ORIGINAL RESEARCH REPORT

Antibacterial Effect of 96% Ethanol Extract of Papaya Seeds (*Carica papaya L.*) on the Growth of *Staphylococcus aureus* and *Klebsiella pneumoniae* causing Pneumonia

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ABSTRACT

Background: Pneumonia is an infectious disease with the highest childhood mortality rate worldwide, commonly caused by *Staphylococcus aureus* and *Klebsiella pneumoniae*, which have developed resistance to antibacterial agents. Papaya seeds have traditionally been used in Indonesian medicine due to their bioactive compounds, which are expected to exhibit antibacterial properties. **Objective:** To analyze the antibacterial effect of 96% ethanol extract of papaya seeds against *S. aureus* and *K. pneumoniae* in vitro. **Material and Method:** This study employed a true experimental design with a posttest-only control group. Ethanol extracts of papaya seeds at concentrations of 10%, 30%, and 50% were tested using the well diffusion method. Erythromycin and chloramphenicol were used as positive controls, and 70% alcohol served as the negative control. Inhibition zone diameters were analyzed using SPSS version 29 with the non-parametric Kruskal-Wallis and Mann-Whitney tests. **Results:** The ethanol extract of papaya seeds inhibited the growth of *S. aureus* starting at a concentration of 10%, with the largest inhibition zone observed at 50%. Against *K. pneumoniae*, the extract demonstrated the lowest effective inhibitory concentration at 30%, which also produced the largest inhibition zone. However, the extract was less effective than the antibiotics used. **Conclusion:** The ethanol extract of papaya seeds exhibits antibacterial activity against both *S. aureus* and *K. pneumoniae*, with a more pronounced effect on *S. aureus*.

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Highlights

1. Papaya seeds are a natural and traditionally used remedy in Indonesia, known for their safety and medicinal properties.
2. The 96% ethanol extract of papaya seeds exhibits antibacterial activity against *Staphylococcus aureus and Klebsiella pneumoniae*.

BACKGROUND

Pneumonia is an inflammatory condition of the lung parenchyma, including the respiratory bronchioles and alveoli, caused by infection. This condition leads to lung tissue consolidation and impaired gas diffusion (Roth, et al., 2018). Bacterial infection is a common cause of pneumonia (Sulung, et al., 2021). Pneumonia can be classified based on the site of acquisition into Community-Acquired Pneumonia (CAP) and Hospital-Acquired Pneumonia (HAP) (Jain, et al., 2025). *Staphylococcus aureus* is a known causative agent of CAP (Self, et al., 2016), while *Klebsiella pneumoniae* is a major cause of nosocomial infections, including HAP (Roes, et al., 2016). According to WHO data, pneumonia is the leading infectious cause of death in children under five, accounting for 15% of all deaths in this age group and causing approximately 740,180 deaths globally in 2019. In Indonesia, around 19,000 deaths from pneumonia were reported during the same year (Faisal, et al., 2024).

Staphylococcus aureus is a Gram-positive bacterium belonging to the Staphylococcaceae family. It appears as irregularly clustered cocci, is coagulase- and catalase-positive, and stains violet on Gram staining. *S. aureus* is part of the normal human flora but can cause opportunistic infections when it invades sterile areas such as body tissues or the bloodstream (Khairunnisa, et al., 2023). *Klebsiella pneumoniae* is a Gram-negative, rod-shaped (bacillus) bacterium belonging to the Enterobacteriaceae family. It ferments lactose, reduces nitrate, and is indole-negative. *K. pneumoniae* is known for causing opportunistic infections, including HAP and potentially septicemia (Tarina & Kusuma, 2017).

The primary treatment for bacterial pneumonia is antimicrobial therapy (Feldman & Richards, 2018). Appropriate antimicrobial use is strongly associated with reduced mortality (Pereira, et al., 2018). However, inappropriate antibiotic use remains common in many countries, including Indonesia (Zuhriyah, et al., 2018). Antibiotic resistance has become a critical global issue, with increasing reports of resistance among pneumonia-causing bacteria (Ramaditya, et al., 2018; Wang, et al., 2020). In response, research into alternative treatments, including natural remedies such as papaya seeds, is increasingly important.

The papaya plant (*Carica papaya L.*) is widely cultivated and consumed in Indonesia. It has demonstrated antifungal and antibacterial properties, with various parts of the plant, including the seeds, contributing to its medicinal value (Ilvani, et al., 2019; Khasanah, et al., 2020). Papaya seeds contain secondary metabolites such as flavonoids, alkaloids, saponins, tannins, terpenoids, and phenols, which have shown antibacterial activity against both Gram-positive and Gram-negative bacteria (Setyani, et al., 2020; Syarifah, et al., 2015).

