Systematic Review

Antibacterial effect of alpha-mangostin from *Garcinia mangostana.* L against oral streptococci and staphylococci biofilms: a systematic review

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ABSTRACT

Introduction: Interactions among competing bacteria, which inhibit each other's growth to maintain the balance of microorganisms in the biofilm, can influence oral cavity homeostasis. Natural products contain compounds with the potential to combat various diseases, including caries. Alpha-mangostin from *Garcinia mangostana.* L exhibits antibacterial properties against oral streptococci and staphylococci, acting through several mechanisms, including the disruption of peptidoglycan, which ultimately leads to cell brittleness and rupture. This study aims to assess the impact of antibacterial alpha-mangostin on oral streptococci and staphylococci biofilm. **Methods:** The research methodology employed secondary data collection through a systematic review study. We conducted searches across databases including PubMed, ScienceDirect, and Google Scholar to identify Indonesian and English references encompassing textbooks, research findings, reviews, and internet articles relevant to the topic published between 2014 and 2024. Following a thorough screening process, we selected articles deemed pertinent for inclusion in the review. Subsequently, these articles underwent evaluation for full-text accessibility, language compatibility, and availability of information from the respective journals, resulting in the selection of 20 articles. **Results:** Analysis was carried out on 20 articles. Ten articles described the effects of alpha-mangostin's inhibit oral biofilm, 6 articles discussed the effects of alpha-mangostin's antibacterial activity against *Streptococcus mutans* and *Streptococcus sanguis*, 3 article state mechanism alpha-mangostin inhibit membrane enzymes such as F(H+)-ATPase and the phosphoenolpyruvate-sucrose phosphotransferase system on *Staphylococcus aureus.* Additionally, one article described inhibition mechanisms of aldolase, glyceraldehyde-3-phosphate dehydrogenase, and lactic dehydrogenase on *Staphylococcus epidermidis.* **Conclusion:** Alpha-mangostin inhibits and disrupts biofilm defense mechanisms. It possesses antimicrobial properties effective against oral streptococci and staphylococci, including *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus aureus* and *Staphylococcus epidermidis.* These properties operate through various mechanisms, including enhancing the permeability of bacterial cell walls, ultimately leading to bacterial cell death.

KEYWORDS
Oral biofilm, alpha-mangostin, oral streptococci, staphylococci

INTRODUCTION

Biofilms are surface-bound microbial communities enveloped by self-synthesizing extracellular polymeric substances such as proteins, polysaccharides, and nucleic acids.[1,2] Virulent biofilms are responsible for various infectious illnesses, including oral disease in humans. Dental caries, a prevalent and costly biofilm-dependent disease globally, stems from virulent biofilms.[3]

Bacterial cells within biofilms shield themselves within an intricate architecture eluding host defense mechanisms and antimicrobial agents, resulting in chronic and resistant infections.[4] For microorganisms involved in caries progression, virulence factors such as the production of an extracellular polysaccharide-rich biofilm matrix, environmental acidification, and maintenance of an acidic pH microenvironment near tooth enamel must be controlled when addressing tooth decay development.[5,6]

Garcinia mangostana Linn. (mangosteen) contains the antibacterial xanthone alpha-Mangostin. Southeast Asians have long utilized mangosteen fruit pericarp as traditional medicine to treat skin infections, wounds, and diarrhea.[7,8] Extensive reports on alpha-Mangostin have demonstrated its broad pharmaceutical significance, including anti-inflammatory, anti-tumor, cardioprotective, anti-diabetic, antibacterial, antifungal, antiparasitic, antioxidant, antiobesity, and antibacterial activities.[9] Alpha-Mangostin, as a member of the xanthone class, is 9H-xanthene substituted by methoxy, oxo, and hydroxy groups at positions 7, 9, 2, with hydroxy groups at positions 1, 3, and 6.[10]

In vitro, alpha-Mangostin (a-MG) exhibits rapid bactericidal activity against several gram-positive pathogens. Alpha-Mangostin (a-MG) shows rapid bactericidal activity against several gram-positive pathogens in vitro.[11,12] It rapidly damages the cytoplasmic membrane of methicillin-resistant *Staphylococcus aureus* (MRSA), leading to the loss of cytoplasmic components.[12,13] Notably, previous studies have shown that gram-positive pathogens did not develop resistance to the natural product alpha-Mangostin using a multi-step resistance selection assay.[9,14,15] Hence, it is crucial to investigate the effect of alpha-Mangostin on the formation of S*treptococcus sanguinis* and *Streptococcus mutans biofilms*.

