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ANTIMICROBIAL ACTIVITY OF THE ETHANOLIC EXTRACT OF *DURIO ZIBETHINUS* RIND AGAINST ESBL-PRODUCING *ESCHERICHIA COLI* AND *KLEBSIELLA PNEUMONIAE*

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ABSTRACT

Background: *Durio zibethinus* (durian) contains secondary metabolites with antibacterial potency, such as alkaloids, flavonoids, saponins, tannins, and glycosides. Indonesia is one of the world's largest producing countries of durian, yet the thorny part of the fruit rind often ends up as waste. Investigations of durian rind for its antimicrobial activity will maximize the benefits and prevent waste accumulation.
Objective: In this experimental study, we analyzed the antimicrobial activity of ethanolic extract of durian rind against extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *K. pneumoniae* in vitro.
Methods: This study used a one-group posttest-only design. The disc diffusion method for antimicrobial susceptibility testing was used to test the ethanolic extract of durian rind against ESBL-producing *E. coli* and *K. pneumoniae*, each with six experimental repetitions to observe the inhibition zone produced around discs containing the extracts at various concentrations (12.5%, 25%, 50%, 75%, 80%, and 100%).
Results: The ethanolic extract of durian rind showed an inhibition zone against ESBL-producing *E. coli* at the extract concentration of 50%, with an average inhibition zone of 3.57 mm. The inhibition zone was also observed against ESBL-producing *K. pneumoniae* at the extract concentration of 75%, with an average inhibition zone of 3.73 mm.
Conclusions: The ethanolic extract of durian rind showed inhibition zones against ESBL-producing *E. coli* and *K. pneumoniae*, showing its potential antimicrobial activity in vitro.

Keywords: *Durio zibethinus*, *E. coli*, *K. pneumoniae*, antimicrobial susceptibility test.

ABSTRAK

Latar belakang: *Durio zibethinus (durian) mengandung metabolit sekunder yang memiliki potensi antibakteri, antara lain alkaloida, flavonoid, saponin, tanin, dan glikosida. Indonesia adalah salah satu negara penghasil terbesar durian di dunia, namun bagian kulit durian yang berduri seringkali hanya menjadi sampah. Uji aktivitas antimikroba diharapkan dapat menambah manfaat dan mencegah terbuangnya kulit durian.*
Tujuan: *Pada penelitian eksperimental ini, peneliti menganalisis secara in vitro aktivitas antimikroba ekstrak etanol kulit durian terhadap E. coli dan K. pneumoniae penghasil extended-spectrum beta-lactamase (ESBL).*
Metode: *Penelitian ini menggunakan desain one-group posttest-only. Uji kepekaan antimikroba dengan metode difusi cakram dilakukan untuk mengamati zona hambat yang ditimbulkan ekstrak etanol kulit durian terhadap pertumbuhan E. coli dan K. pneumoniae penghasil ESBL, dengan enam kali pengulangan untuk setiap konsentrasi ekstrak yang diujikan, yaitu 12.5%, 25%, 50%, 75%, 80%, dan 100%.*
Hasil: *Ekstrak etanol kulit durian pada konsentrasi 50% menunjukkan zona hambat terhadap E. coli penghasil ESBL, dengan zona hambat rata-rata 3.57 mm. Zona hambat juga tampak terhadap K. pneumoniae penghasil ESBL pada konsentrasi ekstrak 75%, dengan zona hambat rata-rata 3.73 mm.*
Kesimpulan: *Ekstrak etanol kulit durian menunjukkan daya hambat terhadap pertumbuhan E. coli dan K. pneumoniae penghasil ESBL, sehingga berpotensi antimikroba secara in vitro.*
Keyword: *Durio zibethinus, E. coli, K. pneumoniae, uji kepekaan antimikroba*

