Grape Juice on Paracetamol-Induced Hepatotoxicity and Nephrotoxicity

Andrew Johan [1*], Irene Uli [2], Yosefani Fortunella Yasmine [2]

Abstract

Background: Paracetamol, an analgesic and antipyretic widely available without prescription, can cause acute renal failure and severe liver necrosis when consumed in high doses. Its recommended dosage for adults is less than 4 grams per day, with toxicity reported at 10 grams per day. The nephroprotective and hepatoprotective effects of antioxidants, particularly those found in grapes, have been debated. This study aimed to explore the effects of paracetamol and grape extract on serum creatinine and alanine transaminase levels in Wistar rats. Methods: The study, approved by ethical clearance No. 76/EC/FK UNDIP/VII/2021, was conducted at Semarang Public University Laboratory, Indonesia. Twenty-four male Wistar rats (170-200g) were divided into four groups: a control group, a paracetamol-only group (700 mg/kg body weight), a paracetamol (700 mg/kg) plus 1 ml grape juice group, and a paracetamol (700 mg/kg) plus 3 ml grape juice group. Treatments were administered for 14 days, after which blood samples were collected to measure serum creatinine and alanine transaminase levels using spectrophotometry. Results: Paracetamol administration significantly increased serum alanine transaminase levels from 55.42 IU/L ± 4.74 in the control group to 74.28 IU/L ± 11.69. Co-administration with grape juice further elevated these levels, indicating a potential exacerbation of paracetamol-induced hepatotoxicity. Serum creatinine levels also increased with paracetamol treatment, and further increases were observed with the addition of grape juice. Conclusion: The study concludes that grape juice, known for its high antioxidant content, may aggravate the hepatotoxic and nephrotoxic effects of paracetamol. These findings suggest caution when consuming paracetamol with grape juice to avoid increased toxicity risks.

Keywords: Paracetamol, Grape juice, Alanine transaminase, Serum creatinine, Antioxidants

Significance | Grape juice elevates alanine transaminase and creatinine, exacerbating paracetamol toxicity. Caution advised when consuming paracetamol with grape juice.

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Introduction

Paracetamol is an analgesic and antipyretic drug that is often used widely in various countries. Paracetamol is widely provided in drug stores without a prescription from doctors (Chiew et al., 2018). The side effects could be acute renal failure and severe liver necrosis (Arzuk et al., 2018). The recommended dosage of paracetamol for adults should be lower than 4 grams/day. The toxicity due to paracetamol is reported at 10 grams/day in adults (Martinez-De la Torre et al., 2020). Renal failure causes dysfunction of the kidneys to remove waste from the body's metabolism. Assessment of glomerular function can be done using an examination of serum creatinine levels, which is an endogenous marker (Kashani et al., 2020). Creatinine is a waste product of creatine phosphate in muscles. Creatinine is an ideal test because constant creatinine is produced as a result of body metabolism. It is not reabsorbed and is secreted by the proximal tubule. Creatinine is cleared from the

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blood circulation by the kidneys. Decreased filtration function in the kidneys is characterized by an increase in serum creatinine levels (Gama et al., 2023). Unlike creatinine, alanine transaminase is a cytosolic enzyme found in the liver. The half-life of alanine transaminase is approximately 47 ± 10 hours. The levels of serum alanine transaminase become higher in liver disease. Hepatocellular injury triggers the release of these enzymes into the circulation (Yu et al., 2019).

Previous studies reported that antioxidants might be protective against renal and liver injury (Xiang et al., 2022; Touzani et al., 2022). However, other studies have shown the opposite effects of antioxidants. Resveratrol contained in grapes induced a prooxidant effect, causing cell damage (Posadino et al., 2015). Polyphenolic antioxidants potentiate the efficacy of chemotherapeutic agents by exacerbating oxidative stress in cancer cells (Chikara et al., 2018).

In this study, it was proposed to explore the effect of grapes, which have a high natural antioxidant content. Grapes are a source of polyphenols containing flavonoids, anthocyanins, tannins, and resveratrol. Grape juice has the highest antioxidants compared to orange, acai, and apple juices (Denkova-Kostova et al., 2020). The nephroprotective effect of polyphenols is mainly found in grapes and wine. This is because the grape content causes an increase in plasma antioxidant capacity and a decrease in cytochrome P-450. Flavonoids have antiapoptotic and antifibrotic properties. Flavonoids from grapes also show nephroprotective effects against acute kidney injury (Ali et al., 2019). Apple extract was reported to show benefits in animals exposed to cadmium. Grape juice decreased tubular necrosis in rats (Handan et al., 2020), and ameliorated bone formation (Ruiz et al., 2018). However, it was also reported that grapes aggravated drug bioavailability, such as fexofenadine and cyclosporine (Chen et al., 2018). This study aimed to understand the effects of paracetamol and grape extract on serum creatinine and alanine transaminase compared to previous reports.

