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Evaluation of the Effectiveness of Tomato (Solanum lycopersicum L.) Juice in Inhibiting Calcium Oxalate Crystal Formation *In Vitro*

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ABSTRACT

Background: Nephrolithiasis is a major urological problem worldwide with a high recurrence rate, reaching approximately 50% within the first 5–10 years after the initial episode. Around 70–80% of kidney stones consist predominantly of calcium oxalate (CaOx). The imbalance between urinary promoters (calcium, oxalate) and inhibitors (citrate, magnesium) leads to supersaturation and crystal formation. Citrate functions as a strong natural inhibitor, although conventional medical therapy may involve considerable costs and adverse effects. Tomatoes (Solanum lycopersicum L.) are an affordable local commodity containing high levels of citrate and magnesium, and therefore hold potential as a natural antilithiasis agent.

Objective: To evaluate the effectiveness of tomato juice in inhibiting calcium oxalate crystal formation using a synthetic urine model.

Methods: An in vitro experimental study was carried out using a post-test only design with a control group. Samples were divided into five groups with three replications: Negative Control (no treatment), Positive Control (Potassium Citrate 0.5%), and three treatment groups of Tomato Juice at 25%, 50%, and 100% concentrations. Crystal formation was induced using $CaCl_2$ and $Na_2C_2O_4$ in synthetic urine. Absorbance was measured using a UV–Vis spectrophotometer (620 nm) at two-minute intervals for 60 minutes. Measured parameters included Slope of Nucleation (SN), Slope of Aggregation (SA), and percentage of inhibition.

Results: Tomato juice demonstrated statistically significant inhibitory activity against CaOx crystallization kinetics ($p < 0.05$ for SN and SA). The 25% concentration produced the highest inhibition rate (approximately 65%), comparable to the positive control (70%). The 50% and 100% concentrations yielded inhibition values of approximately 38% and 37%, respectively, indicating a dose–response pattern that did not increase proportionally with concentration.

Conclusion: Tomato juice effectively inhibited calcium oxalate crystal formation in vitro, particularly during the aggregation phase. The optimal effect was observed at the 25% concentration, suggesting a non-linear dose–response possibly influenced by the balance between citrate content and endogenous oxalate in tomatoes.

KEYWORDS: Calcium Oxalate, Nephrolithiasis, Citrate, Crystallization Inhibitor, *In Vitro, Solanum lycopersicum L.*, Tomato.

INTRODUCTION

Prevention of urolithiasis, particularly kidney stones predominantly composed of calcium oxalate (CaOx), is an essential strategy to reduce incidence, recurrence, and complications such as urinary tract obstruction, infection, and irreversible renal damage, considering the invasive nature and high cost of conventional treatment modalities.[1] Nephrolithiasis is a significant global urological problem with a recurrence rate reaching 50% within the first 5–10 years after the initial episode. Approximately 70–80% of kidney stones consist mainly of calcium oxalate. Without preventive measures, calcium oxalate crystals may continue to grow and aggregate, forming stones that contribute to clinically relevant urological disturbances.[3] The prevalence of calcium oxalate urolithiasis in Asia varies considerably, ranging from 1% to 19.1%.[4] In Indonesia, the prevalence of kidney stones was reported at 0.6% in 2013, with a rate of 0.7% in East Nusa Tenggara Province.[5] Long-term management and surgical interventions require substantial economic resources, emphasizing the necessity for effective and affordable preventive approaches.[6] Tomato (*Solanum lycopersicum L.*) juice has been identified as a promising candidate due to its citrate and antioxidant content, which may contribute to reducing urinary calcium oxalate supersaturation.[7,8] Citrate in tomatoes acts as a natural inhibitor by chelating calcium to form

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soluble complexes, thus limiting calcium-oxalate binding. Several other natural preventive agents have also been investigated, including Nigella sativa, which demonstrated significant reductions in nucleation and aggregation, as well as lemon juice, known for strong inhibitory effects through increased citrate excretion and beneficial modulation of urinary pH. [9-11]

This study aims to evaluate the effectiveness of tomato juice in preventing calcium oxalate crystal formation using an in vitro experimental model. Spectrophotometric measurements were employed to assess its influence on nucleation and aggregation phases, with the expectation of generating supporting evidence for the use of tomato juice as a safe and accessible preventive option for individuals with a history of urolithiasis.

