Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2021, Article ID 3423001, 22 pages
https://doi.org/10.1155/2021/3423001

Review Article

The Current Strategies in Controlling Oral Diseases by Herbal and Chemical Materials

Mohammad Nima Motallaei,[1] **Mohsen Yazdanian**,[1] **Hamid Tebyanian**,[2] **Elahe Tahmasebi**,[1] **Mostafa Alam**,[3] **Kamyar Abbasi**,[4] **Alexander Seifalian**,[5] **Reza Ranjbar**,[1,6] **and Alireza Yazdanian**[7]

[1]*Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[2]*Science and Research Branch, Islamic Azad University, Tehran, Iran*
[3]*Department of Oral and Maxillofacial Surgery, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4]*Department of Prosthodontics, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[5]*Nanotechnology and Regenerative Medicine Commercialization Centre (Ltd), The London Bioscience Innovation Centre, London, UK*
[6]*School of Dentistry, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[7]*Department of Veterinary, Science and Research Branch, Islamic Azad University, Tehran, Iran*

Correspondence should be addressed to Mohsen Yazdanian; myazdaniandr@gmail.com and Hamid Tebyanian; tebyan.hamid@yahoo.com

Received 18 May 2021; Accepted 26 July 2021; Published 23 August 2021

Academic Editor: Mary Anne Medeiros Bandeira

Dental plaque is a biofilm composed of complex microbial communities. It is the main cause of major dental diseases such as caries and periodontal diseases. In a healthy state, there is a delicate balance between the dental biofilm and host tissues. Nevertheless, due to the oral cavity changes, this biofilm can become pathogenic. The pathogenic biofilm shifts the balance from demineralization-remineralization to demineralization and results in dental caries. Dentists should consider caries as a result of biological processes of dental plaque and seek treatments for the etiologic factors, not merely look for the treatment of the outcome caused by biofilm, i.e., dental caries. Caries prevention strategies can be classified into three groups based on the role and responsibility of the individuals doing them: (1) community-based strategy, (2) dental professionals-based strategy, and (3) individual-based strategy. The community-based methods include fluoridation of water, salt, and milk. The dental professionals-based methods include professional tooth cleaning and use of varnish, fluoride gel and foam, fissure sealant, and antimicrobial agents. The individual-based (self-care) methods include the use of fluoride toothpaste, fluoride supplements, fluoride mouthwashes, fluoride gels, chlorhexidine gels and mouthwashes, slow-release fluoride devices, oral hygiene, diet control, and noncariogenic sweeteners such as xylitol. This study aimed to study the research in the recent five years (2015–2020) to identify the characteristics of dental biofilm and its role in dental caries and explore the employed approaches to prevent the related infections.

1. Introduction

Oral cavity provides an environment that leads to the colonization and growth of an extensive range of microorganisms. Bacteria are the most prevalent of them. The highest bacterial accumulation is found as a biofilm on the tooth surface (dental plaque). The loss of mucosal surface reduces the microbial load on the mucosal surfaces [1, 2]. These microbes normally exist on all oral surfaces and are necessary for the normal physiological growth of the oral cavity [3]. Static microflora contributes to the host health by preventing the establishment and colonization of exogenous microorganisms and potential pathogens and regulating the inflammatory response of the host to oral commensal bacteria [4]. The oral bacterial population with almost 1000 species is very complicated [5]. The clinical treatment of caries usually deals with the restoration of hard tissues considering the functional and aesthetic needs. However,

this does not treat the illness but treats its outcomes. In clinical settings, a common method for the management of dental caries is the elimination of contaminated tissues to prevent the further progress of the disease. The areas surrounding the restoration gradually undergo caries, so a small restoration must be substituted by a greater restoration and dental tissues are increasingly eliminated. Repetition of this cycle leads to extensive loss of dental tissue, pulpal involvement, and finally tooth loss [6]. Admittedly, an inadequate understanding of dental caries as a biological process leads dentist to such a problem. Considering the developments in genetics, particularly molecular biology, findings make it possible for us to replace the old paradigms with new ways of caries prevention and treatment. Dental decay is caused by an ecological imbalance in mouth microflora. These imbalances can be influenced by environmental and biological reasons. Dental caries can be controlled by managing the above mentioned changes [7, 8]. In this review, we aimed to study the recent research to identify the characteristics of dental biofilm and its role in dental caries and also explore the employed methods to prevent the related infections.

2. Caries and Its Stages

Dental caries is a chronic and preventable disease caused by dental biofilm activity. This disease is multifactorial and is initially caused by an imbalance of mouth microflora as a result of existence of carbohydrates on the tooth. Caries is characterized by local demineralization of the teeth and loss of dental structure. Some biofilm bacteria metabolize the existing carbohydrates and produce acids. These acids can reduce the pH and reach lower than the critical limit (5.5 for enamel and 6.2 for dentine) if they remain in the biofilm for a long time. This acidic environment affects the biofilm composition and tooth surface. Therefore, acidogenic and acidophilic bacteria increase, which results in a more acidic environment. Calcium and phosphate are removed from the tooth surface, as a result of which demineralization occurs due to the loss of minerals. If pH returns to its normal level, calcium and phosphate can return to the tooth structure and cause remineralization [9]. Dental caries is created on the surface and subsurface areas of the tooth following a dynamic trend of demineralization and remineralization. These events occur several times over time and are influenced by several factors like the type and number of biofilm microorganisms, diet, oral hygiene, genetics, tooth anatomy, fluoride consumption, and salivary content and composition. These factors are specific to each individual and vary from tooth to tooth and from place to place [9]. As demineralization continues, primary caries occurs, a lesion with no cavities called white spot lesion (WSL) on enamel. Most primary caries can be terminated or remineralized; i.e., they are reversible. Dental caries becomes cavitated as it progresses. Cavitated lesions often need restorative intervention and are irreversible. Moderate lesions are lesions that have not extended the internal one-third of the dentin, and advanced or deep lesions are those that have extended the internal one-third of the dentin [9].