2. Materials and Methods

The present study was approved by ethical clearance number No. 76/EC/FK UNDIP/VII/2021. The research was carried at Laboratory of Semarang Public University in Indonesia for the treatment of Wistar rats.

2.1 Study Design

The present research was design as Post test Only Control Group Design (Fig.1)

2.2 Animal treatment

Wistar rats at 170 -200 gram body weight were obtained from public University of Semarang, Central Java, Indonesia. The rats were kept at 25 ± 5 °C in a well-ventilated animal plastic chambers under a 12:12 h light/dark cycle, with free access to animal chow and water. Twenty four male rats were randomly divided into 4 groups consisting of six rats in each group. The first group was given standard food and aquadest, the second group was given paracetamol 700 mg/kgbw, the third group was given 1 ml grape juice and paracetamol 700 mg/kgbw, and the forth group was given 3 ml grape juice and paracetamol 700 mg/kgbw. The treatment was given for 14 days, and on day 15th, the rats' blood were harvested for measurement of serum creatinine and alanine transaminase levels. Serum creatinine levels were measured base on red cromophore in serum mixed with picric acid. It is shown by a spectrophotometer at 510 nm. Alanin transferase determination were based on purple colour of formazan produced by the reduction of the tetrazolium salt with NADH. The absorbances of formazan in spectrphotometer were read at 500 nm.

3. Results

3.1 Effects of Paracetamol on levels of Alanine Transferase

Paracetamol toxicity was reported in previous several studies. Paracetamol is an antipyretic analgesic drug which is an inhibitor of COX-1 and COX-2 in peripheral tissues . Intake of a high dosage of paracetamol can cause hepatotoxicity. The levels of serum alanine transaminase are an indicator of liver damage . The present study revealed that paracetamol increased the serum alanine transaminase from 55.42 IU/L ± 4.74 in the control group to 74.28 IU/L ± 11.69 in rats treated with paracetamol 700 mg/KgBW for 14 days (Table 1).

Previous studies had reported the side effects of paracetamol leading to liver injury. Paracetamol ruins the functions of mitochondria, causing higher levels of oxidative stress . Paracetamol gives rise to the prooxidant product named N-acetyl-p-benzoquinone imine (NAPQI) that should be neutralized by the enzyme glutathione peroxidase . Aminophenols in paracetamol elevate the levels of reactive oxygen species (ROS) .

3.2 Effects of Paracetamol and Grape Juice on Levels of Alanine Transaminase

In this study, the rats were administered paracetamol 700 mg/KgBW + 1 ml grape juice (P1 group) and 700 mg/KgBW + 3 ml grape juice (P2 group). The levels of serum alanine transaminase were elevated in these groups (Table 1). People who take drugs with fruit juice may worsen the adverse effects. Grape juice increases the side effects by increasing the area under the curve (AUC) . It has been declared that grape juice inhibits the activity of cytochrome P450 enzymes in the intestinal tract . Red wine extended plasma peak levels of felodipine . This study cautions against administering drugs with fruit juice.

3.3 Effects of Paracetamol and Grape Juice on Levels of Serum Creatinine

Previous studies reported that juice of fruit increased levels of drugs, thereby elevating adverse effects. It could lower the

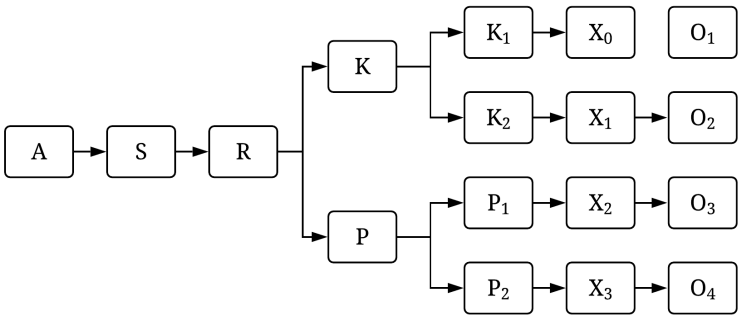

Figure 1. The design of the present study. A: Rats get adaptation to new enviroment for 7 days, S: Sample of healthy rats after the adaptation, R: Randomisation to four groups, K1: Control group, the rats were not given paracetamol nor apple, K2:Rats were given 700 mg/kgBW/day paracetamol for 14 days, P1: Rats were given 700 mg/kgBW/day paracetamol and 1ml/day grape juice for 14 days, P2: Rats were given 700 mg/kgBW/day paracetamol and 3 ml/day grape juice for 14 days, O1, O2, O3, O4:Levels of serum creatinine and alanine transferase

