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Mechanism of inhibiting periodontitis pathogenesis with various variations of inhibitors on *Porphyromonas gingivalis*: Systematic literature review

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Abstract

Background: Periodontal disease is the most prevalent disease worldwide with a prevalence of 20% to 50%, including periodontitis. Periodontitis involves complex interactions between specific pathogenic bacteria and host immune response. Microbial infections in subgingival biofilms are mainly caused by gram-negative bacteria including *Porphyromonas gingivalis*. Inhibition of *Porphyromonas gingivalis* virulence is one way to prevent periodontitis. This inhibition can be done in several ways through peptide inhibitors, quorum sensing inhibitors and natural inhibitors.

Objective: This study aims to explain the mechanism of inhibiting periodontitis pathogenesis with various inhibitors on *Porphyromonas gingivalis.*

Methods: his study employed a systematic literature review design by searching for articles based on predetermined inclusion and exclusion criteria. The search strategy used keywords and Boolean Operators from two databases (EBSCO and ProQuest).

Results: he use of SAPP as a peptide inhibitor can inhibit the activity of *Porphyromonas gingivalis* gingipains, suppressing cytokine levels and inhibit colonization of *Porphyromonas gingivalis*. The use of furanone, D-ribose and BMK-Q101 as quorum sensing inhibitors can reduce *Porphyromonas gingivalis* in biofilms, inhibit the biosynthesis of autoinducer-2 so as to suppress the virulence factors of *Porphyromonas gingivalis.* The use of prenyl flavonoid as a natural inhibitor is a potent inhibitor of Arg-gingipain (Rgp) and Lys-gingipain (Kgp) and completely suppress the growth of *Porphyromonas gingivalis*.

Conclusion: Inhibition of *Porphyromonas gingivalis* using peptide inhibitor, quorum sensing inhibitors and natural inhibitor can suppress virulence factors and inhibit biofilm formation of *Porphyromonas gingivalis* thus inhibiting the pathogenesis of periodontitis.

Keywords: *Porphyromonas gingivalis*; Peptide Inhibitors; Quorum Sensing Inhibitors; Natural Inhibitor; Periodontitis

1. Introduction

Periodontal disease occurs due to interaction between microorganisms and their host in the biofilm, causes an imbalance and pathological transformation [1]. According to the Global Burden of Disease Study, periodontal disease is the 11th most prevalent disease in the world. The prevalence of periodontal disease is 20% to 50% worldwide [2]. World Health Organization states that it is necessary to control periodontal disease to reduce the prevalence of

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periodontal disease as it is one of the oral diseases that contribute to the global burden of chronic diseases and is a major public health problem [3].

Periodontitis is a multifactorial inflammation associated with the accumulation of dental plaque (biofilm) and is characterized by progressive destruction of the supporting tissues of the teeth, including the periodontal ligament and alveolar bone. Periodontitis involves a complex interaction between host immune response, environmental factors such as smoking and specific pathogenic bacteria, especially a gram-negative anaerobic bacteria includes *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* [4]. Opportunistic *Porphyromonas gingivalis* antigens can trigger periodontitis cases by 40-100%. As many as 85.75% of *Porphyromonas gingivalis* bacteria were found in subgingival plaque with chronic periodontitis [5].

Porphyromonas gingivalis is associated with the severity of periodontal disease and is identified as one of the main causative agents of periodontitis [6]. *Porphyromonas gingivalis* is a major pathogen that can impair innate immunity in several ways that can alter biofilm composition and change host homeostasis [7]. Inhibition of *Porphyromonas gingivalis* is one way to prevent periodontitis disease. This inhibition can be done in several ways, namely through peptide inhibitors, quorum sensing inhibitors and natural inhibitors.

