citrate, phosphorus, and oxalate levels were measured to evaluate the effects of the treatments.

Along with the assessment of the diuretic effect, urine volume, pH, and the ion levels of sodium, potassium, and chloride were measured six hours post-treatment on day 15 (6-hour post-treatment).

2.7.2. Biochemical Analysis of Serum

Blood samples, which were collected from the retro-orbital plexus under light anesthesia, were centrifuged to separate the serum, which was assayed for important parameters such as calcium, magnesium, uric acid, blood urea nitrogen, and creatinine levels. These serum markers were indicative of kidney function and systemic biochemical changes due to urolithiasis.

2.7.3. Biochemical Analysis of Kidney

Then the kidneys were weighed, harvested, cleaned, and rinsed with ice-cold physiological saline. Then a kidney from each animal was homogenized in Tris-HCl buffer (0.02 mol/L, pH 7.4) to form a 10% homogenate which was analyzed for oxalate, catalase, calcium, uric acid, phosphate, and urea.

2.8. Histopathological alterations

The kidney samples were fixed in 10% buffered formalin for at least 24 hours to preserve the morphology of tissues, an important step to maintain cellular architecture during further processing. Following fixation, the tissues were dehydrated in a gradual series of ethanol (70%, 80%, 90%, and 100%), followed by clearing in xylene. Then, the samples were embedded in paraffin wax to facilitate easier sectioning. Serial sections were prepared, 4-5 µm thick, by a microtome and mounted on glass slides. The glass slides were kept at 37°C for more than a day to complete adherence. The paraffin sections were further treated with H&E staining, being one of the common histological approaches for detail contrast of cellular components. For staining, the sections were deparaffinized in xylene, rehydrated through descending concentrations of ethanol, immersed in hematoxylin for about 5-10 min, rinsed with distilled water, and then stained with eosin for about 2-3 min before a further rinse.

2.9.Statistical Analysis

All data were analyzed using GraphPad Prism version 8.4 and the result have been given as Mean ± SEM. For statistical analysis, the tests used were one-way ANOVA followed by Dunnett's post hoc test. The result of less than 0.05 was considered significant with a satisfactory indication of differences between experimental groups and controls.

3.0. Results and Discussion

Urolithiasis, commonly known as kidney stones, is a condition whereby calculi form in the urinary tract due to supersaturation of calcium oxalate in the urine(Allam, 2024). The induction of urolithiasis is usually achieved through the administration of sodium oxalate in its various forms, which induces rapid formation of CaOx crystals in renal tubules, thus simulating pathological conditions similar to those in humans(Sayed *et al.*, 2023).Ethnomedicine treatment has received attention to help alleviate some of the adverse effects of NaOx-

induced urolithiasis. Herbal extracts, such as *Bryophyllum pinnatum* and *Lagenariasiceraria*, have significant antiurolithiatic actions through reduction in urinary oxalate levels and prevention of crystal deposition in the kidneys(Takawale*et al.*, 2012; Pandhare *et al.*, 2021). However, another important endpoint is the oxidative damage via alteration of antioxidant enzymes before the application of any treatments or medicines that sometimes leads to stress-mediated nephrotoxicity(Kumar and Sindhu, 2024b, 2024a). Application of ethnomedicines, therefore, emerges as an attractive alternative for the management of urolithiasis, helping to indicate their application in traditional medicine and their integration into modern therapeutic approaches.Such treatments help in restoring normal renal physiology and often improve biochemical parameters related to the kidney. The present study has underlined the phyto-constituents responsible for therapeutic action and attracted special attention toward such potential plants as candidates for developing novel plant-based treatments for urolithiasis.

3.1. Effect of Ethnomedicine on the Survival and Growth of Rat

There was no significant impact on the survival of rat upto 2000 mg/kg dose exposure in any of the treatment group and all rats were found to be physiologically healthy and in range of bodyweight.

