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EFECTIVENESS OF *Carica papaya* SEEDS ETHANOL EXTRACT WITH METRONIDAZOLE AGAINST *Porphyromonas gingivalis* IN ANTIBACTERIAL AND ANTIBIOFILM ACTIVITY

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ABSTRACT

Porphyromonas gingivalis promotes the growth of periodontal biofilm. Metronidazole is one of the adjunctive therapies for periodontitis. The combination of metronidazole with natural products such as *Carica papaya* seeds ethanolic extract, which has proven to have antibacterial effects is expected to reduce the side effects caused by metronidazole. Objective: To determine the antibacterial and antibiofilm effects of *C. papaya* seeds ethanolic extract combined with metronidazole against *P. gingivalis*. In vitro laboratory experiment using post-test only control group design. The sample used were 100% *C. papaya* seeds ethanolic extract, combination of 1000 µg/mL metronidazole with extract 3.125%, 6.25%, 12.5%, 25%, 50%, and 100%, 1000 µg/mL and 2000 µg/mL metronidazole as positive control, and distilled water as negative control. Antibacterial test was performed using plate count method and antibiofilm using microtiter plate biofilm assay method. Results: *Carica papaya* seeds ethanolic extract alone showed effective antibacterial and antibiofilm effects against *P. gingivalis*. The combination of 1000 µg/mL metronidazole with extract 6.25% to 100% showed an antibacterial effect equivalent to 2000 µg/mL metronidazole. The combination of 1000 µg/mL metronidazole with 100% extract showed antibiofilm effects in 1, 3, and 24 hours time incubation. The combination of extract and 1000 µg/mL metronidazole demonstrated the best antibiofilm effect during the biofilm maturation phase. Conclusion: The combination of 1000 µg/mL metronidazole with ethanol extract of *C. papaya* seeds exhibited antibacterial and antibiofilm effects against *P. gingivalis*.

Introduction

Natural products have been widely developed and utilized as alternative treatments for various diseases. Their growing popularity is due to affordability, cultural acceptance, and a lower risk of side effects compared to synthetic drugs.. Among the various natural products,

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papaya (*Carica papaya*) stands out as a widely used plant with a broad range of therapeutic benefits. *Carica papaya* is native to tropical regions and is found in many countries with warm climates. According to 2022 data, Indonesia ranks among the top five largest producers of papaya in the world (FAO, 2022). The fruit, leaves, and flowers of *C. papaya* are commonly consumed by people as everyday food, while other parts like the stem, skin, and seeds are often discarded as organic waste (Kumoro, Alhanif, & Wardhani, 2020). However, *C. papaya* seeds are rich in proteins, lipids, and fiber, making them a potential alternative source of energy. Compounds found in *C. papaya* seeds, such as tocopherol phenolates, carotenoids, and benzyl isothiocyanate, demonstrate bactericidal, bacteriostatic, and fungicidal effects (Dotto & Abihudi, 2021; Singh et al., 2020).

Studies have demonstrated the antibacterial activity of aqueous, acetone, methanol, and ethanol extracts of *C. papaya* seeds against both Gram-positive and Gram-negative bacteria (Dagne, Dobo, & Bedewi, 2021). The ethanol extract of *C. papaya* seeds has demonstrated antibacterial effects against *Staphylococcus aureus* and *Enterococcus faecalis*, which are common causes of root canal infections (Arun, Ramesh, & Sankar, 2023). Furthermore, the ethanol extract of *C. papaya* seeds, when used as a mouthwash, has proven effective in reducing inflammation and bleeding in cases of halitosis, gingivitis, and periodontitis (Rangaraju, Mousin, Babu, & Dasappa, 2019). *Porphyromonas gingivalis* is considered a primary etiological agent of periodontitis, as it promotes the growth of periodontal biofilm through quorum sensing with other periodontal pathogens (Serbanescu et al., 2022). Several virulence factors of *P. gingivalis*, such as fimbriae, heme, capsule, lipopolysaccharides (LPS), and gingipains, contribute to the destruction of periodontal tissue by activating inflammatory mediators, attacking host cells, and enabling the pathogen to persist in the periodontal pocket. These invasion and survival mechanisms of *P. gingivalis* contribute to the inflammation of the gingiva, alveolar bone resorption, and increase the risk of developing coronary artery disease (Aleksijević et al., 2022).

