Malaysian Journal of Microbiology, Vol 22(4) 2026, pp. 561-570
DOI: http://dx.doi.org/10.21161/mjm.251087

Malaysian Journal of Microbiology
Published by Malaysian Society for Microbiology
(In SCOPUS since 2011)

A review and bibliometric analysis of farnesol as a natural anti-cariogenic agent: Targeting the virulence factor of *Streptococcus mutans*

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Received 3 June 2025; Received in revised form 9 July 2026; Accepted 12 July 2026

ABSTRACT

Aims: Dental caries remains a prevalent global health issue, primarily driven by the virulence of *Streptococcus mutans*. While fluoride and chlorhexidine are common preventive agents, their limitations have led to increased interest in natural alternatives. Farnesol, a naturally occurring sesquiterpene alcohol, has shown promising anti-cariogenic properties by targeting bacterial virulence without promoting resistance. This review systematically examines the anti-cariogenic properties of farnesol targeting *S. mutans*, complemented by a bibliometric analysis to elucidate research trends, thematic progression and knowledge gaps within this field.
Methodology and results: A literature search was conducted using the Scopus database with the keyword "Farnesol and *Streptococcus mutans*," yielding 42 relevant articles published from 2002 to 2024. Key studies were examined through bibliometric keyword analysis, with VOSviewer employed to perform the analysis and generate visual representations of keyword co-occurrence networks. The bibliometric analysis identified main research clusters such as biofilm inhibition and regulation of virulence-associated genes, development of targeted delivery systems, *in vivo* efficacy validation, integration into dental restorative materials and combinatorial therapeutic strategies. Farnesol disrupts *S. mutans* biofilm formation, compromises membrane integrity and modulates the expression of virulence genes such as *luxS*, *gtfB* and *brpA*. Synergistic effects with agents like apigenin, myricetin and fluoride have been documented. Advanced delivery systems, including liposomes and nano-formulations, enhance its bioactivity.
Conclusion, significance and impact of study: Farnesol offers a promising anti-virulence strategy for caries prevention, with demonstrated efficacy and potential for clinical translation. Further research is needed to refine formulations, assess long-term safety and validate outcomes through clinical trials.

Keywords: Anti-cariogenic, bibliometric, farnesol, *Streptococcus mutans*, VOSviewer

INTRODUCTION

Streptococcus mutans is a key contributor to dental biofilm formation and the progression of dental caries, particularly in children and the elderly. While dental caries is a universally recognized global health issue, it remains a disproportionately severe public health burden in Southeast Asia. Recent epidemiological data indicate that oral disorders account for nearly half of all-cause disease prevalence across the Association of Southeast Asian Nations (ASEAN), with permanent and deciduous dental caries contributing the largest share (Cao *et al*., 2026). Within this region, high-sugar diets and limited access to oral healthcare exacerbate disease severity, highlighting an urgent need for sustainable anti-cariogenic strategies (The Lancet Regional Health–Southeast Asia, 2025). Developing these strategies is particularly challenging because biofilm-associated infections caused by *S. mutans* are difficult to eradicate due to their structural complexity and increased resistance to conventional antimicrobial agents. These infections not only compromise oral health but also have broader implications, such as nutritional deficiencies, growth delays and reduced quality of life (Rusali *et al*., 2019).

Conventional anti-cariogenic agents such as fluoride, chlorhexidine, triclosan and stannous compounds have been demonstrated to effectively inhibit the formation of dental biofilms. However, their long-term use raises safety concerns, including toxicity, microbial dysbiosis and the potential for antimicrobial resistance (Deus and Ouanounou, 2022; Chen *et al*., 2023). Moreover, increasing reports of reduced sensitivity to these agents highlight the urgent need for safer and more sustainable alternatives. Natural products have emerged as promising candidates for targeting biofilm-producing microorganisms. Farnesol, a sesquiterpene alcohol found

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ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 22(4) 2026, pp. 561-570
DOI: http://dx.doi.org/10.21161/ mjm.251087

in various essential oils, are increasingly being explored due to its ability to disrupt membrane integrity, inhibit biofilm development and interfere with quorum-sensing pathways in multiple microbial species. In contrast to bactericidal agents, farnesol targets bacterial virulence rather than viability, potentially reducing the selective pressure that drives resistance and offering a promising alternative approach (Fernandes *et al.*, 2018).

Thus, this review aims to examine the potential of farnesol as a promising anti-cariogenic agent against *S. mutans* by summarizing evidence on its mechanisms of action, biofilm-inhibitory properties and therapeutic relevance. To provide a broader perspective on its research progression, this review incorporates a bibliometric analysis of published literature related to its anti-cariogenic properties. This dual approach not only summarises the mechanistic evidence regarding its effects on *S. mutans* virulence but also identifies emerging research themes, knowledge gaps and future directions. To the best of our knowledge, this is the first review that combines bibliometric mapping with an in-depth evaluation of farnesol's anti-caries potential, thereby offering a broader understanding of its scientific development and translational prospects.

MATERIALS AND METHODS

Data collection and analysis

A Scopus search of "Farnesol and *S. mutans*" keyword resulted in 56 documents. The papers were retrieved up to 31st December 2024 and screened based on the inclusion and exclusion criteria, as described by Sheikh *et al*. (2023). The inclusion criteria involved articles with the keyword mentioned in the title, abstract or keywords and research done in the last 22 years (2002-2024). The exclusion criteria included reviews (12 documents) and conference papers (2 papers). Upon applying these criteria, a total of 42 original articles were selected for the subsequent bibliometric analysis. The search strategy is illustrated in Figure 1. A keyword analysis of the selected articles was conducted using VOSviewer (version 1.6.19) according to Fadhlina *et al*. (2024). Keywords with a minimum of 2 occurrences were selected for the analysis using a full counting method. A total of 155 keywords were analysed after removing irrelevant keywords such as human, nonhuman, controlled study, priority journal, unclassified drug, etc. Network and overlay visualization were used to present the analysed data.

