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RESEARCH ARTICLE

Antibakteri Ekstrak Kulit Buah Naga Merah (Hylocereus polyrhizus) terhadap *Klebsiella pneumoniae* Penghasil ESBL

Antibacterial Extract of Red Dragon Fruit (Hylocereus polyrhizus) Peel Extract against ESBL-Producing Klebsiella pneumoniae

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Abstract

The rising prevalence of infections caused by Extended-Spectrum Beta-Lactamase (ESBL)-producing Klebsiella pneumoniae necessitates the search for alternative antibacterial agents. Red dragon fruit (Hylocereus polyrhizus) peel is a potential source of bioactive compounds. This study aimed to evaluate the in vitro antibacterial activity of red dragon fruit peel extract against ESBL-producing K. pneumoniae. The bacteria were isolated and identified via culture on MacConkey agar, Gram staining, and biochemical tests. The peel was extracted using 96% ethanol via maceration. Antibacterial activity was assessed using the disk diffusion method on Mueller-Hinton agar with extract concentrations of 20%, 40%, 60%, 80%, and 100% (v/v), with three replicates per concentration. Meropenem (10 µg) and DMSO served as positive and negative controls. The extract exhibited concentration-dependent antibacterial activity, with mean inhibition zone diameters increasing from 5,6 ± 0,3 mm at 20% to 6,1 ± 0,2 mm at 100%. The positive control produced a 30,2 ± 0,5 mm zone, while the negative control showed no inhibition. One-way ANOVA confirmed significant differences between groups (p-value < 0,05). Red dragon fruit peel extract demonstrated promising in vitro antibacterial activity against ESBL-producing K. pneumoniae, although its potency was considerably lower than meropenem.

Keywords: *Hylocereus polyrhizus, Klebsiella pneumoniae, bioactive compounds*

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Abstrak

Meningkatnya prevalensi infeksi yang disebabkan oleh *Klebsiella pneumoniae* yang memproduksi *Extended-Spectrum Beta-Lactamase* (ESBL) memerlukan pencarian agen antibakteri alternatif. Kulit buah naga merah *(Hylocereus polyrhizus*) adalah sumber potensial senyawa bioaktif. Penelitian ini bertujuan untuk mengevaluasi aktivitas antibakteri in vitro dari ekstrak kulit buah naga merah terhadap *K. pneumoniae* penghasil ESBL. Bakteri diisolasi dan diidentifikasi melalui kultur pada *MacConkey agar*, pewarnaan Gram, dan tes biokimia. Kulitnya diekstraksi menggunakan etanol 96% melalui maserasi. Aktivitas antibakteri dinilai menggunakan metode difusi disk pada *Mueller-Hinton agar* dengan konsentrasi ekstrak 20%, 40%, 60%, 80%, dan 100% (v/v), dengan tiga replikasi per konsentrasi. *Meropenem* (10 µg) dan DMSO berfungsi sebagai kontrol positif dan negatif. Ekstrak menunjukkan aktivitas antibakteri yang bergantung pada konsentrasi, dengan diameter zona penghambatan rata-rata meningkat dari 5,6 ± 0,3 mm pada 20% menjadi 6,1 ± 0,2 mm pada 100%. Kontrol positif menghasilkan zona 30,2 ± 0,5 mm, sedangkan kontrol negatif tidak menunjukkan penghambatan. *ANOVA* satu arah mengkonfirmasi perbedaan yang signifikan antar kelompok (*p-value* < 0,05). Ekstrak kulit buah naga merah menunjukkan aktivitas antibakteri in vitro yang menjanjikan terhadap *K. pneumoniae* penghasil ESBL, meskipun potensinya jauh lebih rendah daripada meropenem.

Kata Kunci: Hylocereus polyrhizus, Klebsiella pneumoniae, senyawa bioaktif

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Highlight:

- Red dragon fruit (*Hylocereus polyrhizus*) peel extract demonstrated concentration-dependent antibacterial activity against ESBL-producing *Klebsiella pneumoniae*.
- The study found that higher concentrations of the extract resulted in larger inhibition zones, with the 100% concentration producing the most significant result (6,1 ± 0,2 mm).
- While its potency is significantly lower than the antibiotic meropenem, the extract shows promise as a preliminary candidate for adjunctive therapy in addressing antibiotic resistance.