The management of periodontitis typically involves mechanical debridement, such as scaling and root planing. In addition, antibiotics like metronidazole, amoxicillin, and azithromycin are often used as adjunctive therapy to enhance treatment outcomes (Saquib et al., 2021). Metronidazole is commonly prescribed for conditions like gingivitis, acute necrotizing ulcerative gingivitis (NUG), and periodontitis (Newman, Takei, Klokkevold, & Carranza, 2019). This broad-spectrum nitroimidazole antibiotic is highly effective against anaerobic bacteria, including *Bacteroides fragilis*, *Fusobacterium fusiform*, *Prevotella intermedia*, and *Porphyromonas gingivalis*. Despite its many benefits, studies indicate that metronidazole may lead to a range of side effects including headaches, nausea, gastrointestinal discomfort, and metallic taste (Weir & Le, 2023).

The combination of aqueous extracts from *Panax ginseng* and *Symphytum officinale* with 500 mg/mL metronidazole exhibit a synergistic effect in producing antibacterial and antibiofilm activities against *P. gingivalis* (Ibrahim, Al-Mizraqchi, & Haider, 2023). Additionally, 20 µg metronidazole has shown synergistic effects when combined with ethanol extracts from *Punica granatum*, *Commiphora molmol*, and *Azadirachta indica*, effectively inhibiting the growth of *P. gingivalis*, *A. actinomycetemcomitans*, and *Treponema denticola* (Saquib et al., 2021). Based on these findings, this study aims to evaluate the effectiveness of combining ethanol extracts from *C. papaya* seeds with metronidazole against the growth and biofilm formation of *P.*

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gingivalis as a key pathogen in periodontitis. This combination may offer a potential alternative treatment for periodontitis.

Materials and Methods

This study is an in vitro laboratory experiment with a post-test only control group design conducted at the Microbiology Center of Research and Education (MiCORE), Faculty of Dentistry, Universitas Trisakti, Jakarta. The ethical clearance was approved by the Ethics Committee for Health Research at the Faculty of Dentistry, Universitas Trisakti, Jakarta (759/S1/KEPK/FKG/6/2024). The test solution used were distilled water as negative control, metronidazole infusion at 1000 µg/mL and 2000 µg/mL as positive control, 100% *C. papaya* seeds ethanol extract, and the combination of 1000 µg/mL metronidazole with *C. papaya* seeds ethanol extract at concentrations of 3.125%, 6.25%, 12.5%, 25%, 50%, and 100%.

Carica papaya seeds ethanol extract

The *C. papaya* seeds ethanol extract used in this research was prepared using the maceration method at Indonesian Spice Medicinal and Aromatic Plants Instrument Standard Testing Institute (BPSI-TROA) in Bogor, West Java, Indonesia. The *C. papaya seeds* were dried at 37°C for three days, then ground into a fine powder. This powder was soaked in 96% ethanol for 24 hours, then being filtered. Ethanol was removed using a rotary evaporator, resulting in a 100% concentration extract. The extract was then serially diluted with distilled water to achieve concentrations of 50%, 25%, 12.5%, 6.25%, and 3.125%.

Phytochemical Test

The phytochemical test was conducted at BIOFARMAKA IPB to identify the secondary metabolites present in the ethanol extract of *C. papaya* seeds.

Antibiotic Preparation

The antibiotic stock used was metronidazole infusion 5 mg/mL (OGB Dexa). For the combination with extract, metronidazole was diluted to concentrations of 1000 µg/mL and 2000 µg/mL using distilled water.

