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RESEARCH **Open Access**

Papaya Juice Treatment Increases Body Weight and Decreases Urea Levels in Lead acetate-exposed Wistar Rats

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Abstract
Lead (Pb) exposure poses significant health risks due to its non-degradable nature and profound toxicity, causes oxidative stress and organ damage, particularly targeting the kidneys. Urea nitrogen levels rise as a result of decreased renal filtration rate and urea excretion. This study investigates the potential of papaya juice, rich in flavonoids, vitamins C, E, and beta-carotene, as a protective agent against Pb-induced nephrotoxicity. A Completely Randomized Design experiment was conducted, involving six treatment groups of Wistar rats. Papaya juice was administered at doses of 3.6, 7.2, and 14.4 g/200g body weight (BW) to Groups P1, P2, and P3, respectively, prior to exposure to 50 mg/kg BW of lead acetate. Group PC received vitamin E (400 IU/kg BW) and lead acetate, while Group NC was exposed to lead acetate alone. Group NT served as the control. Following a 28-day treatment period, the P3 group exhibited the most significant improvements, with a notable increase in body weight (22.50 grams) and a substantial decrease in urea nitrogen levels (18.24 mg/dl). These findings underscore the efficacy of papaya juice treatment in mitigating Pb-induced nephrotoxicity, suggesting a potential therapeutic regimen for alleviating lead toxicity in exposed populations. Eventually, the optimal dosing for papaya juice treatment, either at 14.4 g per 200 g body weight for rats or consumption of one medium-sized papaya for humans, yields compelling benefits. This regimen demonstrates significant efficacy in increasing body weight and lowering serum urea levels in rats subjected to Pb acetate exposure.

Keywords: Papaya Juice, Body Weight, Urea Levels, Lead Acetate.

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1. INTRODUCTION

Lead (Pb) is classified into two types: organic lead and inorganic lead. Organic lead pollution is caused by the use of leaded gasoline in the form of Tetra Ethyl Lead (TEL), which easily evaporates and dissolves in fats (Kamilatussaniah, Yuniastuti, & Iswari, 2015). The air pollution resulting from TEL emissions from motor vehicles in Indonesia will persist as long as the government permits the use of this substance in vehicles. will persist as long as the government permits the use of this substance in vehicles. This situation is deeply concerning because transportation emissions constitute the primary source of pollution in Indonesian urban areas, accounting for 85% of pollution, thereby rendering humans susceptible to exposure to hazardous substances. Inorganic lead pollution in the environment stems from industrial processes such as battery recycling, ceramic tableware manufacturing, paint production, and water pipe construction. Humans are exposed to organic and inorganic Pb particles in the environment through inhalation, oral ingestion, or skin adsorption. Lead that enters the body enters the bloodstream. Lead entering the body circulates in the bloodstream with a half-life of approximately 30 days before being distributed to various organs or soft tissues, including the liver, kidneys, brain, heart, lungs, spleen, and hard tissues such as teeth, bones, and hair, primarily as lead phosphate (Collin et al., 2022; Wulandari, 2020; Gusnita, 2012).

Lead is a non-degradable and highly toxic heavy metal (Rizal, 2022; Kumar et al., 2020). Accumulation of Pb2+ ions in biological systems causes oxidative damage and health problems such as central nervous system dysfunction, reproductive dysfunction, hematopoietic disorders, liver and kidney damage, cardiovascular issues, immune system dysfunction, and carcinogenic effects (Wulandari, 2020). A survey conducted by the Environmental Control Agency of West Java Province in May 2008 found that a significant portion of elementary school students in Bandung City in 2008 had blood lead levels exceeding the threshold of 10 ug/dl, leading to anemia (Wulandari, 2020). The presence of lead in the blood at levels of 30–60 g/dL in the renal system can result in severe kidney failure (Collin et al., 2022). The accumulation of Pb2+ ions in the body due to lead poisoning increases the levels of Reactive Oxygen Species (ROS) compounds such as hydroperoxides, hydrogen peroxide, and singlet oxygen. This occurs due to a decrease in antioxidant defenses in the body, leading to the induction of oxidative stress, cell damage, and impaired organ function, including the kidneys, accompanied by an elevation in Blood Urea Nitrogen (BUN) levels (Yuniarti et al., 2021; Kumar et al., 2020; Wani, Ara, & Usmani, 2015). Lead poisoning affects kidney disorder in 75% of Semarang car painting workers. This is due to the presence of Pb chromate molybdate and Pb sulfate compounds in car paint. These compounds can enter the body through the respiratory, digestive, and skin systems (Muliyadi, 2015).

