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The Quorum Sensing Mechanism of *Aggregatibacter actinomycetemcomitans* in Pathogenesis of Periodontitis: Systematic Literature Review

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Abstract

Background: Periodontitis is one of the most prevalent oral diseases worldwide and a significant public health concern. Periodontitis characterized by inflammation of the tissues supporting the teeth. It is primarily caused by bacteria in the subgingival biofilm, with *A. actinomycetemcomitans* and *P. gingivalis* as a key pathogens. These bacteria contribute to oral dysbiosis, leading to periodontal tissue damage. *A. actinomycetemcomitans* is particularly virulent, utilizing quorum sensing (QS) to regulate biofilm formation and enhance its pathogenicity, playing a significant role in the development and progression of periodontitis.

Objective: This study aims to explain the quorum sensing mechanism in the pathogenesis of periodontitis caused by *A. actinomycetemcomitans.*

Methods: This 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 across three databases (PubMed, Ebsco, ScienceDirect).

Results: The variation between wild-type (*Aa-WT*) and *LuxS* mutant (*Aa-LuxS*) strains of *A. actinomycetemcomitans* impacts its pathogenicity. Quorum sensing (QS) interactions between *A. actinomycetemcomitans* and other periodontopathogens *(P. gingivalis, T. denticola, P. intermedia)* amplify virulence, promoting biofilm formation and disease progression. AI-2 regulates key processes, underscoring *A. actinomycetemcomitans* significant role in periodontitis.

Conclusion: The quorum sensing mechanism in *A. actinomycetemcomitans*, through AI-2 production, is essential for microbial communication and biofilm formation, influencing the bacterium's virulence and role in periodontitis.

Keywords: AI-2; Quorum Sensing; *Aggregatibacter actinomycetemcomitans*; Biofilm; Periodontitis

1. Introduction

Periodontitis is a significant public health issue with a relatively high prevalence. It is an oral disease that affects the supporting tissues of the teeth, including the gingiva, periodontal ligament, cementum and alveolar bone [1]. The Global Burden of Disease from 1990 to 2010 showed that severe periodontitis was the sixth most prevalent disease, with a prevalence of 11.2%, affecting approximately 743 million people worldwide [2]. This disease impacts approximately 20-50% of people worldwide, and its global burden is expected to rise in the future, primarily due to the aging of the general population [3].

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Periodontitis can be defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or microbial groups, leading to progressive damage to the periodontal ligament and alveolar bone, and resulting in increased pocket depth and gingival recession [4]. Periodontitis is a complex condition primarily driven by bacteria present in the subgingival biofilm. According to The Human Microbiome Project Consortium, over 700 bacterial species have been identified in the oral cavity. However, only a small number of pathogens exhibit higher virulence, including *A. actinomycetemcomitans* and *P. gingivalis*. These two bacteria have been shown to be strongly associated with the onset and progression of periodontitis, demonstrating rapid destructive progression [5].

The composition of the oral microbiome can change due to various factors, such as genetic factors, maternal transmission, systemic conditions, and environmental factors like diet, oral hygiene, and medications. A dynamic ecosystem or microbiome composition can lead to oral dysbiosis, which may result in periodontal tissue diseases [6]. Dysbiosis induced by *A. actinomycetemcomitans* may result from immunological damage caused by its virulence factors. *A. actinomycetemcomitans* exhibits numerous virulence factors with varying capabilities, allowing this bacterium to consistently colonize the oral cavity, modulate the host immune system, invade periodontal tissues, destroy connective tissue, and inhibit tissue healing. This bacterium interacts with the host cell's extracellular and intracellular receptors, leading to exacerbated inflammation and subsequent tissue damage [7]. This bacterium is the most frequently isolated from infected periodontal pockets among hundreds of organisms identified in the oral cavity and is considered the most virulent among other periodontal pathogens. It is a small, rod-shaped, gram-negative facultative anaerobe with fastidious growth requirements [8,9]. Each bacterium or microbe has its own quorum sensing (QS) activity, which is believed to influence its interaction with tissues. Quorum sensing refers to the process of communication between similar or different cells through the release or detection of signaling molecules known as inducers [10].

This study aims to examine the quorum sensing mechanism involved in the pathogenesis of periodontitis caused by *A. actinomycetemcomitans.* The research seeks to clarify this process using insights from previous studies, providing a basis for future investigations.

2. Material and methods

This type of research is a literature review study using a Systematic Literature Review design. The research is conducted by searching for several pieces of literature 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 AND NOT). The literature search was focused on journal articles in English and Indonesian, with a publication year range from 2014 to 2024 (the last 10 years). The keywords used were quorum sensing AND *A. actinomycetemcomitans* AND periodontitis.

