


Antibacterial and Antimicrobial Effects of Xanthorrhizol in the Prevention of Dental Caries: A Systematic Review

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Background: Xanthorrhizol is one of the numerous phytochemicals whose pharmacological benefits have been explored for its antibacterial and antimicrobial effects. In light of the role bacteria play for initiating tooth decay, this present systematic review assessed xanthorrhizol's effect against dental caries.

Methods: The electronic databases including Pubmed, Scopus and Embase were searched up to September 2020, Studies examining the antibacterial and antimicrobial effects of xanthorrhizol in the prevention and treatment of dental caries.

Results: Eleven studies met the criteria for final inclusion. Findings from these studies showed that xanthorrhizol showed significant inhibition of notable caries causing bacteria including *Streptococcus mutans*, *Streptococcus sanguinis*, *Enterococcus faecalis* and *Bacillus cereus*. Furthermore, there was no reported toxicity. However, it could not selectively target the growth of cariogenic bacteria.

Conclusion: So far, studies exploring the use of xanthorrhizol as a potential drug for the prevention and treatment of dental caries have shown promising outcomes. However, more work needs to be done especially in areas such as optimal dose or concentration, in addition, in vitro, in vivo and clinical studies and selective targeting of cariogenic bacteria has been performed.

Keywords: xanthorrhizol, antibacterial, antimicrobial, dental caries

Introduction

Dental caries (also known as tooth decay) is the most prevalent oral disease as well one of the most common chronic diseases across the globe.¹ The formation of caries also describes the carious lesions or cavities resulting from the destruction of the cementum, enamel, and dentin.² Although dental caries are complex in pathogenesis, the process of decay is initiated by Early life stages of cariogenic bacteria joining the dental biofilm, leading to initiation of the disease at a later stage.³ Some diseases responsible for dental caries in human include diabetes, anemia, oral cancer, eating disorders, etc.

As part of the bacterial flora in the oral cavity, *Streptococcus sanguinis* (*S. sanguinis*) and *Streptococcus mutans* (*S. mutans*) can be observed. In the pathogenesis of dental caries,⁴ certain microorganisms are the most dominant. Moreover, as is the case with *S. sanguinis*, they are concerned with periodontal and systemic diseases such as bacteremia and endocarditis.⁵

Biofilms are complex microbial communities. In the oral cavity, the number of phylotypes was estimated to exceed 19,000.⁶ It is composed of proteins, hydrated

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polysaccharides, glycopeptides, extracellular DNA and lipids.⁷ A biofilm is composed of several organism species including viruses, fungi and bacteria, existing at a stage or density interface, and embedded in an extracellular matrix that is self-secreted.⁷ The extracellular matrix surrounding the bacteria limits the penetration of antimicrobial drugs into the deeper sections of the biofilm. Apart from promoting competition for space, cohabitation of several organisms as well enhances the cooperative interactions such as horizontal gene transfer, metabolic cooperation and other synergies. This improves the ability of microorganisms to survive, thus become resistant to antimicrobial drug.^{8,9}

Since biofilms act as a group rather than a separate cell, coordination, communication and signaling from cell to cell are vital.¹⁰ Quorum sensing, the secretion and identification by its representatives of diffusible molecules can result in sudden changes in the behavior of microbial species.¹¹ The resistance of biofilms to therapy is controlled by three physiological processes.^{12,13} Firstly, there is a delayed or reduced penetration of any antimicrobials because of repulsion by the exopolysaccharide matrix. Secondly, the presence of persistent metabolically inactive cells capable of putting up with antimicrobial attacks prevents the colony from being utterly eliminated. Finally, the shut proximity of alternative cells offers rise to associate degree exaggerated chance of sharing resistance-encoding mobile genetic components. They will become 10–1000 times more resistant to the effects of antimicrobial agents when cells live in a biofilm.¹³ This poses a challenge for therapeutically targeting cariogenic bacteria residing in the biofilm.