3. Dental Plaque

Dental plaque is a soft and sticky layer accumulated on the tooth surface. Dental plaque, also called biofilm, mostly consists of bacteria and their products, extracellular matrix, and water. Biofilm is not sticky food debris or accidental accumulation of opportunistic microorganisms; it is the accumulation of a series of organized events. The formation of dental plaque involves the formation of the pellicle, initial attachment, and plaque maturity [10]. Plaque forms as follows: a clean tooth surface is immediately exposed to the salivary byproducts, gingival crevice fluid (GCF), and some compounds resulting from bacteria. These products are absorbed by the surface with a negatively charged hydroxyapatite, creating a layer called acquired pellicle. The dental pellicle is covered with positively charged molecules, which contain more than 180 proteins, peptides, and glycoproteins such as proline-rich proteins, histidine-rich proteins, phosphoproteins (e.g., statherin), creatine, mucin, and other molecules that act as the binding sites for bacteria [10]. Some bacterial products like glycosyltransferases and glucans are also found in the pellicles. Interestingly, the main compound of a pellicle is stable in different areas of the oral cavity and among individuals. The bacteria attached to the tooth surface are not directly connected to the enamel; they are bound to the enamel through pellicle [10]. Primary bonding is initiated a few minutes after brushing the colonization. A cell wall with negatively charged bacteria facilitates its connection to the positively charged receptors of the pellicle. The early stages of transfer and interference with the surface are similar and nonspecific for all bacteria. Specific involvement of the binding molecules of the bacterial cell wall and pellicle receptors determines whether the bacteria remain in contact with the surface or not. Only a small part of oral bacteria can bind to the pellicle receptors, which constitutes the most common biofilm bacteria over a short time after tooth cleaning. During the early hours, streptococci form over 60–80% of biofilm bacteria. These bacteria along with *Haemophilus*, *Neisseria*, *Actinomyces*, and *Veillonella* species are known as primary colonizers. They initially create a wide range of nonspecific and reversible Van der Waals connections with pellicle (more than 50 nm). Then, they make stronger and irreversible short-range connections (10–20 nm) with pellicle receptors by their specific surface molecules [10].

Streptococci create different adhesion mechanisms. They have different adhesion mechanisms such as products of glycosyltransferases, glucan-binding proteins, and pili, while other bacteria such as actinomycetes bind to the surface using their fimbriae [11]. These bacteria provide new adhesion sites for other bacteria and change the environment with their metabolic activity, thereby affecting the biofilm viability (e.g., reducing the ambient oxygen) [11]. Plaque matures as follows: the primary colonizing bacteria bound to the tooth surface provide new receptors for the bacteria to help induce coadhesion via binding. The bacteria of different species or even strains of a species can specifically bind to specific bacteria. *Fusobacterium* coaggregates with all oral bacteria, while *Veillonella*, *Capnocytophaga*, and *Prevotella*

coaggregate with streptococci or actinomycetes. Most of this adhesion between various bacteria is performed through lectin-like receptors (proteins that identify the carbohydrates). Thus, they can be inhibited by lactose or other galactosidase or amino acids like L-arginine [10, 12]. Secondary colonizers like *P.Int*, *FN*, *Prevotella loescheii*, *Capnocytophaga*, and *PG* cannot bind to the clean tooth surface but can bind to bacteria in the dental plaque. Some specific structures in dental biofilm such as corn cob and test-tube brush are created due to the adhesion of cocci to filamentous bacteria. In this stage of plaque maturity, the bacteria secret extracellular polysaccharide, which constitutes the biofilm scaffold [10, 13]. If the dental plaque remains for about 7 days, it provides a favorable environment for the colonization of some aerobic Gram-negative bacteria, which are called secondary colonizers, including *PG*, *Aggregatibacter actinomycetemcomitans*, and *Treponema denticola* [10, 13].

4. Dental Biofilm

A healthy dental biofilm is mostly composed of commensal nonpathogenic microbes. These microbes are not completely independent and are regularly linked with each other and host tissues like gingiva even in a healthy state. The host provides the surfaces for colonization, and beneficial bacteria prevent the colonization of pathogenic bacteria [4, 14]. The advantages of this connection are manifested in conditions such as antibiotic sore mouth when inhibition of normal flora leads to the growth of opportunistic pathogens [4]. Studies have shown that commensal bacterial species such as *S. salivarius*, *S. sanguis*, and *Atopobium parvulum* can induce biofilm health-related conditions. Nevertheless, further research is needed to explore this issue. It has been shown that *S. salivarius* inhibits the quorum sensing process and mutans biofilm formation, which results in its anticaries properties [15–17]. The commensal bacteria in biofilm are involved in the immune system development. They do this by presenting diverse antigens to the host immune system. The commensal bacteria create a cascade of signals that induce the host resistance, while pathogenic bacteria induce severe inflammation in the host. Hence, proinflammatory cytokines are produced in a low number in oral epithelial cells, which induces the expression of E-selection in vascular endothelial tissues and produce IL8 [10]. The commensal bacteria induce the innate immune response of the host, which strategically juxtaposes the neutrophils with subgingival bacteria and junctional epithelium. The main bacteria with the highest variation in the oral cavity include *S*, *Staphylococcus*, *Peptostreptococcus*, *P*, *Haemophilus*, *Veillonella*, *Leptotrichia*, *Treponema*, *Propionibacterium*, *Actinomyces*, *Fusobacterium*, *Corynebacterium*, *Eikenella*, *Gemella*, *Granulicatella*, *Rothia*, *Porphyromonas*, *Capnocytophaga*, *L*, *Neisseria*, and *Eubacteria* [18–20]. Oral health depends on the conservation of its normal microflora. A disease occurs once the species are imbalanced and pathogens become dominant. Oral health and disease are dynamic processes in which the ecology of communities is a determinant factor, not an organism. Understanding the meaning of and identifying the molecular changes among the disease and health conditions provide the clinicians with the ability to diagnose and reverse the disease in early stages [21].