One of the peptide inhibitors obtained by *Porphyromonas gingivalis* is Streptococcal ArcA Anti-P. gingivalis Peptide (SAPP) which can bind tightly to the surface of *Porphyromonas gingivalis* and can suppress virulence factors in *Porphyromonas gingivalis* [8]. One of the quorum sensing inhibitors (QSI) is D-ribose and (5Z)-4-bromo5-(bromomethylene)-2(5H)-furanone which can inhibit biofilm formation in the oral cavity. The use of quorum sensing inhibitors is one of the protective ways to maintain oral health [9]. Natural inhibitors such as polyphenols have been investigated because of various biological functions such as antimicrobial, anti-inflammatory, antioxidation, and anticancer. The largest class of polyphenols is flavonoids which can inhibit the virulence of *Porphyromonas gingivalis* [10].

This study aims to examine the mechanism of inhibition of periodontitis pathogenesis with various variations of inhibitors on *Porphyromonas gingivalis*. The research seeks to clarify this process using insight from previous studies, providing a basis for future investigations.

2. Material and methods

This type of research is literature review study using a Systematic Literature Review design. The research is conducted by searching for several literatures that relevant to the discussed topic as references.

2.1. Research Strategy

The search for literature from journals or articles in this study was conducted using a search strategy with keywords and Boolean Operators (AND, OR, and NOT). The literature search was focused on journal articles in English within the last 10 years from 2014 to 2024. The keywords used were peptide inhibitor OR quorum sensing inhibitor OR natural inhibitor AND *Porphyromonas gingivalis* OR biofilm AND periodontitis.

2.2. Inclusion and Exclusion Criteria

The data collection strategy used was to apply inclusion and exclusion criteria based on the PICO framework, which consists of population, intervention, comparison and outcome.

Table 1 PICO Framework for Inclusion and Exclusion Criteria

PICO Framework	Inclusion	Exclusion
Population	Periodontitis	Other diseases in periodontal tissue
Intervention	Inhibition with various inhibitors in *Porphyromonas gingivalis*	Inhibition with other inhibitors on *Porphyromonas gingivalis*
Comparison	-	-
Outcome	Pathogenesis of periodontitis	Pathogenesis of other periodontal diseases

2.3. Analysis and Synthesis Data

Data was collected from two online databases, EBSCO and ProQuest, using Boolean Operators and predefined keywords. Data limitation and crawling were applied based on the inclusion and exclusion criteria. Literature were selected by reading the titles and abstracts according to the research topic and inclusion-exclusion criteria. The titles and abstracts of literature that did not match these criteria were excluded. The remaining data collection was selected by full text reading. Literature publications that did not pass full text reading were not selected. The quality of the studies was assessed based on the CRAAP criteria and the CASP critical appraisal method.

3. Results and discussion

This systematic literature review identified a final selection of 5 articles that matched the inclusion criteria.

