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The Inhibitory Activity of Tetracycline and Doxycycline at Concentrations of 0.05–1.6% Against the Bacterium *Porphyromonas gingivalis*

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Abstract

Porphyromonas gingivalis is a key pathogen in the pathogenesis of periodontitis and plays a major role in periodontal tissue destruction. Mechanical therapy such as scaling and root planing is not always effective in eliminating this bacterium, especially in areas that are difficult to access, thus requiring the use of adjunctive antibiotics. Tetracycline and doxycycline are known to exhibit activity against anaerobic bacteria, their effectiveness at various concentrations against P. gingivalis has not been directly compared. This study aimed to quantitatively compare the inhibitory effect of Tetracycline and Doxycycline on the growth of P. gingivalis across various concentration ranges. The study employed a laboratory experimental design utilizing colony counting assay (measuring Colony-Forming Units - CFU/mL) and disc diffusion assay (measuring inhibition zone diameter). Tetracycline and Doxycycline were tested at concentrations ranging from 0.05% to 1.6%. The P. gingivalis bacterial suspension was adjusted to the 0.5McFarland standard, inoculated on Mueller-Hinton Agar (MHA), and incubated anaerobically at 37∘C for 48 hours. Chlorhexidine was used as a positive control, and sterile aquadest as a negative control. Data were statistically analyzed using the non-parametric Kruskal-Wallis test followed by Mann-Whitney post-hoc test. Results: This study demonstrated that tetracycline and doxycycline possess antibacterial activity against Porphyromonas gingivalis, with effectiveness increasing alongside higher concentrations. Doxycycline was shown to be more effective than tetracycline at the same concentration. The MIC of tetracycline was 0.4% and the MBC was 0.8%, while the MIC of doxycycline was 0.2% and the MBC was 0.4%. Statistical analysis and inhibition zone measurements confirmed significant differences between concentrations and indicated that higher concentrations of both antibiotics performed comparably to the positive control. Tetracycline 0.4% and doxycycline 0.2% effectively inhibited P. gingivalis, with doxycycline exhibiting stronger antibacterial potential.

Keywords: *Porphyromonas Gingivalis, Tetracycline, Doxycycline, Colony Count Assay, Disc Diffusion Assay*

1. Introduction

Approximately 50% of adults worldwide suffer from periodontitis, which is one of the leading causes of tooth loss (Chen et al., 2021; Tonetti et al., 2017). Recent studies indicate that up to 90% of the population may experience some form of periodontal disease, demonstrating the widespread nature of this condition (Aulia Ramadhani et al., 2021; Nathania et al., 2023). Data from the 2018 Indonesian Basic Health Research (Riskesdas) reported that the prevalence of periodontitis in Indonesia reached 74.1%. According to the World Health Organization (WHO) in 2024, the global prevalence of periodontitis among adults is approximately 19%, with poor oral hygiene and smoking identified as major risk factors.

Periodontitis affects not only oral health but also systemic health and overall quality of life. Several systemic diseases, including diabetes mellitus, cardiovascular diseases, and respiratory diseases, have been associated with this chronic inflammatory condition (Ma et al., 2020; Hajishengallis & Chavakis, 2021). This problem is particularly significant in Indonesia due to the high prevalence of diabetes, with approximately 75% of diabetic patients reported to experience periodontal complications (Wildan et al., 2023).

Porphyromonas gingivalis is a Gram-negative anaerobic bacterium that plays a crucial role in the pathogenesis of periodontitis. This disease is characterized by inflammation, destruction of periodontal tissues, and resorption of alveolar bone. The pathogenicity of *P. gingivalis* is supported by several virulence factors, including lipopolysaccharides (LPS), gingipains, and fimbriae, which facilitate bacterial adhesion and modulation of host immune responses (Zhou et al., 2022).

The interaction of these virulence factors accelerates periodontal tissue destruction and contributes to the association between periodontal disease and systemic conditions such as diabetes mellitus and cardiovascular diseases. As a result, periodontitis has become a significant public health concern that extends beyond oral health issues (Pussinen et al., 2022).