5. Bacterial Groups in the Caries Process

The newest molecular biology methods of microorganisms related to caries are *B. dentium*, *B. adolescentis*, *SM*, Scardovia wiggsiae, *B. longum*, *Selenomonas* spp., *P.* spp., and *L.* spp. [16]. Studies have indicated that early streptococci on the newly cleaned tooth surface mostly include *S. sanguinis*, *S. oralis*, and *S. mitis* strains, and the content of their mutans is only 2% or less. It has also been shown that most primary colonizers belong to the *S. mitis* group. The amount of microflora actinomycetes increases over time so that the smooth surfaces of most bacteria in the mature plaque include actinomycetes and nonmutans streptococci. Mutans are found in small numbers [22] and are more abundant in white spot lesions (WSLs) than in healthy regions. However, nonmutans streptococci still constitute most WSL bacteria. It has been shown that the initial members of microflora can singly dissolve enamel in the absence of mutans and lactobacilli [22]. In cavitated dentinal lesions, including rampant caries, mutans constitute about 30% of microflora, which indicates that mutans are linked with progressive carious lesions. Nevertheless, some studies have shown that the dentinal caries of mutans is less frequent in deep lesions, and lactobacilli, *Prevotella*, and bifidobacteria are more prominent. These results indicate that microflora on the tooth surfaces change as caries progresses [22]. *S. mutans* is Gram-positive cocci. The oral *S* spp. are normal flora but are also opportunistic and can cause dental caries [23]. They include *SM*, *S. sobrinus*, *S. rattus*, *S. cricetus*, *S. ferus*, *S. downei*, and *S. macacae*. Virulence has numerous factors that induce its demineralization [23] (Table 1).

6. Extracellular Polymeric Substance [24]

The extracellular polymeric substance [24] of the biofilm plays a pivotal role in maintaining the bacterial integrity and adhesion. New studies on the biology of EPS have reported several roles for the scaffold resulting from EPS, which are vital for the biofilm [25, 26]. Some of these roles include surface adhesion, spatial and chemical heterogeneity in biofilm, competitive or collaborative interactions, and improved resistance to antimicrobials [25]. The construction of EPS matrix relates to the existing substrates, production and secretion of e-materials, and shear forces. The key part of EPS content in oral biofilms which is related to caries is polysaccharides, especially the glucans derived from *SM* [27]. In addition to these, polysaccharides result from other bacteria (e.g., actinomycetes, *Streptococcus salivarius*, and *Streptococcus gordonii*), and combination compounds of starch glucan exist in this matrix. Further, this matrix contains eDNA [28] (proteins derived from bacteria with properties similar to amyloid), host GP which are able to participate in the scaffold with G such as glucan-eDNA compounds [29]. The function and structure of this class of extracellular polymers are still not known completely and

Table 1: Virulence factors of *SM*.

Property	Description
Making acid	Capability to make lactic acid
Aciduricity	Capability to tolerate low pH
IPS	Capability to consume IPS to continue making lactic acids with the lack of fermentable carbohydrates
EPS	Making matrix of the biofilm

require further studies. Glucans are composed of glucose components, which are connected byα 1–4 and α 1–6 glycosidic bonds and are created by the coordinated activity of streptococcal exoenzymes called glucosyltransferase [3, 27, 30]. Interestingly, these extracellular enzymes can bind to the tooth structure in the active state and produce glucans locally, thereby providing new binding sites for the bacteria. In addition to these, glucosyltransferase enzymes bind to other oral microorganisms (e.g., commensal *S*, actinomycetes, *L*, and even *Candida albicans*) and make them G producers [3, 27, 30].

The G produced on the tooth surface increase the surface bacterial aggregation. They also cause new interspecies interaction and increase cell-cell adhesion [3]. These extracellular polymers aggregate on different areas of tooth surface on the cell membrane, each having a complementary role in the EPS matrix formation and biofilm development. Some of these roles are surface adhesion, cell-cell adhesion, and cell cluster development found in the biofilm systems [31]. The biofilm matrix is developed three-dimensionally with biofilm maturation and production of extracellular polymers, covering cell clusters, building bridges between them, and creating a firmly divided structure. This heterogeneous structure resulting from EPS explains the presence of microbial clusters in various sizes and composition in the human oral biofilm [32–34]. The EPS sediment on the surface and its development affect the mechanical properties of biofilm like the binding strength of biofilm to the surface and its integrity [35]. A well-formed biofilm is hardly removed from the tooth surface and has reinforced viscoelastic properties that help it to remain on the surface during the shear stresses exerted by liquids [35]. The structure of the EPS matrix can be locally altered by dextranases, DNAs, and protolithic enzymes to create new binding sites for the following bacteria that have not been able to join the biofilm. The stiffness of the biofilm matrix is increased over time. The physicochemical properties of biofilm protect the buried bacteria by inhibiting the access of drugs and increasing their AM resistance. For instance, EPS can bind to cationic AM like CHX and AM peptides and prevent their permeation into the depth of biofilm, thus preventing their toxic effect [3, 34].