3.2. Effect of Ethnomedicine on the Biochemical Parameters

This study provides strong evidence on the efficacy of various treatment regimens in improving urinary, serum, and kidney parameters in the context of kidney stones, as depicted in Figures 1-6.

In brief, as shown in Figure 1, urine volume exhibited no significant change on day 0. However, as the treatment duration increased to 14 and 28 days, the groups treated with natural extracts and ethnomedicines (T5, T9, and T10) demonstrated significant improvement compared to the disease control. The same trend was observed for urine volume and urinary crystal urea, with these parameters showing a significant improvement in the treated groups compared to the disease control and individual ethnomedicine treatments. In contrast, urine volume and pH decreased notably in the disease control group, leading to more concentrated urine, which promotes crystal formation and stone growth. The effective treatments, on the other hand, increased both urine volume and pH, which diluted the urinary components, reducing the risk of crystal aggregation. The combination therapies further boosted urine volume and pH, demonstrating their role in reducing the risk of urolithiasis by promoting diuresis and creating a less acidic environment, which inhibits crystal growth.

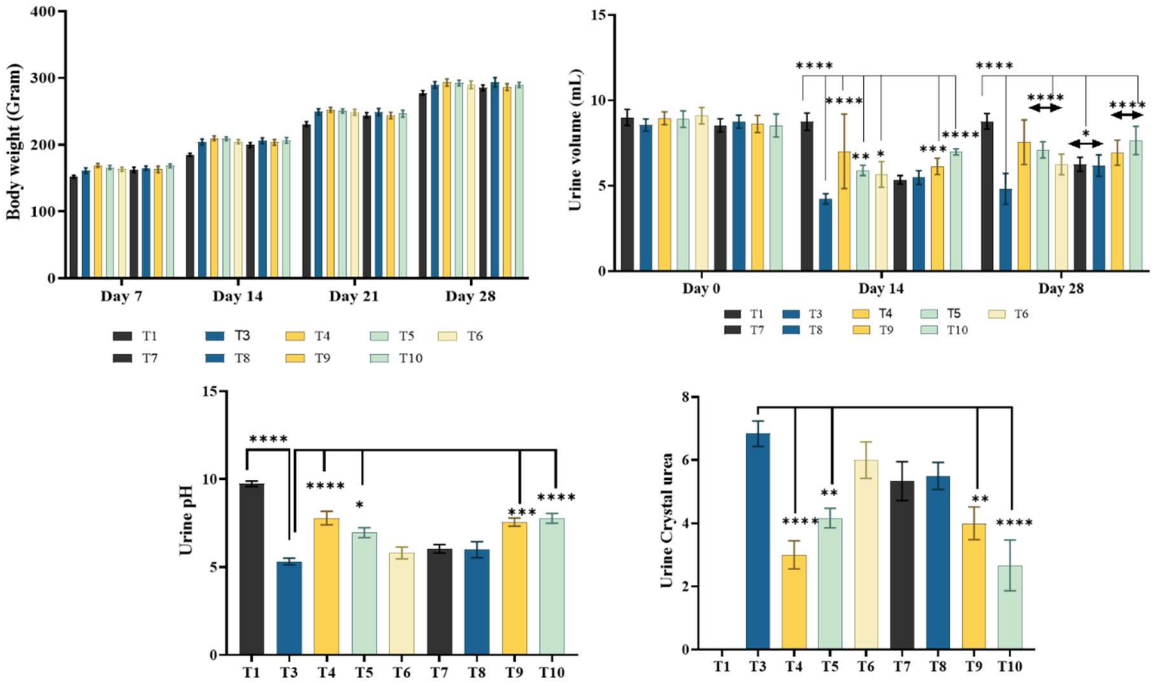

Figure 1: No significant difference ($p>0.05$) in the body weight of rats was observed, while significant changes ($p<0.05$) were noted in urine parameters, including volume, pH, and crystal urea.