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1. Introduction

The genus *Durio* (durian) consists of at least 30 species and is native to the tropical countries of Southeast Asia, including Indonesia (Sumatra, Borneo), Peninsular Malaysia, Thailand, and the Philippines [1]. Over time, it has been widely distributed across Asia, including Sri Lanka, India, and the surrounding islands [1]. Durian is usually cultivated and marketed for its instantly edible flesh and is considered a delicacy in Asia. The outer part of durian (the durian rind), which is spiky and thick, accounts for more than 50% of the total durian weight and usually ends up as waste, thus requiring manipulation for utilization. Research indicates that durian possesses a rich composition of secondary metabolites such as anthocyanins, polyphenols, and flavonoids, but the non-edible parts (seed and rind) revealed higher phytochemical compositions than the flesh [2]. Phytochemicals in plants exhibit antimicrobial effects due to their bioactive compounds, which serve as natural defense mechanisms against pathogens, for example, by directly disrupting microbial cell membranes or interfering with their metabolic processes, leading to cell death [3]. Phytochemicals such as phenolic compounds (flavonoids, phenolic acids, tannins, etc.) have shown antibacterial and antibiofilm properties [4]. The study of plant phytochemicals for their antimicrobial activity is essential due to the growing threat of antimicrobial resistance (AMR) and the limited availability of new antibiotics. Phytochemicals derived from a wide range of plant species offer a promising alternative to combating multidrug-resistant (MDR) bacteria, with diverse mechanisms of action that can disrupt bacterial functions.

Various studies have demonstrated that different parts of the durian plant, including its rinds, seeds, and leaves, possess compounds that inhibit pathogenic bacteria, making durian a promising candidate for natural disinfection and food preservation [5]-[11]. In one of the studies, the durian rind methanolic extracts and essential oils were proven to possess strong to medium antimicrobial activities [5]. The durian rind extract has been shown to have antimicrobial activity against Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, and *Klebsiella pneumoniae* [12]-[14]. However, to our knowledge, no accessible report exists on the antimicrobial activity of durian rind extract against problematic multidrug-resistant (MDR) bacteria, including beta-lactam-resistant strains. The proposed mechanism of action and the synergistic effect of some phytochemical compounds against/with antibiotics were reviewed elsewhere [15], and researchers detected some of those compounds in durian rind [16,17]. Given the proposed synergistic mechanisms with antibiotics such as beta-lactams, these phytochemical compounds may reduce antibiotic tolerance in MDR bacteria [15]. In this study, we analyzed the antibacterial activity of durian rind ethanolic extract against

extended-spectrum beta-lactamase (ESBL)--producing *Escherichia coli* and *K. pneumoniae* in vitro.

2. Methods

2.1. Preparation and phytochemical screening of the extract

Durian was obtained from local sellers around Medan City, North Sumatra, Indonesia. Four kilograms of durian rind were washed and cleaned thoroughly under running tap water, drained, and cut into small pieces. Afterward, the durian rinds were dried under indirect sunlight and covered with black cloth. The dried durian rinds were ground to get the fine materials (*simplisia*), which were then stored in a clean container. Five grams of the *simplisia* were used in the qualitative phytochemical screening. A total of 400 g of the *simplisia* was soaked in 4000 ml of 70% ethanol. The solvent was removed using a rotary evaporator. The resulting filtrate from the maceration process yielded the ethanolic extract of durian rind in paste form. The paste was kept in a sterile bottle and refrigerated, then diluted in sterile aquabidest to reach the tested concentrations, each in a separate sterile container right before the experiment. The extraction steps and phytochemical screening of durian rind were performed at the Biology Laboratory, Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara.

2.2. Antimicrobial activity test of durian rind ethanolic extract

This study used a one-group post-test design to analyze the inhibition zone formed by durian rind ethanolic extract following a disc diffusion method for an antimicrobial sensitivity test. Ethical clearance was obtained from the ethical committee for health research of the Faculty of Medicine Universitas Sumatera Utara with the letter number 561/KEPK/USU/2023. Durian rind ethanolic extract at concentrations of 12.5%, 25%, 50%, 75%, 80%, and 100% was tested against extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae*. The bacterial strains were identified from patients with significant bacteriuria using the Vitek-2 compact automated system (bioMérieux) and obtained from Universitas Sumatera Utara Hospital. The American Type Culture Collection (ATCC) 25922 *E. coli* and ATCC 700603 *K. pneumoniae* were used as control strains.