Bacterial Culture

The *P. gingivalis* ATCC 33277 strain was obtained from the MiCORE laboratory, Faculty of Dentistry, Universitas Trisakti. The *P. gingivalis* ATCC 33277 culture was inoculated in Brain Heart Infusion-Broth (BHI-B) (Sigma Aldrich) medium. The mixture was then homogenized using a vortex (Biosan) and incubated anaerobically for 24 hours at 37°C. The absorbance was measured using a microplate reader (Safas) at a wavelength of 600 nm, with a value of 0.1 and equal to the McFarland 0.5 standard (1.5 x 10^8 CFU/mL).

Antibacterial Test

The antibacterial effect was tested using microdilution with the plate count method. A total of 100 µL of *P. gingivalis* was added to 100 µL of each test solution. The mixture was then incubated anaerobically for 48 hours and diluted 1.000 times. Each test solution was taken 10 µL and spread onto Brain Heart Infusion-Agar (BHI-A) (Oxoid) media and incubated for another 24 hours. Finally, the bacterial colonies were counted manually. This test was repeated three times.

Antibiofilm Test

The antibiofilm effect was tested using the microtiter plate biofilm assay method. A 200 µL suspension of *P. gingivalis* was added to a 96-well plate and incubated for 48 hours. After incubation, the supernatant was discarded. In each treatment group, 200 µL of test solution was added to 5 wells with biofilm and 2 wells without biofilm. The plate was incubated anaerobically at 37°C and observed at 1, 3, and 24-hour

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intervals. The wells were rinsed twice with PBS (Biomatik), then dried and fixed by briefly passing them over a flame. Crystal violet solution (0.05% w/v) was added to stain the biofilm that had formed. The wells were then rinsed and dried, then 200 µL of 96% ethanol was added to each well. The intensity of the crystal violet stain in the wells was measured in optical density (OD) using a microplate reader at a wavelength of 490 nm.

Statistical Analysis

The normality of the data was assessed using the Shapiro-Wilk test. For the antibacterial test, one-way Analysis of Variance (ANOVA) was applied, along with post hoc Tukey HSD in order to determine the significant differences between the test groups ($P<0.05$). For the antibiofilm test, Kruskal-Wallis test was applied, followed by post hoc Mann-Whitney tests ($P<0.05$).

Results and Discussion

Phytochemical test

The phytochemical test identified that ethanol extract of *C. papaya* seeds contains flavonoids and saponins (Table 1).

Table 1. Results of the phytochemical test of *C. papaya* seeds ethanol extract

No	Secondary metabolites	Test results
1	Alkaloid	Negative
2	Saponin	Positive
3	Tanin	Negative
4	Phenol	Negative
5	Flavonoids	Positive
6	Triterpenoid	Negative
7	Steroid	Negative
8	Glycosides	Negative

Antibacterial test

The antibacterial test showed a reduction in total bacterial colony compared to negative control. The test group with the lowest bacterial colony count, which was significantly different from the negative control, was the combination of 1000 µg/mL metronidazole with 6.25% $(226.3\pm26.63)\times10^5$ CFU/mL, 12.5% $(299\pm93.95)\times10^5$ CFU/mL, 25% $(148\pm116.97)\times10^5$ CFU/mL, 50% $(253\pm201.65)\times10^5$ CFU/mL, 100% $(173\pm48.13)\times10^5$ CFU/mL, 100% extract $(222\pm106)\times10^5$ CFU/mL, and 2000 µg/mL metronidazole $(40\pm4.36)\times10^5$ CFU/mL (Figure 1 and Table 2).

