Quorum sensing *Streptococcus mutans* and *Lactobacillus salivarius* (prospects of prevention of dental caries in the future): narrative review

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Abstract

Background: Dental caries is the most widespread infectious disease, affecting millions of people worldwide. *Streptococcus mutans* is a major caries-causing microorganism in which its acidogenic and aciduric properties and its ability to adhere to tooth surfaces mediate its ability to produce extracellular polysaccharides from sucrose, all of which are virulence factors associated with the pathogenesis of dental caries. *Lactobacillus salivarius* is a type of lactic acid bacteria that can inhibit the growth of pathogenic bacteria through communication between bacterial cells called Quorum Sensing (QS).

Purpose: To analyze the mechanism of Quorum Sensing *Streptococcus mutans* and *Lactobacillus salivarius*.

Method: This study uses a narrative review method. The literature sources used in compiling the review are digital databases such as Pubmed, Sciencedirect, and Google Scholar regarding QS *S. mutans* and *L. salivarius.*

Discussion: Several literatures report that *Lactobacillus salivarius* can inhibit the growth of *S. mutans* through downregulation of genes that play a role in biofilm formation. The K35 and K43 proteins resulting from the activation of the *L. salivarius* gene work by inhibiting the expression of the LuxS gene resulting in downregulation of the VicK, VicR and ComC genes which act as coding for the glucosyltransferase (gtfBCD) gene for *S. mutans* biofilm formation and decreased autoinducer-2 signaling molecules. (AI-2) is used in the QS mechanism.

Conclusion: *Lactobacillus salivarius* in the oral cavity has prospects as an agent for preventing dental caries in the future by inhibiting the growth of *S. mutans* through the QS mechanism.

Keywords: dental caries, quorum sensing, *Streptococcus mutans*, *Lactobacillus salivarius*, biofilm

Introduction

Dental caries is known as the most widespread infectious disease, affecting millions of people worldwide, and causing a large economic burden on society [1, 2]. Dental caries is an irreversible local infection that can lead to progressive tooth decay depends on the aggregation of the tooth surface biofilm and repeated exposure to dietary carbohydrates [3, 4].

Among cariogenic microbes, *Streptococcus mutans (S. mutans)* is the main agent causing dental caries and has an important role in its development [1, 2]. *S. mutans* are Gram-positive oral bacteria found in dental biofilms and one of the most studied microorganisms associated with dental caries. *S. mutans* exhibits a high level of virulence, mainly due to its ability to produce large amounts of organic acids (acidogenicity) from metabolized sugars, can survive at low pH, and can attach to the tooth surface which mediates its ability to produce extracellular synthesis extra polysaccharides (EPS), which is a key virulence factor associated with the pathogenesis of dental caries [4, 5].

In biofilm communication occurs between *S. mutans* and other bacteria. Communication that occurs between bacterial species is known as Qurom Sensing (QS). Quorum Sensing is a biological process by which bacteria can communicate and regulate gene expression involved in processes related to biofilm formation, acid tolerance, virulence, and pathogenicity. QS is also known as a communication system between cells by producing and releasing small signaling molecules known as autoinducers [6].

In recent years, research has been conducted to discuss the *Lactobacillus salivarius (L. salivarius)* strain which can inhibit the formation of *S. mutans* biofilms [7]. There has been no study that specifically discusses the inhibition of *L. salivarius* on the formation of *S. mutans* biofilms through the QS mechanism to prevent dental caries. Therefore, the authors are interested in conducting an analysis using the literature review method regarding quorum sensing *S. mutans* and *L. salivarius* in the oral cavity for the prospect of preventing dental caries in the future.

Method

The method used in this research is a literature review with a narrative review research design. The articles used come from secondary data in the form of research results, research articles, and review articles obtained from digital databases in the form of PubMed, ScienceDirect, and Google Scholar. Articles to be reviewed are selected based on inclusion criteria: articles published within 10 years (2012-2022), use Indonesian and English and can be accessed free full text. Articles that match the inclusion criteria are collected and reviewed according to the topics studied.

Discussion

Lactobacillus salivarius can be used as an inhibitor of *S. mutans* biofilm formation to reduce the possibility of multiplication which causes acid buildup on the tooth surface. The mechanism of decreasing gene expression through communication between bacteria is known as Quorum Sensing (QS). *S. mutans* have acidogenic and aciduric properties which can cause demineralization of tooth enamel and cause caries [8]. *S. mutans* produces three types of glucosyltransferases (gtfBCD) which utilize the glucose portion from sucrose synthesis as a substrate to synthesize polymers through chemical bonds and utilize the fructose portion from other sucrose synthesis to produce lactic acid through the glycolysis mechanism [9].