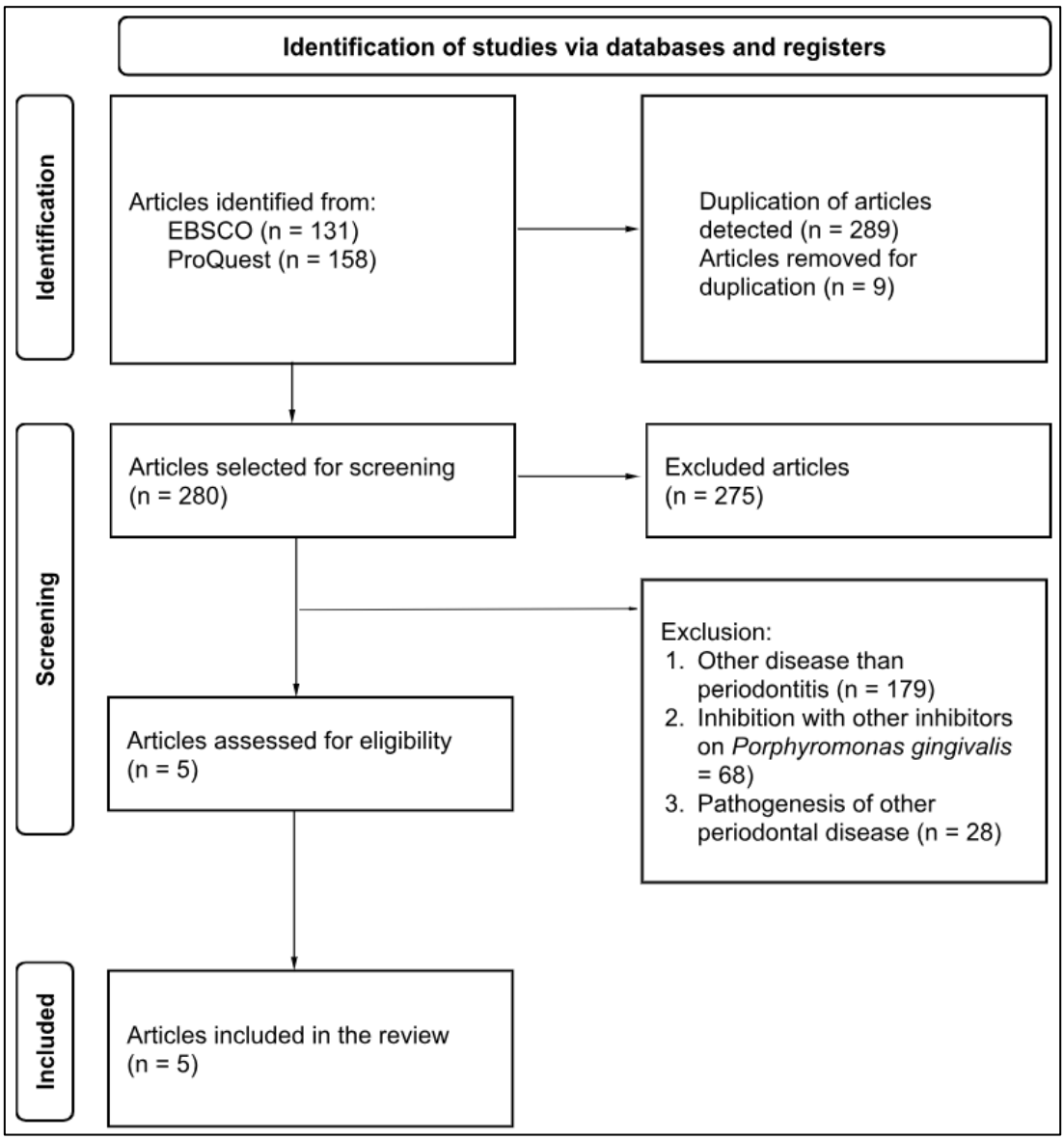

Figure 1 PRISMA Flow Chart of Selection Process

Table 2 Results of Literature

No.	Author Name, Year	Research Result
1.	Ho, et. al., 2020	SAPP can suppress the gingipain activity of Porphyromonas gingivalis due to decreased cytokine. SAPP are effective in suppressing Porphyromonas gingivalis activity and manipulating microbial species to reduce microbial communities.
2.	Ho, et. al., 2018	SAPP suppressed the virulence of fimA and rgpA/B genes. SAPP caused a significant reduction of Porphyromonas gingivalis in the microbial biofilms and decreased the number of other bacteria, making it a promising therapeutic agent against chronic periodontitis.
3.	Ben Amara, et. al., 2018	Manipulation of quorum sensing signals using quorum sensing inhibitor can reduce autoinducer-2 expression by periodontopathogens, thus showing a decrease bacteria in biofilm so as to prevent periodontitis infection.
4.	Kariu, et. al., 2017	Prenyl flavonoids as natural inhibitor can inhibit Porphyromonas gingivalis and can be used as a development of periodontitis treatments that suppress gingipain, Porphyromonas gingivalis growth and biofilm formation.
5.	Cho, et. al., 2016	Quorum sensing inhibitor showed a decrease in bone destruction and a decrease in the amount of Porphyromonas gingivalis in the biofilm. The use of quorum sensing inhibitor on bacteria in vivo suggests a new approach to the prevention and treatment of periodontitis.