Therefore, it is essential to evaluate the antibacterial activity of papaya seed (*Carica papaya L.*) extract against *S. aureus* and *K. pneumoniae.* This study aimed to contribute to the understanding of alternative antimicrobial agents in the prevention and treatment of infectious diseases, particularly pneumonia. In this context, we assessed and compared the antibacterial effects of papaya seed extract against *S. aureus* and *K. pneumoniae* using the well diffusion method.

OBJECTIVE

The study aimed to analyze the antibacterial effect of 96% ethanol extract of papaya seeds at varying concentrations on the in vitro growth of *Staphylococcus aureus* and *Klebsiella pneumoniae* using the well diffusion method.

MATERIAL AND METHOD

This study was a true experimental design employing a post-test only control group, conducted in vitro using the agar well diffusion assay. The samples were divided into two main groups: a control group and an intervention group. The control group included a negative control (70% ethanol), an erythromycin control for *Staphylococcus aureus*, and a chloramphenicol control for *Klebsiella pneumoniae*. The intervention group was subdivided into three subgroups, based on the concentration of papaya seed ethanol extract administered to *S. aureus* and *K. pneumoniae* isolates—10%, 30%, and 50%.

The research was conducted from December 2023 to May 2024 at the Medical Microbiology Laboratory, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. The preparation of the ethanol extract of papaya seeds was performed using the maceration method at the Testing Service Unit (*Unit Layanan Pengujian/ULP*) Laboratory, Faculty of Pharmacy, Universitas Airlangga.

Laboratory equipment used included an incubator, oven, autoclave, Petri dishes, micropipettes, test tubes, tweezers, stirring rods, aluminum foil, Erlenmeyer flasks, wire gauze, analytical scales, various glass containers, alcohol burners, sterile cotton swabs, sterile toothpicks, calipers, and lamps. The materials used comprised Mueller-Hinton Agar (MHA; Oxoid, UK), 96% and 70% ethanol (Onemed, Indonesia), antibiotics (Erythromycin and Chloramphenicol; Oxoid, UK), and McFarland standard solution.

Preparation of papaya seed ethanol extract

Young, fresh, and undamaged Thailand cultivar papayas were selected from Lamongan, East Java, Indonesia. The seeds were removed from the fruit, washed, and air-dried. The dried seeds were sorted and ground into a fine powder using a blender, then stored in a sealed container. The ethanol extract was prepared using the maceration method, where the powdered seeds were soaked in 96% ethanol for 48 hours. The resulting filtrate was concentrated using a rotary evaporator to obtain a thick extract (Torar, 2017). The concentrated extract was then diluted with a solvent to achieve concentrations of 10%, 30%, and 50%.

Antibacterial activity assay

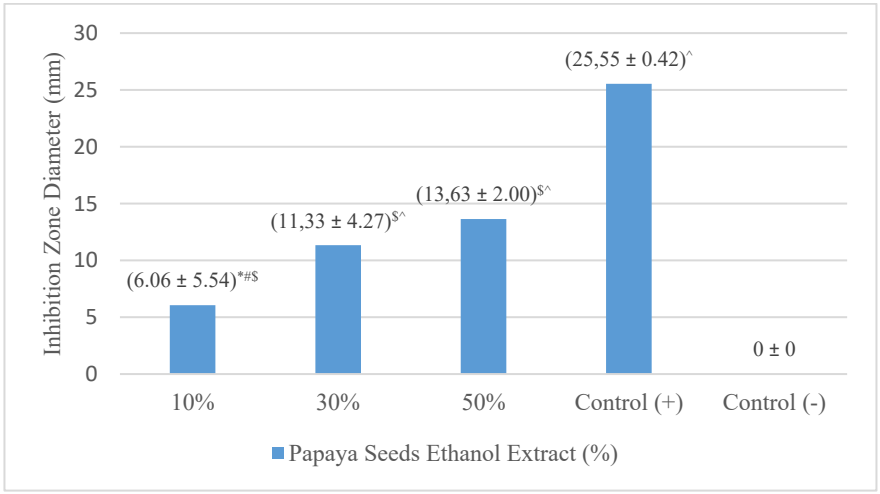
The antibacterial activity was assessed using the well diffusion method. Bacterial suspensions of *S. aureus* and *K. pneumoniae*, adjusted to the turbidity of the McFarland 0.5 standard, were evenly spread onto Mueller-Hinton (Oxoid, United Kingdom) agar plates. Wells were created in the agar and filled with the papaya seed extract at concentrations of 10%, 30%, and 50%. The negative control was 70% ethanol, while the positive controls were erythromycin (for *S. aureus*) and chloramphenicol (for *K. pneumoniae*). Each treatment was performed in five replicates. Plates were incubated at 37°C for 24 hours. After incubation, the diameter of the inhibition zones (clear areas around the wells) was measured in millimeters using a digital caliper.