Fluoride is the most common therapeutic modality for dental caries.^{13,14} Fluoride decreases bacteria's acid resistance and is most effective at acidic pH levels. Fluoride enhances glycolysis in *S. mutans* under acidic conditions. The anti-caries effect of fluoride not only consists of remineralization but also inhibition of acidogenic bacteria in acidic conditions. Although the most powerful anti-caries agent today is fluoride,¹⁴ dental caries remain a public health problem in today's world. Thus, there is the need to establish new therapeutic alternatives that may complement current treatment modalities.

Dental Caries is mainly a disorder of infection, thus numerous studies have focused mainly on the transmission and presence of certain groups of bacteria as the major determinants of caries. *S. mutans* have been shown to be one of the key pathogens involved in the development of dental caries, especially in children.^{15–21} From a microbiological

standpoint, preventive approaches might include efforts to prevent or delay transmission of *S. mutans* to the child, the development of topical antimicrobial agents aimed at preventing key bacteria from reaching pathological levels, vaccination or gene therapy and methods to stimulate salivary flow.^{2,22} However, the clinical efficacies of these strategies have so far been ineffective.²

Phytochemicals (plant-derived natural products) with abilities to inhibit bacteria growth are an attractive alternative to conventional oral biocides for long-term caries prevention. Phytochemicals have been shown to reduce the development of dental plaque, influence bacterial adhesion, and reduce symptoms of oral diseases.²³ For instance, eucalyptus globules and ethyl acetate extracts of acacia nilotica have been observed for their potent antimicrobial effects.²⁴ Natural products have advantage over conventional antimicrobial agents which suppress even health-associated oral microbial communities, and thus disrupting key health benefits of the resident oral microbiome.²⁵

Xanthorrhizol (Figure 1) is one of the numerous phytochemicals whose medical benefits have been explored. This is a bioactive substance isolated from the *Curcuma xanthorrhiza* rhizome (Java turmeric).²⁶ Xanthorrhizol (1,3,5,10-bisabolatetraen-3-ol) has a molecular weight of 218.33 g/mol and a solubility of 28.90 µg/mL.²⁷ Thus, the surface of a biofilm is supposed to penetrate readily.²⁷ It has been reported to possess numerous pharmacological abilities including antimicrobial, anti-hyperglycemic,

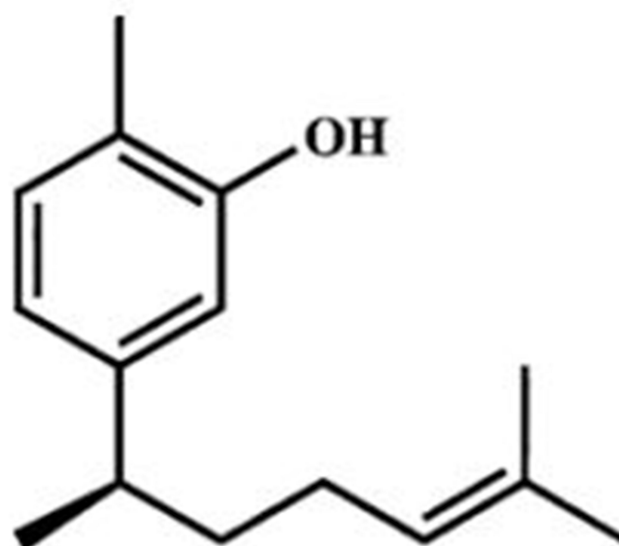


Figure 1 Chemical structure of xanthorrhizol.

antibacterial, anti-inflammatory, antifungal, anticancer and neuroprotective properties.²⁸⁻³¹ In light of the role bacteria play for initiating tooth decay, this present systematic review assessed xanthorrhizol's effect against dental caries.

Materials and Methods

We adopted the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)³² guidelines in conducting the present study.

