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Anticariogenic Potential of Piper sarmentosum Water Extract in Oral Health: A Review of Antibacterial and Antibiofilm Mechanisms

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Abstract

Dental plaque formation by mutans streptococci is the main cause of dental caries worldwide. Plant phenolic compounds offer a diverse array of anticariogenic mechanisms of action in the prevention of dental caries. *Piper sarmentosum* is a traditional medicine and an edible culinary plant that has been well documented for its phenolic compounds, and recently, the leaves' water extract has been commercially available. However, numerous antibacterial studies have shown that this plant extract successfully inhibits bacteria other than mutans streptococci, and no antibiofilm properties have been properly studied. To address this challenge, this paper reviews the anticariogenic properties of *P. sarmentosum* leaf extract in terms of antibacterial and antibiofilm as well as predicts the possible antibiofilm targets by several well-studied compounds, mainly vitexin, quercetin, and naringenin, that are present in the water extracts. This provides insights into dental caries management using plant extracts while maintaining the balance of the oral microbiota in a eubiotic state. Hence, *P. sarmentosum* leaves' crude extracts or the phytocompounds could be integrated into the oral health application.

Keywords : Piper sarmentosum; biofilm; *Streptococcus mutans*; *Streptococcus sobrinus*

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1.0 INTRODUCTION

Dental caries or tooth decay is the most common oral health condition worldwide (Cui et al., 2026). The interaction between the microorganism and the sugar from dietary intake through the oral cavity is the main cause of dental caries. Oral microorganisms, especially bacteria, can ferment the sugar present in the oral cavity and produce a layer of biofilm on the tooth surface called dental plaque (Ghamari et al., 2025). The planktonic motile bacteria turn out to be sessile in the biofilm and start to cause the biofilm environment to be acidic (Chen et al., 2021). The acids released cause the smooth tooth surface, known as enamel, to continuously corrode and form a deep lesion, contributing to dental caries (Fernández et al., 2022). Oral streptococci are the most abundant bacterial species that live as biofilms in the human oral cavity (Klein, 2022). For years, mutans streptococci, consisting of *Streptococcus mutans* and *Streptococcus sobrinus*, have belonged to the group of cariogenic bacteria that primarily cause dental caries (Bhardwaj et al., 2024).

Despite this, researchers have developed numerous strategies to prevent dental plaque formation (Zhu et al., 2023). One of the strategies was the use of phenolic substances (Schestakow et al., 2023). Plants were the potential source of phenolic compounds since many secondary metabolites are phenolic-based (Schestakow et al., 2023). Plant-based phenolic compounds

offer diverse mechanisms of action toward bacterial biofilm formation by inhibiting the bacterial cell surface proteins, enzymes, and quorum-sensing signalling molecules that assist in biofilm formation (Oulahal & Degraeve, 2022). For instance, plant salicylic acid acts as a noncompetitive inhibitor for glycosyltransferases (GTFase) by binding to the allosteric site and preventing the conversion of sucrose into biofilm glucan (Ham & Kim, 2020). Furthermore, plant-derived phenolics are cost-effective in terms of production due to easy access to the compound from a wide variety of renewable plant sources, as compared to the synthesis of nanoparticles or probiotics (Homayouni et al., 2023; Oulahal & Degraeve, 2022; Pandey & Jain, 2020).

P. sarmentosum, known as *Kaduk* in the Malaysian community, is a traditional medicine and an edible culinary plant found in tropical regions in Northeast India, Southeast Asia and parts of China (Ware et al., 2023). This plant has been proven to exert antibacterial activities toward two Gram-positive strains, mainly methicillin-resistant *Staphylococcus aureus* (MRSA) and wild-type *S. aureus,* as well as three Gram-negative strains – *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli* (Hussain et al., 2012). There is a presence of abundant phenolic substances in this plant, and one of the major phenolic compounds is myristicin, which exerts antibacterial activity (Carvalho et al., 2022; Junairiah et al., 2023; Setty et al., 2020). In recent times, water extract of *P. sarmentosum* has been commercialised mainly by Thailand compared to ethanolic and methanolic extracts (Oriental Heritage Herbalists, 2026). Therefore, this paper discusses the anticariogenic potential of *Piper sarmentosum* leaves water extracts (WEPS) in terms of bioactive compounds, antibacterial and antibiofilm mechanisms for oral health application.