One approach to inhibit bacterial virulence is the use of antibiotics. Antibiotics have been shown to be effective in the management of periodontitis, particularly in severe cases, and are often prescribed as adjuncts to non-surgical periodontal therapy such as scaling and root planing (SRP). However, concerns have arisen regarding long-term effectiveness due to the emergence of antibiotic-resistant bacteria in periodontal pockets (Ardila et al., 2023; Kissa et al., 2023).

Local antimicrobial therapy in the form of subgingival irrigation has emerged as a practical and cost-effective alternative, particularly following SRP. This approach allows high concentrations of antibiotics to be delivered directly to periodontal pockets, minimizing systemic effects and reducing the risk of antimicrobial resistance and bacteremia caused by persistent pathogens such as *Porphyromonas gingivalis* (Waghmare et al., 2013).

Tetracycline has demonstrated advantages in periodontal therapy due to its antibacterial activity against periodontal pathogens as well as its non-antimicrobial properties, including anti-inflammatory effects and inhibition of matrix metalloproteinases (MMPs). Previous studies have shown that tetracycline hydrochloride can inhibit oral bacteria at various concentrations (Setiawati, 2008; Kusumawati et al., 2025). However, no studies have specifically evaluated the inhibitory effects of tetracycline and doxycycline against *Porphyromonas gingivalis*. Therefore, this study aims to evaluate the antibacterial effectiveness of tetracycline and doxycycline at concentrations of 0.05%–1.6% against *Porphyromonas gingivalis*.

2. Method

2.1 Periodontitis

Definition of Periodontitis

Periodontitis is a chronic inflammatory disease that causes progressive destruction of periodontal tissues, including the gingiva, cementum, periodontal ligament, and alveolar bone. It is primarily triggered by excessive accumulation of subgingival plaque bacteria that induce a host inflammatory immune response. Periodontitis is highly prevalent in Indonesia, reaching 74.1% according to Riskesdas 2018, while the global prevalence among adults is estimated at 19%. Clinically, the disease leads to loss of periodontal attachment, alveolar bone resorption, and ultimately tooth loss.

Etiology of Periodontitis

The primary etiological factor of periodontitis is the formation of pathogenic subgingival biofilm, particularly involving Porphyromonas gingivalis. This bacterium invades periodontal pockets and stimulates an inflammatory response aimed at eliminating pathogens, but excessive production of cytokines, proteinases, and prostaglandins results in collateral destruction of periodontal tissues, including the periodontal ligament and alveolar bone.

Pathogenesis

Periodontitis develops through sequential stages starting from initial and early lesions characterized by mild inflammation and gingivitis, progressing to established and advanced lesions marked by chronic inflammation, increased neutrophil infiltration, collagen degradation by matrix metalloproteinases, alveolar bone resorption, and deep periodontal pocket formation.

2.2 Tetracycline and Its Derivatives

Tetracycline

Tetracycline is a broad-spectrum bacteriostatic antibiotic widely used as an adjunctive therapy in periodontal treatment, particularly in aggressive periodontitis. Besides inhibiting Gram-positive and Gram-negative bacteria, tetracycline suppresses bone resorption, enhances collagen synthesis, and supports periodontal tissue repair. However, inappropriate use may contribute to antimicrobial resistance, influenced by bacterial mutation, incomplete antibiotic courses, and misuse without prescription.

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Mechanism of Action

Tetracycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, preventing aminoacyl-tRNA attachment and halting peptide elongation. Its ability to penetrate Gram-negative bacteria through passive diffusion and active transport enables effective intracellular antibacterial activity.

Route of Administration and Dosage

Tetracycline is commonly administered orally at 250–500 mg four times daily, while intravenous dosing is typically 500 mg every 6–12 hours depending on clinical conditions. Common side effects include tooth discoloration, gastrointestinal discomfort, dizziness, and hypersensitivity reactions.

Contraindications

Tetracycline is contraindicated in pregnant women and children under eight years due to risks of permanent tooth discoloration and impaired bone development. It should also be avoided in patients with renal impairment or hypersensitivity to tetracyclines, and its absorption may be reduced by antacids and iron supplements.

Doxycycline

Doxycycline is a broad-spectrum tetracycline derivative effective against Gram-positive and Gram-negative bacteria and is widely used in periodontal therapy. It inhibits matrix metalloproteinases (MMP-8 and MMP-9), thereby reducing inflammation and alveolar bone resorption, and also suppresses collagenase activity in gingival crevicular fluid.