3.1. Peptide inhibitors in *Porphyromonas gingivalis*

The DNA concentration of bacteria cultured with Streptococcus ArcA derived anti-P. gingivalis Peptide (SAPP) was significantly lower than bacteria cultured without SAPP. The number of *Porphyromonas gingivalis* found in dental plaque samples that have been exposed to SAPP shows a decrease of 3.7 times, indicating that SAPP can eliminate biofilm-forming bacteria. The gingival sulcus fluid concentration of IL-8 levels was lower in chronic periodontitis patients compared to healthy patients [11]. The result of IL-6, IL-8, and MCP-1 levels in media exposed to *Porphyromonas gingivalis* decreased significantly, this occurs because the virulence factor produced by *Porphyromonas gingivalis* is gingipains. The administration of SAPP can make cytokine levels return to normal because SAPP can inhibit the activity of *Porphyromonas gingivalis* gingipains so that *Porphyromonas gingivalis* fails to manipulate cytokine levels. *Porphyromonas gingivalis* can express IL-1, IL-6 and TNF-α, which are proinflammatory cytokines that can cause periodontal tissue damage [12]. The group of mice exposed to *S. gordonii* / *P. gingivalis* and SAPP 30 μM SAPP showed the best results. This shows that the administration of SAPP in the mice model can significantly inhibit alveolar bone loss.

Research using dental plaque samples of chronic periodontitis patients found that administration of Streptococcus ArcA derived anti-P. gingivalis Peptide (SAPP) to Human Oral Keratinocytes (HOK) and Human Periodontal Ligament Fibroblasts (HPLF) did not damage cell membranes, indicating that SAPP has no impact on human oral viability. SAPP derivatives P34 and P35 caused a significant decrease in *Porphyromonas gingivalis* concentration of more than 20 times or more than 50% in microbial biofilms. SAPP derivative P33 can suppress the expression of fimA and rgpA/B genes by about 60%. Reduced expression of FimA genes (I, II, III, and IV) will inhibit colonization of *Porphyromonas gingivalis* strains. The reduction of *Porphyromonas gingivalis* in biofilm affects the colonization of periodontal pathogens such as *T. forsythia, T. denticola* and *F. nucleatum*. This bacterium is a gram-negative red complex bacterium, a periodontal pathogen that is often found in the subgingiva of chronic periodontitis patients [13]. *Porphyromonas gingivalis* is a key pathogen that can increase the virulence of the entire microbial community in biofilms so that it can trigger chronic periodontitis and SAPP can suppress the virulence of *Porphyromonas gingivalis. Porphyromonas gingivalis* in low numbers can still interfere with the body's immune response and disrupt the symbiosis between oral bacteria [14]. The development of periodontitis and SAPP can be used as a preventive to prevent the pathogenesis of chronic periodontitis.

3.2. Quorum sensing inhibitors in *Porphyromonas gingivalis*

Research was conducted using a mice model and using quorum sensing inhibitors (QSI) in the form of BMK-Q101 and D-ribose to prevent biofilm growth. The results of linear measurements of the interproximal area and the distance between the alveolar bone crest and the cemento enamel junction of the *Porphyromonas gingivalis* and *Fusobacterium nucleatum* dual infection group resulted in significantly more severe bone loss. Quorum sensing is a microbial communication mechanism in response to environmental changes such as nutrient availability and bacterial density [15]. The quorum sensing inhibitor of autoinducer-2-treated group showed a significant reduction in alveolar bone loss by 40%. The results of residual bone volume measurement in the dual infection group caused more bone tissue loss than the QSI-treated group. The residual bone volume of the MI-M2 and M2-M3 interproximal areas appeared to be larger in the QSI-treated and control groups than in the double-infection group. The group infected by *Porphyromonas gingivalis* and *Fusobacterium nucleatum* showed greater bone loss to the furcation area than the control group [16]. The group with QSI showed a 93% reduction in oral bacteria. The expression of TNF-α, IL-1β, IL-6, NF-κB, MMP-8 and MMP-13 increased in the *Porphyromonas gingivalis* group [17]. This shows that QSI can suppress the expression of *Porphyromonas gingivalis* genes that can trigger chronic periodontitis to cause alveolar bone loss.