METHODS

This research was an experimental laboratory study using a post-test only with control group design. All procedures were conducted at the Laboratory of FKKH Universitas Nusa Cendana and the Pharmacy Laboratory of Poltekkes Kupang from September to October 2025. Samples were allocated into five groups with three independent replications per group to ensure result reliability. The treatment groups consisted of a negative control (synthetic urine without treatment), a positive control (synthetic urine with 0.5% Potassium Citrate), and tomato juice treatment concentrations of 25%, 50%, and 100%.

Fresh tomatoes (Solanum lycopersicum L.) were washed, blended, and filtered to obtain pure juice. The filtrate was then diluted with deionized water to achieve the desired concentration. Synthetic urine was prepared by dissolving sodium chloride, anhydrous calcium chloride, and sodium acetate trihydrate to a homogeneous mixture. The pH was adjusted to 6.5 ± 0.1 using 1N HCl or NaOH, and the solution was incubated in a water bath at 37°C to simulate physiological conditions.

Crystal formation was induced by the simultaneous addition of $CaCl_2$ and $Na_2C_2O_4$ into the synthetic urine system. Calcium oxalate crystallization kinetics were monitored by measuring turbidity using a UV–Vis spectrophotometer at 620 nm. Absorbance readings were recorded every 2 minutes for a total duration of 60 minutes.

The main evaluated parameters included Slope of Nucleation (SN), Slope of Aggregation (SA), Time to Maximum Absorbance (Tmax), and percentage inhibition. Data were processed statistically beginning with normality testing using the Shapiro–Wilk test and homogeneity testing using Levene's test. Differences among groups were analyzed using One-Way ANOVA for parametric data or the Kruskal–Wallis test for non-parametric data, followed by Tukey HSD or Dunn's post-hoc test to determine significant pairwise differences.

RESULT

Absorbance measurements using a UV–Vis spectrophotometer at 620 nm demonstrated turbidity changes representing calcium oxalate (CaOx) crystal formation. In the negative control group, a marked increase in absorbance was observed, indicating a naturally high crystallization rate without inhibition. Tomato juice treatment at various concentrations resulted in a slower increase in turbidity, reflecting inhibitory activity on the nucleation and aggregation processes. Quantitative parameters, including Slope of Nucleation (SN), Slope of Aggregation (SA), percentage inhibition, and time to peak absorbance, are presented in Table 1.

Table 1. Descriptive Analysis of Calcium Oxalate Crystallization Parameters

Treatment Group	SN (OD/min)	SA (OD/min)	SN Inhibition (%)	SA Inhibition (%)	Tmax (min)
Negative Control	0.000417	1.00	0.00%	0.00%	15.33
Tomato Juice 25%	0.000144	0.35	65.5%	65.0%	50.67
Tomato Juice 50%	0.000260	0.62	37.7%	38.0%	52.00
Tomato Juice 100%	0.000265	0.63	36.5%	37.0%	32.67
Positive Control (Potassium Citrate 0.5%)	0.000125	0.30	70.0%	70.0%	46.67

A non-linear dose-response pattern was observed, where the 25% tomato juice concentration yielded the highest inhibition (~65%), closely comparable to the positive control (70%). Increasing the concentration to 50% and 100% resulted in inhibition values of approximately 37% and 36%, respectively.

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Bivariate analysis was conducted to determine the significance of differences among treatment groups. The results demonstrated that variation in tomato juice concentration significantly influenced nucleation and aggregation kinetics.