2.0 Antibacterial Activity of *P. sarmentosum* Leaves Extract

Numerous studies have been conducted on the antibacterial properties of *P. sarmentosum* leaf extract, especially on Gram-negative *E. coli* and Gram-positive *S. aureus*. In the case of *E. coli*, an isolated phenylpropanoid sarisan from the *P. sarmentosum* methanolic leaves crude extract was shown to have inhibition toward *E. coli* with a minimal inhibitory concentration (MIC) at 0.1 mg/ml (Masuda et al., 1991). However, the *P. sarmentosum* methanolic leaves crude extract was not effective in inhibiting *E.coli* tested via the disc diffusion test (Fernández et al., 2012; Vaghasiya et al., 2007; Zaidan et al., 2005). Later findings show that MIC for both *P. sarmentosum* ethanolic and methanolic leaves crude extract were 100 mg and 0.502 mg/mL, respectively, exhibiting mild inhibition towards *E. coli* when tested using the broth microdilution method (Lee et al., 2014; Saad & Yusuf, 2014). Few subsequent studies using the broth dilution method with different extraction techniques were carried out, with even the lowest MIC value of *P. sarmentosum,* as shown in Table 1. The result is incomparable due to different maceration methods and broth dilution methods. Untachai et al. (2018) used the broth macrodilution method, which consumes large amounts of broth, while Samappito et al. (2021) used the broth microdilution method.

An antibacterial test conducted by Saad et al., (2014) on *S. aureus* showed that the ethanolic extract of *P. sarmentosum* leaves inhibits *S. aureus* at a MIC value of 50 mg/ml. The MIC determination using broth macrodilution by Untachai et al. (2018) on the other hand shows that 5-day ethanolic leaf extract confers a high MIC value at 0.0125 mg/ml compared to 5-day methanolic extract with MIC 0.00625 mg/ml, which exhibited the strongest antibacterial activity. Methanolic extract in another study shows a MIC value of 6.25 mg/ml for *S. aureus* (Yusof et al., 2019). The same result was obtained by Samappito et al. (2021) using 80% methanolic extract. One more study using methanolic extract resulted in an MIC of 7.5 mg/ml for *S. aureus* (Ibrahim & Mohd Nazir, 2019). All the research shows that the MIC values are not consistent, and bacterial susceptibility towards the extracts is dependent on the condition of sample preparation and the extraction used to extract the *P. sarmentosum* sample. In addition, there was a lack of WEPS antibacterial studies compared with ethanolic and methanolic extracts over the years, especially against cariogenic bacteria. A recent WEPS antibacterial study by Tran et al., (2025) shown stronger inhibition towards both *E. coli* and *S. aureus* at 0.016 mg/mL, which has the same or high antibacterial effectiveness as methanolic and ethanolic extracts from previous research. On the other side, the main difference between the dental biofilm of the eubiotic and dysbiotic main difference is in terms of microbial load and diversity, in which the dysbiotic has low diversity and a high count of cariogenic microbes, caries-causing microbes (Bowen et al., 2018; Valm, 2019). The high load of cariogenic bacteria, for instance, *S. mutans,* can withstand the inhibition by oral commensal bacteria such as *Streptococcus salivarius*, *Streptococcus gordonii*, *Streptococcus sanguinis* and *Actinomyces naeslundii* (Baty et al., 2022). The main concern arises when plant extracts that exert strong antibacterial activity may strip off these commensal bacteria together with cariogenic bacteria, thereby disrupting the eubiotic state of the oral microbiota. Hence, even though plant extract exhibiting antibacterial activity could serve the purpose of inhibition of the growth of cariogenic bacteria, it will ultimately result in the removal of beneficial oral bacteria at the same time.

Table 1: Studies on *E. coli* with the lowest value of MIC.

Solvent	Sample-solvent ratio	Extraction duration	Extraction temperature	Extraction method	MIC Value (mg/ml)	Reference
80% Methanol	1:10	35 minutes	20 ± 1°C	Maceration (Sonicator Assisted)	0.39	(Samappito et al., 2021)
100% Methanol	1:5	3 days	100°C (10 minutes)	Maceration	0.0125	(Untachai et al., 2018)