7. Fighting Dental Caries

The caries-preventive strategies can be classified into three groups depending on the role and responsibility of the individuals doing them (Figure 1): (1) community-based strategies, (2) dental professionals-based strategies, and (3) individual-based strategies. The dental professionals-based strategies include professional tooth cleaning and use of varnish, fluoride gel and foam, fissure sealant, and antimicrobial agents. The individual-based (self-care) strategies consist of using fluoride toothpaste, fluoride supplements, fluoride mouthwashes, fluoride gels for personal use, chlorhexidine gels and mouthwashes for personal use, slow-release fluoride devices, oral health, diet control, and noncariogenic sweeteners like xylitol [36]. Recent studies (2015–2020) are mentioned in Table 2.

8. Communal Activity-Based Methods

8.1. Fluoridation of Water, Salt, and Milk. Fluoridation of drinking water has been used as an affordable practical way to reduce socioeconomic inequalities related to dental caries. Fluoridation of drinking water decreases dental caries by 30–50%, and termination of water fluoridation in conditions with inadequate alternative sources of fluoride increases caries by 18% [149]. Fluoridation of salt includes many advantages of water fluoridation, and consumers can choose to use it. The fluoride-containing salt will have different effects depending on the type of consumer. In high-consumption families, it can cause fluorosis [150]. Fluoridation of milk is beneficial for school children, especially for their permanent teeth. An advantage of this method is that it can be used in the high-risk group. Its consumption rate is also controllable. Moreover, individuals have the right to choose it or not. Fluoride in milk is absorbed more slowly than the fluoride in water due to the presence of calcium in milk [150, 151].

9. Dental Professionals-Based Methods

9.1. Professional Tooth Cleaning. Karlstad program can be used for biofilm control. In this program, the application of topical fluoride and diet, daily oral hygiene, and tooth cleaning with certain intervals are presented by a trained specialist. Further, this is done every two weeks in this program because studies have shown that the biofilm remaining for two to three weeks leads to the formation of WSL and caries. These intervals can be increased to three months in people with good oral health [152].

9.2. Use of Varnish, Gel, and Fluoride. The individuals aged <18 years are advised to use fluoride varnish every 3–6 months. Tooth caries due to the application of fluoride varnish has been reported to reduce 46% in permanent dentition and 33% in primary dentition [153, 154]. APF and NaF gels are used professionally. Studies have reported 26% reduction in caries in permanent dentition and 20% in

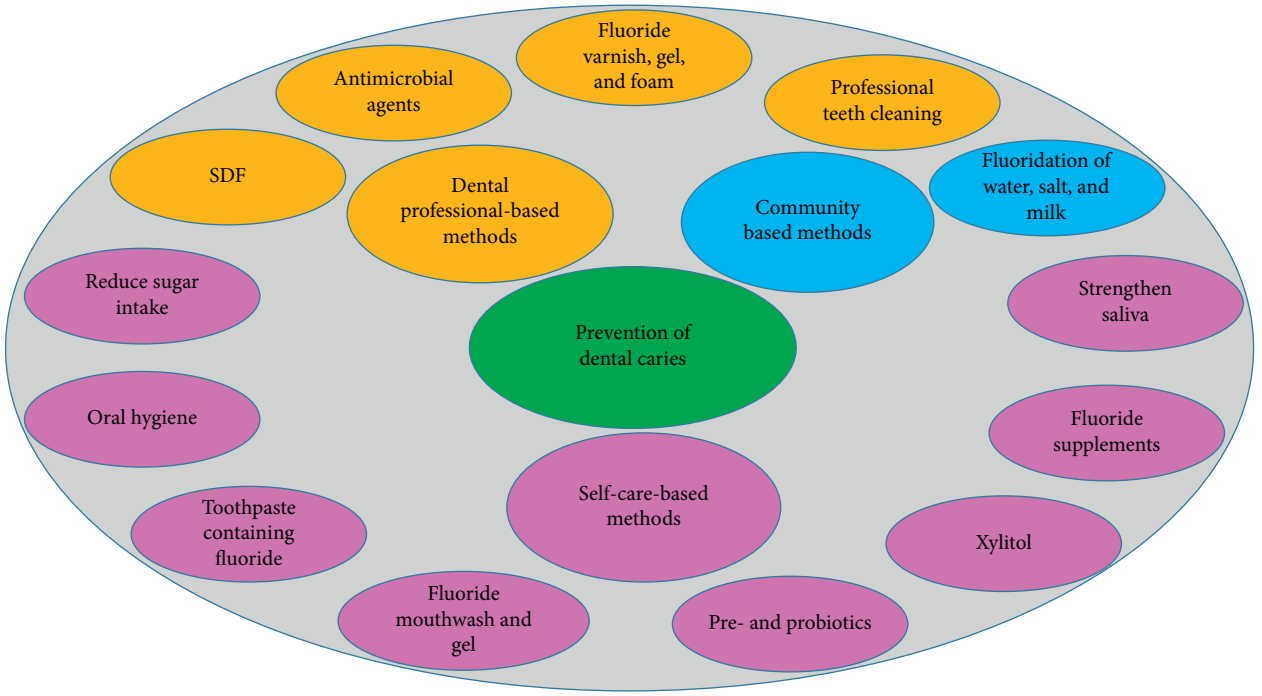

Figure 1: Prevention strategies of dental caries.

Table 2: Recent strategies in dental caries prevention.