2.2. Inclusion and Exclusion Criteria

The data collection strategy used involves applying 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	The Quorum Sensing Mechanism of *Aggregatibacter actinomycetemcomitans*	Quorum Sensing mechanisms in other bacteria
Comparison	-	-
Outcome	Pathogenesis of Periodontitis	Pathogenesis of other periodontal diseases

2.3. Analysis and Synthesis Data

Data was collected across several databases, including PUBMED, EBSCO, and ScienceDirect, using Boolean Operators and predefined keywords. Limitations and data crawling were applied based on the inclusion and exclusion criteria. Articles were selected by carefully reading the titles and abstracts individually, ensuring they aligned with the research topic and inclusion-exclusion criteria. The titles and abstracts of articles that did not match these criteria were excluded. The data collection process continued with reading the full text of the selected articles. The gathered literature was further screened through full-text reading, and the quality of the studies was assessed based on the CRAAP criteria and the JBI critical appraisal method.

3. Results and discussion

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

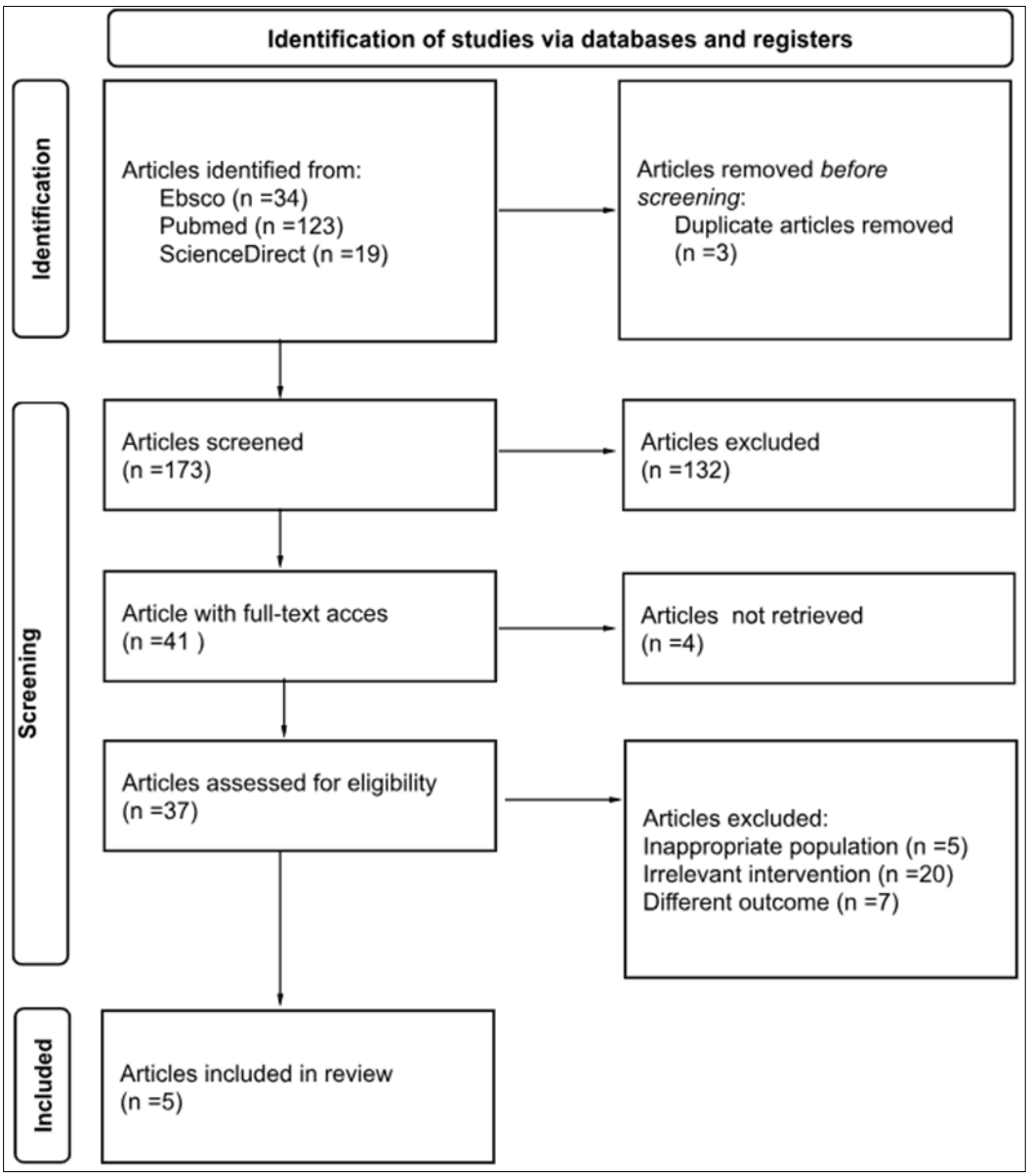

Figure 1 PRISMA Flow Chart of Selection Process

Table 2 Results of literature

No.	Author Name, Year	Research Result
1.	Bachtiar et al., 2014	The *Aa-Wild type* strain is capable of inhibiting the growth of *C. albicans.* However, the Aa-*LuxS* mutant is unable to inhibit the growth of *C. albicans* due to its inability to produce AI-2.
2.	Bachtiar & Endang W., 2020	*Aa-WT* and *Aa-Y4* are capable of producing AI-2, while the *LuxS* mutant *(Aa-LuxS)* cannot produce AI-2. The presence of AI-2 produced by *A. actinomycetemcomitans* can reduce the biofilm mass of *C. albicans* without affecting the viability of *S. mutans*. An imbalance in the interaction between *C. albicans and S. mutans* may increase the risk of periodontal damage.
3.	Torrungruang et al., 2015	The presence of *P. gingivalis*, along with high levels of *A. actinomycetemcomitans*, *T. denticola,* or *P. intermedia*, indicates a high risk of severe periodontitis in the studied group. Although *A. actinomycetemcomitans* is not the most common pathogen in severe periodontitis, its role can become a significant risk factor if its numbers exceed a certain threshold and/or interact with other pathogens.
4.	Ryu et al., 2016	In *A. actinomycetemcomitans*, the receptor that interacts with AI-2 is RbsB (Ribose Binding Protein). D-galactose effectively inhibits the formation of periodontal disease biofilms by targeting AI-2, preventing it from binding to its original receptor.