3.0 *P.sarmentosum* Leaves Extract Effects on Bacterial Biofilm

Over the years, very little research has been carried out on the effects of the *P. sarmentosum* extract on the bacterial biofilm. However, all the research conducted is not mainly on a single plant but gathers more than one plant altogether, which means that in the end, the outcome focuses on the single plant that exerts strong antibacterial activity or antibiofilm activity on microorganisms other than bacteria. In 2010, Taweechaisupapong et al. studied the antimicrobial effects and antibiofilm effects of *Boesenbergia pandurata* rhizomes and *P. sarmentosum* leaf ethanolic extract and oils. This study showed that no zone of inhibition was formed on the disc diffusion assay, and the MIC value was not determined at the fixed concentration range for any bacteria that tested using *P. sarmentosum* extract. Hence, the antibiofilm study was only focused on the *B. pandurate* extract on the fungi *Candica albicans* due to the strong MIC value of this microorganism. The next study, followed by Puttipan et al. (2017), also uses the same 95% *P. sarmentosum* ethanolic extract as Taweechaisupapong et al. (2010), and no zone of inhibition was observed for *P. sarmentosum*; therefore, the MIC was not determined for *P. sarmentosum* instead antiobiofilm assay was performed on 95% *Caesalpinia sappan* ethanolic extract that has a clear zone of inhibition. However, no antibiofilm assay was performed by Puttipan et al. (2017) for *P. sarmentosum* extract in their experiment, even though *S. mutans* was used in antibacterial and other assays. In the same year, Teanpaisan et al. screened Thai medicinal plant extracts' antibacterial and antibiofilm activity against oral microorganisms. Throughout the study, the ethanolic extract of *P. sarmentosum* did not form any zone of inhibition with biofilm-forming bacteria *S. mutans* and *A. actinomycetemcomitans*. Thus, MIC and MBC determination as well as antibiofilm assay were performed only on *Piper betle* extract, which shows the larger zone of inhibition during agar well diffusion assay. The last study was done by Leesombun et al. (2023) using *Piper* species extract against biofilm formation by methicillin-resistant *Staphylococcus pseudintermedius* (MRSP). This study showed that 97% ethanolic *P. sarmentosum* extract exerts lower antibiofilm activity at 18.9% of biofilm inhibition than *P. betle* with 59.13% of biofilm inhibition. Table 2 outlines the involvement of *P. sarmentosum* in bacterial biofilm research. Overall, no proper research has been carried out to investigate the antibiofilm activity of this plant throughout the years

Table 2: The involvement of *P. sarmentosum* in bacterial biofilm research from the year 2010 until the year 2023

Year	Bacteria tested	Antibacterial Inhibition Zone	MIC	Outcome	Reference
2010	*S. mutans*, *Lactobacillus* sp, *A. actinomycetemcomitans*	None	No inhibitory effect	Antibiofilm assay omitted	(Taweechaisupapong et al., 2010)
2017	*S. mutans* DMST9567, *S. mutans* DMST41283, and *S. intermedius* DMST42700	None	Not performed	Antibiofilm assay not performed	(Puttipan et al., 2017)
2017	*Enterobacter faecalis* ATCC 19433, *Lactobacillus fermentum* ATCC 14931, *Lactobacillus salivarius* ATCC 11741, *S. sobrinus* ATCC 33478, *S. mutans* ATCC 25175, *A. actinomycetemcomitans* ATCC 33384, *Fusobacterium nucleatum* ATCC 25586	None	Not performed	Antibiofilm assay not performed	(Teanpaisan et al., 2017)
2023	MRSP	Not specified	2.048 mg/ml	No biofilm inhibition	(Leesombun et al., 2023)

4.0 Overview of Regulation of Biofilm Formation in Mutans Streptococci

4.1 LuxS/AI-2 quorum-sensing system

LuxS/AI-2 quorum-sensing system is one of the widely studied quorum-sensing and interspecies as well as intraspecies communication in *S. mutans* (Cai et al., 2021; Rocha et al., 2020; Wright & Ramachandra, 2022; Zheng et al., 2023). This system is involved in biofilm formation, acid tolerance and acid production in *S. mutans* (Yuan et al., 2021; Zhu et al., 2023). The conserved gene, *luxS* involved in many cellular processes, as the knockdown of this gene suppresses the *gtfD* expression, affects the ABC transporters and carbohydrate transport, disrupts the activated methyl cycle (AMC), and reduction in biofilm mass (Liu et al., 2021; Yuan et al., 2021; Zheng et al., 2023). The system uses a furanosyl borate diester, basically known as autoinducer-2 (AI-2), which is a byproduct derived from LuxS-mediated methyl metabolism that acts as a signal molecule (Polizzi et al., 2022; Zhu et al., 2023).