METHODS

This study comprises a systematic review. This study used the keyword *oral biofilm, alpha-Mangostin, oral streptococci, Streptococcus mutans, Streptococcus sanguis, staphylococci, Staphylococcus aureus, and Staphylococcus epidermidis.* Each keyword with a phrase related to oral streptococci and staphylococci was utilized to conduct a thorough literature search across PubMed, ScienceDirect, and Google Scholar databases. Selected literature includes original or review articles published between 2014 and 2024, written in English.

Journals not either of these languages and those lacking full-text availability were excluded, as were those failing to specify the nature of the work and exposure to chemical compounds of alpha-Mangostin. Following a thorough screening process, we selected articles deemed pertinent for inclusion in the review and articles that are not relevant to the discussion are excluded. Subsequently, these articles underwent evaluation for full-text accessibility, language compatibility, and availability of information from the respective journals, resulting in the selection of 20 articles. Mendeley, a reference management software, was employed to organize references and gather journal data.

Following the application of exclusion criteria, 20 articles were selected (explained in Diagram 1 in the PRISMA Flowchart).

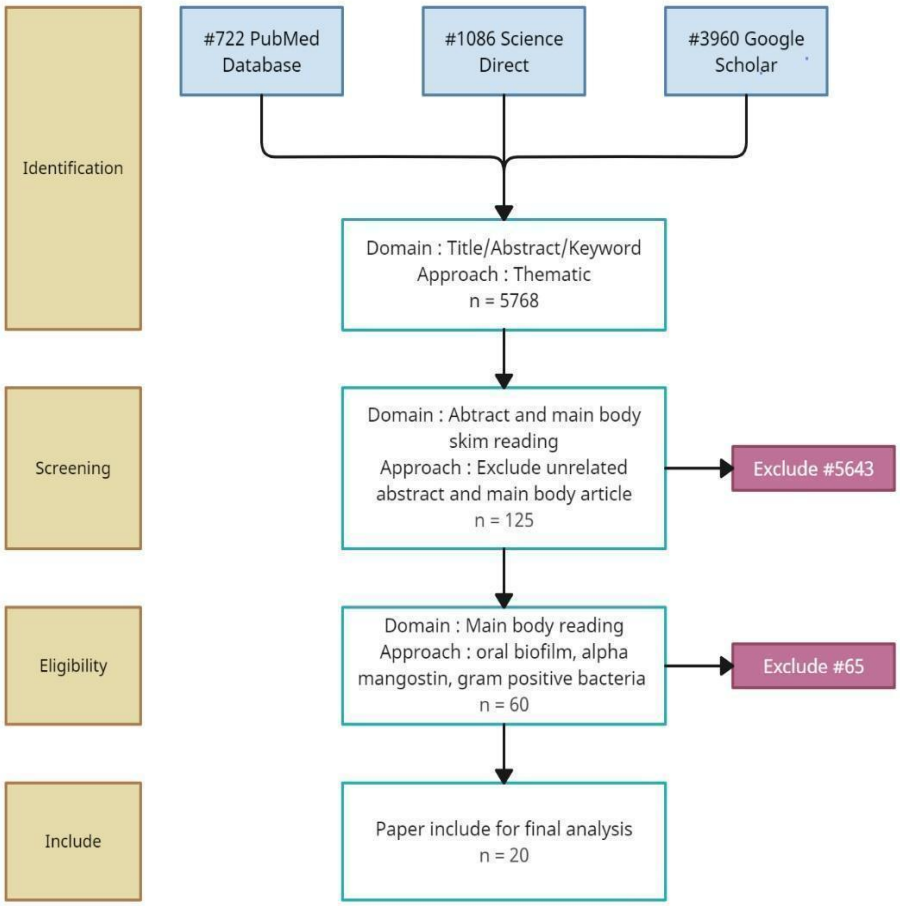

Diagram 1. PRISMA Flowchart

RESULTS

In this study, literature was obtained from three databases: PubMed (n= 722), ScienceDirect (n= 1,086), and Google Scholar (n= 3,960). Subsequently, a skim reading of the abstracts and main bodies was conducted (n=125), followed by a thorough reading of the main bodies (n=60).