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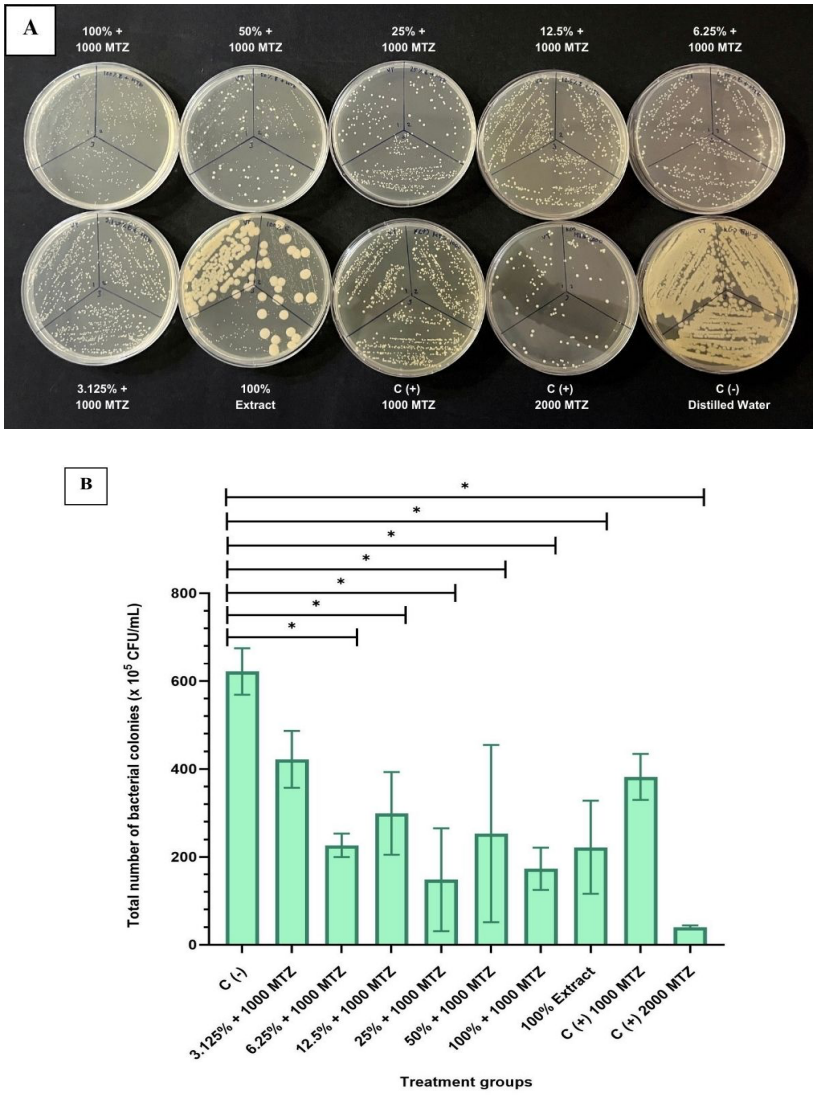

Figure 1. The results of antibacterial test of *C. papaya* seeds ethanol extract against *P. gingivalis* using the plate count method. MTZ = metronidazole (µg/mL). (A) Colonies of *P. gingivalis* on a petri dish. (B) Total bacterial colony count in the treatment groups. * = significantly different ($p<0.05$) to negative control according to Tukey HSD test.

Table 2. Results of the post-hoc test for the antibacterial test of the *C. papaya* seeds ethanol extract against the negative and positive controls.

Treatment groups	C (-)	3.125% + 1000 MTZ	6.25% + 1000 MTZ	12.5% + 1000 MTZ	25% + 1000 MTZ	50% + 1000 MTZ	100% + 1000 MTZ	100% Extract	C (+) 1000 MTZ	C (+) 2000 MTZ
C (-)	-	0.269	0.001*	0.012*	<0.001*	0.003*	<0.001*	0.001*	0.108	<0.001*
C (+) 1000 MTZ	0.108	1.000	0.583	0.980	0.125	0.787	0.222	0.548	-	0.007*
C (+) 2000 MTZ	<0.001*	0.002*	0.352	0.067	0.908	0.204	0.759	0.382	0.007*	-

* = significantly different ($p < 0.05$) according to Tukey HSD post-hoc test.

Antibiofilm test

After 1 hour of incubation, the combination of 1000 µg/mL metronidazole with 100% extract showed a significantly lower OD (0.06±0.06) than negative control (0.62±0.18). Similarly, the 100% extract group showed an OD of 0.16±0.06 (Figure 2).