Based on Figure 1, S-ribosylhomocysteinase (LuxS), the enzyme responsible for the biosynthesis of AI-2 catalyzes the conversion of S-ribosylhomocysteine (SRH) to the AI-2 precursor 4,5-dihydroxy-2,3-pentanedione (DPD) and homocysteine (HCY) in the final step of the AMC pathway (Liu et al., 2021; Souissi et al., 2021; Zhu et al., 2023). The DPD produced is unstable, leading to spontaneous cyclisation to give rise to AI-2 molecules (Yuan et al., 2021). This AI-2 is transported extracellularly via ABC transporters, accumulates, and binds to the histidine kinase receptor to initiate downstream signal transduction and enable gene transcription and virulence (Wright & Ramachandra, 2022; Zhu et al., 2023). The AI-2 is also able to bind to the histidine kinase sensor protein coded by *comD* from the ComABCDE quorum-sensing pathway (Polizzi et al., 2022). This signal is necessary for biofilm formation and the upregulation of the cariogenic genes such as *spaP*, *fruA*, *gtfB*, *gtfC* and *gtfD* (Zhu et al., 2023). The crosstalk between the LuxS and ComABCDE systems occurs by induction of expression of ComCDE and ComE-regulated genes by DPD (Aqawi et al., 2023).

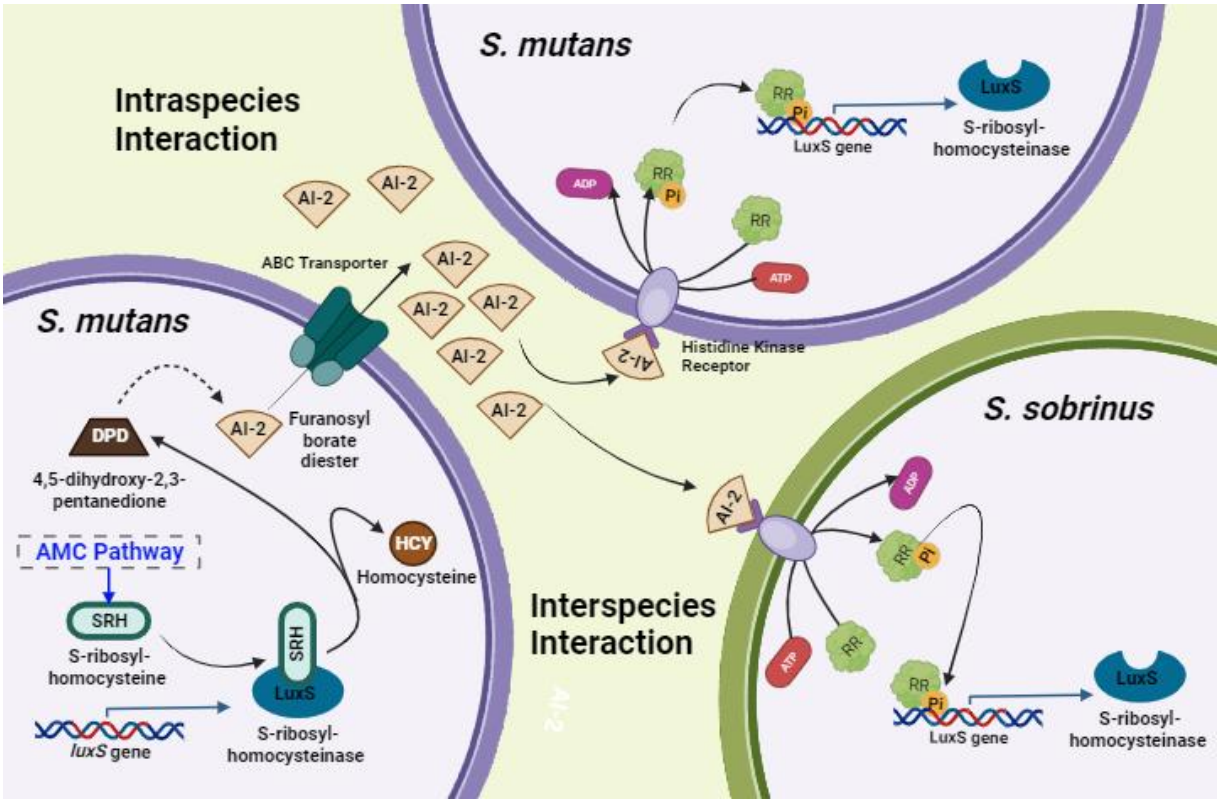


Figure 1 : LuxS/ AI-2 Q quorum-sensing in both intraspecies and interspecies interactions. Adapted from Wright & Ramachandra, (2022) and Zhu et al., (2023). Created using BioRender.com