Analysis was carried out on 20 articles in Table 1. Ten articles described the effects of alpha-Mangostin's inhibit oral biofilm, 6 articles discussed the effects of alpha-Mangostin's antibacterial activity against *Streptococcus mutans* and *Streptococcus sanguis*, 3 article state mechanism alpha-Mangostin inhibit membrane enzymes such as F(H+)-ATPase and the phosphoenolpyruvate-sucrose phosphotransferase system on *Staphylococcus aureus.* Additionally, one article describes inhibition mechanisms of aldolase, glyceraldehyde-3-phosphate dehydrogenase, and lactic dehydrogenase on *Staphylococcus epidermidis*.

Table 1. Data analysis presentation

No	Title	Researcher and Year	Design	Aims	Methods	Result
1	Antimicrobial and anti-inflammatory effects of α-mangostin soluble film.	Tangsuksan, et al.[1]	In vitro study	to determine the antimicrobial activity and antibiofilm formation of α-mangostin (α-MG) soluble film	· Antimicrobial assays against *Streptococcus mutans,* · Time-killing kinetic studies against the organisms and inhibition of biofilm formation by the broth microdilution method. · The antiinflammatory effect of the α-MG film was investigated in nitric oxide production.	The α-MG film is effective against *S. mutans,* without significant cytotoxicity in vitro. Thus, this new product may have potential advantage in preventing those common oral infections.
2	A-Mangostin disrupts the development of *Streptococcus mutans* biofilms and facilitates their mechanical removal.	Nguyen et al.[2]	In vitro study	To examine whether aMG, a xanthone purified from *Garcinia mangostana* L grown in Vietnam, disrupts the development, acidogenicity, and/or mechanical stability of *S. mutans* biofilms.	· A saliva-coated hydroxyapatite (sHA) biofilm model to assess the bioactivity of aMG	aMG could be an effective anti-virulence additive for the control and/or removal of cariogenic biofilms.
3	α-Mangostin and lawsone methyl ether in tooth gel synergistically increase its antimicrobial and antibiofilm formation effects in vitro	Nittayananta, et al.[3]	In vitro study	to develop a herbal tooth gel containing α-MG and LME plus fluoride and determine its antimicrobial, anti-biofilm formation, anti-cancer, anti-inflammatory, wound healing, and enamel microhardness effects.	· Antimicrobial assays against *Streptococcus mutans were* performed. The microbes ultrastructural morphology was assessed using Transmission Electron Microscopy. The effect on microbial biofilm formation was tested by a broth microdilution. Cell viability was assessed with MTT assay. The anti-inflammatory effect was investigated by measuring inhibition of nitric oxide production. Enamel microhardness was measured via Vickers microhardness testing.	The tooth gel containing α-MG and LME synergized its antimicrobial activity and antibiofilm formation and inhibited oral cancer cell proliferation. Incorporating fluoride into the tooth gel increased enamel microhardness. Thus, the herbal tooth gel containing α-MG and LME plus fluoride may be useful for preventing dental caries and promoting oral health
4	In vitro activity of alpha-mangostin in killing and eradicating *Staphylococcus epidermidis* RP62A biofilms.	Sivaranjani et. al.[4]	In vitro study	To evaluate the antibiofilm and mature biofilm eradication ability of α-MG against *Staphylococcus epidermidis* RP62A (ATCC 35984) biofilms.	- The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of α-MG against *S. epidermidis* RP62A. · Multi-passage resistance analysis and confirmed through scanning electron microscopy (SEM) analysis.	The present study exemplifies that α-MG could plausibly assist in eliminating biofilm infections associated with multidrug-resistance staphylococci.