Sterile blank discs (Oxoid) were separately soaked in the ethanolic extract of durian rind at concentrations of 12.5%, 25%, 50%, 75%, 80%, and 100% for at least two hours at room temperature. The sterile blank discs were soaked in the non-prediluted extract to obtain a concentration of 100%. Following the overnight cultures of the bacterial strains in blood agar, the bacterial suspension was prepared for each strain and adjusted to the turbidity of 0.5 McFarland using a digital densitometer (DEN-1 Biosan). One microliter of each bacterial suspension was poured separately using a micropipette with sterile filtered tips onto a Mueller-Hinton (Oxoid) agar plate, then spread evenly on the agar surface using a sterile spreader. The disks soaked in different extract concentrations were then transferred individually using sterile tweezers onto the surface of the inoculated agar plate, with at least 2 cm of space between the adjacent discs. The agar plates were then incubated for 18-24 hours at 37°C. After incubation, the antibacterial activity of the extract was observed visually by measuring the inhibition zone (clear zone) diameter around each disc using digital calipers. Six experimental repetitions were done for each tested concentration of the extract. The bacterial cultures, disc diffusion method, and inhibition zone observations were conducted at the Department of Microbiology Laboratory, Faculty of Medicine, Universitas Sumatera Utara.

3. Results

3.1. Phytochemical Screening of the Extract

The ethanolic extract of durian rind contains secondary metabolites, including alkaloids, saponins, flavonoids, tannins, and glycosides (Table 1).

Table 1. The phytochemical screening tests of durian rind

Phytochemical	Test	Result
Alkaloids	Bouchadart	positive
	Meyer	negative
	Dragenndoff	positive
	Wagner	positive
Steroids and terpenoids	Salkowski	negative
	Lieberman-Burchard	negative
Saponins	96% ethanol	positive
Flavonoids	5% $FeCl_3$	positive
	Shinoda	positive
	10% NaOH	negative
	H_2SO_4	negative
Tannins	1% $FeCl_3$	positive
Glycosides	Molisch	positive

3.2 Antimicrobial activity of durian rind ethanolic extract

The disc diffusion tests of durian rind ethanolic extract against the ESBL-producing *E. coli* strain showed inhibition zones starting at the 50% extract concentration, with an average diameter of 3.57 mm. At the highest extract concentration (100%), the average diameter of the inhibition zone was 4.65 mm. The extract exhibited an inhibition zone starting at a concentration of 50% with an average diameter of 3.57 mm. At the extract concentration of 100%, the average diameter of the inhibition zone against ESBL E. coli was 4.65 mm. The inhibition zone against ESBL K. pneumoniae appeared at the lowest concentration of 75% with an average diameter of 3.73 mm and reached an average diameter of 4.97 mm at the highest concentration of 100% extract (Figure 1).

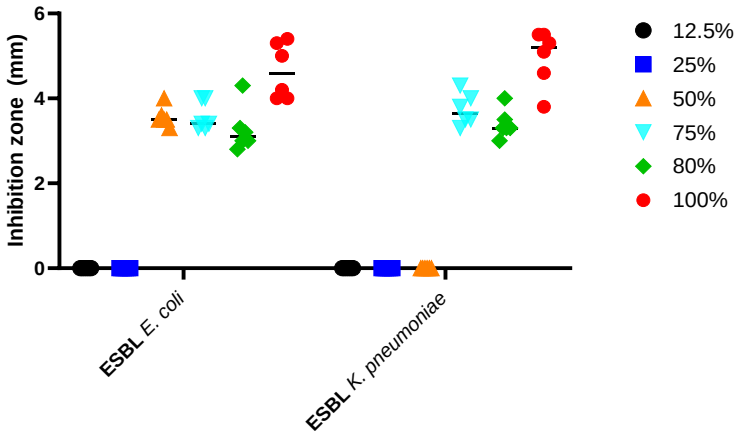

Figure 1. Inhibition zones of durian rind ethanolic extract against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*.