Search Strategy

The Pubmed, Embase and Scopus databases were assessed from the inception of each database till September 2020, to perform a literature search on studies which investigated the antimicrobial and antibacterial effects of xanthorrhizol. These databases were searched for articles published in English language without restriction on publication year. The search keywords were “xanthorrhizol”, “Curcuma xanthorrhiza”, “antimicrobial”, “antibacterial” and “dental caries”. Only original articles (experimental and clinical) were included. However, articles types such as reviews, letters and conference proceedings were excluded. Afterwards, articles from the initial search were screened for duplicates (using Endnote software version 8), followed by screening their titles and abstracts for conformity to the eligibility criteria. Furthermore, references of retained articles were manually screened for possible inclusion of relevant studies. Quality assessment of the relevant studies was conducted using RevMan software version 5.3.

Data Extraction

With the aid of a predesigned data extraction form, two authors were charged with the independent entry of its contents. In the case of disagreements, a third author was consulted and consensus were reached based on factual evidences. The data extracted from the included studies were as follows: first author name and year, study type, xanthorrhizol concentration, antibacterial activity and major finding(s). The antibacterial and antimicrobial activity of xanthorrhizol against any of the studied microorganism was defined in terms of at least of the following:

- Minimum inhibitory concentration (MIC) (expressed in $\mu\text{g/mL}$), defined as the lowest concentration of xanthorrhizol required to inhibit the growth of a bacteria compared with the control, in vitro.

- Colony forming unit (CFU) [expressed in \log_{10} (CFU/mL)].
- Cell viability (expressed as a percentage).

Results

Initially, 313 records were identified from the literature search following the removal of duplicates, 295 articles were retained. Afterwards, a further 258 articles were excluded after screening of their titles and abstracts. Thus, the full-texts of 37 articles were screened for eligibility, from which 11 articles met all criteria for final inclusion (Figure 2). Except for one clinical study, all others were in vitro studies. Table 1 presents the major characteristics of the included studies.

Antibacterial Effect of Xanthorrhizol

Studies by Hwang et al^{28,33} showed that revealed the fast antibacterial activity of xanthorrhizol against *S. mutans*. Moreover, in both studies, xanthorrhizol had the highest antibacterial activity against all the five Streptococcus species. Rukayadi and Hwang³⁴ further observed that the antibacterial effect of xanthorrhizol on treated *S. mutans* biofilms was dependent on the concentration, exposure time and maturation periods (4, 12, 20 and 24 hours) of biofilm. While 5 $\mu\text{mol/l}$ xanthorrhizol treated biofilms of *S. mutans* at the adherent period (4 h) were completely removed, those treated with 50 $\mu\text{mol/l}$ xanthorrhizol at the

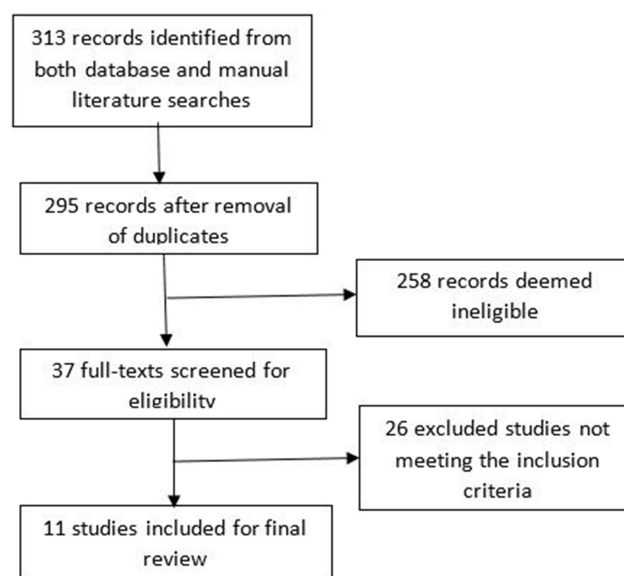


Figure 2 PRISMA diagram depicting the process of study inclusion. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.³²