5	Deciphering the antibacterial mode of action of alpha-mangostin on *Staphylococcus epidermidis* RP62A through an integrated transcriptomic and proteomic approach.	Sivaranjani et al.[6]	In vitro study	To identify the impact of α-MG on *Staphylococcus epidermidis* RP62A through integrated advanced omic technologies.	· The differential expression pattern of genes/proteins were analyzed in the absence and presence of α-MG using RNA sequencing and LC-MS/MS experiments. · Bioinformatic tools were used to categorize the biological processes, molecular functions and KEGG pathways of differentially expressed genes/proteins. · qRT-PCR was employed to validate the results obtained from these analyses.	Transcriptomic and proteomic profiling of α-MG-treated cells indicated that genes/proteins affected by α-MG treatment were associated with diverse cellular functions. The qRT-PCR analysis substantiated the results obtained from transcriptomic and proteomic profiling studies.
6	Inhibition of biofilm formation by alpha-mangostin- loaded nanoparticles against *Staphylococcus aureus.*	Nguyen et al.[7]	In vitro study	To investigate the antibiofilm activity of alpha-mangostin (AMG)-loaded nanoparticles (nanoAMG) against *Staphylococcus aureus*, including the methicillin-resistant strain MRSA252.	· *S. aureus* was cultured to measure the effect of biofilm formation. · Bacterial adhesion assay · Then, Confocal microscopy Polyvinyl qRT-PCR was performed to evaluate the expression of the genes. · Statistical analysis	The result of this study was that AMG-coated nanoparticles had enhanced biological activity as compared to free AMG, indicating that nanoAMG could be a new and promising inhibitor of biofilm formation to tackle *S. aureus,* including strains that are resistant to multiple antibiotics.
7	The antibacterial effects of apacaries gel (polyphenol from mangosteen extract) *on Streptococcus mutans:* An in vitro study	Juntavee et al.[8]	In vitro study	To evaluate the antibacterial effects of apacaries gel on *Streptococcus mutans* in vitro.	- Mangosteen pericarp powder was extracted. The amount of phenolic compounds was determined using the Folin-Ciocalteu method. The time-kill kinetics were investigated. Mangosteen extract and papain were mixed with gel base to develop apacaries gel. The inhibition zone of the Apacaries gel was determined using agar well diffusion methods	Apacaries gel can effectively inhibit *S. mutans strain* ATCC25175. Apacaries is capable of S. mutans inhibition better than both mangosteen extract or papain separately
8	Antimicrobial activity of α-mangostin against *Staphylococcus* species from companion animals *in vitro* and therapeutic potential of α-mangostin in skin diseases caused by *S. epidermidis*	Park YS, et al.[9]	In vitro study	To investigate the antimicrobial activity of α-mangostin against *Staphylococcus* species from companion animals *in vitro* and the therapeutic potential of α-mangostin in skin diseases caused by *S. pseudintermedius.*	· Bacterial strains · Antimicrobial susceptibility testing · Time-kill kinetics Assay Three · Field emission-scanning electron microscopy · Biotinylation of a-MG a-MG	The antimicrobial activity of a-MG against G (+) bacteria pathogens, including *S. aureus, S. epidermidis,* from human clinical specimens, have already been demonstrated. However, the antimicrobial activity of a-MG against *Staphylococcus* species originating from companion animals has not been characterized.
9	Anti-biofilm activity of α-mangostin isolated from *Garcinia mangostana* L.	Nguyen et al.[16]	In vitro study	To examine the anti-biofilm activity of α-mangostin (αMG) isolated from *Garcinia mangostana* L. grown in Vietnam, against a	- Extraction and isolation of αMG - Biofilms of S. mutans were formed on hydroxyapatite disk (sHA) surfaces - Multispecies biofilm preparation - Determination of surface GtfC activity	A brief exposure to αMG may suppress biofilm formation by targeting key enzymes involved in biofilm formation