Furthermore, treatment with the standard drug Cystone (T4) at a dosage of 500 mg/kg body weight resulted in a significant improvement in these parameters, reinforcing its well-established efficacy in managing urolithiasis. Notably, the combination of extracts from P. nigrum, M. alba, and V. vinifera with Nausadar (T10) produced results that were statistically significant and comparable to those achieved with Cystone, highlighting the therapeutic potential of these herbal combinations. Additionally, kidney weight showed a statistically significant reduction in the T4, T5, T9, and T10 groups compared to the disease control (T3).

When analyzing catalase activity in kidney homogenates, an opposite pattern emergedthere was a significant increase in the treated groups compared to the disease control (Figure 2). The reduced catalase activity in the disease control group suggests increased oxidative stress in renal tissues. Elevated oxidative stress, due to higher levels of reactive oxygen species, can lead to further cellular damage and inflammation, exacerbating the pathological changes in kidney tissues. The treatment groups, however, showed a rise in catalase activity, indicating enhanced antioxidant defense mechanisms (Figure 2). This increase in antioxidant activity likely helps protect kidney tissues from oxidative damage, supporting tissue recovery and preventing further injury. The combination of herbal extracts likely enhances therapeutic outcomes beyond what individual herbs can achieve due to their complementary mechanisms of action, including antioxidant, anti-inflammatory, diuretic, and nephroprotective effects, which together promote better renal health. The observed synergistic effects of the combined treatments suggest that the phytochemical properties of each component work in harmony to increase their overall effectiveness.

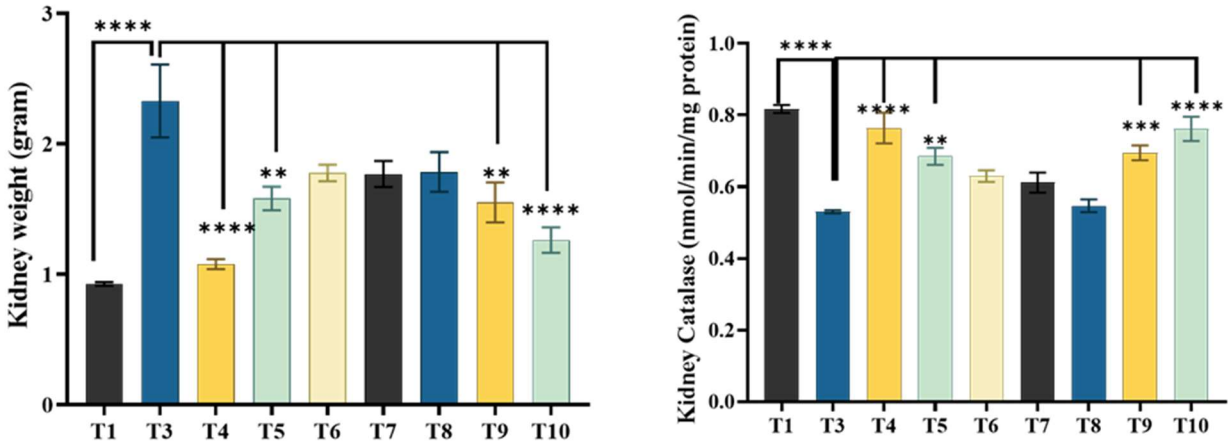

Figure 2: Significant changes ($p<0.05$) in kidney weight and antioxidant catalase activity.

Similarly, calcium and uric acid levels in serum, kidney, and urine were measured, showing a decline in the treated groups, indicating a positive correlation with the use of ethnomedicines compared to the disease control. In contrast, the disease control group showed a sharp increase in these parameters, indicating worsening urolithiasis (Figure 3).