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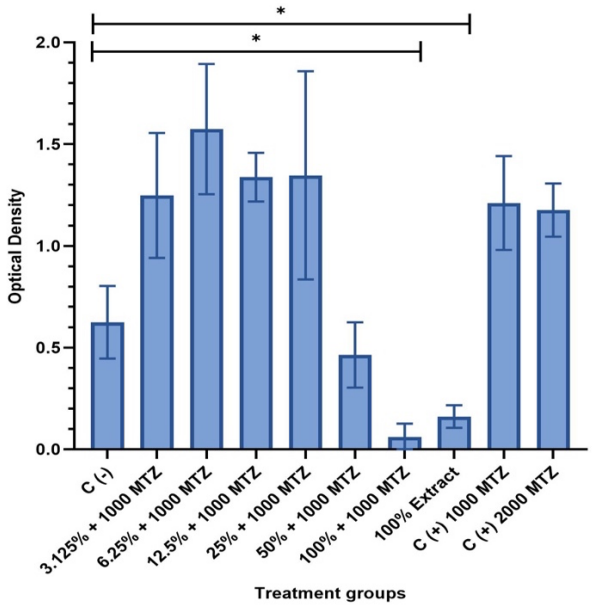

Figure 2. The results of antibiofilm test after 1 hour of incubation compared to the negative control. * = significantly different ($p < 0.05$) according to the Mann-Whitney test.

After 3 hours of incubation, the combination of 1000 µg/mL metronidazole with 100% extract showed a significantly lower OD (0.07±0.06) than the negative control (0.45±0.08). Similarly, the 100% extract group showed an OD of 0.09±0.06 (Figure 3).

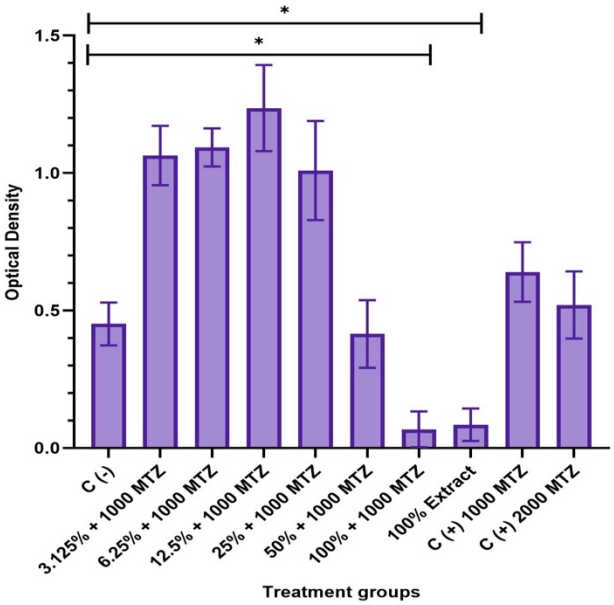

Figure 3. The results of the antibiofilm test after 3 hour of incubation compared to the negative control. * = significantly different ($p < 0.05$) according to the Mann-Whitney test.

After 24 hours of incubation, the combination of 1000 µg/mL metronidazole with 6.25% extract showed a significantly lower OD (0.18±0.05) than the negative control (0.38±0.07). Other groups with significant differences included the combination of 1000 µg/mL metronidazole with 25% extract (0.14 ± 0.05), 100%

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extract (0.11 ± 0.05), and 100% extract alone (0.04 ± 0.03) (Figure 4).

