JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v14i6.52065
JKD (DMJ), Volume 14, Number 6, November 2025 : 304-310

EFFECT OF LEMON PEEL (*CITRUS LIMON*) EXTRACT ADMINISTRATION ON THE MACROSCOPIC AND MICROSCOPIC CHARACTERISTIC OF WISTAR MALE RATS KIDNEYS WITH HYPERURICEMIA

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Keywords:
Kidney,
Citrus limon,
Rats,
Uric acid,
Hyperuricemia

Received: 25 June 2025
Revised: 31 July 2025
Accepted: 4 August 2025
Available online: 1 November 2025

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ABSTRACT
Background: Excessive purine intake increases serum uric acid levels, which may result in renal complications such as tubular injury and nephrolithiasis. Lemon (*Citrus limon*) peel contains vitamin C, flavonoids, and citrate, which exhibit antioxidant properties and act as inhibitors of crystal formation in the urinary tract. **Objective:** This study aimed to evaluate the effects of graded doses of lemon peel extract (Citrus limon) on the renal macroscopic morphology and histopathological features of male Wistar rats with induced hyperuricemia and to compare outcomes across control, positive control, and treatment groups. **Methods:** Thirty male Wistar rats were randomly assigned into five groups (n=6 each): negative control (K0), positive control (K1), and treatment groups (P1, P2, P3) receiving lemon peel extract at doses of 17.5, 35, and 70 mg/kgBW, respectively. Hyperuricemia was induced using Maggi® cube broth (140 mg/200gBW) and potassium oxonate (50 mg/200gBW). Serum uric acid levels were measured pre- and post-intervention to confirm induction and assess therapeutic efficacy. Kidney tissues were evaluated macroscopically and microscopically following euthanasia on day 35. **Results:** No significant macroscopic alterations were observed across groups, with all kidneys showing smooth, elastic surfaces. Histological analysis revealed reduced tubular epithelial cell degeneration in all treatment groups compared to the positive control, with the most notable reduction observed in the 70 mg/kgBW group. However, inflammatory cell infiltration in the interstitial area did not differ significantly between K1 and treatment groups. **Conclusion:** Lemon peel extract mitigated tubular cell degeneration in the kidneys of hyperuricemic Wistar rats, with the highest dose (70 mg/kgBW) demonstrating the most pronounced effect. Nonetheless, it did not significantly attenuate interstitial inflammation.

INTRODUCTION
An individual's health and physiological functions are profoundly influenced by dietary patterns. Diets rich in purines, particularly from animal protein, can elevate serum uric acid levels, predisposing individuals to hyperuricemia and subsequent complications such as nephrolithiasis and gouty arthritis. Purines are metabolized into uric acid, the end-product of purine catabolism. When purine intake or endogenous production increases, uric acid crystallization may occur, particularly in joints and renal tissues. Persistent hyperuricemia results from this metabolic imbalance and is associated with excessive monosodium urate (MSU) crystal accumulation[1].

Chronically elevated uric acid levels may lead to renal complications, including urate nephropathy and urolithiasis. Kidney stone formation occurs due to

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supersaturation of lithogenic substances—such as uric acid and calcium oxalate—in the urine, compounded by a deficit of crystallization inhibitors. Uric acid excretion is considered excessive when it exceeds 600 mg/24h on a purine-free diet or 800 mg/24h on a regular diet. The risk of nephrolithiasis markedly increases when excretion surpasses 900 mg/24h[2].

Allopurinol is a commonly prescribed xanthine oxidase inhibitor for managing hyperuricemia and gout. However, it is associated with adverse effects, including potential nephrotoxicity. As a result, there is growing interest in non-pharmacological or plant-based alternatives, including those rich in natural antioxidants. Vitamin C is a known uricosuric agent that enhances uric acid excretion by inhibiting reabsorption in renal tubules. Lemon (Citrus limon) peel is a rich source of vitamin C, flavonoids, and citrate—bioactive compounds with antioxidant and lithiasis-inhibiting properties. Flavonoids neutralize free radicals and mitigate purine-induced oxidative stress, while citrate inhibits the nucleation and aggregation of calcium-based crystals[3,4].

Despite the potential of lemon peel as a natural nephroprotective agent, few studies have directly investigated its effect on renal structure in hyperuricemic conditions, particularly in relation to both macroscopic morphology and histopathological parameters. This study was conducted to address this research gap and evaluate the therapeutic potential of lemon peel extract in a hyperuricemic rat model.