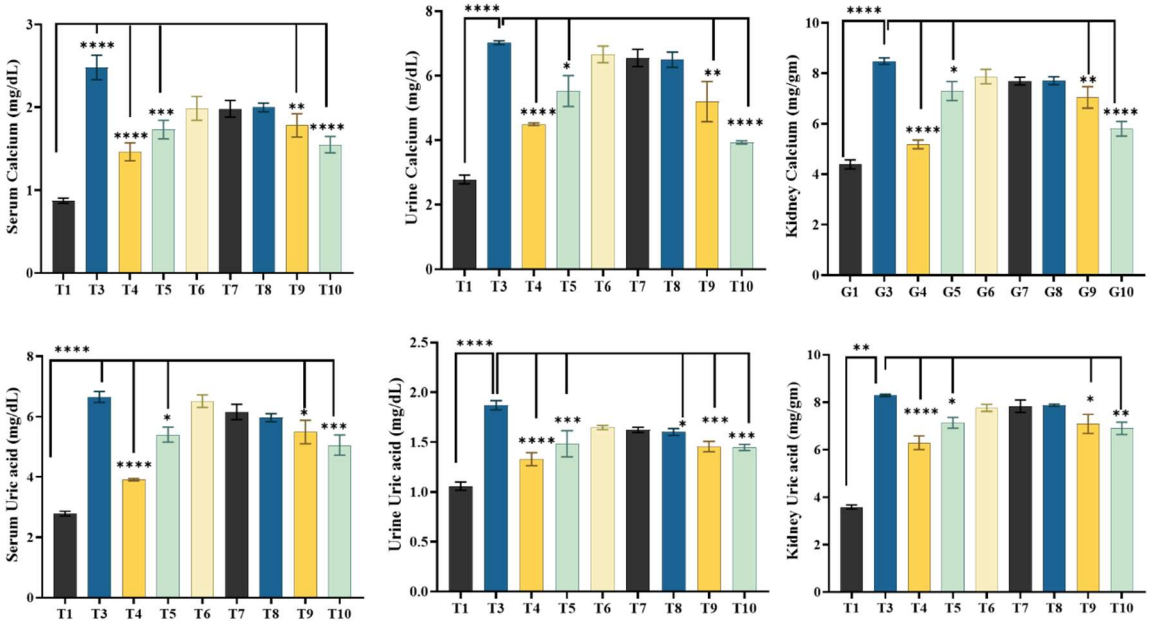

Figure 3: Significant changes ($p<0.05$) in both urine and serum parameters, such as calcium and uric acid.

Magnesium and citrate levels in urine and serum, known to inhibit crystal formation in the urinary tract, also displayed significant changes. In the disease control group, magnesium and citrate levels were notably reduced, creating an environment conducive to crystal aggregation and stone formation (Figure 4). Lower citrate levels are particularly linked to a reduced ability to prevent calcium crystal precipitation, further promoting stone formation. Conversely, the treated groups, including the standard and effective treatment groups, exhibited

significant increases in magnesium and citrate levels, restoring the balance of these critical inhibitors and likely contributing to reduced crystal formation and improved histopathological outcomes. Other serum parameters, such as BUN, creatinine, and phosphorus, showed an opposite trend compared to magnesium and citrate, with significant declines observed in the T4, T5, T9, and T10 groups compared to the disease control (T3) (Figure 4). Additionally, urea, phosphate, and oxalate levels followed a similar pattern, with notable declines in the treated groups compared to the disease control, indicating a positive treatment response (Figure 5).