LuxS/AI-2 quorum-sensing system in *S. sobrinus* are not well established. Since the *luxS* gene and LuxS enzyme are highly conserved across a diverse range of Gram-positive and Gram-negative streptococcal species, AI-2 is also produced by the *S. sobrinus* (Liu et al., 2021; Yoshida et al., 2005). A study conducted by Yoshida et al. (2005) showed that the *luxS* gene deficit *S. mutans* was complemented by *S. sobrinus,* leading to biofilm formation and AI-2 activity by this mutant almost the same as

when complemented with wild-type *S. mutans*. Thus, the finding elucidates that there are interspecies interactions between the *S. mutans* and *S. sobrinus* via the LuxS/AI-2 quorum-sensing system, and this AI-2-mediated quorum-sensing regulates the glucosyltransferase genes for sucrose-dependent biofilm formation.

4.2 CSP-ComABCDE quorum sensing pathway

The CSP-ComABCDE quorum-sensing pathway plays an important role in biofilm formation, genetic competence and bacteriocin production. This system is composed of two operons, *comAB* and *comCDE* (Aqawi et al., 2023). The *comAB* operon code for the ComAB ATP-binding cassette (ABC) transporter, a transmembrane protein (Aqawi et al., 2023; Wright & Ramachandra, 2022). On the other hand, *comCDE* comprises *comC*, *comD* and *comE,* encodes for precursor for competence-stimulating peptide (CSP), histidine kinase sensor protein (HK) and cognate response regulator (RR) (Rocha et al., 2020; Wright & Ramachandra, 2022).

Figure 2 illustrates that the precursor CSP encoded is cleaved by the ComAB ABC transporter into 21-CSP and transported extracellularly to be converted into 18-CSP autoinducer by the extracellular membrane-bound protease SepM (Bernabè et al., 2022; Zhu et al., 2023). The 18-SCP molecule binds to ComD histidine kinase sensor membrane protein when it reaches a critical extracellular concentration (Aqawi et al., 2023; Bernabè et al., 2022). This binding activates the kinase activity of the HK sensor protein and results in activation and autophosphorylation of ComE RR (Aqawi et al., 2023; Bernabè et al., 2022; Zhu et al., 2023). The phosphorylated ComE RR induce the activation of the downstream genes involved in the biofilm formation pathway, *Com*RS competence pathway, and bacteriocin BlpRH pathway (Bernabè et al., 2022; Rocha et al., 2020; Zhu et al., 2023). Zhang et al. (2022) stated in the study on the effect of antibacterial agent SCH-79797 that *S. mutans* with *comD* and *comE* mutant genes form a biofilm with reduced biomass and compromised architectural integrity. Unlike *S. mutans*, *S. sobrinus* has all the CSP-ComABCDE quorum-sensing pathway except lacking in *com*C, which makes *S. sobrinus* unable to produce its CSP to induce the pathway (Conrads et al., 2014). In addition, the *ComA*, *B*, *D* and *E* gene sequences vary in *S. sobrinus* from those of *S. mutans* (Song et al., 2013).