INTRODUCTION

In recent decades, antibiotic resistance has become a global challenge that threatens the effectiveness of treating various infectious diseases (Ahmed et al., 2024; Kemenkes, 2023; Nazir et al., 2025). One pathogen that shows a high level of resistance is *Klebsiella pneumoniae*, an opportunistic Gram-negative bacterium that often causes serious infections such as pneumonia, urinary tract infections, and wound infections, especially in patients with low immunity (Bernarda et al., 2023; Suryanditha et al., 2024). The *World Health Organization* (WHO) categorizes *K. pneumoniae* as a critical priority pathogen with an antibiotic resistance rate of 21.4%, which is largely due to the irrational use of antibiotics (Kaslam et al., 2021). This condition demands the exploration of alternative

sources of treatment based on natural ingredients as a solution to the problem of antibiotic resistance (Riwu et al., 2022).

One of the plants that has begun to be widely researched as a natural source of antibacterial is the red dragon fruit (*Hylocereus polyrhizus*) (Diyatri et al., 2023). In Indonesia, the type of red dragon fruit with red skin and flesh is the most widely cultivated variety. In addition to the pulp, the skin of dragon fruit is also known to contain bioactive compounds such as *phenols*, *flavonoids*, *alkaloids*, and *terpenoids* that have the potential to be antibacterial agents (Sari et al., 2021; Sari et al., 2023). Despite this, dragon fruit peel has received less attention in previous studies, especially as a therapeutic candidate against antibiotic-resistant pathogens.

Several studies have shown that red dragon fruit peel extract has antibacterial activity against various pathogenic bacteria. The extract is reported to be effective against *Staphylococcus aureus* and *Staphylococcus epidermidis* (Bakhriansyah et al., 2021; Lisnayetti et al., 2022; Wijayanti et al., 2022). The content of vitamin C, lycopene, and *polyphenols* in red dragon fruit has also been linked to synergistic antioxidant and antibacterial effects (Nishikito et al., 2023). In addition, red dragon fruit extract was able to inhibit the growth of *Enterococcus faecalis*, which strengthens the argument for its therapeutic potential (Yesudanam et al., 2024). However, these studies have predominantly targeted Gram-positive or oral pathogens, leaving a significant gap regarding its efficacy against highly resistant Gram-negative bacteria.

Specifically, there have been no studies evaluating the effectiveness of red dragon fruit peel extract against *K. pneumoniae*, which employs a complex resistance mechanism through the production of Extended-Spectrum β-Lactamases (ESBL). This absence of targeted research presents a clear scientific gap. Based on the established phytochemical profile of the peel, this study is designed to systematically evaluate its potential as a natural alternative against this critical pathogen. Therefore, this study aims to evaluate the *in vitro* antibacterial activity of red dragon fruit (*Hylocereus polyrhizus*) peel ethanol extract at various concentrations against ESBL-producing *K. pneumoniae* using the disk diffusion method.

METHOD

This *in vitro* experimental study, conducted with three biological and technical replicates per treatment, used an ESBL-producing *K. pneumoniae* strain (ATCC 700603) (Agnesia et al., 2023; Liberty, 2024). Bacterial identification was confirmed through subculture on *MacConkey agar*, Gram staining, and biochemical tests (hydrogen sulfide (H_2S), indole, and motility) (Jung dan Hoilat, 2024). For the assay, the inoculum was standardized to a 0.5 McFarland standard. Red dragon fruit (*Hylocereus polyrhizus*) peel extract was prepared by macerating dried peel powder in 96% ethanol (1:10 w/v) three times for 24 hours each; the combined filtrate was filtered (Whatman No. 1), evaporated, and the crude extract yield was calculated. The extract was diluted with Dimethyl Sulfoxide (DMSO) to concentrations of 20%, 40%, 60%, 80%, and 100% (v/v), ensuring a final DMSO concentration on disks not exceeding 5%. Sterile 6-mm paper disks were impregnated with 20 µL of each solution, dried, and placed on *Mueller-Hinton agar* plates inoculated with the standardized bacteria. A 10 µg meropenem disk and a DMSO-only disk served as positive and negative controls, respectively. After incubation at 37°C for 18–24 hours, inhibition zones were measured (mm). Data were analyzed using SPSS version 26; after confirming normality (Shapiro-Wilk) and homogeneity of variance (Levene's test), a one-way ANOVA followed by Tukey's post-hoc test was applied, with

significance set at p-value < 0,05. This research has obtained ethical approval with number: UMI012502110 on March 10, 2025, from the Research Ethics Committee of the Indonesian Muslim University.