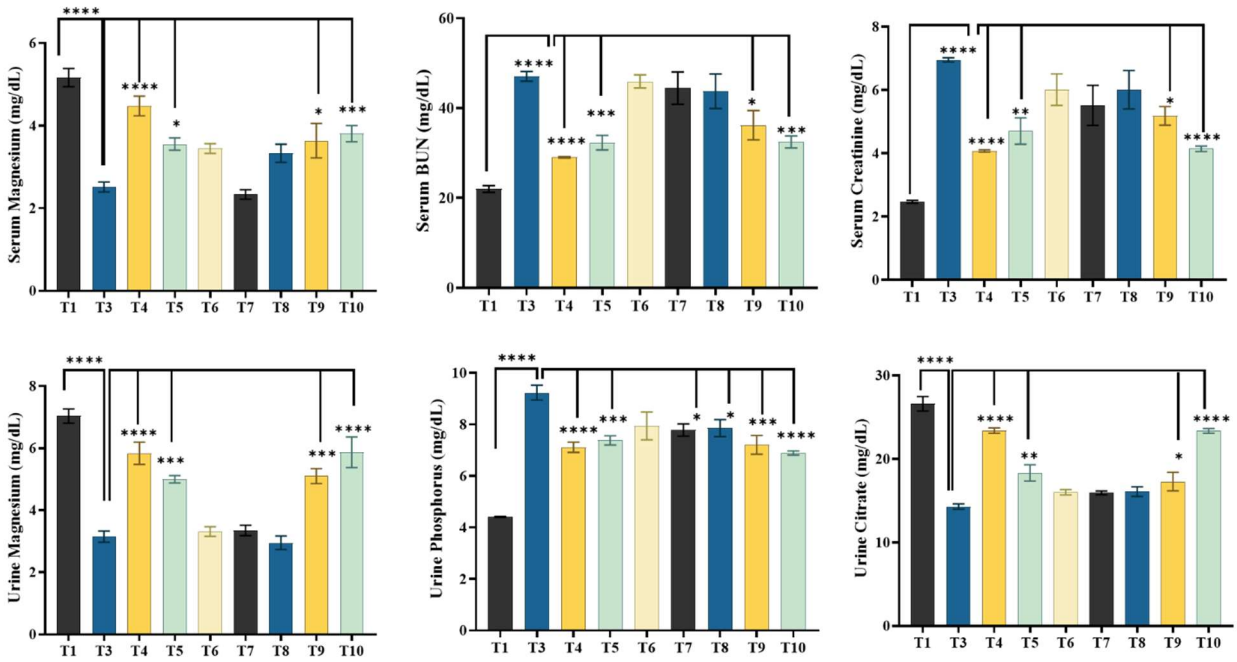

Figure 4: Significant changes ($p<0.05$) in both serum and urine parameters, including magnesium, phosphorus, and citrate.