Chronic lead poisoning causes fatigue, anxiety, decreased appetite, decreased concentration, and hypertension (Wulandari, 2020; Rosyidah, 2010). Research results indicate that lead toxicity can lead to weight loss in rats and hinder their growth. This is attributed to decreased appetite and disrupted nutrient absorption due to metabolic disturbances in the body (Ramah, Nabila, & El-shewey, 2015). Curative efforts for lead toxicity can rapidly reduce blood lead levels and excrete lead through urine, but may cause side effects such as Calcium Disodium Ethylenediamine Tetraacetic Acid (CaNa2EDTA) inducing encephalopathy, and the combination of Dimercaprol and CaNa2EDTA causing increased liver enzymes and nausea (Flora & Pachauri, 2010). Preventive measures are prioritized over curative actions.

Papaya contains phenolic compounds such as flavonoids that prevent lipid peroxidation. Besides its sweet taste, papaya fruit contains vitamins such as Ascorbic Acid (vitamin C), Tocopherol (vitamin E), and beta-carotene, which act as antioxidants by scavenging radicals caused by Pb exposure (Sari, & Santika, 2023; Suhartono, Nijka, Anhar, Sari, & Marisa, 2015).

This study aims to determine whether papaya juice treatment increases weight and decreases urea levels in Wistar rats exposed to lead acetate.

2. RESEARCH METHOD

This study employed a completely randomized design experimental approach (CRD). According to Federer's (2008) formula, the number of male white rats (*Rattus norvegicus*) Wistar strain used in this study was 24. There were six treatments, which were repeated four times:

Groups	Treatment	dose	Exposure
P1	papaya juice	3.6 g/200 g BW/day	Pb acetate at 50 mg/kg BW/day.
P2		7.2 g/200 g BW/day	
P3		14.4 g/200 g BW/day	
Positive Control (PC)	Vit. E (α-tocopherol)	400 IU/kg BW/day	
Negative control (NC)	-	-	
Non Treatment (NT)	-	-	-

The rats were administered the treatment for 28 days before blood samples were obtained on the 29th day. The detailed procedures are provided in the research stage section.

The research was conducted at the Laboratory of the Center for Food and Nutrition Studies at Gajah Mada University (UGM) Yogyakarta, which had applied for permission from the Health Ethics Committee at Surakarta State University and received a letter No: 1.117/XII/HREC/2017.

The test animals were male white rats (*Rattus norvegicus*) Wistar aged 13-14 weeks, weighing 180-250 g, and were healthy (actively moving, willing to eat, not physically disabled, who were fed standard pellet feed and aquadest drink given ad libitum). Rats were acclimatized for 7 days before and 28 days after treatment. The rats were kept in a laboratory environment with a temperature of (25^{o}C) and 12 hours of light (light-dark) alternated.

The following materials were used in the study: California variety ripe papaya acquired straight from papaya producers in Rajek Wetan Tirtoadi Mlati Sleman, Lead Acetate Pb(CH3.CO2)2Pb.3H2O Merck Darmstadt, Germany, Vitamin E (Alpha-tocopherol) or NaturE® 100 IU, and Ureum diasys®. The tools used include a UV-visible spectrophotometer, cuvette, centrifuge, set of animal cages, micropipette, analytical balance, vortex mixer, centrifuge, blender, volume pipette, measuring pipette, oral syringe, microtube Eppendorf, glass beaker, test tube rack, incubator, and aluminum foil. The research stage includes:

1) Determination of Papaya Varieties The

The papaya plants were identified at Gadjah Mada University's Faculty of Biology, Plant Systematics Laboratory. According to the test results based on Certificate Number: 01226/S. Tb/I/2018, the papaya is *Carica papaya L.* var. Calina IPB - 9, also known as the California papaya.

2) Papaya Juice Making Papaya

Ripe fruit, or ready to harvest, aged ± 3 months, orange flesh, sweet and distinctive aroma of papaya. The ripe papaya is then peeled and blended without the addition of water to make juice. Every day, new papaya juice is prepared and stored in a clean container. Using a gastric probe, white rats (*Rattus norvegicus*) strains Wistar were given papaya juice orally twice a day.

3) Serum Making

Blood was drawn from the orbital vein area of the rat's eye. 3 mL of blood was drawn, collected in an Eppendorf tube without anticoagulant, and allowed to settle at room temperature for 30 minutes. After that, the sample was centrifuged for 20 minutes at 3000 rpm. The clear part (serum) is separated and used to test serum urea levels.