5.	Velusamy et al., 2017	The wild-type strain has the ability to produce AI-2, whereas the *LuxS* mutant lacks the capacity to synthesize this autoinducer. This limitation leads to a slight increase in biofilm formation and exopolysaccharide (EPS) production, contributing to the development of periodontitis.

3.1. Variations in *Aggregatibacter actinomycetemcomitans* strains

The differences between the wild-type strain and the *LuxS* mutant strain of *A. actinomycetemcomitans* play an important role in understanding its behavior and pathogenicity. The wild-type strain, which represents the natural, unmutated form of *A. actinomycetemcomitans* can produce autoinducer-2 (AI-2) through the *LuxS* pathway. This AI-2 molecule plays a key role in inhibiting *Candida albicans* biofilm formation, helping *A. actinomycetemcomitans* dominate the oral cavity and contribute to the pathogenesis of periodontitis. On the other hand, the *LuxS* mutant strain, which has undergone genetic modification to eliminate the production of AI-2, shows no significant inhibition of *C. albicans* growth [11]. The wild-type strain, capable of producing AI-2, outcompetes other microorganisms, leading to an increase in *A. actinomycetemcomitans* population and virulence factors, which contribute to periodontitis [12]. The comparison between these strains confirms the role of AI-2-dependent gene regulation, including outer membrane proteins, transcription regulators, and fimbriae components. Additionally, the virulence factor leukotoxin is reduced threefold after the *LuxS* gene is inactivated.

Findings from other studies further illustrate the complex interplay between *A. actinomycetemcomitans* and other microorganisms within the oral biofilm. These interactions, often mediated by AI-2 signaling, reveal how this bacterium not only regulates its own virulence but also influences the behavior of other biofilm-associated species. *Aa-WT* (wild-type strain) and *Aa-Y4* (laboratorium strain) can inhibit the formation of hyphae in *Candida albicans*, where hyphae is its pathogenic form. *C. albicans* has specific genes related to hyphal formation and adhesion which function to invade the host and regulate *C. albicans* virulence factors. By suppressing the expression of hyphal genes, and maintaining the expression of a non-invasive yeast form gene, these bacteria keep *C. albicans* in its yeast form, thereby reducing its pathogenic potential in biofilm. Meanwhile, in *S. mutans*, the viability or microcolony formation was unaffected. However, genes in *S. mutans*, such as gtfB (water-insoluble) and gtfC (semi-soluble in water), significantly increased with the presence of AI-2, while gtfD (water-soluble) decreased when the biofilm was cultured with media containing AI-2 for 48 hours. The imbalance between these two biofilm microorganisms makes their interaction complex, potentially worsening periodontal conditions [13].

