Effect of quorum sensing tyrosol (antibiofilm and antibacteria) in *Streptococcus mutans*: narrative review

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Abstract

Background: *Streptococcus mutans* is a gram-positive bacteria in the form of a cocci, which is a normal flora of the oral cavity. *Streptococcus mutans* forms a biofilm layer consisting of a matrix of Extracellular Polymeric Substances. Biofilm can be a health problem, one of which is dental caries. Tyrosol is *Quorum Sensing* which is owned by *Candida albicans* and has anti-biofilm and antibacterial properties on *Streptococcus mutans.*

Purpose: To analyze the effect of *quorum sensing* tyrosol (antibiofilm and antibacterial) on *Streptococcus mutans.*

Method: This study uses the narrative review method. The literature sources used come from the digital databases ScienceDirect, Pubmed, and Proquest. Inclusion criteria published in the period 2005-2022, in the form of research results or review articles, and can be accessed in full text.

Discussion: Some literature states that tyrosol can cause a decrease in *Streptococcus mutans* biofilm formation. Tyrosol synthesizes the *Flo8* gene which plays a role in hypha formation and virulence. *Flo8* can induce ALS1 to inhibit AgI/II synthesis. The phenolic content in tyrosol can suppress the production of *glucosyltransferases* produced by *S. mutans*, causing a decrease in biofilm formation, damage the cytoplasmic membrane and inhibit bacterial DNA synthesis.

Conclusion: Tyrosol can inhibit biofilm formation and antibacterial *S. mutans* by involving the *QS* mechanism. The phenolic content in tyrosol has anti-biofilm and antibacterial properties on *S. mutans.*

Keywords: biofilm, *Streptococcus mutans*, tyrosol, *Quorum Sensing*

Introduction

Streptococcus mutans (*S. mutans*) is a gram-positive bacterium, in the form of a cocci, and is a normal flora in the human oral cavity. *S. mutans* can metabolize various carbohydrates into organic acids (acidogenicity) and can survive under very low pH conditions (aciduric) [1, 2]. Based on its oxygen requirements, *S. mutans* is a facultative anaerobic bacteria that can produce *Adenosine Triphosphate* (*ATP)* with or without oxygen [3].

In the oral cavity, *S. mutans* forms a biofilm by involving the *Quorum Sensing (QS)* mechanism to communicate between microorganisms in a biofilm. Biofilm is a collection of microorganisms that are tightly attached in an *Extracellular Polymeric Substances* (*EPS*) matrix [4]. *S. mutans* biofilms are quite a serious problem because they can cause various infections in the oral cavity, one of which is dental caries, and in other body organs (systemic infection) through focal infections [5-7].

Preventing the development of biofilm can be done in several ways, including direct signal degradation, inhibiting the attachment of signal molecules to receptors, administering analogs of signal molecule receptors, or it can also be done through inhibiting the signal transduction cascade [8].

Tyrosol is one of the *QS* possessed by *Candida albicans* (*C. albicans*) whose activity begins at 0-24 hours and plays an important role in the transition of yeast cells turning into hyphae [9]. In *C. albicans* tyrosol, its function is to accelerate the transition of yeast cells turning into hyphae [10].

Inhibition of biofilm formation through the *QS* mechanism by tyrosol by inhibiting bacterial communication to reduce the *QS* process or what is usually called the *Quorum Quencing* (*QQ*) [11]. Apart from *QS*, the phenolic content in tyrosol can inhibit the formation of biofilms from *S. mutans* and can have antibacterial properties [12, 13].

Research on the interaction between *C. albicans* and *S. mutans* has been widely carried out, but there has been no research that specifically discusses the effects of *quorum sensing* tyrosol (antibiofilm and antibacterial) on *Streptococcus mutans*. This makes the author interested in conducting a literature review.

Method

The method in this research uses narrative review with research design. The article comes from secondary data obtained from the digital databases Sciencedirect, Pubmed, and Proquest. Articles must meet the inclusion criteria: published in the period 2005-2022, in the form of research results or review

articles, and can be accessed in full text. Articles that meet the criteria are then reviewed.

Discussion

In biofilms bacteria use several survival strategies to evade the host's defense system with the help of *EPS* controlled by the *QS* system [14]. The *QS* system consists of an enzyme catalyzed process to produce chemical molecular signals by involving protein transcription activators [15-17]. *QS* is very important for various activities of microorganisms including functioning as a modulator of protein synthesis, adaptation to territorial environmental conditions, adhesion to surfaces, and biofilm formation [18, 19].