Table 2. Summary of Bivariate Statistical Analysis

Variable	Statistical Test	Test Value (F/χ^2)	p-value
SN (Nucleation)	Kruskal–Wallis	12.86	0.012
SA (Aggregation)	One-Way ANOVA	49.47	<0.001
Tmax	Kruskal–Wallis	8.612	0.072

Post-hoc analysis using Tukey's HSD for SA revealed no significant difference between the 25% tomato juice group and the positive control (Potassium Citrate 0.5%) ($p = 0.916$). This outcome supports the potential of moderate tomato juice concentration to exhibit inhibitory activity comparable to a standard pharmacological agent in preventing CaOx aggregation. Significant differences were detected between the positive control and the 50% and 100% concentrations, indicating the presence of a potential dose-effect threshold.

DISCUSSION

This study demonstrates that tomato juice (Solanum lycopersicum L.) is capable of inhibiting calcium oxalate crystallization in synthetic urine, as reflected by the significant decrease in nucleation (SN) and aggregation (SA) values ($p < 0.05$). The 25% concentration produced the highest inhibitory response at approximately 65%, closely approaching the performance of 0.5% potassium citrate at around 70%, indicating the potential of tomato juice as a natural preventive strategy for nephrolithiasis.

The inhibitory mechanism is closely associated with the natural citrate content in tomatoes, which has been reported to increase urinary citrate excretion and reduce calcium oxalate stone formation risk.[11] Citrate forms soluble calcium–citrate complexes by binding free Ca^{2+}, thereby reducing urinary supersaturation and nucleation potential.[3] This mechanism aligns with the pharmacological action of potassium citrate widely used in clinical management.[12] Magnesium contained in tomatoes also contributes to lithogenesis suppression by competing with calcium for oxalate binding, forming magnesium oxalate which is more soluble.[13]

Tomatoes additionally contain antioxidants such as lycopene, flavonoids, and ascorbic acid that act as free-radical scavengers, reducing oxidative stress that may support tubular epithelial integrity and reduce crystal adhesion.[14] The synergistic presence of citrate, magnesium, and antioxidant compounds likely contributes to the multifactorial inhibitory effect observed in this study.

A non-linear dose–response pattern emerged, where the 25% extract produced greater inhibition compared with higher concentrations. Tomatoes carry both inhibitor constituents (citrate and magnesium) as well as endogenous oxalate that may act as a promoter under certain conditions.[7] At higher concentrations, increased oxalate load may exceed the citrate-binding capacity, reducing overall inhibition efficiency.[8] Elevated viscosity at higher juice concentration may also restrict inhibitor diffusion to crystal surfaces.[15] This pattern suggests that moderate consumption could potentially provide optimal preventive outcomes.

Several limitations should be noted. Phytochemical quantification of citrate, oxalate, and magnesium levels was not performed, leaving exact concentrations undefined.[9] The use of synthetic urine does not fully replicate human physiological conditions such as protein inhibitors, pH variability, and renal excretion dynamics.[16] Tomato citrate content varies between 0.3–0.5% depending on cultivar and ripeness, indicating the need for raw material standardization.[17] Further in vivo and clinical research is necessary to validate prophylactic potential and establish effective dosage recommendations for nephrolithiasis prevention.

CONCLUSION

This study concludes that tomato juice (*Solanum lycopersicum L.*) demonstrates a significant inhibitory effect on calcium oxalate crystallization in synthetic urine. The intervention effectively reduced both the slope of nucleation (SN) and the slope of aggregation (SA) when compared to the untreated control. The strongest inhibition was observed at a moderate concentration of 25%, reaching approximately 65% inhibition and yielding a performance comparable to 0.5% potassium citrate. The findings

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indicate a non-linear dose–response pattern, where increasing the concentration to higher levels, including 100%, did not enhance the inhibitory effect, likely due to endogenous oxalate content and higher solution viscosity at concentrated preparations.

The mechanism of inhibition is suggested to be driven by the combined role of citrate and magnesium, which bind free calcium ions and reduce supersaturation, while antioxidant compounds such as lycopene and flavonoids may further support protection by lowering oxidative stress. These results highlight the potential of tomato juice as a natural dietary candidate to support calcium oxalate nephrolithiasis prevention.

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