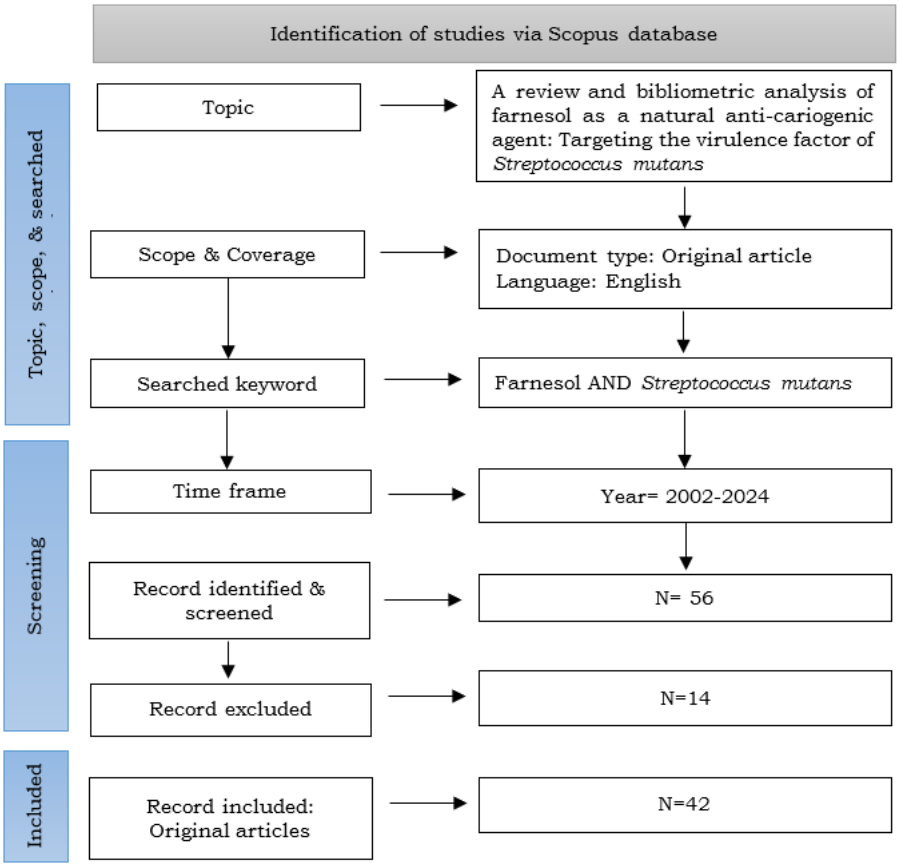

Figure 1: Flow diagram of the search strategy.

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 22(4) 2026, pp. 561-570
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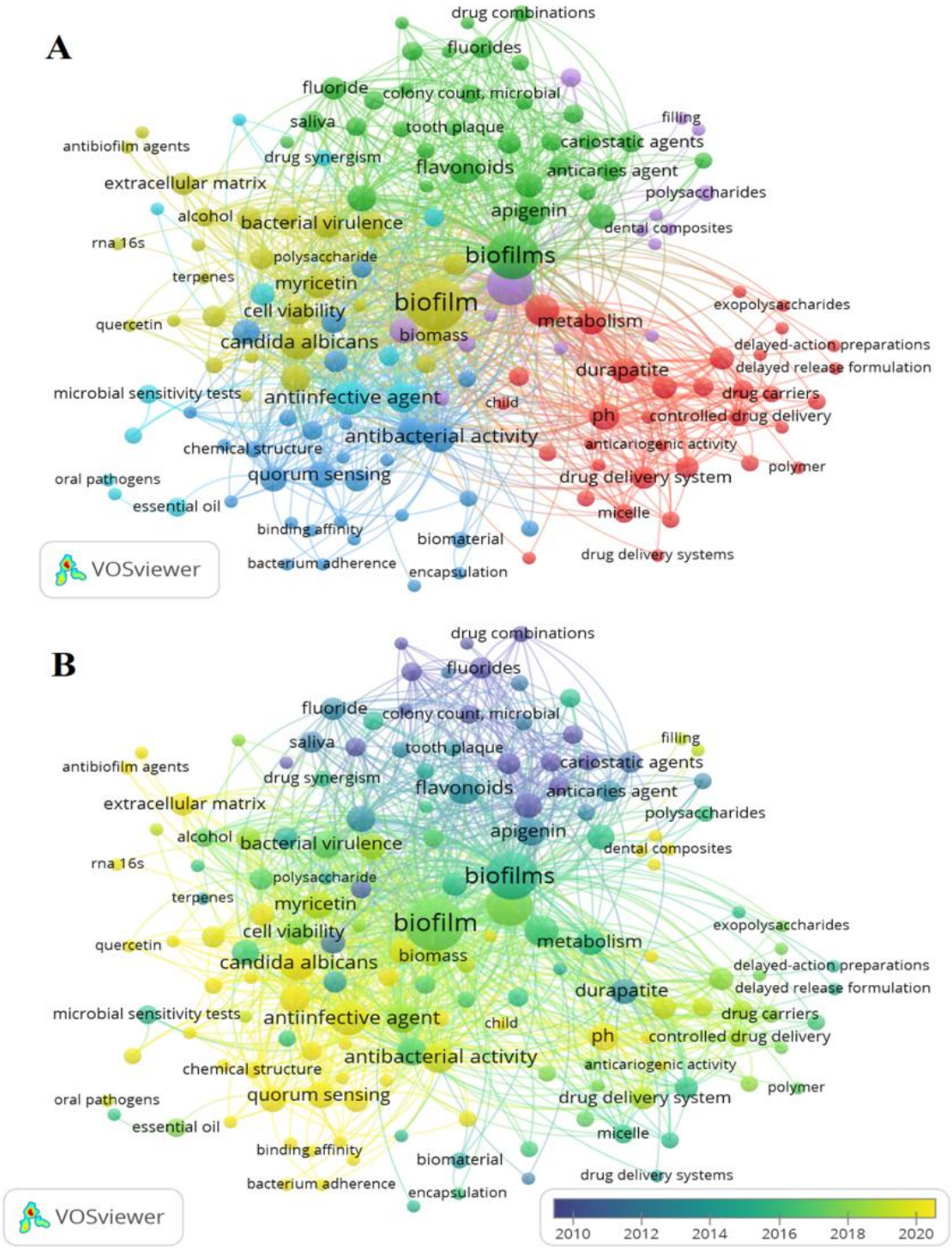

Figure 2: Network (A) and overlay (B) visualizations of the keyword analysis. The size of each node reflects the frequency of keyword occurrences. The node colours indicate distinct thematic clusters (A) in the network map and the average publication year of the studies (B) in the overlay map.