S. mutans biofilm formation involves the luxS gene which is controlled by *QS* to code for an enzyme in the production of *(S)-4,5-dihydroxy-2,3-pentandione* (DPD), which is a precursor of AI-2 furanone. DPD then synthesizes Al-2 to activate ComC, then becomes *Competence-Stimulating Peptide* (*CSP*) [20]. CSP binds to the *histidine kinase* (ComD) receptor thereby initiating phosphorylation for activation of the *regulatory receptor* (ComE). Activated ComE then regulates transcription of the *glucosyltransferase* gene which plays a role in the *S. mutans* biofilm formation process [21-23].

Tyrosol is a phenolic derived from the amino acid tyrosine through a reduction reaction [24]. Tyrosol is one of the *QS* possessed by *C. albicans* because it can produce and secrete small molecule signals [23]. Research conducted by Arias *et al.*, by placing tyrosol and *S. mutans* in acrylic resin and hydroxyapatite media, resulted in a reduction in the number of *S. mutans* biofilms. This research concluded that there was involvement of the *QS* system in the process of inhibiting biofilm attachment [25].

Other research states that tyrosol can inhibit bacterial biofilm formation by releasing genes involved in hypha formation [25, 26]. *Flo8* is thought to be the gene in question, because *Flo8* is the main gene in the process of forming hyphae [12]. *Flo8* is also involved in biofilm maturation, virulence, and adhesion of *C. albicans* to tooth surfaces [27].

Flo8 is a LisH domain that is regulated by the *Efg1* [12]. The *flo8* gene has a denser, more complete phenotype and can survive in aerobic or microaerophilic conditions than the *efg1* [24, 28]. *Flo8* in eukaryotic microorganisms including *C. albicans* has a LUFS domain containing 100 proteins with various functions, including being able to interact with other transcriptional regulators in the hyphal development process [12].

Flo8 stimulates competition between *C. albicans* and *S. mutans* because of its ability to synthesize ALS1, namely the *Agglutinin-Like Sequence* (*ALS*) family which plays a role in the adhesion of *C. albicans* [23, 29, 30]. ALS1 can inhibit the synthesis of Antigen I/II (AgI/II), when *S. mutans* binds to *salivary glycoproteins*, resulting in disruption in the process of biofilm formation [30, 32]. AgI/II has a structurally complex function in *S. mutans* because it mediates attachment to the dental salivary pellicle through interaction with the host *scavenger receptor glycoprotein GP340* [1].

Research carried out by Cenci *et al* by placing *S. mutans* and *C. albicans* in a 24-well microplate and then adding hydroxyapatite to the media. Next, the media was scanned using an electron microscope, and it was seen that the *S. mutans* biofilm had poor attachment to hydroxyapatite when grown together with *C. albicans* [33].

Apart from inhibiting AgI/II synthesis, ALS1 can also bind to *glucosyltransferases* produced by *S. mutans* to form glucan in situ [34, 35]. Increasing the amount of glucan will increase the ability of ALS1 in the adhesion process and coaggregation of *C. albicans* [30]. Another source states that increasing the amount of glucan produced by *S. mutans* will increase the virulence ability of *C. albicans* and potentially increase competition [28].

Research conducted by Brusca *et al.*, stated that *C. albicans* and *S. mutans* grown in the same media for a short time can increase coaggregation between the two, but when left for a longer time it can cause a decrease in the number of *S. mutans* biofilms. while the biofilm on *C. albicans* increased [23].

The phenolic content in tyrosol is also a concern. Phenolics can have antibacterial properties, namely by binding to proteins in the bacterial cell wall, then entering the bacterial cell and damaging the cytoplasmic membrane, as well as inhibiting the synthesis of DNA. Other research states that the phenolic content in tyrosol is able to bind and inhibit the synthesis of *Adenosine Triphosphate* (ATP) from *S. mutans* [36-38].

Phenolics are also able to inhibit the formation of bacterial biofilms by suppressing the *QS* mechanism of bacteria (39). Other research also states that phenolic content can suppress the production of *glucosyltransferases* produced by *S. mutans*, causing a decrease in biofilm formation [40].

Conclusion

From the review above, it can be concluded that tyrosol can inhibit *S. mutans* biofilm formation by involving the *QS* mechanism. The Flo8 gene induces ALS1 to disrupt the synthesis of AgI/II in salivary glycoproteins. The phenol content in tyrosol functions as an antibiofilm and also antibacterial in *S. mutans*.