Statistical analysis

Data analysis was conducted using IBM SPSS for Windows, version 29 (IBM Corp., Armonk, N.Y., USA). The dataset was first subjected to normality and homogeneity of variance tests, with a significance level set at p=0.05. To assess the effect of varying extract concentrations on bacterial growth, the Kruskal-Wallis test was used. When significant differences were found, the Mann-Whitney U test was performed as a post-hoc analysis to determine pairwise differences between extract concentrations.

RESULT

Figure 1 presents the results of the inhibitory test of papaya seed ethanol extract at varying concentrations on the growth of *Staphylococcus aureus*.



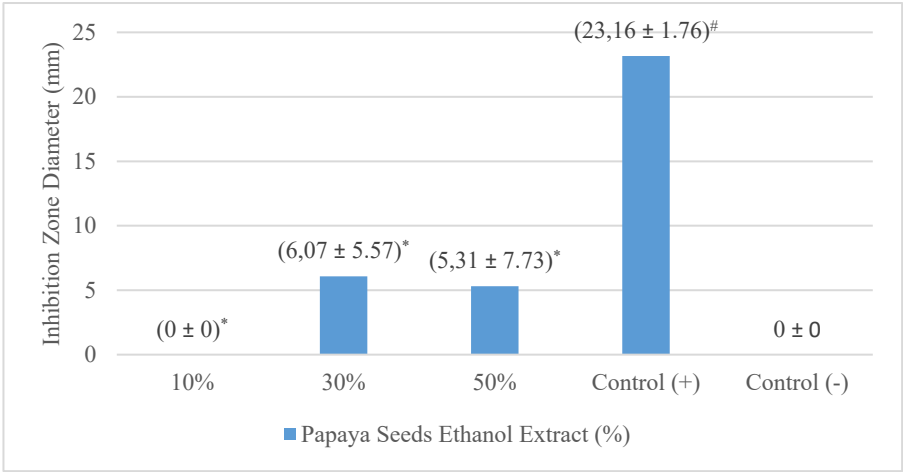
Legends: * = significant with 30%; # = significant with 50%; $ = significant with control +; and ^ =significant with control -).

Figure 1. Diameter of inhibition zone in various concentration of papaya seeds (*Carica papaya L.*) ethanol extract against *Staphylococcus aureus* bacteria.

According to Figure 1, the results demonstrate that inhibition zones formed after the administration of papaya seed ethanol extract in concentrations of 10%, 30%, and 50%. This indicated that the extract is capable of inhibiting *Staphylococcus aureus* growth at concentrations as low as 10%. The 50% concentration produced the largest inhibition zone, with a diameter of 13.63 mm. However, compared to the positive control (erythromycin), the extract exhibited a weaker antibacterial effect. The data indicated a dose-dependent relationship, where higher concentrations of papaya seed ethanol extract corresponded to larger inhibition zone diameters.

Furthermore, the Kruskal-Wallis nonparametric test yielded a statistically significant result ($p<0.001$), suggesting that varying extract concentrations resulted in significantly different inhibition effects on *S. aureus.* Subsequent analysis using the Mann-Whitney test confirmed significant differences between most concentration pairs, except between 30% and 50%, and between 10% and the negative control (70% ethanol). This suggests that increasing the concentration from 30% to 50% did not produce a statistically significant increase in inhibitory activity.

Figure 2 below presents the results of the inhibitory effect of papaya seed ethanol extract at different concentrations on the growth of *Klebsiella pneumoniae.*



Legends: * = significant with control +; # = significant with control -.

Figure 2. Results of inhibition zone diameters of concentration variants of papaya seeds (*Carica papaya L.*) ethanol extract against *Klebsiella pneumoniae* bacteria.

According to Figure 2, inhibition zones were observed only at 30% and 50% concentrations of the papaya seed ethanol extract, indicating that *Klebsiella pneumoniae* exhibited resistance to lower concentrations, as no inhibition was observed at 10%. The largest inhibition zone recorded was 6.07 mm at the 30% concentration. Compared to the positive control (chloramphenicol), the extract showed significantly weaker antibacterial activity.

The Kruskal-Wallis nonparametric test revealed a significant difference in inhibition zone diameters among treatment groups ($p<0.001$), indicating that varying concentrations of the papaya seed ethanol extract had significantly different effects on *K. pneumoniae* growth. However, Mann-Whitney post-hoc analysis showed that there were no statistically significant differences in inhibition between the extract concentrations themselves (10%, 30%, and 50%). Significant differences were only observed between each extract concentration and the positive control (chloramphenicol), as well as between chloramphenicol and the negative control (70% ethanol).