Table 1. The Effects of Paracetamol and Grape Juice to Rats on Serum Alanine transferase Levels

Groups	**Alanine transferase+SE**
Control(K1)	52,42± 4,74
K2	74, 28 ± 11, 69
P1	254,90 ± 147,9*
P2	261, 20 ± 98, 38

*K1: Control group, the rats were not given paracetamol nor apple, K2: Rats were given 700 mg/ kgBW/day paracetamol for 14 days, P1: Rats were given 700 mg/kgBW/day paracetamol and 1ml/day grape juice, P2: Rats were given 700 mg/kgBW/day paracetamol and 3ml/day grape juice, *P < 0.05 The levels of alanine transferase were increased in rats treated with paracetamol and grape juice.*

Table 2. The levels of serum creatinine in the control and treated rats

Groups	**Creatinin mg/dl + SE**
K1	1.44 ± 0.18
K2	1.38 ± 0.17
P1	1.56 ± 0.17
P2	*2.04 ± 0.26

K1: Rats were not given paracetamol nor apple, K2: Rats were given 700 mg/ kgBW/day paracetamol for 14 days, P1: Rats were given 700 mg/kgBW/day paracetamol +1ml/day grape juice, P2: Rats were given 700 mg/kgBW/day paracetamol + 3ml/day grape juice

concentration of a drug in human blood; however, it was also declared that fruit juice could increase the toxicity of medication .

N-acetyl-p-benzoquinone imine (NAPQI) is known as a metabolite of paracetamol that exerts reactive oxygen species. Paracetamol decreases the enzyme superoxide dismutase and increases levels of serum creatinine in albino rats . Previous studies revealed that prolonged administration of fruit juice increased the absorption of drugs . In the present study, grape juice elevated the serum levels of creatinine in rats treated with paracetamol. It is a warning not to take paracetamol with grape juice.

4. Discussion

The substantial increase in serum ALT and creatinine levels in rats treated with both paracetamol and grape juice suggests a potentiating effect of grape juice on paracetamol-induced hepatotoxicity and nephrotoxicity. Paracetamol is metabolized into a toxic compound, N-acetyl-p-benzoquinone imine (NAPQI), which is usually neutralized by glutathione. However, excessive intake overwhelms this detoxification pathway, leading to oxidative stress and cellular damage in the liver and kidneys.

The antioxidant properties of grape juice, primarily due to its polyphenolic compounds such as resveratrol, flavonoids, and tannins, were expected to provide a protective effect against paracetamol toxicity. Contrary to this expectation, the results showed an exacerbation of toxicity. This could be attributed to the prooxidant effect of polyphenols under certain conditions, which might exacerbate oxidative stress rather than alleviate it. Additionally, grape juice may interfere with drug metabolism by inhibiting the cytochrome P450 enzymes, thus increasing the bioavailability and toxicity of paracetamol.

5. Conclusion

The study reveals that co-administration of grape juice and paracetamol significantly exacerbates hepatotoxicity and nephrotoxicity in rats, as evidenced by elevated serum alanine transaminase (ALT) and creatinine levels. While grape juice contains polyphenolic antioxidants like resveratrol and flavonoids, which were hypothesized to mitigate oxidative damage, the findings indicate a contrary outcome. The prooxidant activity of these compounds under specific conditions appears to intensify oxidative stress, thus worsening the toxic effects of paracetamol. Additionally, grape juice may interfere with drug metabolism by inhibiting cytochrome P450 enzymes, leading to increased bioavailability and toxicity of paracetamol. This study underscores the potential risks of consuming fruit juices, particularly grape juice, alongside medications like paracetamol, highlighting the need for caution in such practices.

Author contributions

A.J. conceptualized the study, designed the methodology, and prepared the original draft. I.U. handled data curation, performed formal analysis, and contributed to the review and editing of the manuscript. Y.F.Y. was responsible for investigation, acquiring resources, and creating visualizations. All authors have read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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