				strongly biofilm producing *Streptococcus mutans*, a major causative agent of dental caries	· Determination of GtfB surface activity absorbed on S. mutans cell	
10	Antibiofilm activity of α-mangostin extracted from *Garcinia mangostana* L. against *Staphylococcus aureus*	Phuong et al.[11]	In vitro study	To isolate a-mangostin (AMG) from the peels of mangosteen (*Garcinia mangostana* L.), grown in Vietnam, and to investigate the antibiofilm activity of this compound against three *Staphylococcus aureus (S. aureus*) strains, one of which was methicillin-resistant *S. aureus* (MRSA) and the other two strains were methicillin- sensitive *S. aureus* (MSSA).	· AMG in the n-hexane fraction was isolated on a silica gel column and chemically analyzed by HPLC and NMR. · Biofilm biomass was quantified using crystal violet. The viability of cells was observed under confocal microscopy using LIVE/DEAD BacLight stains. · Biofilm composition was determined using specific chemical and enzyme tests for polysaccharides, proteins and DNA. · Membrane-damaging activity was assessed by measuring the hemolysis of human red blood cells in the presence of AMG.	The results provide evidence that the isolated AMG has inhibitory activity against biofilm formation by *S. aureus,* including MRSA. Thus, isolated AMG has a high potential to develop a novel phytopharmaceutical for the treatment of MRSA.
11	Antibiofilm activity of alpha-mangostin-loaded nanoparticles against *Streptococcus mutans*	Nguyen et al.[10]	In vitro study	To investigate the antibiofilm activity of alpha-mangostin (AMG)-loaded nanoparticles (nanoAMG) against the dental caries pathogen *Streptococcus mutans.*	· AMG was isolated from the peels of *Garcinia mangostana* L. using silica gel columns and chemically analysed. · NanoAMG was prepared using the solvent evaporation method combined with high-speed homogenization. · The nanoparticles were characterized using dynamic light scattering, field emission scanning electron microscopy (FE-SEM), and Fourier transform infrared spectroscopy (FTIR). · The toxicity of nanoAMG in the fibroblast NIH/3T3 cell line was determined using the MTT method. · Biofilm biomass was quantified using crystal violet. Cell viability was observed under confocal microscopy using LIVE/DEAD BacLight staining.	AMG-coated nanoparticles can enhance AMG bioactivity and can be used as a new and promising antibiofilm agent.

12	In Vitro evaluation of mangostanin as an antimicrobial and biocompatible topical antiseptic for skin and oral tissues	Munar-Bestard et al.[12]	In vivo study	To evaluate the antibacterial efficacy and biocompatibility of mangostanin (MGTN), a xanthone derived from *Garcinia mangostana* L., against commercial antiseptics across various bacterial strains (*S. mutans, S.aureus*, etc)	- Antimicrobial assays of different concentrations (0.002, 0.001, and 0.0002%) ofMGTN and Scanning Electron Microscope (SEM)	MGTN demonstrated significant antimicrobial activity against all tested pathogens concurrently exhibiting negligible cytotoxic effects on human gingival fibroblasts as well as on three- dimensional (3D) models of human epidermis and oral epithelium
13	Anticariogenic and anticarcinogenic effects of *Garcinia Mangostana* L. pericarp extracts on cariogenic bacteria and on cancer cell lines with molecular docking study	Mahendra et al.[13]	In vitro study	To explore the role of mangosteen pericarp extract on oral cariogenic organisms, anticarcinogenic potential on oral cancer and cervical cancer cell lines grown in-vitro, role of alpha-mangostin, an active component of mangosteen pericarp on genes commonly expressed in oral cancer using molecular docking technique.	- The Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) values were also determined. The anticancer potential of the crude ethanolic extract of mangosteen against two cancers - oral cancer cells and cervical cancer cells grown in vitro were also investigated. The viability of the cancer cells was assessed by doing a MTT assay, indicating the cytotoxic potential of mangosteen	The results highlight the fact that mangosteen is effective as an anticariogenic against Streptococcal species of microorganisms and anticarcinogenic agent. The pericarp showed promising results as an anticancer agent by inducing apoptosis in both oral cancer and cervical cancer cell lines.
14	Formulation of toothgel from mangosteen (*Garcinia mangostana* L.*)* pericarp extract purified and its antibacterial activity against bacteria of plaque formation	Djamaan, et al.[14]	In vitro	to determine the effectiveness of the dichloromethane extract of mangosteen pericarp as an active substance in tooth gel against bacteria of plaque formation had been done.	- Preparation of mangosteen Pericarp Extract - Preparation of Toothgel Formulas - Antibacterial activity determination of the dichloromethane mangosteen pericarp extract tooth gel against bacteria of plaque formation by diffusion agar method	The extract from mangosteen pericarp was effective againts dental plaque forming bacteria. These result supported the potential use of this Indonesian originally natural product as an antiplaque agent. Further
15	Antibacterial effect of metabolites from stem cells from human deciduous teeth with alpha-Mangostin and EGCG on *Staphylococcus aureus and Streptococcus mutans*	Sidarningsih, et al.[15]	In vitro study	to prove the inhibitory effect of SHED metabolite in combination with α-mangosteen and EGCG against *S. aureus and S. mutans* bacteria.	- The study isolated and characterized metabolites from SHED in a specific medium. Subsequently, the combination of metabolites with α-mangostin and EGCG was made in a 1:1 ratio. The bacterial inhibition zones were measured on disk paper placed on bacterial growth media	Combining SHED metabolites with α-mangostin and EGCG exhibits antibacterial properties against *S. aureus and S. mutans* bacteria. The combination of SHED metabolites with α-mangostin has higher inhibition results than the combination of SHED metabolites with EGCG.
16	Indonesian Mangosteen Fruit (*Garcinia mangostana* L.) Peel Extract Inhibits *Streptococcus mutans* in Biofilms In vitro	Widyarman, et al.[25]	In vitro study	to analyze mangosteen peel extracts' ability to inhibit *S. mutans* has biofilms growth in vitro.	- Mangosteen peel extract effects on the *S. mutans* ATCC-3198 ATCC-3327 in biofilms growth were evaluated by a crystal violet biofilm assay	Mangosteen peel extract is effective at inhibiting *S. mutans* biofilms, and this antibiofilm agent can be an alternative therapy in preventing caries and periodontal disease. Future studies are needed to explore this effect