D-ribose and [(5Z)-4-bromo-5-(bromomethylene)-2(5H)-furanon] are known as representative compounds of the quorum sensing (QS) autoinducer-2 (AI-2)/LuxS inhibitory system. *Porphyromonas gingivalis* uses the AI-2 system for signaling and biofilm attachment while LuxS for virulence expression control. From the micro-CT results, bone damage and alveolar bone crest (ABC) and cemento enamel junction (CEJ) range of the QSI group showed lower results than the infection group. It can be concluded that D-ribose and furanone compounds as QSI can suppress the growth of *Porphyromonas gingivalis* in biofilm, inhibit the biosynthesis of AI-2 from *Porphyromonas gingivalis* and inhibit the LuxS gene. Without QSI, *Porphyromonas gingivalis* can increase bacterial cell density and can secrete Rgp and Kgp associated with LuxS proteins. *Porphyromonas gingivalis* can perform quorum sensing by releasing Rgp and Kgp, which are one of the virulence factors that can affect proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and IL-8 [18]. *Porphyromonas gingivalis* can release LuxS protein which release leukotoxin, the expression of the most powerful bacterial virulence factor so that it can cause periodontal tissue damage [19].

3.3. Natural inhibitors in *Porphyromonas gingivalis*

Research using prenyl flavonoids from extracts of Epimedium species shows inhibitory properties against gingival pain. Compounds 8, 10 and 11 significantly inhibited gingipain and the overall growth of *Porphyromonas gingivalis* at 12.5 μM. Compound 8 is a potent inhibitor of Rgp and Kgp, so it can suppress gingipain significantly. Gingipain R (RgpA and RgpB) and gingipain K (Kgp), have been isolated from many strains of *Porphyromonas gingivalis g*rowing under different conditions which are directly involved in periodontal pocket colonization which causes periodontal tissue damage [20]. Compounds 6, 7, 8 and 13 showed inhibition of the growth of *Porphyromonas gingivalis*, especially compounds 6 and 8 significantly inhibited biofilm formation by *Porphyromonas gingivalis*. This shows that prenyl flavonoids from Epimedium species can be used as inhibitors of *Porphyromonas gingivalis* because they show satisfactory results, it can suppress gingipain and Kgp and Rgp which influence the growth of *Porphyromonas gingivalis* in biofilms so that they can inhibit the pathogenesis of periodontitis.

4. Conclusion

Inhibition of *Porphyromonas gingivalis* using peptide inhibitors can inhibit *P. gingivalis* virulence activities such as gingipains, fimA, and rgpA/B, as well as suppress *P. gingivalis* in biofilms. Quorum sensing inhibitors can prevent biofilm growth by suppressing Autoinducer-2 and the LuxS gene so that they inhibit the expression of Arg-gingipain (Rgp) A and B and Lys-gingipain (Kpg). Natural inhibitors are strong inhibitors of Arg-gingipain (Rgp) and Lys-gingipain (Kpg) so that biofilm formation is inhibited. Variations of inhibitors can suppress virulence expression and inhibit biofilm formation in *Porphyromonas gingivalis*, thus preventing the pathogenesis of periodontitis.

Compliance with ethical standards

Acknowledgments

There is no conflict interest declared by authors in this study.

Disclosure of conflict of interest

No conflict interest to be disclosed.

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