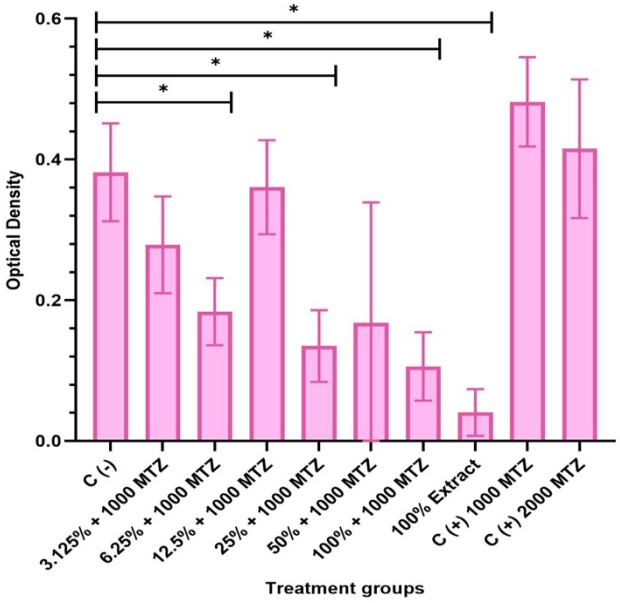

Figure 4. The results of the antibiofilm test after 24 hour of incubation compared to the negative control. * = significantly different ($p < 0.05$) according to the Mann-Whitney test.

Table 3. The results of the post-hoc test for the antibiofilm test of the *C. papaya* seeds ethanol extract against the negative and positive controls at 1, 3, and 24 hours of incubation.

Controls	Time	Treatment groups									
		C (-)	**3.125% + 1000 MTZ**	**6.25% + 1000 MTZ**	**12.5% + 1000 MTZ**	**25% + 1000 MTZ**	**50% + 1000 MTZ**	**100% + 1000 MTZ**	**100% Extract**	**C (+) 1000 MTZ**	**C (+) 2000 MTZ**
C (-)	1 hours	-	0.021*	0.021*	0.021*	0.083	0.248	0.021*	0.021*	0.021*	0.021*
	3 hours	-	0.021*	0.021*	0.021*	0.021*	1.000	0.021*	0.021*	0.043	0.386
	24 hours	-	0.083	0.021*	0.0386	0.021*	0.081	0.021*	0.021*	0.083	0.384
C (+) 1000 MTZ	1 hours	0.021*	0.773	0.149	0.386	0.386	0.021*	0.021*	0.021*	-	0.773
	3 hours	0.043*	0.021*	0.021*	0.021*	0.021*	0.021*	0.021*	0.021*	-	0.149
	24 hours	0.083	0.021*	0.021*	0.043*	0.021*	0.020*	0.021*	0.021*	-	0.384
C (+) 2000 MTZ	1 hours	0.021*	1.000	0.149	0.083	0.386	0.021*	0.021*	0.021*	0.773	-
	3 hours	0.386	0.021*	0.021*	0.021*	0.021*	0.564	0.021*	0.021*	0.149	-
	24 hours	0.384	0.146	0.020*	0.245	0.020*	0.080	0.020*	0.020*	0.384	-

* = significantly different ($p < 0.05$) according to Mann-Whitney test.

Discussion

This study showed that 100% ethanol extract of *C. papaya* seeds significantly inhibit *P. gingivalis*, which aligned with previous studies on other bacteria such as *P. aeruginosa* and *S. aureus* (Torar, Lolo, &

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Citraningtyas, 2017). The antibacterial test results showed that 1000 µg/mL metronidazole alone did not significantly inhibit *P. gingivalis* growth. This can be explained that metronidazole as a prodrug requires the metabolism of anaerob bacteria to become its active form. If the conversion to its active form is not optimal, the concentration of active metronidazole may not be sufficient to work effectively (Dingsdag & Hunter, 2018). To achieve an effective therapeutic effect, metronidazole is often combined with other antibiotics, such as amoxicillin (Karrabi, Baghani, & Venskutonis, 2022).

However, 2000 µg/mL metronidazole was able to inhibit *P. gingivalis* growth significantly. When 1000 µg/mL metronidazole was combined with the extract at concentrations ranging from 6.25% to 100%, it significantly inhibited *P. gingivalis* growth. This suggests that the extract can enhance the effectiveness of 1000 µg/mL metronidazole. The antibacterial effect of this combination of 1000 µg/mL metronidazole and 6.25 to 100% extract was equivalent to 2000 µg/mL metronidazole. This suggest that a lower dose of metronidazole (1000 µg/mL) is sufficient to inhibit *P. gingivalis* growth when combined with the extract. A similar result was found in a previous study that the combination of amoxicillin and *C. papaya* seeds methanol extract was more effective in inhibiting the growth of *Escherichia coli* compared to amoxicillin alone (Bridge et al., 2015).