Treatment	Type of study	Methods	Outcomes	Ref/year
Stannous fluoride products	In vivo	The groups were as follows: the test group using stannous fluoride products and the control group.	The analysis showed no effect of stannous fluoride products.	[37]/2018
Sodium fluoride dental protective agent combined with pit and fissure sealant	In vivo	The groups were as follows: in the control group pit and fissure sealant was used, and in the test group sodium fluoride tooth protector joined with pit and fissure sealant was used.	The combined group had better results.	[38]/2019
GI and RBS	In vivo	The groups were as follows: GI and RBS.	Groups were the same in the survival of GI and RBS.	[39]/2017
Ozone, sealant, and fluoride varnish	In vivo	The groups were as follows: (1) control; (2) fluoride varnish; (3) sealant; (4) ozone.	The use of fissure sealant, fluoride varnish, and ozone is suggested for prevention of occlusal pit and fissure caries.	[40]/2016
Silver diamine fluoride (SDF)	In vivo	SDF (38%) or Pl was applied topically. The primary outcome was caries arrest (Nyvad criteria).	Topical 38% SDF was effective in arresting cavities.	[41]/2018
RBS and GI	In vivo	The groups were as follows: RBS, GI sealant, and control.	The RBS was higher than the GI sealant in prevention of caries.	[42]/2018
F coating joined with PRF or PTS	In vivo	The groups were as follows: group A, PTS; B, PRF; C, 0.5% F coating + pit and fissure sealing; D, 0.5% fluoride + preventive resin filling; E, control.	Groups C and A had a certain effect on prevention of dental caries, but group D was better.	[43]/2018
Lactobacillus paracasei	In vivo	The groups were as follows: probiotic milk or control (standard milk).	Probiotic milk reduced salivary *S. mutans* count.	[44]/2018
MIV and MIPP	In vivo	The groups were as follows: FTP, using MIV + MIPP application, and control.	Groups were the same in ICDAS scores and EDI sum.	[45]/2018

Table 2: Continued.

Treatment	Type of study	Methods	Outcomes	Ref/year
CXT and FJ	In vivo	The groups were as follows: CXT or FJ.	GIC sealants were effective in preventing caries.	[46]/2018
PTS and FV	In vivo	The groups were as follows: resin-based fissure sealant or FV was applied.	Groups were the same in caries prevention.	[47]/2017
Xylitol-containing chewing gum	In vivo	The groups were as follows: in the test group xylitol gum + oral health education were used, and in control group oral health education alone was used.	Both groups had a reduction in the caries rate.	[48]/2017
MIn	In vivo	The groups were as follows: CE or MIn.	MIn group was better in prevention of caries.	[49]/2019
PTS combined with fluorine protective paint	In vivo	The groups were as follows: control, PTS, and PTS + fluorine protective paint.	Pit and fissure sealant + fluoride protective paint can decrease the incidence of dental caries.	[50]/2019
MIn	In vivo	The groups were as follows: HE, MIn, and MI + RA.	MIn group had higher preventive effects against caries than HE group.	[51]/2017
TiF_4 varnish	In vivo/in situ	The groups were as follows: TiF_4 varnish, Duraphat, Pl varnish, and no treatment.	F-varnishes showed caries-preventive effect.	[52]/2019
Silver NP + PTS	In vivo/in situ	The groups were as follows: conventional and silver NP combined with PTS.	Silver NP mixed sealant was more effective than conventional sealant in reducing tooth demineralization.	[53]/2017
Fluoride varnish	In vivo	The groups were as follows: fluoride varnish or Pl.	Quarterly applications of fluoride varnish were not effective in preventing development of dental caries.	[54]/2016
Different fluoride regimens	In vivo	The groups were as follows: G1: control group, fluoride (F) TP (1450 ppm); G2: FTP (1450 ppm) + 0.2% F oral rinse; G3: TP (5000 ppm).	The recommendation was application of FTP (5000 ppm F) or oral rinse (0.2% NaF) + usual TPs.	[55]/2019
Moisture tolerant RBS and GIS	In vivo	The groups were as follows: moisture tolerant RBS or GIS was placed on one side of the mouth, and the other one was placed on the opposing side. DIAGNOdent readings were taken.	Both materials were effective in arresting enamel caries.	[56]/2019
Fluoride varnish Duraphat	In vivo	The groups were as follows: fluoride varnish and control.	Fluoride varnish Duraphat was effective in decreasing caries incidence.	[57]/2019
Low-dose xylitol chewing gum	In vivo	The groups were as follows: xylitol and polyols.	Xylitol group showed a significantly lower increment of dental caries.	[58]/2017
RBS with and without F	In vivo	The groups were as follows: sealants with or without fluoride and control.	The effects of the sealants were similar.	[59]/2018
Xylitol and polyol chewing gum	In vivo	The groups were as follows: xylitol chewing gum, polyol chewing gum, and control group.	Xylitol-containing chewing gum was effective in decreasing caries incidence.	[60]/2018
Oral health education (OHE) and FV	In vivo	The groups were as follows: control, OHE, and OHE + FV.	OHE or OHE + FV reduced the caries incidence.	[61]/2016
FM and D	In vivo	The groups were as follows: participants brushed their teeth with either a D (1150 ppm) or a Pl D without F and either daily application of FM (220 ppm) or not.	FM was effective in remineralization.	[62]/2018
Biannual treatment with FV	In vivo	The groups were as follows: standard yearly intervention with or without FV.	Biannual treatment with FV was not effective in preventing dental caries.	[63]/2017
STB and S	In vivo	The groups were as follows: STB, CR sealant, and ART-GIC sealant.	The groups were the same in preventing caries.	[64]/2015

Table 2: Continued.