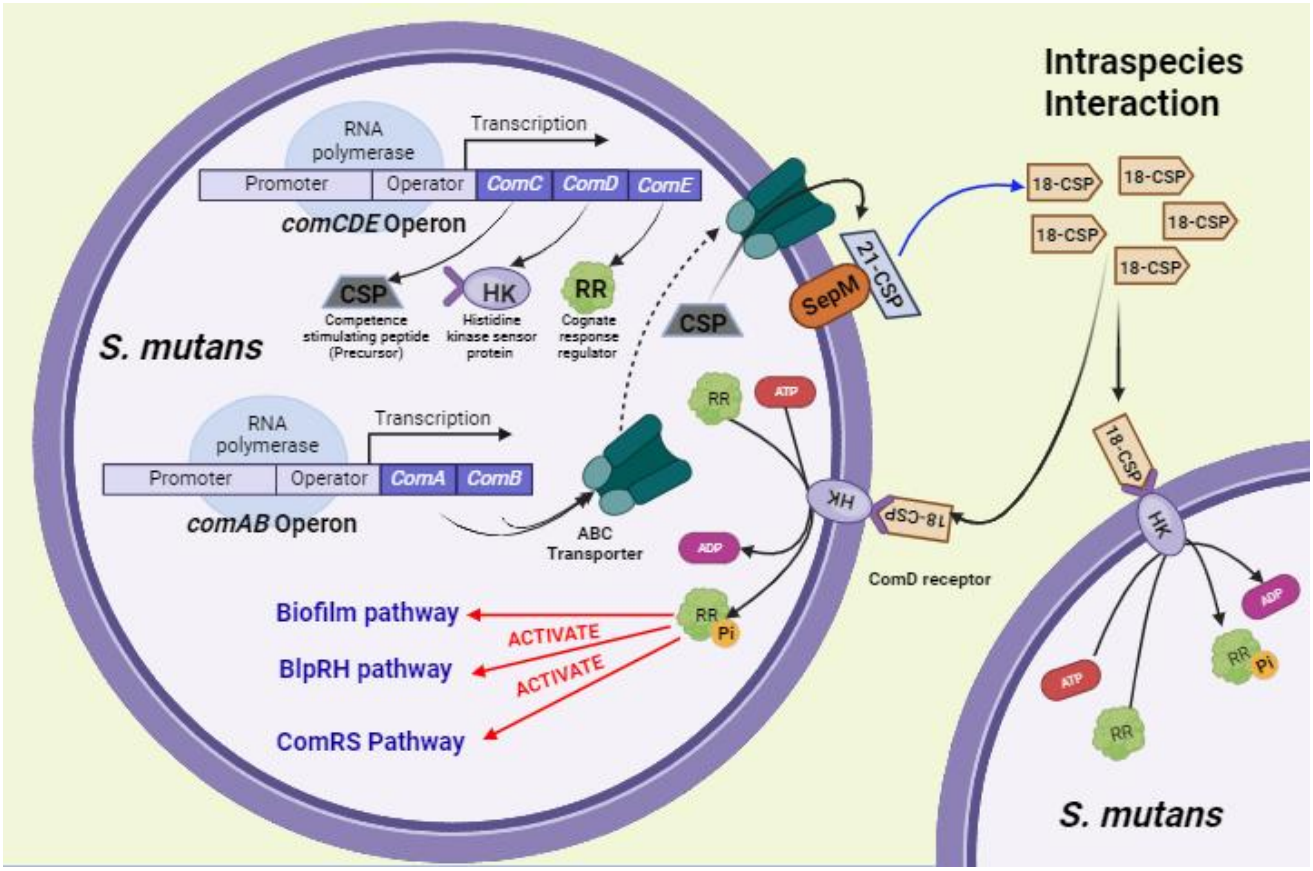


Figure 2 : The ComABCDE two-component transduction pathway in intraspecies *S. mutans* interactions. Adapted from Zhu et al., (2023); Wright & Ramachandra, (2022); Shanmugam et al., (2020); and Rocha et al., (2020). Created using BioRender.com

5.0 VicRK Pathway Regulates Dental Biofilm Formation

ViRK systems are the key regulators of sucrose-dependent and independent biofilm formation (Lu et al., 2020; Shanmugam et al., 2020; Zhu et al., 2023). The *vicRKX* operon consists of three genes, among which are *VicK*, *VicR* and *VicX*. The VicK histidine protein kinase encoded by *VicK* is surface-associated, while *VicR* encodes for a global response regulator (RR) (Deng et al., 2021). *VicX* encoding for a putative hydrolase negatively regulates biofilm formation by reducing the expression of the adhesins and exopolysaccharides (Senadheera et al., 2007). VicK histidine protein kinase senses and transduces the signal from the extracellular environment to the downstream regulatory protein, VicR (Deng et al., 2021). VicR phosphorylated by the kinase activity of VicK histidine protein kinase and in turn positively regulated the transcriptional levels of biofilm-associated genes, for instance, *gtfB*, *gtfC*, *gtfD*, *ftf* and *gbpABCD* by binding to the respective promoter (Deng et al., 2021; Senadheera et al., 2005; Shanmugam et al., 2020). The real relationship between ComCDE and LuxS to the VicRK pathway is not clear, however, Shanmugam et al., (2020) illustrated in a review that LuxS can induce the VicR for sucrose-dependent biofilm formation. Hence, it can be concluded that AI-2 and CSP from LuxS and ComABCDE quorum sensing, respectively able to bind to VicK histidine protein kinase, which in turn phosphorylate VicR to regulate genes involved in biofilm formation, as shown in Figure 3.