METHODS

The type of research conducted was a true experimental laboratory study using a post-test only randomized controlled group design. The treatment involved the administration of lemon peel extract (*Citrus limon*) and a high-purine diet, specifically Maggi® block broth produced by PT. Nestlé Indonesia at a dose of 140 mg/200gBW for Wistar rats, and potassium oxonate at a dose of 50 mg/200gBW to induce hyperuricemia. The outcomes assessed were the macroscopic and microscopic morphology of the kidneys in male Wistar rats (*Rattus norvegicus L.*).

This study was conducted between May and October 2023. All 30 experimental rats underwent a 7-day acclimatization period to allow for adaptation to the new environment. During this period, the rats were fed standard feed and had ad libitum access to drinking water. After the acclimatization phase, on day 8, the rats were randomly divided into five groups, with six rats in each group. They were then fed a standard diet supplemented with a high-purine feed for 14 days.

Blood samples were collected on day 21 to measure serum uric acid levels, confirming the induction of hyperuricemia, which was defined as uric acid levels exceeding 3.0 mg/dL. Following this, the rats in the treatment groups received lemon peel extract orally for 14 consecutive days, with doses of 17.5 mg/kgBW for group P1, 35 mg/kgBW for P2, and 70 mg/kgBW for P3. On day 35, all rats were euthanized, and their kidneys were extracted for macroscopic and microscopic analysis.

The data were processed using IBM SPSS Statistics version 26. Statistical analysis was conducted to examine the effect of lemon peel extract on kidney histology (a ratio scale variable). Variable mapping was performed using a cross-tabulation test, followed by the Kruskal-Wallis test to assess significant differences across groups. If significant differences were found, the Mann-Whitney U test was conducted for pairwise comparisons between groups.

RESULTS

Macroscopic observations

Macroscopic observations of the kidneys in hyperuricemic male Wistar rats showed no visible differences among the experimental groups.

Microscopic observations

Microscopic examination assessed the presence of cloudy swelling in renal tubular epithelial cells and the distribution of inflammatory cells in the interstitial areas.

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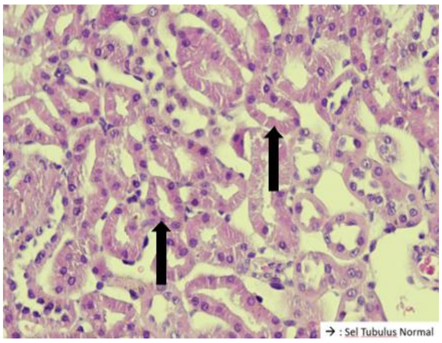

Figure 1. Normal tubule cells

In normal histological sections, as represented in Figure 1, the renal tubules appeared with intact epithelial cells and open lumens (indicated by the black arrow).

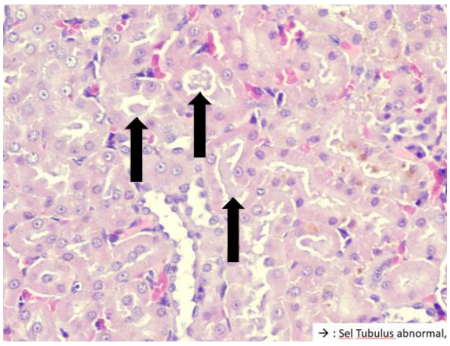

Figure 2. Abnormal tubule cells

In contrast, abnormal histological structures were observed in some samples, as shown in Figure 2, where narrowed lumens and degenerated epithelial cells were evident (black arrow).

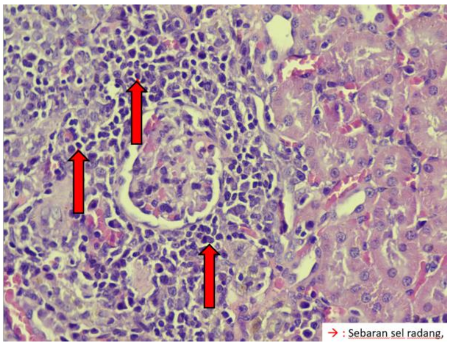

Figure 3. Distribution of inflammatory cells

The presence of inflammatory cells, specifically lymphocytes and plasma cells, infiltrating the interstitial tissue was illustrated in Figure 3 (red arrow).