17	In vitro and in vivo bactericidal and antibiofilm efficacy of alpha-Mangostin against *Staphylococcus aureus* persister cells	Felix, et al.[17]	In vivo and vitro study	To examine the antimicrobial property of alpha mangostin, a natural xanthone molecule, against *methicillin-resistant Staphylococcus aureus* (MRSA) persisters and biofilm.	- *S. aureus* MW2 persister cells were prepared by adding 20 mg/ml of gentamicin to an overnight bacterial culture and incubating for an additional 4 h. - After incubation, the bacterial cells were washed three times with an equal volume of PBS and set to OD600 ~ 0.4 (~2 x 108CFU/ml). - 1 ml of *S. aureus* MW2 persister cells was added with alpha mangostin (2 mg/ml) and vancomycin (4 mg/ml) inside a 2 ml deep well assay block (Corning Costar 3960). - All the experiments were done in triplicate.	The findings reveal that alpha mangostin is active against MRSA persisters and biofilms, and these data further our understanding of the antistaphylococcal activity and toxicity of this natural compound.
18	Alpha-Mangostin extract (*Garcinia mangostana* L.) effectiveness on the biofilm thickness growth of *streptococcus sanguinis*	Praptiningsih, et al.[18]	In vitro study	to determine the effectiveness usage of alpha mangostin toward *Streptococcus sanguinis* biofilm thickness growth.	- Experimental research design, with post-test only control group design with a sample size of 27. The treatment group consisted of alpha mangostin 3.125, 6.25, and 12.5 g/ml and the control group were distilled water. Measurement of *Streptococcus sanguinis* biofilm thickness was carried out by ELISA-reader. The statistical test was carried out using the One Way Anova test.	Alpha mangostin has antibacterial properties that can reduce the thickness of the *Streptococcus sanguinis* biofilm.
19	Antimicrobial effects of *Garcinia mangostana* L. on cariogenic microorganisms	Janardhanan et al.[19]	In vitro study	To assess the antibacterial efficacy of the crude chloroform extract of mangosteen pericarp against cariogenic bacteria.	- The antibacterial effect of mangosteen pericarp was tested using the agar well diffusion method on Trypticase Soy Agar Blood Agar (TSA?BA) and de Man, Rogosa, and Sharpe (MRS) agar media. - The standard antiplaque agent chlorhexidine was used as the positive control. - Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) values were determined by the microbroth dilution method.	The antibacterial bioassay showed the highest activity for *Streptococcus sanguis* (13.6 mm), *Streptococcus mutans* (10.6 mm), respectively. The MBC and MIC values were lowest for *Lactobacillus acidophilus* (MIC 25 mg/ml, MBC 50 mg/ml) and *Streptococcus oralis* (MIC 50 mg/ml, MBC 100 mg/ml).