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

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Keyword analysis

Bibliometric keyword analysis revealed several interconnected research themes (Figure 2A) that represent the scientific focus on the antimicrobial potential of farnesol against *S. mutans*, a key contributor to dental caries. These themes cover a wide range of studies, including molecular mechanisms, drug delivery innovations, biofilm disruption and integration into dental materials. The keywords indicate that researchers are deeply exploring how farnesol and related natural compounds exert antibacterial and antibiofilm effects. The studies mainly investigated their activity against bacterial growth, virulence factors and biofilm formation, often involving techniques like molecular docking, gene expression profiling and minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) testing (Cluster 1: Blue). Farnesol was also found to interfere with quorum sensing, reduce glucosyltransferase activity and limit exopolysaccharide production, which are key elements in *S. mutans* pathogenicity.

Another major theme (Cluster 2: Red) centres on the formulation work, where farnesol is incorporated into nanoparticles, micelles and polymeric systems to enhance its stability, targeting and sustained release in the oral cavity. Keywords like nanocarrier, targeted drug delivery and controlled release highlight efforts to optimise farnesol's delivery, especially for biofilm-related infections. Compounds like quercetin, myricetin and terpenes (Second cluster: Yellow) were studied for their ability to inhibit biomass formation and reduce microbial viability, marking a critical area in overcoming the resilience of biofilms. *In vivo* studies, particularly involving rats, are conducted to examine the efficacy of farnesol-based treatments, often in comparison or combination with standard agents like fluoride, chlorhexidine or flavonoids. These studies measure outcomes like bacterial count, plaque accumulation and enamel demineralisation to assess farnesol's anti-cariogenic potential as presented in the third cluster (green).

An emerging area of interest (Cluster 4: Purple) involves incorporating farnesol into dental restorative materials, such as resin composites and cements, to create materials that are both mechanically strong and antibacterial. These dual-function materials show promise in preventing secondary caries while restoring dental structure. This trend is highlighted in the overlay visualization (Figure 2B) by the yellow nodes, indicating its relevance in more recent publications. Finally, combination therapy is a recurring theme (Cluster 5: Light blue; Cluster 6: Green), with researchers exploring synergistic effects between farnesol and other agents to enhance antimicrobial action and reduce resistance. Keywords such as drug potentiation, synergism and sensitivity testing suggest exploration of optimised antimicrobial regimens for oral pathogens.

The keyword analysis shows that most studies focus on biofilm (58 occurrences) and dental caries (21 occurrences), highlighting the main areas where farnesol is being researched. Common terms such as anti-bacterial activity, anti-infective agents and anti-biofilm activity (9-10 occurrences) also reflect the strong interest in farnesol's potential to fight bacteria and prevent biofilm formation. In summary, the keyword mapping highlights farnesol's role as a natural antimicrobial agent, for which multidimensional strategies are being explored to combat dental caries. These insights can guide future research toward more effective, targeted and sustainable therapeutic approaches for oral health management.

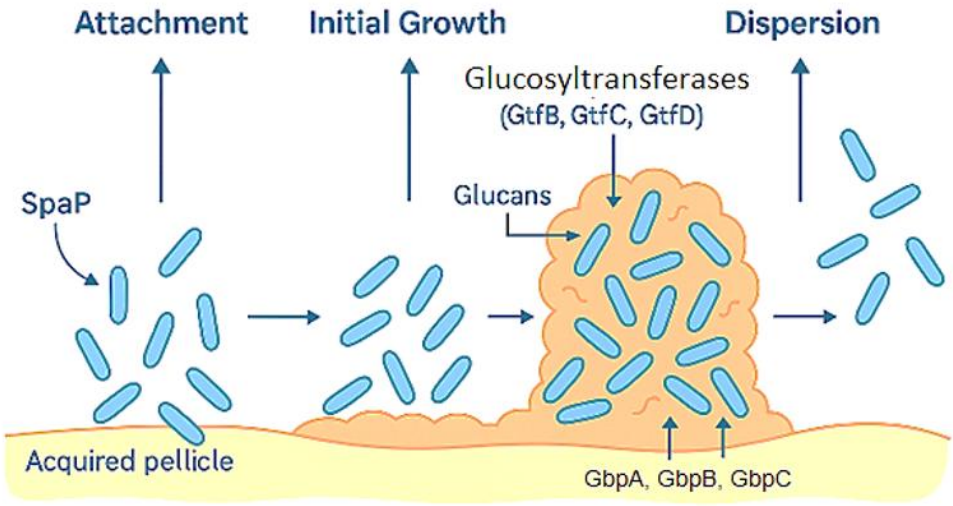

Figure 3: Phases of *Streptococcus mutans*'s biofilm formation (Image generated using ChatGPT by OpenAI).

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 22(4) 2026, pp. 561-570
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RESULTS

Virulence strategies of *S. mutans* in the oral cavity

Streptococcus mutans is a commensal organism commonly found in the dental plaque biofilm of the human oral cavity. It displays substantial genomic diversity due to frequent genome rearrangements, natural genetic transformation and horizontal gene transfer. These features enhance its capacity to adapt to varying environmental conditions within the oral cavity and contribute to its pathogenic potential (Wang *et al*., 2018). The bacterial cell wall comprises a unique rhamnose-glucose polysaccharide (RGP) covalently linked to peptidoglycan. This structural component is essential for maintaining cell wall integrity, stress tolerance and overall virulence (Matsui *et al*., 2010). A major virulence trait of *S. mutans* is its ability to form dense biofilms on tooth surfaces commonly referred to as dental plaque. Biofilm formation protects the bacteria from environmental stresses, host immune responses and antimicrobial agents. This process is tightly regulated by quorum-sensing systems, particularly the Competence Stimulating Peptide (CSP) pathway and the ComDE two-component system (Cross *et al*., 2016; Baker *et al*., 2020).