The extract started from 12.5%, 25%, 50%, 75%, 80%, and 100% concentrations, inhibiting *E. coli* 25922 with diameters of 2.8 mm, 3.8 mm, 4.5 mm, 4.8 mm, 5.0 mm, and 5.2 mm, respectively. At similar concentrations, the extract inhibited *K. pneumoniae* 700603 at the diameters of 3.3 mm, 3.5 mm, 4.0 mm, 4.3 mm, 5.6 mm, and 5.7 mm, respectively (Figure 2)

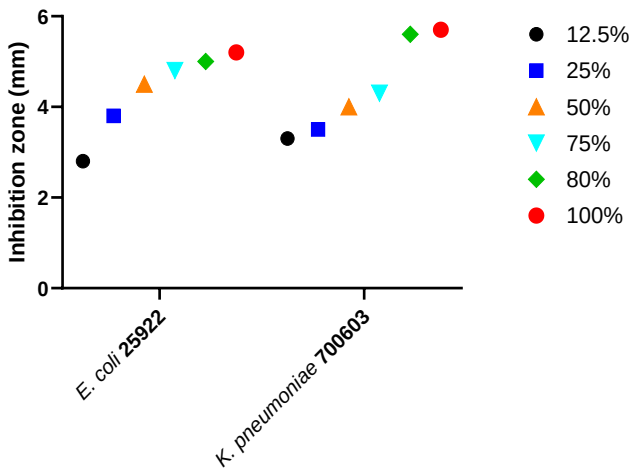

Figure 2. Inhibition zones of durian rind ethanolic extract against ATCC 25922 *Escherichia coli* and ATCC 700603 *Klebsiella pneumoniae*.

4. **Discussion**

The qualitative phytochemical screening results align with previous reports [2,6,13,16,17]. Most of the secondary metabolites detected in this study are known for their antimicrobial activity. Alkaloids exhibit diverse antimicrobial mechanisms, making them significant in combating antibiotic resistance, as research indicates that these nitrogen-containing compounds can disrupt bacterial cell functions through various pathways, including cell wall synthesis inhibition [18], membrane permeability alteration [19], and are involved in the host immune response against bacterial infections [20]. Flavonoids can damage the integrity of bacterial cell membranes, leading to increased permeability and eventual cell lysis [21]. Flavonoids may inhibit the activity of beta-lactamases, enzymes that confer antibiotic resistance, thereby enhancing the efficacy of conventional antibiotics [21]. Flavonoids may also target DNA gyrase, an essential enzyme for bacterial DNA replication [22]. Thus, the antibacterial effect of these phenolic compounds can be effective against Gram-positive and Gram-negative bacteria, although the specific interactions may vary based on the bacterial type [22].

Tannins demonstrate broad-spectrum antibacterial activity as they can be used against Gram-positive and Gram-negative bacteria and disrupt bacterial biofilms [23]. Saponins interact with sterols in microbial cell membranes, leading to pore formation and loss of membrane integrity, leakage of cellular contents, and ultimately causing cell death [24]. Glycosides may inhibit biofilm formation, whereas thioglycosides may disrupt bacterial glycan biosynthesis, which is crucial for bacterial virulence and the ability to infect hosts [25,26]. Analyses of total phenolics and total flavonoid contents of durian revealed that the outer and inner parts of durian rind possess higher concentrations of these phytochemicals compared with other parts of the fruit [2]. Further studies of quantitative phytochemical contents are required to explore the potential benefits of durian. Advanced extraction techniques, bioactivity assays, and characterization of phytochemicals in durian are, however, recommended to reveal its potential antibacterial activity and the possible synergistic activity with standard antimicrobial agents.