RESULTS AND DISCUSSION

Identification results of *K. Pneumoniae*

Figure 1 shows the results of *K. pneumoniae* identification using two methods. Panel A shows bacterial growth on *MacConkey agar* media, where bacterial colonies appear pink to red due to lactose fermentation. The slimy and large colony morphology is consistent with the characteristics of *K. pneumoniae*. Panel B shows the results of Gram staining observed under a microscope at 1000× magnification. The bacteria appear as short pink rods (bacilli) that are pink in color, confirming that these Gram-negative bacteria.

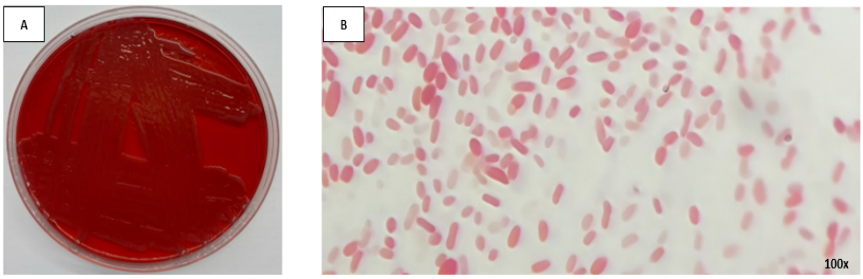

Figure 1. Identification results of *K. pneumoniae*

Figure 2 illustrates the results of biochemical tests using Sulfide, Indole, Motility (SIM) media. The media in the test tubes showed negative results for all three parameters tested. No black precipitate formed (H_2S negative), bacterial growth was limited to the inoculation line (motility negative), and no red ring formed after the addition of Kovac's reagent (indole negative).

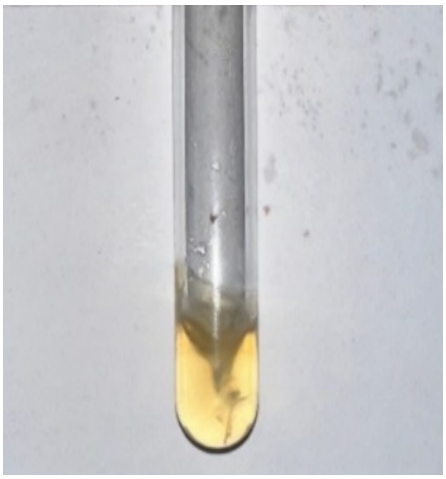

Figure 2. Results of Identification of *K. pneumoniae* by Biochemical Test

Figure 3 presents the results of the antibacterial activity test of red dragon fruit peel extract using the disk diffusion method. Panel A is a bar graph that visualizes the increase in inhibition zone diameter as the extract concentration increases (20%, 40%, 60%, 80%, and 100%). The positive control (meropenem 10 µg) showed the largest inhibition zone

(~30 mm), while the negative control (DMSO) showed no inhibition zone. Panel B shows a photograph of the inhibition zone on *Mueller-Hinton agar* medium. It can be seen that the clarity and diameter of the inhibition zone increased in line with the increase in extract concentration, with a concentration of 100% producing the clearest inhibition zone.

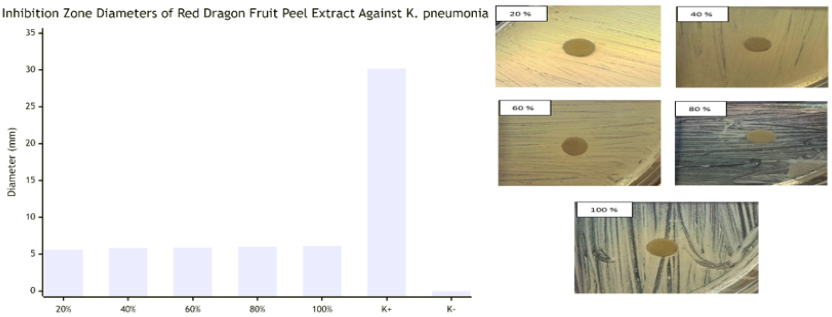

Figure 3. Antibacterial effectiveness test of red dragon fruit peel extract (*Hylocereus polyrhizus*) against *K. pneumoniae*

Table 1 shows the results of biochemical tests for the identification of *K. pneumoniae*. The three tests performed, namely the Hydrogen Sulfide (H_2S) test, Motility test, and Indole test, gave negative results. In the H_2S test, no black precipitate formed on the medium, indicating that the bacteria did not produce hydrogen sulfide. In the motility test, bacterial growth was only visible along the inoculation line without spreading, confirming that *K. pneumoniae* is non-motile. Meanwhile, in the indole test, no red ring formed after the addition of Kovac's reagent, indicating that the bacteria did not produce the enzyme tryptophanase to convert tryptophan into indole.