Extracellular polysaccharides (EPS), primarily synthesized by glucosyltransferases (Gtfs), play a critical role in the initial adhesion to tooth surfaces and in stabilizing the biofilm matrix. Glucan-binding proteins (Gbps) complement this process by interacting with glucans, further strengthening the biofilm architecture (Xiao *et al*., 2010) as illustrated in Figure 3. Additionally, surface adhesins such as SpaP (also known as antigen I/II or P1) and WapA contribute to the initial adherence of *S. mutans* to host salivary glycoproteins, reinforcing its colonization ability (Li *et al*., 2015; Yang *et al*., 2019). In addition to biofilm formation, *S. mutans* ferments dietary carbohydrates to produce lactic acid, creating a highly acidic microenvironment that leads to enamel demineralization. It also thrives under low pH conditions (aciduricity) by modifying its membrane fatty acid composition and utilizing proton-translocating enzymes such as the F_1F_0-ATPase, which expels protons from the cytoplasm (Quivey *et al*., 2016). This acid tolerance is further supported by the acid tolerance response (ATR), which involves the upregulation of stress proteins (DnaK and GroEL) to refold damaged proteins, membrane adaptations to reduce proton permeability and protective DNA repair systems to ensure genetic integrity.

The adaptability of *S. mutans* to the challenging conditions of the oral cavity is largely driven by its genetic regulation and plasticity. Key transcriptional regulators, such as the VicRK and CovR/S systems, control genes crucial for virulence and stress tolerance, allowing *S. mutans* to respond effectively to the fluctuating oral environment (Oliveira *et al*., 2021). Specific gene deletions, including *SMU.1147*, *rgpF* and *sprV*, have been shown to compromise stress tolerance, disrupt biofilm integrity and reduce overall virulence (Shankar *et al*., 2017; Baker *et al*., 2020; Oliveira *et al*., 2021). Additionally, the transcriptional regulator SpxA2 modulates membrane fatty acid composition and ATPase activity, which are essential for acid resistance, a key factor in the bacterium's survival in the acidic environment of the mouth (Baker *et al*., 2020). The SpxA1 regulator also plays a central role in the oxidative stress response, coordinating the activity of enzymes such as superoxide dismutase (Sod) and NADH oxidase (Nox), which protect against reactive oxygen species. These regulatory mechanisms underpin the expression of key virulence-associated proteins that drive pathogenic behaviors such as biofilm development, acid production and environmental persistence. Moreover, manganese uptake systems like SloABC and MntH help maintain metal ion homeostasis, further enhancing resistance to oxidative stress and supporting enzyme activity. Table 1 summarizes these major proteins and their roles in the virulence of *S. mutans*.

In addition to its genetic regulatory mechanisms, *S. mutans* engages in complex interactions with other members of the oral microbiota to establish dominance within the dental biofilm. A key strategy involves the CSP-mediated quorum-sensing system, which regulates not only biofilm maturation and acid resistance but also genetic competence and the production of bacteriocins, such as mutacins (Cross *et al*., 2016; Shankar *et al*., 2017; Baker *et al*., 2020; Oliveira *et al*., 2021). These mutacins inhibit the growth of competing oral bacteria like *S. gordonii* and *S. sanguinis*, thereby promoting *S. mutans* colonization. Furthermore, *S. mutans* secretes membrane vesicles that facilitate interspecies competition by disrupting the biofilms of neighbouring microbes (Cui *et al*., 2022). These vesicles may also carry extracellular DNA (eDNA), released through the action of autolysins like AtlA, which contributes to biofilm stability and horizontal gene transfer. The competence system not only promotes DNA uptake through the ComX sigma factor but also facilitates fratricide, where neighbouring bacteria are lysed to release genetic material and nutrients. By modulating quorum-sensing pathways, *S. mutans* can alter the composition and behaviour of the oral microbiota, an adaptive mechanism that supports its long-term survival and offers promising approaches for targeted anti-cariogenic interventions (Bernabè *et al*., 2022). Emerging evidence also suggests that small regulatory RNAs (sRNAs) and epigenetic mechanisms may fine-tune virulence gene expression, adding a layer of regulatory control and adaptability in the dynamic oral environment (Sy *et al*., 2018).

Antimicrobial activity of farnesol against *S. mutans*

Farnesol, a naturally occurring sesquiterpene alcohol, has demonstrated substantial antimicrobial activity against *S. mutans*. Its multitargeted mechanisms of action, ranging from biofilm inhibition to disruption of membrane integrity, highlight its potential as a therapeutic agent in caries management. One of the primary virulence traits of *S. mutans* is its ability to form robust biofilms on the tooth surface. Farnesol has been shown to significantly inhibit

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

this biofilm formation. An *in vitro* study had reported a 26.4% reduction in biofilm formation at 500 µmol/L and a 37.1% reduction at 1,000 µmol/L, with treated biofilms appearing thinner and containing less extracellular polymeric matrix compared to controls (Cao *et al*., 2017).

In addition to inhibiting biofilm initiation, farnesol also exhibited biofilm-disruptive activity, particularly in mature and mixed-species biofilms. It leads to marked reductions in total biomass and metabolic activity, accompanied by architectural disruption of the biofilm. Notably, farnesol induces the formation of large, tower-like biofilm structures dominated by dead bacterial cells, indicating compromised viability within the biofilm community (Mogen *et al*., 2015; Fernandes *et al*., 2016).

Farnesol impacts the expression of several genes associated with the virulence and stress response of *S. mutans*. It has been reported to downregulate *luxS*, *brpA*, *ffh*, *recA*, *nth* and *smx* genes, which were involved in quorum sensing, DNA repair and cellular metabolism (Cao *et al*., 2017). This gene modulation interferes with biofilm development and may impair the bacterium's ability to adapt to environmental stresses within the oral cavity.

Another key antimicrobial mechanism of farnesol is its ability to compromise bacterial membrane function. Farnesol has been shown to increase membrane proton permeability, leading to disruption of the proton motive force. Furthermore, it reduces glycolytic activity, impeding the energy production necessary for bacterial growth and acidogenesis, which are critical processes in cariogenic activity (Jeon *et al*., 2011).