The inhibition zone against ESBL-producing *K. pneumoniae* was visible at a higher extract concentration (75%) than the concentration against ESBL *E. coli*. Yet, the average diameter was slightly greater (3.73 mm) than the average diameter against ESBL *E. coli* at 75% extract concentration (3.57 mm). The extract concentration of 100% inhibited ESBL *K. pneumoniae* at a slightly greater diameter (4.97 mm) than its inhibition zone against ESBL *E. coli*. Against both of the control strains, however, the extract showed an inhibition zone that started from the lowest concentration tested in this study (12.5%) at the diameter of 2.8 mm for ATCC 25922 *E. coli* and 3.3 mm for ATCC 700603 *K. pneumoniae* (Figure 2). According to the literature, the inhibition zone of <5 mm is classified as no response [5].

Besides the low levels of inhibition zone against ESBL *E. coli* and ESBL *K. pneumoniae*, this study showed the antimicrobial activity of durian rind ethanolic extract, in agreement with previous studies [5]-[8],[12]-[14]. The inhibition zones against ESBL *E. coli* and ESBL *K. pneumoniae* appeared at higher extract concentrations than the control ATCC strains, confirming the superior ability of the MDR strains to counter antimicrobial effects in their environment. Besides, previous studies revealed that bacteria can alter their cell membrane structure to reduce their permeability to phenolic compounds [27] and utilize efflux pumps to expel phenolics or other antimicrobial agents, thereby diminishing their efficacy [4]. Phytochemicals, such as flavonoids and alkaloids, have shown promise in combating MDR bacteria, but their efficacy often depends on concentration and the specific resistance mechanisms at play. Liquid chromatography-mass spectrometry (LC/MS) identified flavonoids, terpenoids, nonflavonoid glycosides, anthocyanins, and phenolics in durian rind, with evidence that durian rind is particularly rich in the flavonoid quercetin [16,17]. Quercetin was suggested for its ability to inhibit ATP synthase required for bacterial energy production, making it difficult for bacteria to develop resistance [28]. However, higher concentrations of phytochemical compounds like quercetin may often be needed to achieve a significant antibacterial effect [29]. Continuous research is necessary to investigate the phyto compounds of durian rind, which is richer in total phenolics and flavonoid contents compared with other durian parts [2], for their potential antimicrobial activity and mechanisms.

A combination of secondary metabolites, including plant metabolites, can be an alternative method to develop a new antimicrobial agent. This method could be a promising approach to combating drug-resistant pathogens. Plant phytochemicals, in combination with conventional antibiotics, can enhance therapeutic effects and minimize side effects [30]. Combining phytochemicals with traditional antibiotics can lower the minimum inhibitory concentration (MIC) needed for effectiveness [31] and thus may reduce required dosages [30]. The phytochemical activity in retarding biofilm formation is another possible synergistic effect that deserves attention because it is a common bacterial resistance mechanism against standard antibiotics [32]. Further, phytochemicals may interact with multiple microbial targets, making it less likely for resistance to develop compared to single-target antibiotics [33]. Further studies are required to explore phytochemicals' synergistic potential with existing antibiotics to maximize therapeutic efficacy and minimize resistance development

5. Conclusions

Despite methodological limitations, this study qualitatively detected alkaloids, saponins, flavonoids, tannins, and glycosides in durian rind. The ethanolic extract of durian rind inhibited the growth of ESBL *E. coli* and ESBL *K. pneumoniae* in vitro, starting at 50% and 75% extract concentrations, respectively. However, given the <5 mm inhibition zones shown by the extract, we recommended that future studies should use different extraction methods and susceptibility test methods to observe the antimicrobial activity of durian rind. Furthermore, it is valuable to investigate the potential synergistic effect of durian rind phytochemical compounds and other antimicrobial metabolites.

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Conflict of Interest

The authors declare no conflict of interest.

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