The antibiofilm test used incubation times of 1, 3, and 24 hours to represent different stages of biofilm development: pellicle formation (1 hour), early adhesion (up to 3 hours), and biofilm maturation (24 hours) (Soesanto, Hepziba, Yasnill, & Widyarman, 2023). A reduction in optical density (OD) values indicates better antibiofilm activity.

The antibiofilm result of this study demonstrated that 100% ethanol extract of *C. papaya* seeds significantly inhibited biofilm formation compared to the negative control, suggesting strong antibiofilm effects against *P. gingivalis*. In contrast, 1000 µg/mL and 2000 µg/mL metronidazole alone during all incubation periods (1, 3, and 24 hours), showed higher OD than negative control. In other word, metronidazole alone did not effectively inhibit biofilm formation. This happen due to *P. gingivalis* biofilm matrix composed of matrix-enclosed polymeric substances (MPE) such as polysaccharides, proteins, and DNA that protect the bacterial cells within biofilm and limit metronidazole's penetration. To enhance the effectiveness of metronidazole against biofilm, the use of nanoparticles or liposomes could improve its ability to penetrate the biofilm (Dos Santos Ramos et al., 2018). Additionally, combining metronidazole with other drugs, such as amoxicillin or quorum sensing inhibitors, may enhance its antibiofilm activity (Hetta et al., 2024).

This study also found that combining 1000 µg/mL metronidazole with 100% extract effectively inhibited biofilm formation at all incubation times. This suggests that *C. papaya* seeds extract not only boosts the antibacterial activity of metronidazole but also has its own antibiofilm potential. At 24-hour incubation time, combining 1000 µg/mL metronidazole with the extract at 6.25% and 25% concentrations significantly inhibited biofilm formation compared to the negative control. This suggests that the strongest antibiofilm effect occurs during the biofilm maturation stage when *P. gingivalis* integrates into the microbial community, interacts with early colonizers, and firmly establishes itself within the biofilm structure.

The antibacterial and antibiofilm effects of the ethanol extract of *C. papaya* seeds on *P. gingivalis* in this study are due to the presence of saponins and flavonoids. Saponins increase the permeability of bacterial cell membranes, which can alter the morphology and destroy the bacterial

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membrane (Li & Monje-Galvan, 2023). This increased membrane permeability allows antibiotics to enter more easily, leading to bacterial death (Maghsoudloo, Bagheri, Aliakbari, & Velisdeh, 2023). Flavonoids inhibit bacterial defense mechanisms, quorum sensing, and biofilm formation. They destroy bacterial membranes, inhibit bacterial nucleic acid replication, and block ATP synthase, causing bacterial death. The antibiofilm mechanism of flavonoids involves enhancing penetration into the biofilm structure and inhibiting bacterial growth and adhesion to surfaces (Majnooni et al., 2023).

A study in India reported different secondary metabolites, including tannins, phenols, alkaloids, proteins, and glycosides, in the ethanol extract of *C. papaya* seeds (Sandhya Rani et al., 2023). The differences in phytochemical results could be attributed to variations in extraction methods, cultivation practices, the age of the papaya at harvest, and the geographical region where the papaya was grown. This difference is also due to variations in plant extraction methods, as the previous study used soxhlet extraction, while this study used maceration (Ulfa, Emelda, Munir, & Sulistyani, 2023).

The limitation of this study was variability during pipetting, which affected result consistency. Additionally, manually counting bacterial numbers was challenging, highlighting opportunities to improve accuracy in future studies.

Conclusions

The combination of 1000 µg/mL metronidazole with ethanol extract of *C. papaya* seeds exhibited antibacterial and antibiofilm effects against *P. gingivalis.* The ethanol extract of *C. papaya* seeds alone exhibits stronger antibacterial and antibiofilm effects against *P. gingivalis* compared to its combination with metronidazole.. The presence of flavonoids and saponins in the extract contributes to these effects.

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