DISCUSSION

The findings of this study demonstrated that the ethanol extract of papaya seeds (*Carica papaya L.*) at varying concentrations can inhibit the growth of *Staphylococcus aureus* and *Klebsiella pneumoniae*. The extract exhibited inhibitory activity against *S. aureus* beginning at a concentration of 10%, while no inhibition zones were observed against *K. pneumoniae* at concentrations below 30%. These results indicated that the extract is more effective against *S. aureus* than *K. pneumoniae*.

Differences in inhibition zone diameters across extract concentrations suggest variability in antibacterial efficacy, likely influenced by several factors, including the size of the bacterial inoculum and the concentration of active substances in the extract. A higher bacterial load can reduce the size of the inhibition zone (Yulianti & Manguntungi, 2018), and uneven distribution of bacterial colonies across the medium may affect zone formation. Furthermore, higher extract concentrations typically allow for faster diffusion and greater antibacterial activity, resulting in larger inhibition zones. The relatively reduced efficacy against *K. pneumoniae* may also be due to the bacteria's intrinsic resistance to certain bioactive compounds in the extract (Ambakesari, et al., 2022).

Papaya seed ethanol extract contains various secondary metabolites, including flavonoids, alkaloids, saponins, tannins, terpenoids, and phenols (Avitka, et al., 2023; Fikriana, et al., 2021; Setyani, et al., 2020), which contribute to its antibacterial properties. Flavonoids inhibit nucleic acid synthesis, disrupt membrane integrity, and interfere with metabolic processes. Alkaloids damage bacterial DNA, leading to nuclear breakdown. Saponins disrupt membrane permeability by lowering surface tension, causing cell lysis. Tannins inhibit key enzymes such as reverse transcriptase and DNA topoisomerase, interfere with protein transport, and destabilize cell wall integrity. Phenols denature proteins and increase membrane permeability, resulting in cell lysis (Pakadang & Salim, 2020).

This study also supported the notion that papaya seed extract is more effective against Gram-positive bacteria (*S. aureus*) than Gram-negative bacteria (*K. pneumoniae*), consistent with findings from Torar, (2017). This discrepancy is attributed to differences in cell wall structure. Gram-positive bacteria possess a thick, polar peptidoglycan layer, which facilitates the absorption of bioactive compounds. In contrast, Gram-negative bacteria have a lipid-rich outer membrane containing lipopolysaccharides, which hinder the penetration of large polar molecules and confer greater resistance ((Mulyono, 2014; Rahayu, et al., 2019; Torar, 2017).

Although the antibacterial potential of papaya seed extract is evident, its activity remains significantly lower than that of the positive controls. Therefore, optimization strategies such as enhancing extraction techniques, selecting appropriate solvents, and isolating dominant active compounds are recommended to maximize the efficacy of *Carica papaya L.* seed ethanol extract against both *S. aureus* and *K. pneumoniae*, particularly in the context of pneumonia treatment.

Strength and limitations

This study provides valuable data for future research, particularly concerning the antibacterial effects of *Carica papaya L.* seed ethanol extract against *Staphylococcus aureus* and *Klebsiella pneumoniae*. However, the study has several limitations. It did not analyze the specific bioactive compounds or their concentrations within the extract. Additionally, the Minimum Bactericidal Concentration (MBC) could not be determined because it is challenging to measure the exact amount of antimicrobial substances

diffusing into the agar medium. Moreover, the study could not establish whether the extract's antimicrobial activity was bacteriostatic or bactericidal, since inhibition of bacterial growth does not necessarily indicate complete bacterial death.

CONCLUSION

This study suggests that ethanol extract from papaya seeds (*Carica papaya L.*) can inhibit the growth of *Staphylococcus aureus* at a minimum inhibitory concentration (MIC) of 10%, and *Klebsiella pneumoniae* at an MIC of 30%. The extract demonstrated greater antibacterial activity against *S. aureus* compared to *K. pneumoniae*, as indicated by the larger inhibition zone diameters. To obtain more precise determinations of MIC and minimum bactericidal concentration (MBC), further research employing alternative methods such as broth and agar dilution assays is recommended.

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Conflict of Interest
No conflict of interest exists for any of the authors.

Ethic Consideration
The study protocol has been declared ethically feasible by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga (No. 91/EC/KEPK/FKUA/2024, on 03-09-2024).

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There is no funding for this study.

Author Contribution
FTAR contributed to conception and design, analysis and interpretation of the data, drafting of the article and critical revision of the article for important intellectual content. EBK contributed to conception and design, critical revision of the article for important intellectual content, and final approval of the article. DRS, MRW and AN contributed to critical revision of the article for important intellectual content, and final approval of the article.

Data Availability
None.

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