Mechanism of Action

Doxycycline acts as a bacteriostatic agent by binding to the 30S ribosomal subunit, preventing aminoacyl-tRNA binding and inhibiting protein synthesis. Its high lipophilicity allows extensive tissue penetration, and it also exhibits non-antimicrobial effects such as inhibition of mitochondrial protein synthesis.

Route of Administration and Dosage

Doxycycline is typically administered orally at 100 mg twice daily on the first day, followed by 100 mg once daily, while sub-antimicrobial dosing for host modulation is 20 mg twice daily. Intravenous administration at 200 mg per day may be used in acute clinical settings.

Contraindications

Doxycycline is contraindicated during pregnancy due to potential adverse effects on fetal bone and tooth development. It should also be avoided in patients with known hypersensitivity reactions or esophageal disorders due to the risk of severe allergic reactions and esophageal irritation.

2.3 Porphyromonas gingivalis

Description of Porphyromonas gingivalis

Porphyromonas gingivalis is a Gram-negative, anaerobic, rod-shaped bacterium classified within the red complex and is a major etiological agent of periodontitis. Its virulence factors, including lipopolysaccharides, fimbriae, and gingipains, promote biofilm formation, immune modulation, tissue destruction, and are associated with systemic diseases such as diabetes and cardiovascular disorders.

Metabolism of Porphyromonas gingivalis

P. gingivalis is an asaccharolytic bacterium adapted to anaerobic, protein-rich subgingival environments, utilizing amino acids and peptides from gingival crevicular fluid and host proteins. Its growth is enhanced through metabolic interactions with other oral microorganisms and requires hemin from host blood as a critical iron source.

Porphyromonas gingivalis in Periodontal Tissues

In periodontal tissues, P. gingivalis can invade epithelial cells, disrupt tissue barriers, and induce proinflammatory cytokine production, contributing to periodontal tissue destruction. The bacterium may also enter the bloodstream through ulcerated epithelium during routine oral activities, linking periodontal infection to systemic inflammatory responses.

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3. Hasil dan Diskusi

3.1 Analysis of Research Results

Analysis of MIC and MBC Results of Tetracycline Against *Porphyromonas gingivalis*

Normality Test Analysis

The normality test was conducted using the Shapiro–Wilk test because the sample size in each group was fewer than 50. The results showed that most treatment groups had significance values greater than 0.05, indicating that the data were normally distributed. Groups that met the normality assumption included the negative control group ($p = 0.497$), tetracycline 0.2% ($p = 0.637$), tetracycline 0.1% ($p = 0.780$), and tetracycline 0.05% ($p = 0.306$). The normality test results for the tetracycline colony count data are presented in Appendix 1.

However, the tetracycline 0.4% group had a significance value of 0.000 ($p < 0.05$), indicating that the data in this group were not normally distributed. This finding served as the basis for selecting the subsequent statistical tests. Since at least one group did not meet the normality assumption, further analysis comparing all groups was more appropriately conducted using a non-parametric test, namely the Kruskal–Wallis test.

Homogeneity of Variance Test

The homogeneity of variance was assessed using Levene's test to determine the equality of variances among treatment groups. The analysis yielded a significance value of 0.000 ($p < 0.05$), indicating that the variances among the treatment groups were not homogeneous. The results of the homogeneity test for the tetracycline colony count data are provided in Appendix 2.

Because one group failed the normality test and Levene's test indicated non-homogeneous variances, non-parametric statistical tests were selected for data analysis. The Kruskal–Wallis test was used to compare multiple groups when the assumptions for ANOVA were not met, followed by the post hoc Mann–Whitney test to identify significant differences between treatment groups.

Statistical Test Analysis

The Kruskal–Wallis test was performed to evaluate differences in the number of *P. gingivalis* colonies among the treatment groups. The results of the Kruskal–Wallis analysis for the MIC and MBC data of tetracycline against *P. gingivalis* are presented below.