While farnesol demonstrates potent standalone activity, its efficacy can be enhanced through combination with other antimicrobial agents. For example, its co-application with arachidonic acid (AA) resulted in a reduction of both MIC and minimum biofilm inhibitory concentration (MBIC) for AA, suggesting a synergistic effect (Haj-Yahya *et al*., 2024). Likewise, combining farnesol with fluoride and apigenin significantly enhanced biofilm inhibition and reduced acid production by *S. mutans* (Koo *et al*., 2003; Koo *et al*., 2005). Moreover, combining farnesol with agents like myricetin or fluoride has demonstrated enhanced inhibition of mixed-species biofilms composed of *S. mutans* and *Candida albicans*, resulting in more effective suppression of biofilm formation and virulence factors than farnesol alone (Rocha *et al*., 2018; Lobo *et al*., 2021; Rocha *et al*., 2022).

In comparative antimicrobial assays, farnesol efficacy against *S. mutans* has been substantiated in multiple studies focused on biofilm and gene regulation. However, its antimicrobial effects are concentration-dependent, with higher doses required for pronounced biofilm inhibition. This limitation indicates the need to balance efficacy and biocompatibility in potential clinical applications (Unnanuntana *et al*., 2009; Fernandes *et al*., 2016). Nevertheless, combination with other natural or synthetic agents may allow for reduced dosages while maintaining antimicrobial effectiveness (Haj-Yahya *et al*., 2024; Koo *et al*., 2005), thus overcoming some of the practical challenges associated with its use.

Farnesol exerts potent antimicrobial and anti-biofilm effects against *S. mutans* through multiple mechanisms, including inhibition of biofilm formation, disruption of membrane integrity and regulation of virulence gene expression. Its efficacy is further enhanced when used in combination with other agents, positioning farnesol as a promising candidate for the development of targeted therapies for dental caries prevention and treatment.

Physicochemical properties of farnesol relevant to its antimicrobial action

Farnesol, a naturally occurring sesquiterpene alcohol, exhibits several physicochemical characteristics that contribute to its antimicrobial efficacy. One of its primary traits is its high hydrophobicity and volatility (Costa *et al*., 2021), which contribute to its ability to interact with and disrupt microbial membranes, primarily through integration into lipid bilayers. Structurally, the aliphatic carbon chain of farnesol (Figure 4) enables insertion into the cytoplasmic membrane, increasing membrane disorder and compromising integrity, ultimately leading to leakage of cellular contents and microbial cell death (Inoue *et al*., 2016).

Moreover, its hydrophobic nature enhances membrane permeability, not only facilitating its own diffusion but also improving the uptake of co-administered antimicrobial agents, making it particularly valuable in combination therapies (Namba *et al*., 2022). It was also reported to potentiate the activity of β-lactam antibiotics by interfering with bacterial cell wall biosynthesis (Kim *et al*., 2018). However, this hydrophobic nature may limit its therapeutic use due to its poor aqueous solubility and chemical instability, including susceptibility to oxidation and enzymatic degradation (Dižová and Bujdáková, 2017). To address these limitations, farnesol can be incorporated into a nanostructured delivery system. This approach may enhance solubility, protect the molecule from degradation and enable controlled release, and targeted delivery (Costa *et al*., 2024; Moghadam *et al*., 2024), thereby improving its bioavailability and therapeutic efficacy against pathogens.

In terms of its metabolism, farnesol is metabolized into farnesyl glucuronide and hydroxyfarnesol in the biological system, which may modulate its physiological activity and reduce its antimicrobial potency, especially when delivered systemically (Staines *et al*., 2004). Therefore, for anti-caries applications, local delivery strategies such as oral rinses, varnishes or controlled-release systems are preferable, as they maintain farnesol in its active, unaltered form at the site of action. In this context, nanostructured formulations not only support stability and bioavailability but also enhance site-specific retention and efficacy at the target site.

As for its toxicity profile, farnesol preferentially induces apoptosis in various tumour cell lines, including human lung cancer and colon adenocarcinoma cells, without significantly harming healthy cells (Yilmaz Öztürk *et al*.,

 ISSN (print): 1823-8262, ISSN (online): 2231-7538

Malays. J. Microbiol. Vol 22(4) 2026, pp. 561-570
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Table 1: Key virulence-associated proteins of *Streptococcus mutans.*

Protein	Function
Glucosyltransferase (Gtf)	Synthesizes glucans from sucrose; critical for biofilm formation (Tang *et al*., 2006)
SpaP (Antigen I/II, P1, PAc) WapA (Wall-associated Protein A)	SpaP facilitates bacterial adherence and colonization (Yang *et al*., 2019). WapA plays critical roles in biofilm formation, cell chain integrity and adhesion to host tissues (Li *et al*., 2015).
Glucan-binding protein (Gbp)	Binds glucans to support biofilm matrix stability (Tang *et al*., 2004)
Competence Stimulating Peptide (CSP)	Mediates quorum sensing and regulates virulence traits (Baker *et al*., 2020)
Lactate Dehydrogenase (LDH)	Catalyzes lactic acid production, key to acidogenicity (Cui *et al*., 2022)
F_1F_0-ATPase	Proton pump aiding survival in acidic environments (Matsui *et al*., 2010)

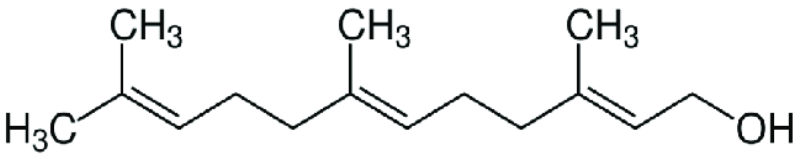

Figure 4: Chemical structure of farnesol.