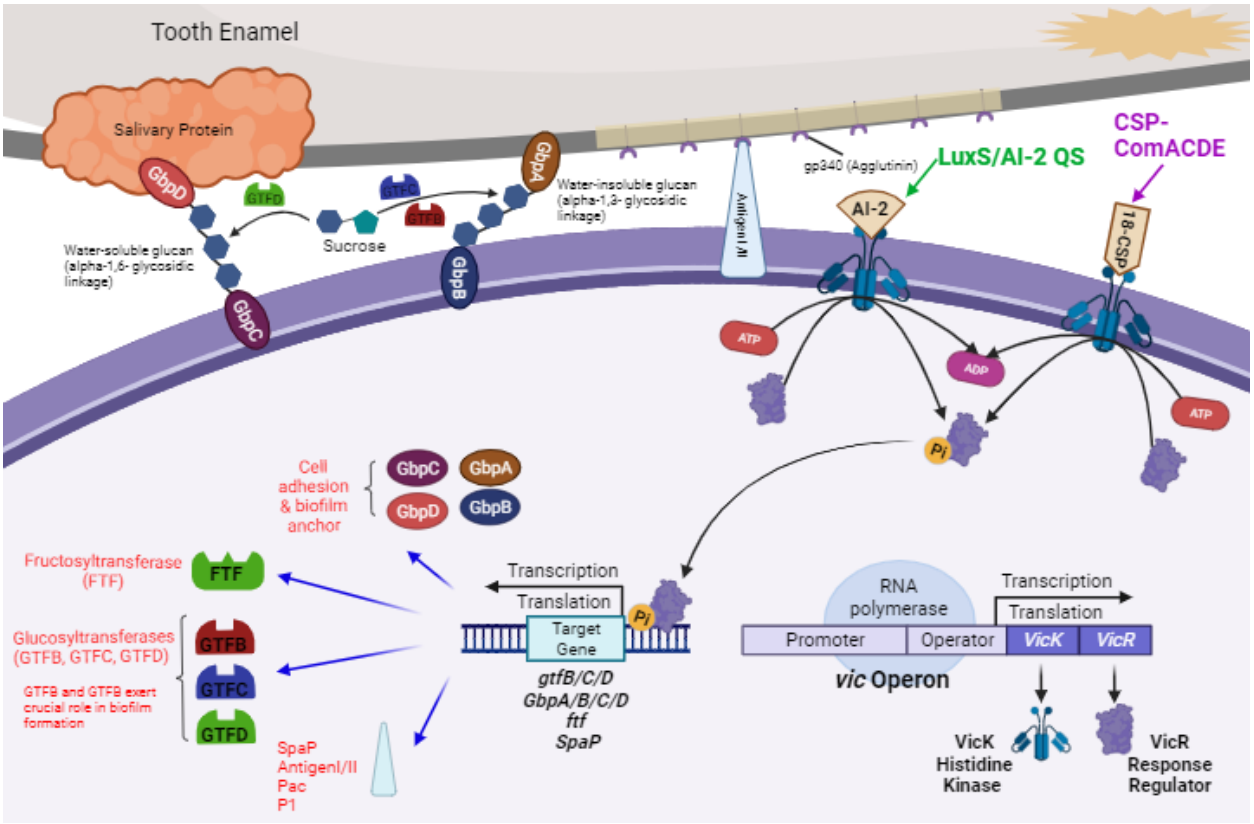


Figure 3 : The VicRK Pathway in regulating the biofilm formation in *S. mutans*. Adapted from Zhu et al., (2023) and Shanmugam et al., (2020). Created using BioRender.com

6.0 Mechanism of Phenolic bioactive compounds in WEPS exhibiting antibiofilm properties

By referring to the LCMS study carried out by Sundar et al. (2019) on WEPS. Several potential phenolic compounds could exert antibiofilm properties, mainly vitexin, quercetin and naringenin (Table 3). These 3 compounds affect LuxS/AI-2 quorum sensing, GTFase and antigen I/II as in Figure 4 . Naringenin and vitexin from *P. sarmentosum* extract are expected to downregulate the *luxS* gene expression that, in turn, affects the synthesis of LuxS enzyme that produces AI-2 signalling molecules. Hence, AI-2 levels in the extracellular environment are expected to be reduced. The reduction in the levels of AI-2 indirectly downregulates the expression of *gtfB*, *gtfC* and *spaP* gene that encodes for gtfB, gtfC and antigen I/II, respectively. Furthermore, quercetin inhibits antigen I/II, preventing adhesion and biofilm formation via sucrose-independent biofilm formation. Hence, *P. sarmentosum* extracts that contain more than one flavonoid and simple phenolics are expected to effectively inhibit *S. mutans* and *S. sobrinus* adhesion and biofilm formation.