Treatment	Type of study	Methods	Outcomes	Ref/year
SDF 12% and SDF 38%	In vivo	The groups were as follows: 12% SDF applied yearly, 12% SDF applied twice a year, 38% SDF applied yearly, and 38% SDF applied twice a year.	Higher concentration or frequency of SDF had more effect in arresting active tooth caries.	[65]/2018
FV and peptide P_{11}-4	In vivo	The groups were as follows: P_{11}-4 + FV or FV.	P_{11}-4+FV was effective in early carious lesions.	[66]/2018
CHX/thymol V or FV	In vivo	The groups were as follows: three-time monthly use of CHX/thymol varnish or semiannual use of FV + semiannual use of Pl V.	The groups were the same in dental caries development.	[67]/2015
FM, EO, and CHX oral rinses	In vivo	The groups were as follows: FM; EO; CHX; control (saline).	FM and CHX had more effect than EO mouth rinse.	[68]/2015
F, CPP-ACP, IR	In vivo	The groups were as follows: A, control (blank); B, control (Irr); C, Irr + F; D, Irr + CPP-ACP, E, Irr + CPP-ACP + F; F, Irr + IR; G, Irr + IR + F; H, Irr + IR + CPP-ACP.	IR + CPP-ACP, IR + F, CPP-ACP + F, and IR were the best effective methods to prevent Irr-dentin-destructions.	[69]/2019
TP containing Arg	In vivo/in vitro	Individuals wearing a dental device: the studies stages were lead-in, Arg-free, washout, and Arg-active stages.	Arg-containing TP can significantly decrease the LA construction.	[70]/2017
Varnish containing chlorhexidine	In vivo	The groups were as follows: Cervitec Plus® or Pl varnishes.	Application of Cervitec Plus® had a significant advancement in patients' oral health.	[71]/2018
Herbal extracts (Tulsi and Black myrobalan) and sodium fluoride	In vivo	The groups were as follows: (1) FM, (2) Tulsi mouth rinse, and (3) Black myrobalan mouth rinse.	Herbal mouth rinses could be tried as an anticaries agent for dental caries.	[72]/2018
FV	In vivo	FV applied every three months.	The use of fluoride varnish every three months prevented the incidence of caries.	[73]/2019
Infiltrant application	In vivo	The groups were as follows: icon infiltrant (DMG) and PFS (Alpha Seal-DFL).	The infiltrant was effective in preventing the caries progression comparable with the conventional sealant.	[74]/2017
Fluoridated milk	In vivo	The groups were as follows: fluoridated milk and nonintervention.	Consumption of fluoridated milk could significantly (34%) reduce the caries.	[75]/2018
PRG filler-containing sealant placed with a self-etching primer/adhesive	In vivo	The groups were as follows: self-etch primed sealant (BeautiSealant, Shofu) or the etch and rinse sealant (Seal it, Spident).	The groups were the same in caries prevention.	[76]/2018
High-fluoride toothpaste	In vivo	The groups were as follows: 5,000 ppm F toothpaste or 1,450 ppm F toothpaste.	High-fluoride toothpaste had more effects than control toothpaste in preventing caries.	[77]/2019
FV	In vivo	The groups were as follows: FV or Pl.	FV application was not effective in children.	[78]/2018
MIn	In vivo	The groups were as follows: HE and MIn.	MIn had more effect than HE in reducing caries.	[79]/2018
Hydrophilic F-releasing sealant and ACP sealant	In vivo	The groups were as follows: Aegis™ or Embrace WetBond™ sealant.	Aegis™ was more effective than Embrace WetBond™ sealant as Aegis™ demonstrated lower caries scores.	[80]/2019
School-based fluoride varnish program	In vivo	Volunteers used FTP at home.	The school-based fluoride varnish program prevented progression of caries.	[81]/2016

Table 2: Continued.

Treatment	Type of study	Methods	Outcomes	Ref/year
Topical F	In vivo	The groups were as follows: (1) annual use of SDF solution (30%); (2) three-time use of SDF (30%) per week; (3) three-time use of 5% FV per week.	Yearly use of SDF solution had more effect than three-time use of FV or SDF solution.	[82]/2018
Nutrition and hygiene education	In vivo	The groups were as follows: intervention and control.	The education intervention reduced the progression of caries.	[83]/2018
Organoselenium-containing pit/fissure sealant (DenteShield™ (DS)) and UltraSeal™ XT Plus (UXT)	In vivo	The groups were as follows: DS and UXT.	The groups had the same results for Caries prevention.	[84]/2019
Fluoride TP	In vivo/in vitro	Volunteers used FD or not.	FD group had lower demineralization.	[85]/2016
Toothpastes with fluoride and hydroxyapatite	In vivo	The groups were as follows: toothpastes with hydroxyapatite and fluoride.	Observation group had significantly higher ($p > 0.05$) acid resistance compared with the group of patients using fluoride toothpaste.	[86]/2018
Ordinary and PB cake (*Bacillus coagulans*)	In vivo	The groups were as follows: (1) 1-week consumption of PB cake, then 4-week washout period, and 1-week consumption of regular cake; (2) consumption of the cakes was reversed.	The addition of PB bacteria led to a slight increase in the number of *SM* bacteria in the saliva.	[87]/2019
Ordinary TB and an interactive power TB	In vivo	The groups were as follows: power TB with Bluetooth technology or an ordinary handy TB.	An interactive power TB was more effective in plaque removal versus a handy TB.	[88]/2019
Food enriched with probiotics	In vivo	The groups were as follows: PB milk and standard milk.	The groups were the same in the incidence of caries.	[89]/2018
Resin infiltration	In vivo	The groups were as follows: 1) FTP + flossing + infiltration; 2) control group (FTP + flossing).	Infiltration group had better results than control group.	[90]/2018
GI sand resin s	In vivo	The groups were as follows: GIS and RS.	GISs presented effective prevention of caries development.	[91]/2016
PB yogurt and gums with xylitol	In vivo	The groups were as follows: PB yogurt or gums with xylitol.	The groups were the same in reduction of *SM* counts.	[92]/2017
Fissurit FX sealant and Grandio Seal nanofilled fissure sealant	In vivo	The groups were as follows: Fissurit FX sealant and Grandio Seal nanofilled fissure sealant.	Fissurit FX and Grandio Seal pit and fissure sealants were similar in caries prevention.	[93]/2019
Photodynamic therapy and US	In vivo	The groups were as follows: PDT with MB and US.	PDT or US postponed side effects.	[94]/2018
Fluoride varnish or fluoride mouth rinse	In vivo	The groups were as follows: semiannual fluoride varnish applications (FV) and fluoride mouth rinses once per week (FMR).	The groups had the same results in dental caries progress.	[95]/2016
PB and normal milk	In vivo	The groups were as follows: PB milk and standard milk.	Long-term drinking of probiotic milk may decrease caries progress.	[96]/2016
Intensive FV	In vivo	The groups were as follows: 3 applications of FV in 2 weeks and extra applications at 1 and 3 months; FV treatment twice a year.	The intensive FV application had no adequate effect to prevent dental caries.	[97]/2018
Erythritol	In vivo	The groups were as follows: erythritol, xylitol, or sorbitol (control) group.	Erythritol consumption had caries-preventive effect.	[98]/2016
Interdental cleaning device	In vivo	The groups were as follows: manual toothbrush + mechanical interdental device or manual toothbrush alone.	The combination group had a superior plaque removal compared to manual brushing alone.	[99]/2018