Table 1 Summary of Included Studies

First Author Name and Year	Study Type	Xanthorrhizol Concentration	Antibacterial/Antimicrobial Activity				Major Finding(s)
			<i>S. mutans</i>	<i>S. sanguinis</i>	<i>E. faecalis</i>	<i>B. cereus</i>	
Hwang et al ²⁸ 2000	In vitro	5 µg/mL	2 µg/mL (MIC)	–	–	–	Xanthorrhizol has fast antibacterial activity and makes it suitable for use as mouthwash or toothpaste.
Hwang et al ³³ 2000	In vitro	–	2 µg/mL (MIC)	4 µg/mL (MIC)	–	–	Xanthorrhizol had the highest inhibition of bacterial growth for all <i>Streptococcus</i> species.
Rukayadi ³⁴ 2006	In vitro	5, 10 and 50 µmol/l	76%–100%	–	–	–	The antibacterial effect of xanthorrhizol depends on its exposure time and concentration as well as on the phase growth of biofilm.
Rukayadi ³⁶ 2006	In vitro	1–10 µg/mL	2.5 µg/mL (MIC)	–	–	–	The antibacterial effect of xanthorrhizol was comparable to that of chlorhexidine.
Kim et al ³⁷ 2008	In vitro	0.1 mg/mL	57.6%	–	–	–	The antibacterial effect of xanthorrhizol was comparable to that of chlorhexidine.
Lee et al ⁴⁴ 2008	In vitro	10%	–	–	–	8 µg/mL (MIC)	Xanthorrhizol had effective antibacterial activity against foodborne pathogens.
Bhat et al ³⁵ 2012	Clinical trial	5%	78%	–	–	–	Xanthorrhizol is an effective disinfectant for toothbrushes and thus could prevent caries.
Yue et al ³⁹ 2016	In vitro	1%	–	–	0.0625%	–	At alkalization state, the antibacterial effect of xanthorrhizol on <i>Enterococcus faecalis</i> was higher than chlorhexidine.
Lee et al ²⁷ 2017	In vitro	0–10 ⁴ ng/mL	0–6.29 log ₁₀ (CFU/mL)	–	–	–	The antibacterial effect of xanthorrhizol showed synergy with photodynamic therapy in preventing caries.
Cho et al ⁵² 2020	In vitro	58.3–233.9 nm (droplet diameter)	5.72 log ₁₀ (CFU/mL)	–	–	–	Nanoemulsions of xanthorrhizol showed stable and strong antimicrobial effects.
Philip et al ⁴⁹ 2020	In vitro	200 µg/mL	4 µg/mL (MIC)	4–8 µg/mL (MIC)	–	–	Xanthorrhizol had the highest inhibition of bacterial growth.

Abbreviations: *S. mutans*, *Streptococcus mutans*; *S. sanguinis*, *Streptococcus sanguinis*; *E. faecalis*, *Enterococcus faecalis*; *B. cereus*, *Bacillus cereus*; MIC, minimum inhibitory concentration; CFU, colony forming unit.

beginning plateau accumulated phase (20 h) and plateau accumulated phase (24 h) were reduced by 89% and 76%, respectively. These effects of exposure time, concentration and phase growth are particularly important as it has been reported that bacteria on the surfaces of toothbrushes can be viable from 24 hours to 7 days.³⁵

Another study by Rukayadi and Hwang³⁶ showed that the antibacterial activity of xanthorrhizol was similar to that of chlorhexidine. Furthermore, coating the well of a microtiter plate with 5 µg/ml xanthorrhizol resulted in a 60% reduction of adherent cells compared to cells in the uncoated wells. Thus, significantly prevented colonization and biofilm formation of *S. mutans*. Kim et al³⁷ also reported that 0.1 mg/mL of xanthorrhizol showed a similar antibacterial activity to 2 mg/mL of chlorhexidine on *S. mutans* biofilms, with a 57% inhibition of cell viability. They attributed the antibacterial mechanism of xanthorrhizol to the disruption of the peptidoglycan layer of *S. mutans*.³⁷