4) Serum Ureum Level Measurement

The serum urea level was measured spectrophotometrically using the enzymatic method. The enzyme urease hydrolyzes urea in the presence of water to produce ammonia and carbon dioxide, which is the basic principle of the experiment. Ammonium ions react with hypochlorite and salicylate to produce a green color. The color intensity is proportional to the concentration of urea in the sample. Methods, reagents, and quality control procedure utilizing Ureum diasys®. The working procedures are as follows:

a. The sample solution, which contained 1 ml of reagent 1A and 0.01 ml of serum, was incubated for 5 minutes at 37°C before adding 1 ml of reagent 2 and incubated at 37°C for another 5 minutes.
b. The blank solution containing 1 ml of reagent 1A and 0.01 ml of distilled water was then incubated for 5 minutes at 37℃, then 1 ml of reagent 2 was added, and incubated for 5 minutes at 37℃.
c. The standard solution containing 1 ml of reagent 1A and 0.01 ml of standard solution reagent was incubated for 5 minutes at 37 °C, then 1 ml of reagent 2 was added and incubated for 5 minutes at 37°C.
d. The blank, standard, and sample were measured using a UV-visible spectrophotometer at a wavelength of 578 nm. The standard reagent concentration is 50 mg/dl. Urea levels were calculated using the following formula:

$$\text{Urea (mg/dl)} = \frac{\Delta\ \text{A Sample}}{\Delta\,\text{A Standard}} \text{ X concentration standard (mg/dl)}$$

5) Weight gain of Wistar Rats

The weighing of rats using an analytical balance was carried out four times every week for 28 days. The rats were also weighed before and after the acclimation process. The one-week acclimation period aimed to stabilize the metabolism of the rats with the conditions in the experimental environment. The weight gain was calculated as the weight of the Wistar rats in the fourth week minus their weight after acclimation. The weight gain data of the rats were then averaged per treatment group.

The data analysis used the Mann-Whitney test. This analysis was used to determine the difference between the two groups of each treatment. Changes in Body Weight of Wistar Rats used The One-Way ANOVA parametric test was used because the data were normally distributed, and the assumption of homogeneity was met. The aim was to determine the effect of giving papaya juice on changes in body weight of rats exposed to Pb acetate. Duncan's test was used to determine the most effective treatment or dose for weight gain.

3. RESULTS AND DISCUSSION

a. Urea levels in Wistar rats

Pb acetate toxicity causes dilation in the lumen of the renal tubules, inflammation, degeneration, damage, and necrosis of renal tubular epithelial cells, accompanied by increased tubular cell permeability and reduced membranes. The renal glomerulus causes the filtrate to cross the lower tubular membrane, back into the interstitium, and into the blood circulation, thereby increasing the retention of nitrogenous wastes in the serum, leading to increased urea levels (Sudjarwo et al., 2019). The previous research showed that there was an increase in blood urea levels in male Wistar rats exposed to lead. Kidney organs damaged by oxidative stress also reduce kidney function and GFR, resulting in increased levels of urea in the blood. Urea is the product of protein catabolism produced by the liver and excreted by the kidneys. If the kidneys are damaged, urea cannot be excreted, leading to an increase in blood urea levels (Sudjarwo et al., 2019).

The results in Table 1 indicate that when rats were given different doses of papaya juice (P1, P2, P3), there was a notable impact on their urea levels. This impact was confirmed by the Kruskal-Wallis test, which showed a significant difference among the groups. The p-value obtained from the test was 0.001, which is less than the commonly used significance level of 0.05. This means that the effect of administering papaya juice at these doses on the urea levels of Wistar rats is statistically significant.

Table 1. A Levels of urea in mice given papaya juice and exposed to lead acetate.

Test Statistics	**Urea levels**
Chi-Square	21,820
df	5
Asymp. Sig.	.001

According to the Mann-Whitney test results in Table 2, the group of rats exposed to Pb acetate at a dose of 50 mg/kg BW/day (NC group) had much higher urea levels (52.06 mg/dl) compared to the group not exposed to Pb acetate (NT group), which had urea levels of 12.07 mg/dl. This increase in urea levels is because the kidneys are not excreting urea as effectively due to a decrease in the glomerular filtration rate (GFR), which happens because of oxidative stress Exposure to Pb2+ ions generates a lot of free radicals, which cause lipid peroxidation. This damages the glomerular membrane, leading to problems like renal tubular vacuolization and hydropic degeneration. In simpler terms, exposure to lead reduces the kidneys' ability to filter waste properly, causing urea levels to rise, and this is due to oxidative stress damaging the kidneys.