20	Formulation and Characterization of a novel palm-oil-based α-Mangostin nano-emulsion (PO-AMNE) as an antimicrobial endodontic irrigant: An in vitro study	Sultan, et al.[24]	In vitro study	To formulate and characterize a palm-oil-in- water-based α-mangostin nano-emulsion (PO-AMNE) endodontic irrigant in order to evaluate its antibacterial efficacy against *Staphylococcus epidermidis, and S.mutans* biofilms, as well as its capacity to remove the smear layer.	- The solubility of α-mangostin in various oils was determined and selected, and surfactants and co-surfactants were used for the nano-emulsion trial. The optimized 0.2% PO-AMNE irrigant antimicrobial efficacy in a tooth model was done using colony-forming units. - The treated teeth were processed by scanning electron microscopic examination for debris and smear layer removal. An Alamar Blue assay was used to evaluate cell viability.	The formulated 0.2% PO-AMNE irrigant was effective, antimicrobial, and biocompatible, which could combat endodontic-infection-related polymicrobial biofilm among strains of *S. mutans* and play a significant role in both community- and population- level interactions in the dental biofilm.

DISCUSSION

Interactions among competing bacteria, which inhibit each other's growth to maintain microbial balance within the biofilm, can significantly impact oral cavity homeostasis. Competitor bacterial activities, such as mutacin produced by *Streptococcus mutans*, can directly impede the growth of *Streptococcus sanguis* bacteria, and vice versa.[8]

Natural products, predominantly derived from plants, harbor a plethora of compounds with potential for combating various diseases, including caries. Among these, several plant-based natural products exhibit inhibitory effects on *Streptococcus mutans* growth, primarily composed of polyphenolic compounds, notably flavonoids, based on their chemical structures.[15] However, their precise mechanism of action against *Streptococcus mutans* survival remains unclear, with potential mechanisms including specific interactions with the cell membrane, altering its permeability and leading to cell death, as well as altering gene expression involved in biofilm formation at the transcriptional level. Additionally, some compounds can hinder enzyme activity in acid production pathways. [8]

Alpha-mangostin, a xanthone extracted from the tropical plant *Garcinia mangostana L.* through ethanolic extraction, inhibits *S. mutans* UA159 acid production. Mechanistic research indicates that alpha-mangostin acts as a multitarget inhibitor, inhibiting membrane enzymes such as F(H+)-ATPase and the phosphoenolpyruvate-sucrose phosphotransferase system, as well as aldolase, glyceraldehyde-3-phosphate dehydrogenase, and lactic dehydrogenase. It inhibits glycolysis in intact cells in suspensions and biofilm formation at concentrations of 12 and 120 M, respectively. Other inhibitory effects of alpha-mangostin include malolactic fermentation involved in alkali production from malate and NADH oxidase, the primary respiratory enzyme for gram-positive bacteria. [9,10]

Alpha-mangostin's antimicrobial properties against gram-positive oral streptococcus bacteria operate through various mechanisms, including disrupting peptidoglycan, leading to cell brittleness and rupture, damaging the mechanical stability of *Streptococcus mutans* and *Streptococcus sanguis* biofilms, and inhibiting glucosyltransferase enzyme activity.[10] Moreover, alpha-mangostin reduces acid production from *Streptococcus mutans*, damages the cell membranes of other microorganisms in biofilms, binds directly to bacterial cell inner membranes, and increases bacterial cell permeability, ultimately resulting in bacterial cell death.[10]

The rapid bactericidal activity of alpha-mangostin (a-MG) on *Staphylococcus aureus, Staphylococcus epidermidis* and other gram-positive bacteria is noteworthy, as is its resistance to resistance development.[11] The bactericidal activity of alpha-mangostin on biofilms is significantly influenced by the age of the biofilm, and it may prove more effective when combined with other antimicrobial compounds.[11] *Streptococcus mutans* bacteria also produce gtfs, which is essential for extracellular matrix protein (EPS) formation. Similar to *Streptococcus sanguis*, *Streptococcus mutans* produces gtfB, gtfC, and gtfD, facilitating glucan formation and aiding in attachment to saliva-coated hydroxyapatite (sHA).[2] Bacteria then colonize and secrete extracellular polymeric substances (EPS) during the lag phase, initiating bacterial colonization and upregulating gene expression under aerobic conditions.[12] Rapid and extensive bacterial multiplication leads to colony formation during the rapid growth or exponential phase.[12-13]

The previous rapid growth phase encompassed both primary and secondary bacterial colonization. Aerobic bacteria such as streptococci and staphylococci species initially colonize the biofilm, multiplying and subsequently reducing oxygen availability within it. This paves the way for secondary bacterial colonization by anaerobic species like *Actinomyces*, *Fusobacterium nucleatum, Prevotella intermedia,* and *Capnocytophaga*.[14] The steady state phase, also termed the stationary and death phase, is characterized by slow or stagnant bacterial growth,

heightened extracellular polymeric substance (EPS) production, and decreased oxygen saturation resulting from bacterial activity in the preceding phase. Prolonged persistence in this state can enhance biofilm protection.[15]