Other studies on *A. actinomycetemcomitans* strains have been conducted in primates. In terms of colonization, the *LuxS* mutant strain of *A. actinomycetemcomitans* has minimal impact on colonization efficiency, showing no significant difference compared to the wild-type strain. This occurs due to the adaptive nature of the *LuxS* mutant strain. However, when it comes to signal transmission responsible for biofilm formation, differences between the two strains are evident. The *LuxS* mutant strain cannot produce the autoinducer AI-2 due to a genetic mutation. This is consistent with previous

research, which also found that the *LuxS* mutant strain can form a biofilm comparable to the wild-type strain by adding DPD (precursor of AI-2) [14].

3.2. Interaction with other Periodontopathogens

Periodontopathogenic bacteria, including *A. actinomycetemcomitans*, cannot independently cause periodontitis. These bacteria must interact with other periodontopathogenic species (*P. gingivalis, T. denticola, P. intermedia*) to induce tissue damage. Such interactions occur through quorum sensing mechanisms, which enhance the virulence factors of each bacterial species (intraspecies communication) as they collectively aim for a common goal, resulting in a synergistic effect. The autoinducer-2 molecule produced by *A. actinomycetemcomitans* regulates iron uptake mechanisms independently, and iron deficiency in the bacteria leads to reduced virulence. Moreover, *A. actinomycetemcomitans* relies on the release of inducer molecules to facilitate communication within a biofilm [15]. Although not the primary pathogen in chronic periodontitis, *A. actinomycetemcomitans* plays a significant role in the pathogenesis of both aggressive and chronic periodontitis. The presence of *A. actinomycetemcomitans* becomes a risk factor for periodontal damage when its population surpasses a certain threshold or when it engages in interspecies interactions with other pathogenic bacteria [12].

3.3. Components of Quorum Sensing in *Aggregatibacter actinomycetemcomitans*

A. actinomycetemcomitans relies on a single inducer molecule, AI-2 (autoinducer-2), produced by the LuxS enzyme encoded by the *LuxS* gene. AI-2 interacts with receptors LsrB (Autoinducer-2 Binding Protein) and/or RbsB (Ribose-Binding Protein), which are essential for activating *qseBC*, a two-component system comprising QseB (response regulator) and QseC (sensor kinase)[10]. This system allows the bacterium to respond to environmental signals and regulate behaviors such as biofilm formation, pathogenicity, antibiotic resistance, microbial interactions, and virulence at high population densities. For the quorum sensing system to function optimally, it must remain undisturbed by external inhibitors or disruptions, as such interference can compromise the bacterial communication networks.

Interference in quorum sensing can arise from various factors, such as the presence of external inhibitors like D-galactose, which competes with AI-2 for receptor binding (e.g., Gbp in F. nucleatum or RbsB in *A. actinomycetemcomitans*). This disruption reduces intracellular signaling, affecting virulence gene expression and biofilm stability [16]. Biofilms, which shield bacteria from immune responses and antibiotics, are critical in exacerbating periodontitis [17]. With a complete quorum sensing system, *A. actinomycetemcomitans* effectively communicates intra- and intercellularly, dominates biofilm formation, enhances virulence alongside other periodontopathogens, and optimizes iron acquisition for survival. These abilities establish its significant role in periodontitis development.

The formation and development of biofilms in the oral cavity are influenced by various environmental changes[18]. As *A. actinomycetemcomitans* becomes dominant within the biofilm, it alters the microbial composition, leading to a shift that favors its growth and contributes to the initiation of periodontal disease. The increase in virulence factors can occur due to the quorum sensing (QS) mechanism of *A. actinomycetemcomitans* and its receptors, enabling the formation of bidirectional interactions with other periodontopathogenic bacteria. These bidirectional interactions stimulate an increase in virulence factors in each bacterial species. For *A. actinomycetemcomitans*, the virulence factors include leukotoxin, CDT, LPS, and collagenase, all of which contribute to periodontal tissue damage [19].

4. Conclusion

The quorum sensing mechanism in *A. actinomycetemcomitans* plays a crucial role in the pathogenesis of periodontitis, heavily relying on the production of AI-2, which facilitates microbial interactions within the biofilm. The wild-type strain *Aa-WT* and laboratory strain *Aa-Y4* are capable of producing AI-2, contributing to increased virulence, while the *LuxS* mutant strain *Aa-LuxS* cannot produce AI-2 and thus does not contribute to periodontitis development. AI-2 plays a pivotal role in microbial communication, enhancing biofilm formation and increasing the pathogenic potential of periodontal disease.

Compliance with ethical standards

Disclosure of conflict of Interest

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

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