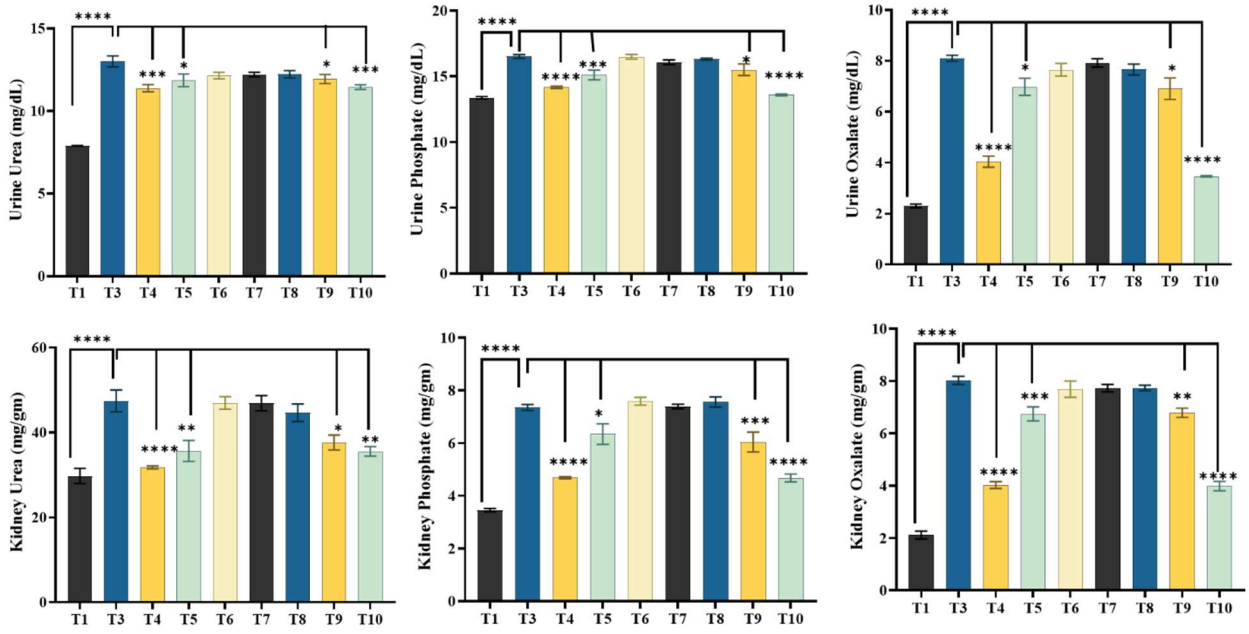

Figure 5: Significant changes ($p<0.05$) in urine and kidney parameters, such as urea, phosphate, and oxalate.

The observed biochemical changes, particularly in sodium, potassium, chloride, urine volume, and urine pH, align with increased diuretic activity, which is critical for flushing out kidney stones and reducing stone-forming substances in the urinary tract. This biphasic response to diuresis, as demonstrated in figure 6, supports the role of these herbal treatments in promoting the removal of kidney stones through enhanced urine flow. The combination of P. nigrum, M. alba, and V. vinifera with Nausadar (T10) demonstrated remarkable efficacy, underscoring the potential for synergistic interactions among these herbal constituents. The response was better when the biochemical and histopathological parameters were combined, which means that the combination works at different levels: the reduction of stone-forming substances, enhancement of diuresis, and offering renal protection.

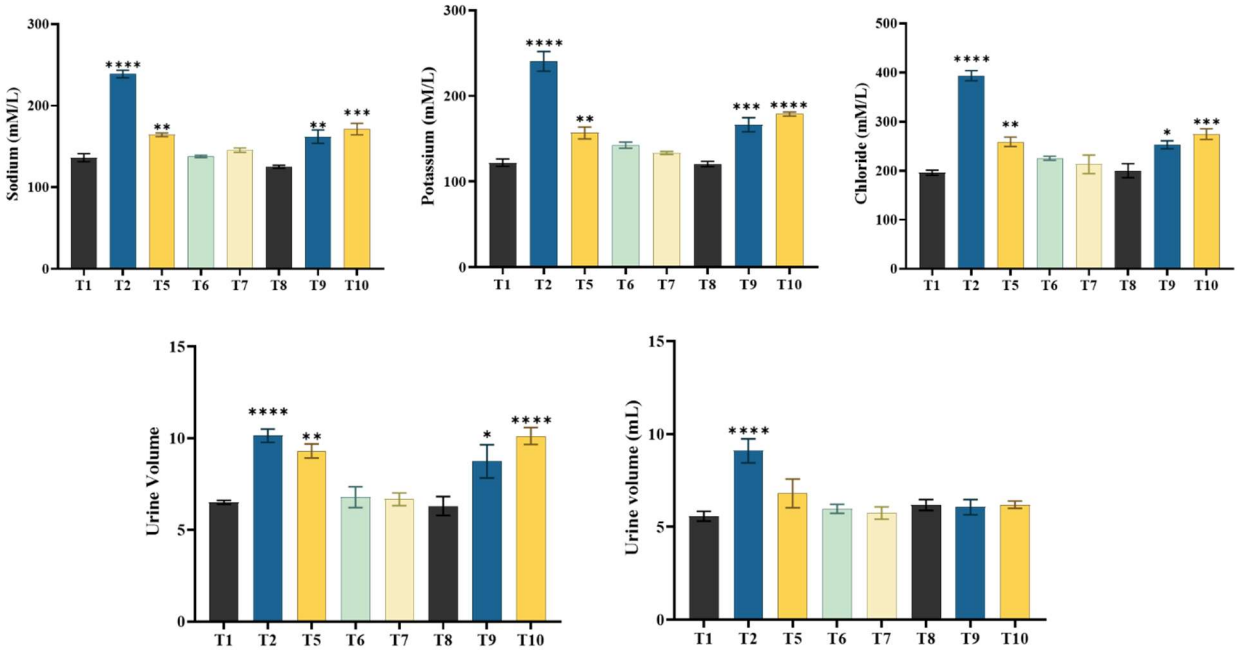

Figure 6: Changes of the parameters of diuretic activity-sodium, potassium, chloride, urine volume and pH-showed significant changes, $p<0.05$, 14 days after exposure, i.e., 6 h posttreatment.