Table 1 Statistical Analysis Results of MIC and MBC Data of Tetracycline Against *P. gingivalis*

Study Group	r (Number of Replications)	p (Significance Value)	Description
Positive control	3	0.002	Statistically significant difference
Negative control	3		
Tetracycline 1.6%	3		
Tetracycline 0.8%	3		
Tetracycline 0.4%	3		
Tetracycline 0.2%	3		
Tetracycline 0.1%	3		
Tetracycline 0.05%	3		

Based on the Kruskal–Wallis test results for all study groups, a significance value of $p = 0.002$ was obtained, with three replications in each group. A p-value less than 0.05 indicates a statistically significant difference between the control group and the various tested concentrations of tetracycline against *Porphyromonas gingivalis*. These findings suggest that at least one treatment group produced a significantly different effect, thereby necessitating further analysis using a post hoc test to identify specific group differences.

Post Hoc Analysis

Based on the results of the post hoc Mann–Whitney test, a consistent pattern of differences among the treatment groups was observed. The results of the Mann–Whitney analysis for the MIC and MBC data of tetracycline against *P. gingivalis* are presented below.

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Table 2 Post Hoc Analysis Results of MIC and MBC of Tetracycline Against *P. gingivalis*

Kelompok	K(+)	K(-)	1,6%	0,8%	0,4%	0,2%	0,1%	0,05%
K(+)	-	0.000*	1.000	1.000	0.911	0.003*	0.000*	0.000*
K(-)	0.000*	-	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
1,6%	1.000	0.000*	-	1.000	0.911	0.003*	0.000*	0.000*
0,8%	1.000	0.000*	1.000	-	0.911	0.003*	0.000*	0.000*
0,4%	0.911	0.000*	0.911	0.911	-	0.029*	0.000*	0.000*
0,2%	0.003*	0.000*	0.003*	0.003*	0.029*	-	0.125	0.000*
0,1%	0.000*	0.000*	0.000*	0.000*	0.000*	0.125	-	0.000*
0,05%	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0,000*	-

Note: (*): Statistically significant difference between groups.

Based on the results of the post hoc Mann–Whitney test, several group pairs showed statistically significant differences. The negative control group and the tetracycline concentration of 0.05% demonstrated significant differences compared with all other groups. Higher tetracycline concentrations (1.6%, 0.8%, and 0.4%) did not show significant differences among each other but differed significantly from lower concentrations (0.2%, 0.1%, and 0.05%). Conversely, the 0.2% and 0.1% concentrations did not differ significantly from each other; however, both showed significant differences compared with nearly all other groups, particularly those with higher concentrations.

3.2 Analysis of MIC and MBC Results of Doxycycline Against *Porphyromonas gingivalis*

Normality Test Analysis

A normality test was conducted to determine whether the data in each treatment group followed a normal distribution. The Shapiro–Wilk test was used because the sample size in each group was fewer than 50 (n = 3). The results of the normality test for the doxycycline colony count data are presented in Appendix 5. Based on the Shapiro–Wilk test results, all groups showed p-values greater than 0.05, including the negative control group (p = 0.567), doxycycline 0.2% group (p = 0.843), doxycycline 0.1% group (p = 0.537), and doxycycline 0.05% group (p = 0.726). These results indicate no significant deviation from normal distribution at the 5% significance level. Therefore, the data for all groups were considered normally distributed. With the normality assumption satisfied, further analysis could proceed using a parametric test, namely One-Way ANOVA, to evaluate differences in mean values among treatment groups.

Homogeneity of Variance Test

A homogeneity of variance test was performed to assess whether variances among treatment groups were equal, which is a requirement for parametric statistical analysis. Levene's test was used for this purpose, and the results of the homogeneity test for the MIC and MBC data of doxycycline are presented in Appendix 6. Based on Levene's test using mean values, a significance value of p = 0.002 was obtained, which is less than 0.05. This result indicates that the variances among groups were not homogeneous and therefore did not meet the assumption of homogeneity. Because the homogeneity assumption was not met, parametric statistical tests such as ANOVA could not be applied. Consequently, differences among treatment groups were analyzed using the non-parametric Kruskal–Wallis test. If statistically significant differences were identified, further analysis was conducted using the post hoc Mann–Whitney test.