Table 3: Antibiofilm activity of the most studied flavonoid occurring in *P. sarmentosum* leaves.

Phenolic Compounds	Mechanism of Action	References
Vitexin	Inhibit biofilm formation by reduce the expression of *spaP, gtfB* and *luxS* genes in *S. mutans*	(Yan et al., 2023)
Quercetin	Concentration range from 16 to 32 mg/mL reduce biofilm dry weight, total protein, viable cells, insoluble and soluble glucans formation as well as pH drop. Biofilm extracellular matrix becomes porous and less interlinked reducing the biofilm thickness. Decrease the expression of antigen I/II preventing adhesion and biofilm formation	(Zeng et al., 2019)
Naringenin	Concentration range from 10-20 µg/mL inhibit *S. mutans* biofilm formation, cell surface hydrophobicity, reduce bacterial aggregation and downregulate gene expression of gtfB, gtfC, and luxS.	(Chen et al., 2022; Moiketsi et al., 2023; Singh & K, 2023; Yue et al., 2018)

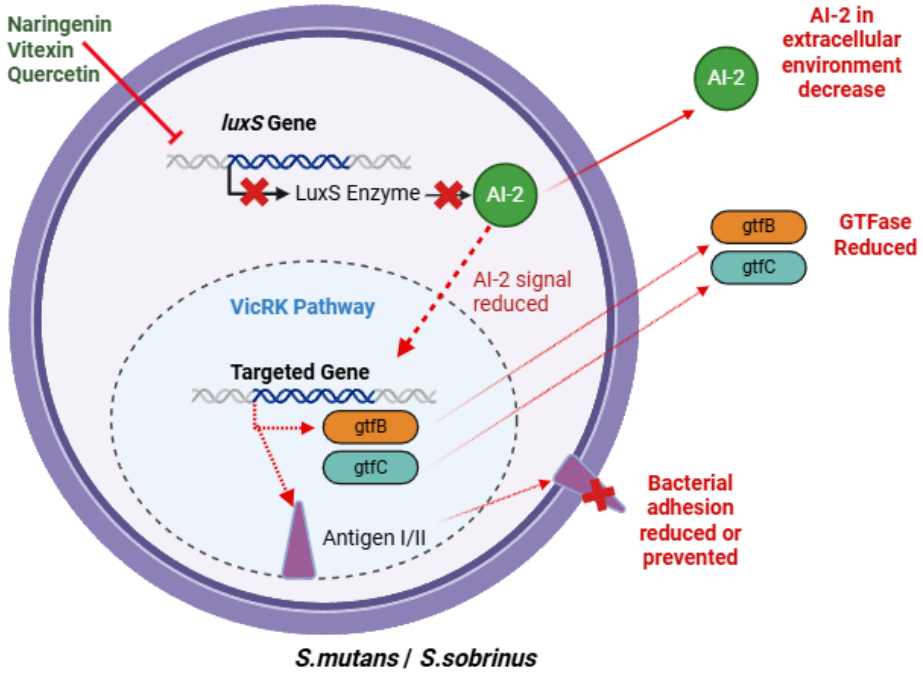


Figure 4: Inhibitory mechanisms of action of flavonoids found in *P. sarmentosum* leaves extract. Created using BioRender.com

7.0 CONCLUSION

This review concludes that *P. sarmentosum* extracts, regardless of the extract types, contain various potent bioactive phytocompounds which could benefit in oral health applications. Even though certain compounds do not inhibit the growth of cariogenic bacteria, it reflects that it is important to maintain a balanced eubiotic oral microbiota, as the antibacterial activity of plant extracts is not selective for beneficial and pathogenic microbes most of the time. Importantly, antibiofilm properties are the most crucial aspect of anticariogenic activity, as they help control dental plaque formation, which could reduce the cariogenic and pathogenic bacterial load in the oral cavity. In addition, the abundance of bioactive compounds in plant extracts increases the efficacy of biofilm inhibition by targeting multiple cariogenic targets involved. Moreover, *P. sarmentosum* extracts should be investigated for the oral toxicity of their phytocompounds to ensure the safety before their application in oral health.

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