The assessment of cloudy swelling was conducted using a scoring system based on the extent of cytoplasmic degeneration or swelling in the tubular cells. A score of 0 indicated no degeneration, while scores of 1 to 3 represented increasing severity, from <25%, 25–60%, to >60% of tubular cells affected, respectively. Similarly, the degree of inflammation was evaluated based on the presence and extent of lymphocyte and plasma cell infiltration in the interstitial space, with scores ranging from 0 (no inflammation) to 3 (diffuse infiltration).

Table 1. *Crosstab Test*

			Scale				Total
			0	**1**	**2**	**3**	
Tubulus group	K0	Count	3	2	0	0	5
		% within group	60%	40%	0%	0%	100%
	K1	Count	0	0	4	2	6
		% within group	0%	0%	66.7%	33.3%	100%
	P1	Count	0	3	2	0	5
		% within group	0%	60%	40%	0%	100%
	P2	Count	0	4	2	0	6
		% within group	0%	66.7%	33.3%	0%	100%
	P3	Count	0	3	1	0	4
		% within group	0%	75%	25%	0%	100%

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Inflammation group	K0	Count	5	0	0	0	5
		% within group	100%	0%	0%	0%	100%
	K1	Count	0	5	1	0	6
		% within group	0%	83.3%	16.7%	0%	100%
	P1	Count	0	5	0	0	5
		% within group	0%	100%	0%	0%	100%
	P2	Count	0	6	0	0	6
		% within group	0%	100%	0%	0%	100%
	P3	Count	0	4	0	0	4
		% within group	0%	100%	0%	0%	100%

Table 1 presented the distribution of tubular degeneration scores across the groups. In the control group (K0), most samples—three out of five rats (60%)—showed no evidence of degeneration, while the remaining two rats (40%) exhibited degeneration in less than 25% of the tubular cells. In the positive control group (K1), the majority—four rats (66.7%)—showed moderate degeneration (25–60%), while two rats (33.3%) demonstrated severe degeneration involving more than 60% of the tubule cells. Among the treatment groups, the P1, P2, and P3 rats generally exhibited mild degeneration. In the P1 group, 60% of the rats had <25% of tubular cells affected, while 40% had degeneration in the range of 25–60%. The P2 group had a similar trend, with 66.7% of rats showing <25% degeneration and 33.3% showing moderate degeneration. The P3 group showed the least degeneration, with 75% of samples in the <25% category and only 25% in the 25–60% category.

In terms of inflammatory cell infiltration, the K0 group showed no inflammation in any of the samples (100% score 0). The K1 group displayed inflammation in all samples, with 83.3% exhibiting mild inflammatory cell infiltration and 16.7% showing a moderate degree. In the treatment groups P1, P2, and P3, all rats (100%) demonstrated mild inflammation, without any cases of moderate or severe infiltration. Statistical analysis using the Kruskal-Wallis test yielded a p-value of <0.05 for both tubule degeneration and inflammation, indicating that there were significant differences among the groups. Further analysis using the Mann-Whitney U test is summarized in Table 2, which revealed more specific intergroup comparisons.

Table 2. Mann Whitney Test

Tubulus group		**K0**	**K1**	**P1**	**P2**	**P3**
	K0	-	0.004*	0.031*	0.026*	0.055
	K1	-	-	0.026*	0.014*	0.021*
	P1	-	-	-	0.827	0.655
	P2	-	-	-	-	0.789
	P3	-	-	-	-	-
Inflammation group		K0	K1	P1	P2	P3
	K0	-	0.004*	0.031*	0.026*	0.055
	K1	-	-	0.026*	0.014*	0.021*
	P1	-	-	-	0.827	0.655
	P2	-	-	-	-	0.789
	P3	-	-	-	-	-

*A value of p <0.05 shows a significant difference

According to Table 2, comparisons between K0 and K1, P1, and P2 groups showed p-values <0.05, indicating statistically significant differences in tubular degeneration between the control and both the positive control and lower-dose treatment groups. However, the comparison between K0 and P3 yielded a p-value >0.05, suggesting no significant difference between the control group and the high-dose treatment group, which may indicate a protective effect of the higher lemon peel extract dose.

All comparisons between K1 and treatment groups (P1, P2, and P3) also showed p-values <0.05, reflecting that the lemon peel extract in all doses significantly reduced degeneration compared to the untreated hyperuricemic group. On the other hand, comparisons among treatment groups (P1 vs P2, P1 vs P3, and P2 vs P3) resulted in p-values >0.05, implying that while all treatment doses were effective, no

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significant difference in tubular degeneration was observed between different dosages.