Statistical Test Analysis

The Kruskal–Wallis test was applied because the data did not meet the assumption of homogeneity required for parametric analysis. This test aimed to determine whether there were statistically significant differences in bacterial colony counts among the treatment groups. The results of the Kruskal–Wallis analysis for the MIC and MBC data of doxycycline against *P. gingivalis* are presented below.

Table 3 Statistical Analysis Results of MIC and MBC Data of Doxycycline Against *P. gingivalis*

Study Group	**r (Number of Replications)**	**p (Significance Value)**	**Description**
Positive control	3	0.002	Statistically significant difference
Negative control	3		

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Doxycycline 1.6%	3		
Doxycycline 0.8%	3		
Doxycycline 0.4%	3		
Doxycycline 0.2%	3		
Doxycycline 0.1%	3		
Doxycycline 0.05%	3		

Based on the Kruskal–Wallis test results for the control group and various doxycycline concentrations, a significance value of p = 0.002 was obtained, with three replications in each group. A p-value less than 0.05 indicates a statistically significant difference among the study groups in inhibiting the growth of *Porphyromonas gingivalis*. These findings suggest that at least one doxycycline concentration produced a significantly different inhibitory effect compared with the other groups, thereby necessitating further analysis to identify which specific groups differed significantly.

Post Hoc Analysis

A post hoc Mann–Whitney test was conducted to determine which group pairs exhibited statistically significant differences following the Kruskal–Wallis test. The results of the Mann–Whitney analysis for the MIC and MBC data of doxycycline against *P. gingivalis* are presented below.

Table 4 Post Hoc Analysis Results of MIC and MBC of Doxycycline Against *P. gingivalis*

Group	K(+)	K(-)	1,6%	0,8%	0,4%	0,2%	0,1%	0,05%
K(+)	-	0.000*	1.000	1.000	1.000	0.073	0.000*	0.000*
K(-)	0.000*	-	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
1,6%	1.000	0.000*	-	1.000	1.000	0.073	0.000*	0.000*
0,8%	1.000	0.000*	1.000	-	1.000	0.073	0.000*	0.000*
0,4%	1.000	0.000*	1.000	1.000	-	0.073	0.000*	0.000*
0,2%	0.073	0.000*	0.073	0.073	0.073	-	0.000*	0.000*
0,1%	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	-	0,001*
0,05%	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0,001*	-

Notes: (*): Statistically significant difference between groups

Based on the Post Hoc Mann–Whitney test results, a clear pattern of differences among the treatment groups was observed. The negative control group showed significant differences compared with all other groups, indicating a markedly different response compared to doxycycline treatment. High concentrations (1.6%, 0.8%, and 0.4%) did not differ significantly from one another but showed significant differences compared with very low concentrations, namely 0.1% and 0.05%. The 0.2% concentration exhibited a pattern similar to the higher concentrations and did not differ significantly from those groups; however, it showed significant differences compared with the 0.1% and 0.05% concentrations. Meanwhile, the 0.1% and 0.05% concentrations showed significant differences compared with almost all other treatment groups.

3.3 Analysis of the Inhibitory Effects of Tetracycline and Doxycycline Against Porphyromonas gingivalis

Normality Test Analysis

Based on the normality test results presented in the table, all treatment groups including the positive control, various concentrations of tetracycline (0.8%, 0.4%, and 0.2%), and various concentrations of doxycycline (0.4%, 0.2%, and 0.1%) showed significance values (p-values) greater than 0.05 in the Shapiro–Wilk test. This indicates no significant difference between the data distribution of each group and a normal distribution. Therefore, the data from all groups can be considered normally distributed and meet the normality assumption for parametric statistical analysis. The results of the normality test for the inhibitory effect of tetracycline and doxycycline against P. gingivalis are presented in Appendix 9.

Homogeneity Test Analysis

Based on the homogeneity test using Levene's Test, the significance value based on the mean was 0.043. This value is less than 0.05, indicating that the variances among the groups were not homogeneous or did not have equal variance. This condition suggests that the assumption of homogeneity of variance required for parametric analysis was not met. Therefore, statistical analysis was continued using the non-parametric Kruskal–Wallis test,

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and if significant differences were identified, a post hoc Mann–Whitney test was performed. The results of the homogeneity test for the inhibitory effect of tetracycline and doxycycline against P. gingivalis are presented in Appendix 10.