Lee et al²⁷ explored the photodynamic potential of xanthorrhizol as an antibacterial agent. When irradiated with light, the antimicrobial activity of CXE appeared at 10² ng/mL, which is lower than the MIC of xanthorrhizol itself and so indicates that CXE can induce the photodynamic reaction by acting as a photosensitizer. Thus, the viability of *S. mutans* cells reduced steadily from 85.2% to 0.0% for corresponding xanthorrhizol concentrations of 10² to 10⁴ ng/mL. The production of reactive oxygen species (ROS) following irradiation of xanthorrhizol, was attributed to antimicrobial photodynamic activity of xanthorrhizol in the prevention of caries.¹³

During the treatment of caries, therapeutic resistance could be encountered. It has been shown that the presence of *Enterococcus faecalis* (*E. faecalis*) in the root canal following endodontic treatment is an indication of therapeutic failure.³⁸ Thus, it is imperative to identify new drugs with capabilities of fully reaching the canal system. To this aim, Yue et al³⁹ compared the antibacterial effect of xanthorrhizol with chlorhexidine on *E. faecalis*. Their results showed that although both xanthorrhizol and chlorhexidine had similar antibacterial effect, xanthorrhizol was more effective in alkalization state. Thus, the effective removal of *E. faecalis* by xanthorrhizol portends a useful strategy for countering resistance during the treatment of caries.

Foodborne pathogens such as Enterobacteriaceae, *Staphylococcus aureus* and Enterococci have been shown to be contributory factors in the development of dental

caries.^{40–43} Thus, pathogenic bacteria inhibition can be useful to prevent caries and periodontal diseases. Lee et al⁴⁴ reported effective activity of xanthorrhizol against gram-positive bacteria including *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus* and *Clostridium perfringens*, even at low concentrations. However, among those tested for gram-negative foodborne bacteria, only *Vibrio parahaemolyticus* and *Salmonella typhimurium* were observed to be xanthorrhizol sensitive, while xanthorrhizol had no effect on *Yersinia enterocolitica*, *Shigella sonnei*, *Escherichia coli* O157:H7 and *Campylobacter jejuni*.

Antimicrobial Effect of Xanthorrhizol

Toothbrushes, when manufactured are free of microorganisms. However, when used for the removal of plaque as well as other debris, they become contaminated with bacteria, leading to infection. Moreover, it has been shown that contamination occurs as fast as 30 seconds to 4 minutes after each use.⁴⁵ There have also been evidence associating the continued use of these toothbrushes contaminated by several micro organisms including *Pseudomonas*, *Candida*, *Streptococcus*, *Klebsiella*, *Lactobacilli*, *Escherichia coli* and *Staphylococcus*, to the development of dental caries.^{46–48} Thus, effective decontamination of toothbrushes is a useful strategy in the prevention of caries, especially as toothbrushes are the most common tool for improving oral hygiene. A clinical trial by Bhat et al³⁵ treated the toothbrushes of 60 children with different antimicrobial agents. Toothbrushes of children in groups 1, 2, 3 and 4 were treated with 3% neem, 5% xanthorrhizol, 0.5% cetylpyridinium chloride and 0.2% chlorhexidine, respectively for 12 hours. Their results showed that the antimicrobial effect of xanthorrhizol on *S. mutans* was higher than chlorhexidine, but lesser than that of neem and cetylpyridinium chloride. Moreover, there was a 78% reduction in *S. mutans* following treatment with xanthorrhizol.

In exploring novel drugs that inhibit bacteria that induce dental caries, it is important that the drug does not deplete the “useful” bacteria of plaque microflora. Philip et al⁴⁹ investigated the efficacy of some antimicrobial agents including xanthorrhizol to ascertain their potentials for selective targeting of *S. mutans* without upsetting the viability of health-associated *S. sanguinis*. Results showed that among the tested natural products, xanthorrhizol had the highest antimicrobial activity. Moreover, for all the agents, there was no significant

difference between their inhibitions of *S. mutans* and *S. sanguinis*. Thus, none of the agents could selectively target the growth of cariogenic bacteria.