Table 1. Results of the biochemical tests for *K. pneumoniae* identification

Test	Result	Interpretation
Hydrogen Sulfide (H_2S)	(-)	No black precipitate formed
Motility	(-)	Growth only along the stab line
Indole	(-)	No red ring formed after adding Kovac's reagent

Antibacterial activity of red dragon fruit peel extract

The antibacterial activity of the ethanol extract of red dragon fruit peel was evaluated using the disk diffusion method. Visual results for the various extract concentrations and controls are presented in Figure 3. The mean inhibition zone diameters for all treatments are summarized in Table 2. The extract exhibited a concentration-dependent effect, with the largest inhibition zone observed at the 100% concentration.

Table 2 shows the diameter of the inhibition zone of red dragon fruit (*Hylocereus polyrhizus*) ethanol extract against ESBL-producing *K. pneumoniae*. Data are presented as mean ± standard deviation (SD) from three replicates (n=3). The results show concentration-dependent inhibitory activity, with an increase in inhibition zone diameter as the extract concentration increases. A 20% extract concentration produced the smallest inhibition zone diameter (5,6 ± 0,3 mm), while a 100% concentration produced the largest diameter (6,1 ± 0,2 mm). The positive control (meropenem 10 µg) showed very strong antibacterial activity with an inhibition zone diameter of 30,2 ± 0,5 mm, consistent with the sensitivity of the bacteria to this antibiotic. No inhibition zone was formed in the negative control (DMSO), indicating that the solvent had no antibacterial effect. Numerically, although the increase in zone diameter from 20% to 100% concentration

was statistically significant ($p < 0,05$), the absolute zone size was relatively small, ranging from 0 to 0,5 mm outside the disk diameter (6 mm).

Table 2. Inhibition zone diameters of red dragon fruit peel extract against ESBL-producing *K. pneumoniae* (Mean ± SD; n=3)

Concentration (%)	Mean Inhibition Zone Diameter (mm) ± SD	Significance
20%	5.6 ± 0.3	a
40%	5.8 ± 0.2	ab
60%	5.9 ± 0.4	ab
80%	6.0 ± 0.3	ab
100%	6.1 ± 0.2	b
Positive Control (Meropenem 10 µg)	30.2 ± 0.5	c
Negative Control (DMSO)	0 mm (no inhibition)	-

*Data are presented as the mean ± standard deviation (SD) from three replicates (n=3). Values followed by different superscript letters in the Significance column indicate a significant difference (significant difference) based on a One-Way ANOVA followed by a Tukey HSD post-hoc test at a 95% confidence level (p-value < 0.05); Positive Control: Meropenem 10 µg; Negative Control: DMSO 10%.

The antibacterial activity of red dragon fruit peel extract against ESBL-producing K. pneumoniae is presented in Table 2. The extract exhibited very weak inhibitory effects, with mean inhibition zone diameters ranging from 5.6 mm at 20% concentration to 6.1 mm at 100% concentration. While a dose-dependent trend was observed, the overall increase in activity was marginal, with only a 0.5 mm difference between the lowest and highest concentrations. The negative control (DMSO) produced no inhibition zone, confirming that the solvent did not influence the results. Conversely, the positive control (Meropenem 10 µg) produced a significantly larger inhibition zone of 30.2 mm, indicating high bacterial sensitivity to the standard antibiotic.

Statistical analysis confirmed the significance of these observations. One-way ANOVA revealed a significant difference in mean inhibition zones among the treatment groups ($F = 2.09$; $p < 0.05$). Subsequent post-hoc analysis using Tukey's HSD test showed that the inhibition zone at 100% concentration (6.1 mm) was significantly larger ($p < 0.05$) than at 20% (5.6 mm), as indicated by their different superscript letters ('b' and 'a', respectively). However, the activity of the 100% extract was not significantly different from the 40%, 60%, and 80% concentrations, which all shared overlapping superscripts ('ab'). Most importantly, all extract concentrations, including the highest at 100%, showed significantly lower activity (p-value < 0.05) compared to the Meropenem control, denoted by the distinct superscript 'c'. These findings demonstrate that while the extract possesses some antibacterial properties, its effectiveness is minimal and clinically insignificant when compared to conventional antibiotics (Hardani et al., 2020; Purwanza et al., 2022; Rukajat, 2018).