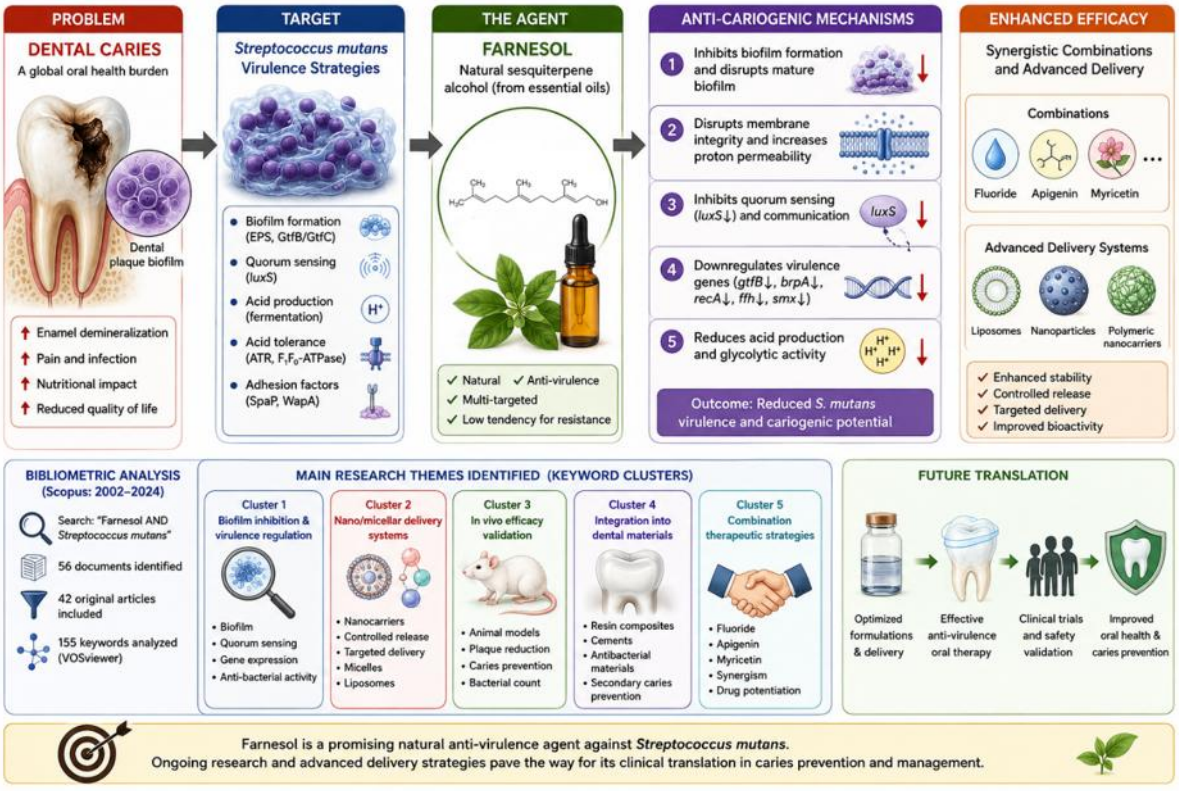

Figure 5: Holistic overview of the anti-cariogenic potential of farnesol against *S. mutans* (Image generated using ChatGPT by OpenAI).

ISSN (print): 1823-8262, ISSN (online): 2231-7538

2022). This selective toxicity is attributed to its ability to induce autophagic and apoptotic pathways (Horn *et al*., 2005; Yilmaz Öztürk *et al*., 2022). In rats, farnesol exhibited low toxicity, as even at high doses (up to 1000 mg/kg/day), it did not cause significant organ damage but led to a reversible increase in hepatic and renal drug-metabolizing enzyme activities, indicating a potential for altered drug metabolism rather than direct toxicity (Horn *et al*., 2005). In summary, the unique physicochemical properties of farnesol, combined with its potent antimicrobial activity and favorable safety profile, highlight its potential as an effective therapeutic agent, particularly for anti-caries applications.

Limitations and future directions

Despite promising preclinical evidence, the clinical translation of farnesol as an anti-cariogenic agent remains limited. Most findings were based on *in vitro* studies using monospecies or simplified biofilm models, which do not fully reflect the complexity of the oral environment, including multispecies interactions, salivary dynamics and host immune responses. In addition, there was a lack of *in vivo* and clinical data to confirm its efficacy, safety, optimal dosage and long-term effects. Formulation challenges also persist due to its hydrophobic nature, which may limit stability and bioavailability in conventional oral care products. Concerns regarding potential cytotoxicity at higher concentrations and its impact on overall oral microbiome balance further highlight the need for cautious interpretation of existing data.

Future research should focus on bridging these translational gaps through well-designed *in vivo* studies and randomized clinical trials to validate its therapeutic potential in real oral conditions. Improvements in drug delivery systems, such as nanoformulations or encapsulation strategies, may enhance its stability and targeted action. In addition, studies integrating microbiome profiling could clarify its ecological effects on oral microbial communities. Exploring synergistic combinations with established preventive agents like fluoride or other natural compounds may also strengthen its clinical applicability in caries management. Figure 5 provides a holistic overview of this review, summarising the key concepts and highlighting the main research themes discussed.

CONCLUSION

Farnesol demonstrates promising potential as an anti-cariogenic agent targeting *S. mutans*, primarily through its capacity to inhibit key virulence factors and impede biofilm development, which are critical in the pathogenesis of dental caries. Its mechanisms of action include perturbation of bacterial membrane integrity and modulation of gene expression involved in quorum sensing and adherence. Additionally, farnesol exhibits synergistic effects when combined with other antimicrobial agents, enhancing its efficacy against cariogenic biofilms. Advances in novel delivery platforms, including nanotechnology-based systems, have shown promise in optimising farnesol's stability and targeted delivery within the oral cavity. Bibliometric analysis reveals an expanding body of research focused on elucidating the molecular interactions and therapeutic applications of farnesol, reflecting a growing scientific consensus on its relevance in oral microbiology and cariology. Despite these promising findings, comprehensive *in vivo* studies and rigorous clinical trials remain imperative to validate its safety profile, pharmacokinetics, and therapeutic efficacy in human subjects. Ultimately, farnesol represents a viable candidate for integration into preventive and therapeutic strategies against dental caries, potentially contributing to improved management of oral biofilm-associated diseases.

DECLARATIONS

The authors declare no competing interests.

FUNDING STATEMENT

The work was supported by the Ministry of Higher Education (MOHE) Malaysia, Fundamental Research Grant Scheme (FRGS) Phase 1 2024 (FRGS/1/2024/SKK12/UIAM/02/1).