The QS mechanism in *S. mutans* uses the CSP-ComDE signaling model. Competence Stimulating Peptide (CSP) encoded from the precursor ComC is an inducer molecule in the form of a small peptide used to regulate gene expression. When CSP accumulates in the environment and reaches a certain threshold concentration, it binds to the membrane-bound receptor histidine kinase (ComD) to regulate signaling responses. The bond formed will trigger the receptor autophosphorylation process and initiate the phosphorylation process and activation of the response regulator (ComE). ComE activation will lead to activation of target genes used in biofilm formation [4, 10].

Lactobacillus salivarius uses a two-component system (TCS) and an inducer molecule in the QS mechanism. The TCS consists of a membrane-bound receptor called histidine protein kinase (HPK) that functions to monitor one or more signaling molecules and a response regulator (RR) that is tasked with modulating the expression of certain genes [11]. The signaling molecule in *Lactobacillus* uses an autoinducer (AI-2), which is a QS signal that plays a role in universal interactions between bacteria [12].

Autoinducer (AI-2) is synthesized by LuxS protein/enzyme. AI-2 is formed from a biosynthetic process of transferring methyl S-adenosyl methionine (SAM) to various substrates which results in the production of S-adenosyl homocysteine (SAH). Toxic SAH can be removed in two ways, through SAH-hydrolase or using Pfs and LuxS enzymes. The Pfs nucleosidase enzyme hydrolyzes adenine from SAH to S-ribosyl homocysteine (SRH). LuxS acts on SRH to produce 4,5-dihydroxy-2,3-pentanedione (DPD) and homocysteine. DPD undergoes further rearrangement to generate active AI-2 molecules [13].

In recent years, many studies have discussed the ability of *Lactobacillus salivarius* againts S. mutans. Ahmed *et al* observed the influence of different *Lactobacillus sp* on S. mutans biofilm formation. The results showed that *Lactobacillus* inhibited LuxS gene expression in *S. mutans* thereby reducing the GtfB gene of *S. mutans* which is responsible for the formation and maturation of biofilms [14].

Wu *et al* identified a *Lactobacillus salivarius* strain isolated from human saliva. In this study, 64 strains of L. salivarius were isolated and their inhibitory activity against *S. mutans* biofilm formation was analyzed using the co-culture method. The co-culture of *S. mutans* with most of the *L. salivarius* strains resulted in a reduction of up to 30% of the total biofilm mass. Two specific strains, expressing K35 and K43 proteins, caused a decrease in biofilm formation, approximately 64.3% and 69.3%, respectively. In this study, quantitative real-time polymerase chain reaction (qRT-PCR) was used to analyze the expression of gtfB, gtfC, and gtfD genes, which encode glucosyltransferases and play an important role in biofilm formation. The K35 and K43 proteins significantly downregulated the gtfB, gtfC, and gtfD genes of *S. mutans*, and showed decreased EPS production [15]. This study is linear with Krzyściak *et al* who reported that *L. salivarius* inhibited the formation of cariogenic S. mutans biofilms [16]. Under the influence of *L. salivarius* the biofilm mass and the number of S. mutans decreased. *L. salivarius* reduced S. mutans attachment by 87% due to decreased GTFs gene expression [17]. Wasfi *et al* examined the ability of Lactobacillus salivarius in inhibiting the expression of the S. mutans gene involved in biofilm formation, the QS mechanism or bacterial survival using a qRT-PCR method. The expression levels of ten genes involved in S. mutans virulence in biofilm-forming cells were analyzed. The selected genes included four genes involved in the QS system (comC, comD, vicK, vicR), four genes involved in EPS formation [three of which were involved in glucan formation (gtfB, gtfC, and gtfD)], one gene involved in fructans formation (sacB), and two genes related to the stress response (aguD and atpD) [18].

Lactobacillus strains released bioactive substances that could inhibit the growth and formation of *S. mutans* biofilms. *Lactobacillus* can inhibit tooth decay and control dental caries, where this inhibitory effect can be attributed to one of the downregulations in several S. mutans virulence genes, namely acid tolerance genes (atpD and aguD genes), EPS-producing genes (gtfBCD and sacB), and gene used in the QS system (vicKR and comCD) [18]. The results of this study support previous research by Wu *et al*.

The studies above agree that *Lactobacillus salivarius* can be used as a dental caries prevention agent where this bacterium is able to inhibit the growth and formation of biofilms and suppress the expression of the S. mutans gene which plays a role in the development of dental caries.

Conclusion

Lactobacillus salivarius in the oral cavity can play a role in preventing dental caries. The K35 and K43 proteins resulting from the activation of the *Lactobacillus salivarius* gene work by inhibiting the expression of the LuxS gene resulting in a downregulation of the VicK, VicR and ComC genes which act as coding for the glucosyltransferase (gtfBCD) gene for *S. mutans* biofilm formation and a decrease in autoinducer-2 signaling molecules (AI-2) used in the QS mechanism.

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