Reference

1. Lemos JA, Palmer SR, Zeng L, Wen ZT, Kajfasz JK, Freires IA, *et al*. The Biology of *Streptococcus mutans*. Fischetti VA, Novick RP, Ferretti JJ, Portnoy DA, Braunstein M, Rood JI, editors. Microbiol Spectr. 2019 Feb 8;7(1):7.1.03.
2. Merritt J, Qi F. The mutacins of *Streptococcus mutans*: regulation and ecology. Molecular Oral Microbiology. 2012 Apr;27(2):57-69.
3. Xu P, Alves JM, Kitten T, Brown A, Chen Z, Ozaki LS, *et al*. Genome of the Opportunistic Pathogen *Streptococcus sanguinis*. J Bacteriol. 2007 Apr 15;189(8):3166-75.
4. Karygianni L, Ren Z, Koo H, Thurnheer T. Biofilm Matrixome: Extracellular Components in Structured Microbial Communities. Trends in Microbiology. 2020 Aug;28(8):668-81.
5. Glodny B, Nasseri P, Crismani A, Schoenherr E, Luger

AK, Bertl K, *et al*. The occurrence of dental caries is associated with atherosclerosis. Clinics. 2013 Jul;68(7):946-53.
6. Ebert C, Tuchscherr L, Unger N, Pöllath C, Gladigau F, Popp J, *et al*. Correlation of crystal violet biofilm test results of *Staphylococcus aureus* clinical isolates with Raman spectroscopic read-out. J Raman Spectroscopy. 2021 Dec;52(12):2660-70.
7. Jamal M, Ahmad W, Andleeb S, Jalil F, Imran M, Nawaz MA, *et al*. Bacterial biofilm and associated infections. Journal of the Chinese Medical Association. 2018 Jan;81(1):7-11.
8. Brackman G, Coenye T. Quorum Sensing Inhibitors as Anti-Biofilm Agents. CPD. 2014 Nov 18;21(1):5-11.
9. Alem MAS, Oteef MDY, Flowers TH, Douglas LJ. Production of Tyrosol by *Candida albicans* Biofilms and its role in quorum sensing and biofilm development. Eukaryot Cell. 2006 Oct;5(10):1770-9.
10. Dizová S, Bujdáková H. Properties and role of the quorum sensing molecule farnesol in ralteion to the yeast Candida albicans. Pharmazie. 2017 Jun;6:307-12.
11. Sikdar R, Elias M. Quorum quenching enzymes and their effects on virulence, biofilm, and microbiomes: a review of recent advances. Expert Review of Anti-infective Therapy. 2020 Dec 1;18(12):1221–33.
12. Cao F, Lane S, Raniga PP, Lu Y, Zhou Z, Ramon K, *et al*. The Flo8 Transcription Factor Is Essential for Hyphal Development and Virulence in Candida albicans□D. Molecular Biology of the Cell, 2006, 17.
13. Rodrigues CF, Černáková L Farnesol, Tyrosol. Secondary Metabolites with a Crucial quorum-sensing Role in Candida Biofilm Development. Genes. 2020 Apr 18;11(4):444.
14. Srinivasan R, Santhakumari S, Poonguzhali P, Geetha M, Dyavaiah M, Xiangmin L. Bacterial Biofilm Inhibition: A Focused Review on Recent Therapeutic Strategies for Combating the Biofilm Mediated Infections. Front Microbiol. 2021 May 12;12:676458.
15. Castillo-Juárez I, Maeda T, Mandujano-Tinoco EA, Tomás M, Pérez-Eretza B, García-Contreras SJ, *et al*. Role of quorum sensing in bacterial infections. WJCC. 2015;3(7):575.
16. Mallick EM, Bennett RJ. Sensing of the Microbial Neighborhood by Candida albicans. Heitman J, editor. PLoS Pathog. 2013 Oct 31;9(10):e1003661.
17. Wongsuk T, Pumeesat P, Luplertlop N. Fungal quorum sensing molecules: Role in fungal morphogenesis and pathogenicity. J Basic Microbiol. 2016 May;56(5):440–7.
18. Papenfort K, Bassler BL. Quorum sensing signal–response systems in Gram-negative bacteria. Nat Rev Microbiol. 2016 Sep;14(9):576–88.
19. Ren T Ting, Yu H Qing, Li X Yan. The quorum-sensing effect of aerobic granules on bacterial adhesion, biofilm formation, and sludge granulation. Appl Microbiol Biotechnol. 2010 Oct;88(3):789–97.
20. Shields RC, Burne RA. Growth of *Streptococcus mutans* in Biofilms Alters Peptide Signaling at the Sub-population Level. Front Microbiol [Internet], 2016 Jul 15. [cited 2023 Nov 14];7. Available from: http://journal.frontiersin.org/Article/10.3389/fmicb.2016.01075/abstract
21. Pourhajibagher M, Alaeddini M, Etemad-Moghadam S, Rahimi Esboei B, Bahrami R, Miri Mousavi RS, *et al*. Quorum quenching of *Streptococcus mutans* via the nano-quercetin-based antimicrobial photodynamic therapy as a potential target for cariogenic biofilm. BMC Microbiol. 2022 Dec;22(1):125.
22. Szafrański SP, Deng ZL, Tomasch J, Jarek M, Bhuju S, Rohde M, *et al*. Quorum sensing of *Streptococcus mutans* is activated by Aggregatibacter actinomycetemcomitans and by the periodontal microbiome. BMC Genomics. 2017 Dec;18(1):238.
23. Brusca MI, Irastorza RM, Cattoni DI, Ozu M, Chara O. Mechanisms of interaction between *Candida albicans* and *Streptococcus mutans* : An experimental and mathematical modelling study. Acta Odontologica Scandinavica. 2013 Jan;71(3-4):416-23.
24. Jagtap SS, Bedekar AA, Rao CV. Quorum Sensing in Yeast. In: Dhiman SS, editor. ACS Symposium Series [Internet]. Washington, DC: American Chemical Society, 2020, 235–50. Available from: https://pubs.acs.org/doi/abs/10.1021/bk-2020-1374.ch013
25. Arias LS, Delbem ACB, Fernandes RA, Barbosa DB, Monteiro DR. Activity of tyrosol against single and mixed-species oral biofilms. J Appl Microbiol. 2016 May;120(5):1240–9.
26. Ni N, Li M, Wang J, Wang B. Inhibitors and antagonists of bacterial quorum sensing. Medicinal Research Reviews. 2009 Jan;29(1):65-124.
27. Fox EP, Bui CK, Nett JE, Hartooni N, Mui MC, Andes DR, *et al*. An expanded regulatory network temporally controls *C andida albicans* biofilm formation. Molecular Microbiology. 2015 Jun;96(6):1226-39.
28. Xu H, Sobue T, Bertolini M, Thompson A, Vickerman M, Nobile CJ, *et al*. *S. oralis* activates the Efg1 filamentation pathway in *C. albicans* to promote cross-kingdom interactions and mucosal biofilms. Virulence. 2017 Nov 17;8(8):1602–17.
29. Nailis H, Vandenbroucke R, Tilleman K, Deforce D, Nelis H, Coenye T. Monitoring ALS1 and ALS3 Gene Expression During In Vitro Candida albicans Biofilm Formation Under Continuous Flow Conditions. Mycopathologia. 2009 Jan;167(1):9-17.
30. Ren Z, Chen L, Li J, Li Y. Inhibition of *Streptococcus mutans* polysaccharide synthesis by molecules targeting glycosyltransferase activity. Journal of Oral Microbiology. 2016 Jan;8(1):31095.
31. Kadosh D, Johnson AD. Induction of the Candida albicans Filamentous Growth Program by Relief of Transcriptional Repression: A Genome-wide Analysis□D. Molecular Biology of the Cell, 2005, 16.
32. Yang C, Scoffield J, Wu R, Deivanayagam C, Zou J, Wu H. Antigen I/II mediates interactions between *Streptococcus mutans* and *Candida albicans*. Molecular Oral Microbiology. 2018 Aug;33(4):283–91.
33. Pereira-Cenci T, Deng DM, Kraneveld EA, Manders EMM, Del Bel Cury AA, Ten Cate JM, *et al*. The effect of *Streptococcus mutans* and Candida glabrata on Candida albicans biofilms formed on different surfaces. Archives of Oral Biology. 2008 Aug;53(8):755–64.
34. Diaz PI, Xie Z, Sobue T, Thompson A, Biyikoglu B, Ricker A, *et al*. Synergistic Interaction between Candida