For inflammatory variables, Table 2 also indicated that comparisons between K0 and K1, P1, P2, and P3 yielded p-values <0.05, showing significant differences in the extent of inflammation. However, comparisons between K1 and the treatment groups, as well as comparisons among the treatment groups themselves, showed p-values >0.05, suggesting that although the extract had a beneficial effect in reducing inflammation, the difference in dosage did not significantly affect the degree of inflammatory cell infiltration.

DISCUSSION

Macroscopic observations

From the findings and analysis conducted by the researchers, the kidneys exhibited a normal macroscopic morphology across all groups. The outer surface appeared smooth, flat, and had a slippery texture with elastic consistency. No cysts, connective tissue thickening, abscesses, or irregular textures were observed in any of the kidney samples. There were no differences in macroscopic appearance between groups receiving lemon peel extract (*Citrus limon*) at doses of 70 mg/kgBW, 35 mg/kgBW, and 17.5 mg/kgBW, compared to the K0 (normal) and K1 (positive control) groups. These findings indicate that both the induction of hyperuricemia via broth and the administration of lemon peel extract did not produce any macroscopic changes in the kidneys of Wistar rats.

Microscopic observations

Microscopically, signs of proximal tubular damage and degeneration were observed in the kidneys of rats in all groups (K0, K1, P1, P2, and P3). These included cloudy swelling, characterized by cytoplasmic swelling and degeneration of the tubular epithelial cells. Notably, calcium oxalate crystals were not identified in any sample. Additionally, inflammatory cell infiltration by lymphocytes and plasma cells was found in the interstitial areas of the kidneys in groups K1, P1, P2, and P3, while no inflammation was observed in the control group (K0).

The presence of inflammatory cell infiltration and tubular swelling formed focal inflammatory zones that contributed to lumen narrowing or closure. The formation of urinary tract stones requires a condition of supersaturation, where the balance between promoters and inhibitors of crystallization is disrupted. Although glycoproteins and citrate are known inhibitors of calcium oxalate stone formation and are normally present in urine, various reactants, including uric acid, can increase the risk of stone formation. Although the mechanism is not entirely understood, it is believed that both inhibitors and promoters play significant roles in crystal nucleation, growth, and aggregation.[5]

Citrate-rich fruits such as lemon have been shown to prevent urinary stone formation due to citrate's role as an effective crystallization inhibitor. Lemon contains citric acid, which is the dominant organic acid[6]. Citric acid reduces calcium oxalate saturation by binding free calcium in urine and acts as a direct inhibitor of crystal growth. Several studies have used supersaturated solutions containing calcium oxalate or phosphate to examine the rate of crystallization and the effects of inhibitory compounds.

It has been proposed that high-molecular-weight compounds, such as acidic glycoproteins, are the primary inhibitors of calcium oxalate crystallization. However, citric acid also contributes to this process. For instance, Pak and Fuller demonstrated that citric acid increases the "permissible rise" of oxalate in urine, allowing more oxalate to be tolerated before precipitation occurs. Kok, Papapoulos, and Bijvoet employed kinetic analysis and discovered that subjects with recurrent stone formation typically exhibited low urinary citrate excretion and high rates of crystal agglomeration, which were normalized following citrate supplementation. Citric acid also inhibits the formation of calcium phosphate stones[7].

Supporting this, Saraswati, *et al* in 2017 reported that citrate in lime juice was effective in dissolving kidney stones, functioning as an inhibitor by binding free calcium ions (Ca^{2+}), thus promoting the formation of calcium citrate or phosphate salts and decreasing calcium crystal formation[8]. This aligns with the present microscopic findings in which calcium oxalate stones were not observed in the K1, P1, P2, or P3 groups.

The comparison of the positive control group with the treatment group showed that lemon peel extract (*Citrus limon*) was able to trigger a significant reduction in the rate of damage or degeneration in renal tubule cells at all doses, namely 70 mg/kgBW, 35 mg/kgBW, and 17.5 mg/kgBW and there was a

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difference in the effect of different doses. The picture of tubule cells in the K0 group compared to the K1, P1, and P2 groups had significant differences while in the P3 treatment there was no significant difference. This shows that the treatment using a dose of 70 mg/kgBW is the optimal dose in reducing the rate of tubule cell degeneration that is close to the kidney condition of the control group. The dose was converted from mice to humans according to the conversion factors in the table.