REFERENCES

Baker, J. L., Saputo, S., Faustoferri, R. C. and Quivey Jr, R. G. (2020). *Streptococcus mutans* SpxA2 relays the signal of cell envelope stress from LiaR to effectors that maintain cell wall and membrane homeostasis. *Molecular Oral Microbiology* **35(3), 118-128.**

Bernabè, G., Pauletto, A., Zamuner, A., Cassari, L., Castagliuolo, I., Brun, P. *et al.* (2022). Exploiting conserved quorum sensing signals in *Streptococcus mutans* and *Streptococcus pneumoniae*. *Microorganisms* **10(12), 2386.**

Cao, L., Zhang, Z.-z., Xu, S.-b., Ma, M. and Wei, X. (2017). Farnesol inhibits development of caries by augmenting oxygen sensitivity and suppressing virulence-associated gene expression in *Streptococcus mutans*. *The Journal of Biomedical Research* **31(4), 333-343.**

Cao, Y., Wong, R. C. W., Jansisyanont, P., Hariri, F., Amir, L. R., Segarra, M. S. *et al.* (2026). Burden and trends of common oral disorders across the Association of Southeast Asian Nations from 1990 to 2021. *International Dental Journal* **76(2), 109395.**

Chen, X., Mou, L., Qu, J., Wu, L. and Liu, C. (2023). Adverse effects of triclosan exposure on health and potential molecular mechanisms. *The Science of The Total Environment* **879, 163068.**

Costa, A. F., da Silva, J. T., Martins, J. A., Rocha, V. L., de Menezes, L. B. and Amaral, A. C. (2024). Chitosan nanoparticles encapsulating farnesol

evaluated *in vivo* against *Candida albicans*. *Brazilian Journal of Microbiology* **55(1), 143-154.**

Costa, A. F., Silva, L. D. C. and Amaral, A. C. (2021). Farnesol: An approach on biofilms and nanotechnology. *Medical Mycology* **59(10), 958-969.**

Cross, B., Garcia, A., Faustoferri, R. and Quivey Jr, R. G. (2016). PlsX deletion impacts fatty acid synthesis and acid adaptation in *Streptococcus mutans*. *Microbiology* **162(4), 662-671.**

Cui, G., Li, P., Wu, R. and Lin, H. (2022). *Streptococcus mutans* membrane vesicles inhibit the biofilm formation of *Streptococcus gordonii* and *Streptococcus sanguinis*. *AMB Express* **12(1), 154.**

Deus, F. P. and Ouanounou, A. (2022). Chlorhexidine in dentistry: Pharmacology, uses, and adverse effects. *International Dental Journal* **72(3), 269-277.**

Dižová, S. and Bujdáková, H. (2017). Properties and role of the quorum sensing molecule farnesol in relation to the yeast *Candida albicans*. *Die Pharmazie* **72(6), 307-312.**

Fadhlina, A., Sheikh, H. I., Arzmi, M. H. and Lestari, W. (2024). A bibliometric review of early childhood caries (2013-2023): Key drivers towards designing new prevention and management strategies. *Malaysian Journal of Medicine and Health Sciences* **20(5), 391-397.**

Fernandes, R. A., Monteiro, D. R., Arias, L. S., Fernandes, G. L., Delbem, A. C. B. and Barbosa, D. B. (2016). Biofilm formation by *Candida albicans* and *Streptococcus mutans* in the presence of farnesol: A quantitative evaluation. *Biofouling* **32(3), 329-338.**

Fernandes, R. A., Monteiro, D. R., Arias, L. S., Fernandes, G. L., Delbem, A. C. B. and Barbosa, D. B. (2018). Virulence factors in *Candida albicans* and *Streptococcus mutans* biofilms mediated by farnesol. *Indian Journal of Microbiology* **58(2), 138-145.**

Haj-Yahya, F., Steinberg, D. and Sionov, R. V. (2024). Trans, trans-farnesol enhances the anti-bacterial and anti-biofilm effect of arachidonic acid on the cariogenic bacteria *Streptococcus mutans* and *Streptococcus sobrinus*. *International Journal of Molecular Sciences* **25(21), 11770.**

Horn, T. L., Long, L., Cwik, M. J., Morrissey, R. L., Kapetanovic, I. M. and McCormick, D. L. (2005). Modulation of hepatic and renal drug metabolizing enzyme activities in rats by subchronic administration of farnesol. *Chemico-Biological Interactions* **152(2-3), 79-99.**

Inoue, Y., Togashi, N. and Hamashima, H. (2016). Farnesol-induced disruption of the *Staphylococcus aureus* cytoplasmic membrane. *Biological and Pharmaceutical Bulletin* **39(5), 653-656.**

Jeon, J.-G., Pandit, S., Xiao J., Gregoire, S., Falsetta, M. L., Klein, M. I. *et al.* (2011). Influences of trans-trans farnesol, a membrane-targeting sesquiterpenoid, on *Streptococcus mutans* physiology and survival within mixed-species oral biofilms. *International Journal of Oral Science* **3(2), 98-106.**

Kim, C., Hesek, D., Lee, M. and Mobashery, S. (2018). Potentiation of the activity of β-lactam antibiotics by farnesol and its derivatives. *Bioorganic and Medicinal Chemistry Letters* **28(4), 642-645.**

Koo, H., Schobel, B., Scott-Anne, K., Watson, G., Bowen, W. H., Cury, J. A. *et al.* (2005). Apigenin and tt-farnesol with fluoride effects on *S. mutans* biofilms and dental caries. *Journal of Dental Research* **84(11), 1016-1020.**

Koo, H., Hayacibara, M. F., Schobel, B. D., Cury, J. A., Rosalen, P. L., Park, Y. K. *et al.* (2003). Inhibition of *Streptococcus mutans* biofilm accumulation and polysaccharide production by apigenin and tt-farnesol. *The Journal of Antimicrobial Chemotherapy* **52(2), 782-789.**

Li, Y., Liu, Z., Zhang, Y., Su, Q. P., Xue, B., Shao, S. *et al.* (2015). Live-cell and super-resolution imaging reveal that the distribution of wall-associated protein A is correlated with the cell chain integrity of *Streptococcus mutans*. *Molecular Oral Microbiology* **30(5), 376-383.**

Lobo, C. I. V., Lopes, A. C. U. D. A. and Klein, M. I. (2021). Compounds with distinct targets present diverse antimicrobial and antibiofilm efficacy against *Candida albicans* and *Streptococcus mutans*, and combinations of compounds potentiate their effect. *Journal of Fungi* **7(5), 340.**