Exposure to Pb also inhibits the synthesis of the Superoxide dismutase (SOD) enzyme (Sudjarwo et al., 2019). Lead easily infiltrates the body, and interacts with carboxylic groups (-COOH) and amino (NH2) groups, also disrupting metabolic processes. The inhibition of SOD enzyme activity happens because lead ions can displace vital minerals like zinc, copper, and manganese, which are cofactors essential for SOD enzymes (Fukai & Ushio-Fukai, 2011; Sudjarwo et al., 2019).

Superoxide dismutase is an enzyme that helps fight oxidative stress caused by superoxide anion free radicals (O_2*). These free radicals can hinder SOD's activity. This hindrance occurs when there's a significant increase in the amount of superoxide anions due to exposure to Pb^{2+} ions, leading to a decrease in SOD activity in neutralizing O_2.

Papaya fruit contains several minerals such as calcium (Ca^{2+}), magnesium (Mg^{2+}), iron (Fe^{2+}), zinc (Zn^{2+}), potassium (K^+), copper (Cu^{2+}), manganese ($Mn^{2+)}$ and sodium $(Na)^+$) (Wall, 2006); Zhai, Narbad, & Chen, 2015; Kordas, 2017). The presence of these minerals can prevent mineral deficiencies, especially copper and manganese which act as cofactors for SOD enzymes (Purlinda & Simanjutak, 2020). Increased SOD enzyme activity can prevent oxidative stress in rats exposed to lead acetate, thus preventing kidney damage and decreased kidney function.

Moreover, a study has demonstrated that a higher dosage of papaya juice can prevent nephrotoxicity by enhancing SOD enzyme activity in the kidney tissue of rats exposed to lead acetate. The papaya juice treatment, especially in the P3 group, increased the antioxidant activity of superoxide dismutase (SOD) the most in the kidney tissue of Wistar rats. In the P3 group, SOD activity increased by 39.24 units per milliliter (u/ml) of kidney tissue compared to 36.46 u/ml in the P2 group and 31.73 u/ml in the P1 group (Purlinda & Simanjutak, 2020).

Additionally, table 2 has been shown serum urea levels decrease with increasing doses of papaya juice, and the effective dose of papaya juice is 14.4 g/200 g BW/day. The higher doses of papaya juice can reduce serum urea levels in rats exposed to lead acetate (Purlinda & Simanjutak, 2020). Furthermore, the flavonoid content of California papaya fruit is measured at 59 milligrams per 100 grams, surpassing that of Malaysian papaya (38.12 mg/100 g), Hong Kong papaya (36.26 mg/100 g), and breeding lines papaya (15.9 mg/100 g) (Iamjud, et al., 2016; Addai, et al., 2013).

Table 2. Average urea levels in rats.

Treatment with	**Urea levels (mg/dl) (Mean ± SD)**	**Test Man Whitney**	**Asymp. sig (2-tailed) Value**
P1	33.13 ±2.02 a	P1 and P2	0.019
		P1 and P3	0.020
		P1 and PC	0.020
		P1 and NC	0.020
		P1 and KS	0.019
P2	27.48 ± 1:29 b	P2 and P3	0.020
		P2 and PC	0.020
		P2 and NC	0.020
		P2 and NT	0.019
P3	18.24±3:08 c	P3 and PC	0.663
		P3 and NC	0.021
		P3and NT	0.020
PC	19.52 ± 1:28 c	PC and NC	0.021
		PC and NT	0.020
NC	52.06±1.96 d	NC and NT	0.020
NT	12.07±0.43 e	-	-

Phenolic compounds, such as flavonoids (quercetin), in papaya have the potential to prevent lipid peroxidation. They contain hydroxyl and carboxyl groups, which allow them to donate more hydrogen atoms to free radicals than certain vitamins, such as vitamin C (ascorbic acid), vitamin E (α-tocopherol), beta-carotene, and mineral content in papaya fruit. Furthermore, phenolic compounds can maintain the integrity of cell membranes by preventing the entry or diffusion of free radicals into cell membranes (Sasmita, 2017; Michalak, 2006; Suhartono, et al., 2015). The phenolic compounds are able to protect and fight against oxidative stress caused by lead exposure (Ramah et al., 2015)