Overall, the change in biochemical parameters of the biphasic response tallies with the typical biochemical disturbances in urolithiasis. The increase in calcium and uric acid levels, being contributory factors for stone formation, underlines the metabolic disturbances that characterize the disease. Such a profile indicates a high impact on renal function and homeostasis. In contrast, marked improvements with treatment by Cystone underline its established role in clinical practice. All these can be explained by the multifactorial mechanisms of its action: enhancement of diuresis, inhibition of crystallization, and reduction of stone-forming substances in the urine and serum. These findings emphasize the role of pharmacological interventions in the management of severe cases of urolithiasis. Whereas the treatment with fruit extracts alone and in combination exhibited certain positive responses, they failed to provide significant changes when compared to the standard control treatment. However, specific parameters of urinary excretion and kidney retention of oxalate, protein, and calcium did show positive responses to certain extracts. Results from the combination devoid of Nausadar (T6) were positive, but the lack of statistical significance would imply that the role of Nausadar is very important in enhancing the action of herbal extracts. This finding indicates that Nausadar might have a bioenhancement effect or potentiate the synergistic action of combined extracts, and hence, Nausadar is an essential ingredient in producing a therapeutic effect. These ethnomedicine groups, T5 (black pepper combined with Nausadar), which showed significant results but less than the three-herb combination with Nausadar. This means that the inclusion of additional herbal components like Piper nigrum, Morus alba, and Vitis vinifera conferred a more potent therapeutic benefit.

3.2. Pathological Findings

Histopathological examination showed that severe damage occurred in renal tissues in the disease control groups, which was marked by very high degrees of tubular dilatation and early cystic formations, as shown in

figure 7. Such structural changes manifest from high damage due to the deposition of calcium oxalate crystals, which blocks normal renal activities and could result in several complications of filtration defects with a heightened risk of renal failure.

Tubular atrophy reflected chronic renal injury that was typified by loss of kidneys to maintain normal tissue architecture subsequent to a prolonged period of insult or injury. Deposition of calcium oxalate crystals, characteristic of nephrolithiasis, was heavy in the disease control groups. This crystal accumulation caused further renal tissue damage and subsequent inflammation as represented by the infiltration of interstitial mononuclear cells. These crystals, along with the inflammatory response, further promote the renal tissue injury in a cyclic manner. In contrast, this histopathological abnormality was significantly reduced in the standard treatment and other therapeutic groups, including those treated with herbal combinations. The improvement in tubular dilatation, atrophy, and deposition of calcium oxalate in these groups indicates restoration of renal tissue by the respective treatments. This restitution of normal renal architecture and function has suggested that these therapies alleviate not only symptomatic manifestations of urolithiasis but also contribute to long-term renal health through structural integrity in the kidney. These encouraging results point to the requirement for further investigation of other herbal combinations and their synergistic interaction in improving renal health. Further studies should be carried out with dose optimization and treatment duration for maximum therapeutic benefit. Besides, it would be of great interest to investigate the exact biochemical pathways through which these selected herbal extracts interact. In vitro and in vivo studies could help elucidate these mechanisms, offering deeper insights into how these treatments function at the molecular level.Given the favorable results in this preclinical study, clinical trials evaluating the efficacy and safety of these herbal combinations in human populations are essential. These trials could pave the way for integrating herbal remedies into standard therapeutic protocols for the management of urolithiasis, potentially offering new, effective, and natural options for patients suffering from kidney stones.