Statistical Test Analysis

The Kruskal–Wallis test was employed because the data did not meet the homogeneity assumption, making parametric analyses such as ANOVA unsuitable. The results of the Kruskal–Wallis test for the inhibitory effects of tetracycline and doxycycline against P. gingivalis are presented below:

Table 5 Statistical Analysis Results of the Inhibitory Effects of Tetracycline and Doxycycline Against P. gingivalis

Study Group	r (Number of Replications)	p (Significance Value)	Description
Positive control	3	0.002	Statistically significant difference
Negative control			
Tetracycline 0.8%			
Tetracycline 0.4%			
Tetracycline 0.2%			
Doxycycline 0.4%			
Doxycycline 0.2%			
Doxycycline 0.1%			

The Kruskal–Wallis test results showed a statistically significant difference among all tetracycline and doxycycline treatment groups against P. gingivalis ($p = 0.002$). These findings indicate that variations in antibiotic concentrations and control groups produced significantly different inhibitory effects, thereby necessitating further analysis to identify which specific groups differed significantly.

Mann–Whitney Test Analysis

A post hoc Mann–Whitney test was conducted to determine which pairs of groups exhibited statistically significant differences after the Kruskal–Wallis test indicated significant differences among the groups. The results of the Mann–Whitney analysis for the inhibitory effects of tetracycline and doxycycline against P. gingivalis are presented below.

Table 6 Post Hoc Analysis Results of the Inhibitory Effects of Tetracycline and Doxycycline Against P. gingivalis

Group	K(+)	K(-)	Tetrasiklin 0,8%	Tetrasiklin 0,4%	Tetrasiklin 0,2%	Doksisiklin 0,4%	Doksisiklin 0,2%	Doksisiklin 0,1%
K(+)	-	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
K(-)	0.000*	-	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
Tetrasiklin 0,8%	0.000*	0.000*	-	0.044*	0.000*	0.080	0.410	0.023*
Tetrasiklin 0,4%	0.000*	0.000*	0.044*	-	0.001*	0.003*	0.866	0.251
Tetrasiklin 0,2%	0.000*	0.000*	0.000*	0.001*	-	0.000*	0.073	0.073
Doksisiklin 0,4%	0.000*	0.000*	0.880	0.003*	0.000*	-	0.047*	0.000*
Doksisiklin 0,2%	0.000*	0.000*	0.410	0.866	0.073	0.047*	-	0,023*
Doksisiklin 0,1%	0.000*	0.000*	0.023*	0.251	0.073	0.000*	0,023*	-

Note:
(*): Statistically significant difference between groups.

Post Hoc Mann–Whitney analysis showed that most treatment pair comparisons had significance values of $p < 0.05$, indicating statistically significant differences between the groups. The positive control group

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demonstrated significant differences when compared with all concentrations of both tetracycline and doxycycline treatments. The negative control group also showed significant differences compared with nearly all treatment concentrations.

Within the tetracycline group, the 0.8% concentration showed significant differences compared with almost all other groups, except for doxycycline at concentrations of 0.4% and 0.2%, which showed no statistically significant difference. Tetracycline 0.4% also demonstrated significant differences with most groups, except with doxycycline 0.2% and 0.1%. Similarly, tetracycline 0.2% showed significant differences with several groups but did not differ significantly from doxycycline 0.2% and 0.1%.

In the doxycycline group, the 0.4% concentration showed significant differences with almost all groups, including doxycycline 0.2%, but did not differ significantly from tetracycline 0.8%. Doxycycline 0.2% did not show significant differences compared with some lower-dose tetracycline groups but differed significantly from doxycycline 0.1%. Overall, doxycycline 0.1% demonstrated significant differences compared with most other treatment groups.

4. Conclusion

Based on the results of this study, tetracycline at a concentration of 0.4% and doxycycline at a concentration of 0.2% demonstrated antibacterial activity against *Porphyromonas gingivalis*. These findings indicate that both antibiotics are effective in inhibiting the growth of *P. gingivalis* at specific concentrations, supporting their potential use as local antimicrobial agents in periodontal therapy.

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