The identification of the bacterial isolate as *K. pneumoniae* was confirmed by its characteristic growth on *MacConkey agar* (pink, mucoid colonies), Gram-negative bacilli morphology, and negative biochemical results for H_2S, motility, and indole tests (Figure 1, 2, Table 1). This profile aligns with standard identification protocols (Herawati et al., 2022; Yang et al., 2024).

The antibacterial testing revealed that the ethanolic extract of red dragon fruit peel (*Hylocereus polyrhizus*) exhibited a statistically significant, concentration-dependent inhibitory effect against ESBL-producing *K. pneumoniae*. The inhibition zone diameter increased from 5,6 mm at 20% concentration to 6,1 mm at 100% (Figure 3, Table 2), a trend confirmed by one-way ANOVA and post-hoc analysis ($p < 0,05$). However, while

statistically significant, the biological relevance of this effect is modest. The absolute increase in inhibition was only approximately 0,5 mm, and the net zone of inhibition (diameter minus the 6-mm disk) ranged from 0 to a maximum of 0,5 mm. This is markedly lower than the potent bactericidal effect demonstrated by the positive control, meropenem (30,2 mm zone) (Maulana et al., 2018).

The weak inhibitory activity observed can be attributed to several factors inherent to both the extract and the pathogen. First, crude plant extracts are complex mixtures where active compounds are present at low, diluted concentrations, limiting their diffusion capability and potency in agar compared to pure antibiotics. Second, *K. pneumoniae* possesses formidable structural defenses. Its thick polysaccharide capsule and *LPS-rich outer membrane* act as significant permeability barriers, likely impeding the penetration of phytochemicals like the flavonoids and polyphenols identified in dragon fruit peel (Gómez et al., 2021). While ESBL enzymes are a primary resistance mechanism against β-lactam antibiotics, they do not directly inactivate the diverse compounds in a plant extract. The observed weak activity is therefore more likely a consequence of these physical barriers and potential efflux pump activity rather than enzymatic degradation.

When contextualized with prior research, our findings align with the general trend that dragon fruit peel extract exhibits milder activity against Gram-negative bacteria. Previous studies reported larger inhibition zones against Gram-positive pathogens like *Staphylococcus aureus* (e.g., 8-12 mm) (Wijayanti et al., 2022). This discrepancy underscores the greater challenge posed by the outer membrane of Gram-negative bacteria like *K. pneumoniae*. The results confirm antibacterial potential but highlight that the crude extract's efficacy against this resilient pathogen is limited in its current form.

A key limitation of this study is the use of the disk diffusion method alone, which provides a preliminary screening but does not determine the minimum inhibitory concentration (MIC) or bactericidal activity (MBC). Consequently, we cannot conclude whether the effect is bacteriostatic or bactericidal, nor quantify the potency required for meaningful inhibition. The in vitro design and use of a single bacterial strain further limit direct clinical applicability.

Research implications and future direction

Despite its limitations, this study successfully addresses a defined research gap by providing the first evidence of red dragon fruit peel extract's activity against ESBL-producing K. pneumoniae. The findings contribute to the growing body of literature on natural products as sources of antimicrobial agents. The potential of this extract likely lies not as a standalone therapy but as an adjuvant or in synergistic combinations. For instance, its bioactive compounds could potentially weaken bacterial cell membranes, enhancing the efficacy of co-administered conventional antibiotics.

CONCLUSION

In conclusion, the ethanolic extract of red dragon fruit (*Hylocereus polyrhizus*) peel exhibited a statistically significant, concentration-dependent antibacterial effect against ESBL-producing *K. pneumoniae*, with inhibition zone diameters increasing from approximately 5,6 mm to 6,1 mm. However, this in vitro activity was markedly lower than that of the standard antibiotic meropenem, and the absolute increase in inhibition was modest. Therefore, while the extract demonstrates promising antibacterial properties, its current potency is limited. It should be regarded as a preliminary candidate for further

investigation rather than a direct therapeutic alternative. The findings suggest its potential role may lie in complementary or adjunctive strategies. Future research must prioritize the isolation of its active compounds, the evaluation of synergistic effects with conventional antibiotics, and advanced formulation approaches to enhance bioavailability and efficacy. Ultimately, in vivo studies are essential to determine its clinical relevance.

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