Table 2: Continued.

Treatment	Type of study	Methods	Outcomes	Ref/year
FTP containing zinc ions	In situ	The groups were as follows: F, F/ZN/ phytate, F/Zn, and F Pl.	Phytate had slight effect on capability of fluoride to prevent more advanced lesion demineralization. Moreover, zinc ions had no bad effect on fluoride ability.	[99]/2018
High-fluoride varnish	In vivo	The groups were as follows: differing frequencies of Duraphat varnish application.	Periodic application of fluoride varnish could be useful in prevention of white spots.	[100]/ 2016
Fluoride varnish	In vivo	The groups were as follows: control and use of FV (every 3 or 6 months).	Results suggested using FV with three-month intervals for prevention of caries.	[101]/ 2019
Fluoride varnish	In vivo	The groups were as follows: (1) dental hygiene + FTP and one-time use of three varnishes: Fluor Protector S, Elmex® fluid, or control (Pl).	FV application had no extra protective benefit.	[102]/ 2016
Toothpaste with nanosized sodium hexametaphosphate	In vivo/in vitro	The groups were as follows: conventional fluoride TP, fluoride TP (1100 ppm), fluoride TP (1100F + micro HMP), and fluoride TP (1100F + nano HMP).	1100F/HMPnano revealed a superior protective effect against enamel demineralization.	[15]/2019
Three different compositions of topical fluoride varnishes	In vivo	The groups were as follows: FV having CPP-ACP; FV having xylitol; FV with 0.9% difluorosilane.	FV having CPP-ACP showed higher decrease in *SM* count.	[103]/ 2019
CHX MR, combination MR, and green tea extract MR	In vivo	Volunteers used different MR.	Green tea mouth rinse was effective in prevention of caries.	[104]/ 2017
Povidone-iodine (PI), CHX, or FV (fluor protector)	In vivo	The groups were as follows: PI, CHX V, or FV and control.	Fluoride varnish showed higher decrease in S. *mutans* count.	[105]/ 2017
Probiotic milk and fluoride mouth rinse	In vivo	The groups were as follows: probiotic milk and fluoride mouthwash.	Groups were the same in reduction of *S. mutans* and PI scores.	[106]/ 2019
Topical fluorides	In vivo	The groups were as follows: group 1, 30% SDF solution yearly; group 2, 30% SDF solution per week; group 3, 5% FV per week.	Application of SDF had more effect on arresting caries than FV.	[107]/ 2016
Milk sweetened with xylitol	In vivo	The groups were as follows: (a) xylitol milk, 8 g/200 ml, one time daily; (b) xylitol milk, 4 g/100 ml, two times daily; (c) sorbitol milk, 8 g/200 ml, one time daily; (d) sorbitol milk, 4 g/100 ml, two times daily; or (e) sucrose milk 8 g/200 ml, one time daily.	There were no significant differences in caries incidence between groups.	[108]/ 2016
Probiotic chewing tablets	In vivo	The groups were as follows: the test group got chewing probiotic tablet and the Pl group got the same tablets without bacteria.	Probiotic chewing tablets could be helpful in reducing caries.	[109]/ 2015
Fluoride TP	In vivo	The selected product was brushed twice daily for 4 months.	Clinpro 5000, Clinpro Crème, and MI paste Plus all could be helpful in reducing white spot lesions.	[110]/ 2019
Probiotic lozenge	In vivo	The groups were as follows: probiotic lozenge and Pl lozenge.	Probiotic group had significantly lower *S. mutans*.	[111]/ 2019
Self-etching adhesives having an AB agent and/or F	In vitro/ in vivo	The groups were as follows: fluoride-containing (One-Up Bond F Plus, OP), MDPB and fluoride-containing adhesive (Clearfil Protect Bond, PB).	The AB group had lower demineralization adjacent to restorations.	[112]/ 2015
CPP-ACP and xylitol gum	In vivo	The groups were as follows: gum containing CPP-ACP and xylitol.	Both gums increase saliva's properties.	[113]/ 2017
Resin infiltration	In vivo	The groups were as follows: test group lesions were treated with resin infiltration + 5% topical NaF application and control group with 5% NaF alone.	Resin infiltration was more effective in reducing the development of initial proximal enamel lesions compared with the other group.	[114]/ 2018

Table 2: Continued.