albicans and Commensal Oral Streptococci in a Novel *In Vitro* Mucosal Model. Deepe GS, editor. Infect Immun. 2012 Feb;80(2):620–32.
35. Xu H, Sobue T, Thompson A, Xie Z, Poon K, Ricker A, *et al*. Streptococcal co-infection augments *C andida* pathogenicity by amplifying the mucosal inflammatory response. Cell Microbiol. 2014 Feb;16(2):214–31.
36. Daglia M. Polyphenols as antimicrobial agents. Current Opinion in Biotechnology. 2012 Apr;23(2):174–81.
37. Quideau S, Deffieux D, Douat-Casassus C, Pouységu L. Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis. Angew Chem Int Ed. 2011 Jan 17;50(3):586–621.
38. Cushnie TPT, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. International Journal of Antimicrobial Agents. 2011 Aug;38(2):99–107.
39. Silva LN, Zimmer KR, Macedo AJ, Trentin DS. Plant Natural Products Targeting Bacterial Virulence Factors. Chem Rev. 2016 Aug 24;116(16):9162–236.
40. Ananda A, Putri DKT, Diana S. Daya Hambat Ekstrak UBI Bawang Dayak (*Eleutherine palmifolia* (L.) Merr) Terhadap Pertumbuhan *Streptococcus mutans*, 2018, 1.