The rats's urea levels in table 2 also did not show a significant difference in P3 and PC groups, as the p-value was $0.663 > 0.05$. This proves that papaya juice at a dose of 14.4 g/200 g BW/day has the same effectiveness as vitamin E at a dose of 400 IU/kg BW/day in preventing decreased kidney function due to Pb toxicity. Tocopherol (Vitamin E) could prevent cell membrane damage caused by ROS (Ramah et al., 2015). In a previous study, Mehdipour et al. also stated that dried Carica papaya juice was comparable to the antioxidant-tocopherol 10 mg/kg/day in lowering lipid peroxides and increasing total antioxidants in the blood of rats (Jang, et al., 2008).

b. Weight Gain of Wistar Rats

Papaya juice contains antioxidants that can prevent oxidative stress. Papaya juice contains antioxidants, such as vitamins C, E, carotenoids, and flavonoids, that can prevent oxidative stress and free radical chain reactions. This, in turn, prevents lipid peroxidation caused by lead exposure (Jang, et al., 2008; Usmayani et al., 2015; Iamjud et al., 2016; Wall, 2006; Suhartono, et al., 2015).

According to Table 3, the One-Way ANOVA test analysis revealed that the papaya juice treatment had a p-value of 0.000 (which is less than 0.05), indicating a significant difference in the mean weight gain among the rats in the six treatments. In simpler terms, this means that the variance in population weights was not consistent.

Subsequently, Duncan's test was employed to determine the effective dose of papaya juice on the weight gain of Wistar rats exposed to lead acetate. The results of this test indicated that the highest weight gain observed was 22.50 grams in the P3 group, compared to 12.75 grams in the P2 group and 6.50 grams in the P1 group. Based on these findings, it can be inferred that the higher the dose of papaya juice treatment, the more significant the increase in the rats' body weight. Therefore, the papaya juice treatment at a dosage of 14.4 grams per 200 grams of body weight was effective in enhancing the body weight of Wistar rats exposed to lead acetate at a dosage of 50 mg per kilogram of body weight per day.

Table 3. Weight Gain of Rats given Papaya Juice and exposed to Pb Acetate.

Treatment	**Weight Gain (g) (Mean ± SD)**
P1	6.50 ± 2.38 a
P2	12.75 ± 2.63 b
P3	22,50 ± 1.73 c
PC	20.50 ± 1.73 c
NC	-13.00 ± 2.16 d
KS	33.25 ± 2.63 e

Note: columns followed by the same letter are not significantly different at the p<0.05 significance level

In rats exposed to lead acetate at a dosage of 50 mg/kg BW/day, there was no significant difference in the mean weight gain of the rats in P3 and PC group (Sadeque et al., 2012). Similar to the results of this study, previous research has shown that both the aqueous extract of Carica papaya and tocopherol have the same ability to prevent hepatotoxicity, necrosis, and fat degeneration in rats induced by Carbon Tetrachloride (CCl_4). Likewise, metabolic disorders such as impaired absorption of nutrients can be prevented by giving vitamin E and papaya juice to rats exposed to Pb acetate, which prevents weight loss in the mice. The results showed that the weight gain in the Healthy Control treatment was 33.25 g, which tended to be higher than that of P3 at 22.5 g. This may be because the period of giving papaya juice was not long enough to observe the effect of increasing body weight in rats exposed to Pb acetate.

The content of vitamin C in papaya is 82.7 mg/100g, which is higher than in other tropical fruits such as mango (26.9 mg/100g), pineapple (7.2 mg/100g), banana (67.0 mg/100g) and oranges (8.0 mg/100g) (Iamjud et al., 2016). Vitamin C supplementation at a dose of 500 mg/day can increase body weight, prevent anemia, and increase the antioxidant activity of SOD in the blood, thereby preventing liver and kidney function disorders (Sancho, Yahia, & González-aguilar, 2011; Eshginia & Marjani, 2013; Ghanwat, 2016). The mechanism of action of vitamin C is to donate H atoms to free radicals such as superoxide and hydroxyl radicals, and to synergize with -tocopherol. Vitamin C can also regenerate -tocopheroxyl radicals, increase iron absorption to compete with Pb in the intestine and prevent anemia. Additionally, it can increase Pb excretion through urine and feces (El-Neweshy & El-Sayed, 2011).

4. CONCLUSION

Optimal dosing for papaya juice, either at 14.4 g per 200 g body weight or consumption of one medium-sized papaya for humans, yields compelling benefits. This regimen demonstrates significant efficacy in increasing body weight and lowering serum urea levels in rats subjected to Pb acetate exposure. Moreover, papaya juice stands out as a natural antioxidant, effectively counteracting the deleterious effects of free radicals induced by lead acetate. Thus, both the specified dosage and the consumption of whole papaya offer promising avenues for mitigating lead toxicity and promoting overall health

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