Matsui, R. and Cvitkovitch, D. (2010). Acid tolerance mechanisms utilized by *Streptococcus mutans*. *Future Microbiology* **5(3), 403-417.**

Mogen, A. B., Chen, F., Ahn, S.-J., Burne, R. A., Wang, D. and Rice, K. C. (2015). Pluronics-formulated farnesol promotes efficient killing and demonstrates novel interactions with *Streptococcus mutans* biofilms. *PloS ONE* **10(7), e0133886.**

Moghadam, Z. S. M., Mansour, F. N., Naseroleslami, M. and Niri, N. M. (2024). Preparation, characterization, and evaluation of the antimicrobial effects of farnesol-and tyrosol-bearing nanoniosomes on *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*. *Medical Journal of Tabriz University of Medical Sciences* **46(2), 175-187.**

Namba, A. M., de Souza Santos, E. L., Garcia, M. T., de Camargo Ribeiro, F., Figueiredo-Godoi, L. M. A., Rossoni, R. D. *et al.* (2022). Farnesol as a potentiator of antimicrobial photodynamic inactivation on *Enterococcus faecalis*. *Photodiagnosis and Photodynamic Therapy* **39, 102928.**

Oliveira, L. T., Alves, L. A., Harth-Chu, E. N., Nomura, R., Nakano, K. and Mattos-Graner, R. O. (2021). VicRK and CovR polymorphisms in *Streptococcus mutans* strains associated with cardiovascular infections. *Journal of Medical Microbiology* **70(12), doi: 10.1099/jmm.0.001457.**

Quivey, Jr. R. G., Faustoferri, R. C., Santiago, B., Baker, J., Cross, B. and Xiao, J. (2016). Acid-adaptive responses of *Streptococcus mutans*, and mechanisms of integration with oxidative stress. *In*: Stress and Environmental Regulation of Gene Expression and Adaptation in Bacteria. de

Bruijn, F. J. (eds.). John Wiley & Sons, Inc., United States. **pp. 897-910.**

Rocha, G. R., Florez Salamanc, E. J., de Barros, A. L., Lobo, C. I. V. and Klein, M. I. (2018). Effect of tt-farnesol and myricetin on in vitro biofilm formed by *Streptococcus mutans* and *Candida albicans*. *BMC Complementary and Alternative Medicine* **18, 61.**

Rocha, G. R., Sims, Jr. K. R., Xiao, B., Klein, M. I. and Benoit, D. S. W. (2022). Nanoparticle carrier co-delivery of complementary antibiofilm drugs abrogates dual species cariogenic biofilm formation *in vitro*. *Journal of Oral Microbiology* **14(1), 1997230.**

Rusali, R., Hamali, N. N., Muhammad Razi, F., Mustafa, N., Harun, N. A. and Mohd Shukri, N. A. (2019). Early childhood feeding practices and its association with early childhood caries. *Journal of Food and Nutrition Research* **7(11), 801-804.**

Shankar, M., Hossain, M. S. and Biswas, I. (2017). Pleiotropic regulation of virulence genes in *Streptococcus mutans* by the conserved small protein SprV. *Journal of Bacteriology* **199(8), e00847-16.**

Sheikh, H. I., Nordin, B., Paharuddin, N., Liew, H. J., Fadhlina, A., Abdulrazzak, L. A. *et al.* (2023). Virulence factors and mechanisms of *Aeromonas hydrophila* infection in catfish Siluriformes: A review and bibliometric analysis. *Desalination and Water Treatment* **315, 538-547.**

Staines, A. G., Sindelar, P., Coughtrie, M. W. H. and Burchell, B. (2004). Farnesol is glucuronidated in human liver, kidney and intestine *in vitro*, and is a novel substrate for UGT2B7 and UGT1A1. *The Biochemical Journal* **384(Pt 3), 637-645.**

Sy, B., Wong, J., Granneman, S., Tollervey, D., Gally, D. and Tree, J. J. (2018). High-resolution, high-throughput analysis of Hfq-binding sites using UV crosslinking and analysis of cDNA (CRAC). *Methods in Molecular Biology* **1737, 251-272.**

Tang, Z. S., Zhu, M. and Liu, Z. (2004). Architecture of *Streptococcus mutans* biofilms. Chinese *Journal of Microbiology and Immunology* **24(2), 103-106.**

Tang, Z. S., Zhu, M. and Liu, Z. (2006). Susceptibility of *Streptococcus mutans* biofilm to antimicrobial agents. *Chinese Journal of Stomatology* **41(5), 266-268.**

The Lancet Regional Health–Southeast Asia. (2025). Oral health in southeast Asia: Addressing inaccessibility. *The Lancet Regional Health-Southeast Asia* **32, 100528.**

Unnanuntana, A., Bonsignore, L., Shirtliff, M. E. and Greenfield, E. M. (2009). The effects of farnesol on *Staphylococcus aureus* biofilms and osteoblasts: An *in vitro* study. *The Journal of Bone and Joint Surgery. American Volume* **91(11), 2683-2692.**

Wang, Y., Wang, X., Jiang, W., Wang, K., Luo, J., Li, W. *et al.* (2018). Antimicrobial peptide GH12 suppresses cariogenic virulence factors of *Streptococcus mutans*. *Journal of Oral Microbiology* **10(1), 1442089.**

Xiao, J. and Koo, H. (2010). Structural organization and dynamics of exopolysaccharide matrix and microcolonies formation by *Streptococcus mutans* in biofilms. *Journal of Applied Microbiology* **108(6), 2103-2113.**

Yang, J., Deng, D., Brandt, B. W., Nazmi, K., Wu, F. and Crielaard, W. (2019). Diversity of SpaP in genetic and salivary agglutinin mediated adherence among *Streptococcus mutans* strains. *Scientific Reports* **9(1), 19943.**

Yilmaz Öztürk, B., Feyzullazade, N., Dağ, İ. and Şengel, T. (2022). The investigation of *in vitro* effects of farnesol at different cancer cell lines. *Microscopy Research and Technique* **85(8), 2760-2775.**

 ISSN (print): 1823-8262, ISSN (online): 2231-7538