It has been shown that biofilm matrix can limit the effectiveness of drugs, thereby making the biofilm resistant to antimicrobial agents.^{50,51} Thus, Cho et al⁵² explored the possibility of the use of xanthorrhizol in the form of nanoemulsion, in order to facilitate the ease of penetration of antimicrobial agents into biofilm. Their results showed effective antimicrobial effects of nanoemulsion xanthorrhizol, via inhibition as well as damaging the biofilm formation by *S. mutans*.

Discussion

To our knowledge, this is the first study to systematically review the antimicrobial and antibacterial capabilities of xanthorrhizol in preventing dental caries. Our findings from the reviewed studies showed that xanthorrhizol has potentials to be an effective drug for the prevention of dental caries. Xanthorrhizol's mechanism against caries-forming bacteria are determined by the substances that comprise xanthorrhizol: chains of phenols and hydrocarbons. The phenol compounds containing the hydroxyl (-OH) functional groups, interact with bacterial cells through the process of adsorption comprising hydrogen bonds and can change the permeability of cell membranes.⁵³ The high concentration of phenol penetrating into cells could lead to protein coagulation and lysis on cell membranes. Furthermore, the formation of hydrogen bonds between the hydroxyl groups of phenol compounds and cell membrane proteins disrupts the permeability of the membrane, thereby causing the vital cell components to exit the cell leading to the inhibition or death of the bacteria.⁵³ It has also been suggested that the suppression of mitogen-activated protein kinase (MAPK) and nuclear factor kappaB (NF- κ B) by xanthorrhizol could be attributed to its antimicrobial effect.⁵⁴

In recent times, novel antimicrobial and antibacterial agents have been explored.^{55–60} Chlorhexidine, which is commonly found in mouthwash has faced limitations due to restricted doses and possible side effects.⁶¹ In contrast, studies involving xanthorrhizol have shown no toxicity in addition to effective antimicrobial and antibacterial activities even at low concentrations. While the MIC of xanthorrhizol is comparable to chlorhexidine, it also suffers from the challenge of not being selective for cariogenic bacterial species.⁴⁹

According to a recent report by the Global Burden of Disease Study, oral diseases are prevalent in 3.5 billion people.⁶² Furthermore, it was revealed that untreated dental caries is the most common health burden.⁶³ Dental caries has been shown to have a negative effect on the quality of life of individuals.⁶⁴ Its economic burden has also been a major concern especially in low and middle-income nations unable to provide services to prevent and treat oral health conditions.⁶⁵ Thus, exploring the use of natural agents such as xanthorrhizol could go a long way in alleviating these burdens, especially as they are cheap, naturally abundant and less toxic.

The present study had limitations. Most of the reviewed studies were in vitro except for one clinical trial. Moreover, in the clinical study, only a few subjects were enrolled and xanthorrhizol was not administered directly on them, rather it was used to disinfect their toothbrushes. Thus, going forward, future randomized control trials with a large number of subjects, preferably those suffering from dental caries can be enrolled in order to fully examine the clinical efficacy of this drug. Furthermore, while no safety concerns were recorded in any of the reviewed studies, it is imperative that further evaluation of nanoemulsion xanthorrhizol be carried out to ascertain its effects on saliva as well as other soft tissues, before being explored as a potential mouthwash.

Conclusion

Findings from the reviewed studies have shown that xanthorrhizol possesses potent antibacterial and antimicrobial activities, implying a potential drug for the prevention and treatment of dental caries. However, there still remains a lot of work to be done in ensuring its full clinical translation. Further researches are necessary, including in vitro, in vivo and clinical studies. Aspects such as optimal treatment dose or concentration of xanthorrhizol, future randomized control trials and selective inhibition of cariogenic bacterial species would also need to be addressed in order to fulfill its potential to be considered as a standard drug.

Disclosure

The authors report no conflicts of interest in this work.

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