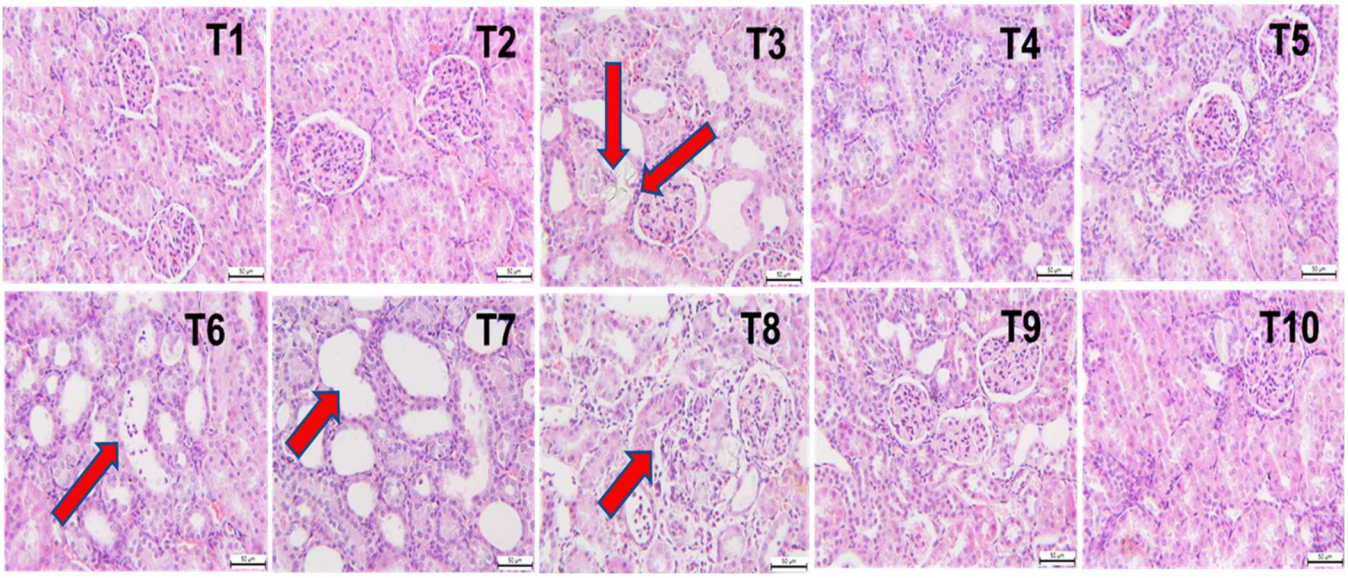

Figure 7: Histopathological findings of kidney tissue from (T1) vehicle control, (T2) FSM standard-treated, and (T3) calculi-induced groups, showing severe changes, including tubular dilatation and initial cystic formation, tubular atrophy, calcium oxalate crystal deposits, and interstitial mononuclear cell infiltration and Calcium oxalate crystals are highlighted with double arrow in T3. (T4) Cystone-treated group, (T5)

Ethnomedicine (*Piper nigrum* with Nausadar) and (T6-T9) curative treatments with individual and combined extracts show progressive improvement, while T10 indicates complete recovery with no significant alterations.

4.0. Conclusion

Present study reveals the efficacy of herbal combinations, such as *P. nigrum, M. alba*, and *V. vinifera* with Nausadar, in managing urolithiasis. These combinations showed significant improvements in urinary, kidney and serum parameters, comparable to the standard drug, Cystone, and demonstrated potential in reducing kidney stone formation by promoting diuresis, balancing urinary pH, and enhancing antioxidant potential. The study also emphasizes the role of Nausadar as acidifier and bioenhancer, contributing to the synergistic effects of the herbal extracts. These findings underscore the promise of integrating ethnomedicines into modern therapeutic strategies for kidney stone management. Further research, including clinical trials, is needed to optimize these treatments for human use.

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