The initial step in biofilm formation entails the development of a distinct biofilm architecture, achieved through both cell-to-cell and cell-to-surface interactions. In light of this, the impact of alpha-mangostin on these interactions was assessed. Findings indicated that inhibiting biofilm formation necessitated the addition of alpha-mangostin during the initial biofilm formation stages.[1]

Disruption of glucan synthesis affects bacterial metabolism, thereby compromising the stability and strength of bacterial attachment within the biofilm.[16] Across the three stages of biofilm formation, alpha-mangostin demonstrates inhibitory effects and damages biofilm defense mechanisms.[17] Furthermore, alpha-mangostin exhibits several anti-streptococci and staphylococci activities, including reducing acid production, which can harm the cell membranes of other microorganisms within the biofilm, directly binding to bacterial cell inner membranes, and enhancing the permeability of alpha-mangostin in bacterial cells, ultimately leading to bacterial cell death.[18]

In vitro studies investigating the efficacy of mangosteen peel against cariogenic bacteria have revealed its potential to inhibit oral streptococci and staphylococci.[19-23] Additional research delves into the effectiveness of alpha-mangostin and its biological action in combating the formation of oral bacterial biofilms in vitro, highlighting its ability to reduce biological mass accumulation, insoluble extracellular material, and enzyme activity for glucan synthesis.[2]

Discrepancies observed in the antibiofilm activity of alpha-mangostin among the test strains in this study could be attributed to differences in biofilm structure. One hypothesis posits that extracellular matrix components in biofilms, such as polysaccharides for NCTC 6175 and MSSA 15981, and surface proteins like FnBPA for MRSA 252, may interact variably with alpha-mangostin.[11]

Numerous studies indicate that alpha-mangostin binds to various unrelated proteins, including human serum albumin, transferrin, and the ATP-binding cassette drug transporter ABCG2 in cancer cells. Previous research has demonstrated alpha-mangostin's interaction with membrane-bound enzymes like F-ATPase and phosphotransferase systems in oral streptococci, along with the catalytic domain of glucosyltransferase C, a key enzyme responsible for biofilm formation by this organism.[24,25] The study investigate the effect antibacterial of alpha-mangostin on biofilm formation in oral streptococci and staphylococci, because previously there had been no research combining the effects of alpha-mangostin on these oral streptococci and staphylococci especially *Streptococcus mutans*, *Streptococcus sanguis, Staphylococcus aureus* and *Staphylococcus epidermidis.* The limitation of this research were difficulty to obtain the full text of articles and limited number of studies that meet the inclusion criteria means that the results may affect the representativeness of the articles. In addition, the studies included in this review differed in methodological quality, which may influence the validity of the results.

CONCLUSION

Alpha-mangostin from *Garcinia mangostin L* inhibits and disrupts biofilm defense mechanisms of oral bacterial biofilm, including *Streptococcus mutans, Streptococcus sanguis, Staphylococcus aureus* and *Staphylococcus epidermidis.* These mechanisms operate to damage the cell membrane of microorganisms, bind directly to the inner membrane of bacterial cells, increase the permeability of bacterial cell walls which ultimately causes bacterial cell death, and reduce biological mass accumulation, insoluble extracellular material, enzyme activity for glucan synthesis. Theoretical implications of this study are the antibacterial effect of alpha-mangostin from *Garcinia mangostana.* L which is effective against oral Streptococci and Staphylococci biofilms by increasing the permeability of bacterial cell walls, which ultimately causes bacterial cell death. while the practical

implications of the results of this study are used as input for researchers as an alternative antibacterial effect of alpha mangostin from *Garcinia mangostana.* L in fighting oral Streptococci and staphylococci biofilms.

Author Contributions: research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used: "Conceptualization, A.L.J., and R.S.P.; methodology, L.L.S.; writing original draft preparation, L.L.S.; writing review and editing, R.S.P., W.S.,A.L.J.,D.K.,Y.S.R.;; supervision. W.S., A.L.J., D.K., Y.S.R.
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