Table 3. Dosage Conversion Factor

	Mice (20 g)	**Rat (200 g)**	**Rabbit (1.5 kg)**	**Human (70 kg)**
Mice (20 g)	1	7	27.8	387.9
Rat (200 g)	0.14	1	3.9	56
Rabbit (1.5 kg)	0.04	0.25	1	14.2
Human (70 kg)	0.0026	0.018	0.07	1

The dose of lemon fruit coolie extract (*Citrus limon*) in rats was 70 mg/kgBW.

- For 200 grams = 200 g / 1000 g x 40 mg = 14 mg
- Conversion factor from 200 g rats to humans 70 kg = 56.0
- In humans 70 kg = 8 x 56.0 = 784 mg
- 784 mg / 70 kg = 11,2 mg/kgBW

Therefore, the optimal human dose of lemon peel extract is estimated at 11.2 mg/kgBW .

The reduction in tubular degeneration is likely attributed to the vitamin C content in lemon peel, which has demonstrated antioxidant activity, as reported in a 2012 study from Pakistan. This suggests that lemon peel extract may have nephroprotective effects. Vitamin C acts as an antioxidant by stabilizing free radicals through electron donation, thereby preventing oxidative chain reactions[9]. Oxidative stress arises from an imbalance between antioxidants and prooxidants, often triggered by antioxidant deficiency or excessive free radical production. While the body naturally produces endogenous antioxidants, additional supplementation with exogenous antioxidants like vitamin C can support oxidative defense mechanisms[10]. Vitamin C helps prevent cell damage by donating electrons to neutralize reactive oxygen species such as hydroxyl radicals, superoxide anions, and lipid hydroperoxides[11]. Under stress, vitamin C becomes a key antioxidant in cells and plasma, serving as a cofactor in the synthesis of collagen, carnitine, and neurotransmitters, which may help strengthen kidney tubular cells[12].

Regarding inflammation, lemon peel extract (*Citrus limon*) did not significantly reduce inflammatory markers, as indicated by comparisons between the K1 group and the treatment groups (P1, P2, and P3), as well as between the K0 group and the other groups. This suggests that the inflammatory conditions in the kidneys of the treated groups did not approach those of the control group. The results indicate that lemon peel extract successfully reduced the rate of renal tubular degeneration in hyperuricemic male Wistar rats. This finding is consistent with the study by Saleem et al. (2012), which showed that vitamin C in lemon peel extract has nephroprotective effects and contributes to tissue strength, reducing tubular degeneration. Furthermore, Anisa et al. (2019) reported that lemon peel extract contains flavonoids and phenols with anti-inflammatory properties[13]. However, in this study, lemon peel extract did not reduce inflammatory cell infiltration in the kidneys of hyperuricemic male Wistar rats.

CONCLUSION

The results showed no macroscopic differences in the kidneys of male Wistar rats among the K0, K1, P1, P2, and P3 groups. All groups exhibited smooth, flat, and consistently elastic kidney surfaces without cysts, connective tissue alterations, abscesses, or jagged textures.

Microscopically, there were significant differences in cloudy swelling of the tubules when comparing K0 with K1, P1, P2, and P3, and between K1 with P1, P2, and P3. However, there were no significant differences in inflammatory markers between K1 and the treatment groups (P1, P2, and P3).

Lemon peel extract (*Citrus limon*) had no effect on the macroscopic appearance of the kidneys in hyperuricemic male Wistar rats but significantly reduced cytoplasmic degeneration (cloudy swelling) in renal tubular cells. The most effective dose was 70 mg/kgBW in rats, equivalent to 11.2 mg/kgBW in humans. However, the extract did not significantly affect the inflammatory response in the kidneys. Therefore, further phytochemical analysis is

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recommended to determine the flavonoid content in lemon peel and explore its potential anti-inflammatory effects.

Although the nephroprotective effect is presumed to be due to flavonoids, vitamin C, and citrate, specific quantification of these constituents via phytochemical test remains to be conducted.

ETHICAL APPROVAL

The researcher's ethical clearance was obtained from Komisi Etik Penelitian Kesehatan (KEPK) Fakultas Kedokteran Universitas Diponegoro Semarang which has the Ethical Clearance number No. 108/EC-H/KEPK/FK UNDIP/IX/2023.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

No specific funding was provided for this article.

AUTHOR CONTRIBUTIONS

Indira Pramesti Poerwanagara: investigation, writing—original draft preparation. Mahayu Dewi Ariani: supervision and review. Endang Mahati: review. Yora Nindita: supervision, writing—review and editing

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