Treatment	Type of study	Methods	Outcomes	Ref/year
Salt fluoridation	In vivo	The groups were as follows: salt containing fluoride and control.	Salt containing fluoride was more effective in prevention of caries.	[115]/2018
Sodium fluoride varnish	In vivo	The groups were as follows: intervention group (fluoride varnish) and control group.	Significant caries reversal was seen in primary dentition after intensive fluoride application after 1 year of study.	[116]/2017
Sour cherry extract	In vivo	The groups were as follows: gum with cherry extract or control.	Sour cherry extract may have effect on prevention of caries.	[117]/2018
Arginine-containing TP	In vivo/in vitro	The groups were as follows: fluoridated TPs (FD) and arginine-containing fluoridated TPs (AFD).	AFD had an anticaries effect like that of ordered fluoridated TPs.	[118]/2018
PBM of major salivary glands	In vivo	The groups were as follows: continuous mode LED light, pulsed mode LED light, and control group.	Results suggested that PBM of salivary glands reduces risk of caries.	[119]/2020
Herbal mouthwash	In vivo	The groups were as follows: herbal mouthwash, chlorhexidine mouthwash, or Pl mouthwash.	The effectiveness of herbal mouthwash in decreasing plaque formation was similar to chlorhexidine.	[120]/2018
Filling intervention health education	In vivo	The groups were as follows: intervention group receiving filling of teeth; and health education group.	Intervention group had better results.	[121]/2015
CHX and F MR	In vivo	The groups were as follows: (a) CHX (0.12%) + NaF (0.2%); (b) NaF (0.2%); (c) CHX (0.12%); (d) control.	Groups a and c had similar plaque formation.	[89]/2018
Resin infiltration	In vivo	The groups were as follows: resin infiltration or control.	Progression of caries was significantly higher in control versus infiltration group.	[122]/2018
Probiotic *Lactobacillus reuteri*	In vivo	The groups were as follows: probiotic lozenges and Pl lozenges.	Probiotic lozenges reduced bacterial counts significantly.	[123]/2018
GIC sealant	In vivo	The groups were as follows: sealant application with or without extra light curing.	Caries prevention in both groups was similar.	[124]/2019
Propolis dental varnish	In vivo	Propolis varnishes were used in different concentrations (1%, 2.5%, 5%, and 10%).	Propolis V has AM activity.	[125]/2020
Resin infiltration	In vivo	The groups were as follows: infiltration and control.	Resin infiltration was more effective in reducing caries progression.	[126]/2016
GIS covered with resin-based agents	In vivo	Fuji VII was used and covered with G-Coat Plus or Heliobond.	The results were the same in both groups in incidence of caries.	[127]/2017
CPP-ACP	In vivo	The groups were as follows: stannous F gel (0.4%) with or without CPP-ACP.	CPP-ACP was not effective in decreasing caries development.	[128]/2015
New sealant	In vivo	The groups were as follows: Select Defense™ sealant; control.	Test group had lower incidence of WSLs.	[129]/2016
Atraumatic restorative treatment by chlorhexidine: disinfection or incorporation	In vivo	The groups were as follows: group (a) CHX having GIC; group (b) CHX; group (c) regular GIC.	Both chlorhexidine disinfection and incorporation showed higher efficacy in inhibiting residual microbes compared to conventional ART.	[130]/2017
Fluoride-releasing resin composite	In vitro	The groups were as follows: intervention group (F having adhesive resin) and control.	The materials used in test group were not effective in prevention of WSL.	[131]/2017
Fluoridated milk	In vivo/in vitro	Volunteers used an intraoral appliance. They dipped it in fluoridated milk for 5 minutes and once every other day drank the same milk.	Drinking fluoridated milk once per day prevented enamel demineralization.	[132]/2018
Toothbrush with paste and Munident	In vivo	The groups were as follows: normal TP and Munident.	Munident (herbal) TP group had significantly lower *S. mutans*.	[133]/2017

Table 2: Continued.

Treatment	Type of study	Methods	Outcomes	Ref/year
Fluoride TP and GC Tooth Mousse	In vivo	The groups were as follows: fluoride TP, CPP-ACP crème, and fluoride TP + CPP-ACP crème.	All groups had the same results; combination groups did not have additive benefits.	[134]/2020
MIPP and Er: YAG laser	In vitro	The groups were as follows: (a) MIPP; (b) Er: YAG laser; (c) MIPP + Er: YAG laser; (d) saliva; (e) control.	Group c was the most effective group in the treatment of WSLs.	[135]/2020
Probiotic bacterium *Lactobacillus reuteri*	In vivo	The groups were as follows: probiotic lozenge and Pl lozenge.	Probiotic lozenges did not prevent progressing of WSL.	[136]/2016
RMGI cement varnish	In vivo	The varnish was applied to teeth.	Application of RMGI cement varnish could be useful in preventing WSLs.	[137]/2015
Probiotic *Streptococcus dentisani*	In vivo	The probiotic was applied in a buccoadhesive gel.	*S. dentisani* was able to buffer oral pH, especially after multiple dosing.	[138]/2020
Semiannual fluoride varnish application	In vivo	The groups were as follows: typical oral health program with or without FV twice a year.	Applications of FV + typical oral health program did not decrease caries progress.	[139]/2016
CPP-ACP	In vivo	The groups were as follows: test group receiving CPP-ACP paste monthly and control group.	Test group had lower WSL compared to the control patients.	[140]/2016
Peptide P_{11}-4	In vivo	The groups were as follows: P_{11}-4 or FV.	Application of P_{11}-4 significantly reduced the size of early carious lesions. This reduction was higher than fluoride varnish application.	[24]/2020
CHX MR and neem MR	In vivo	The groups were as follows: group a: CHX MR; group b: neem MR; group c: control.	Both MR significantly decreased PI index.	[141]/2017
TiF_4 V	In vivo/in vitro	TiF_4, NaF (2.45% F), or control (Pl V).	TiF_4 V was the only treatment able to improve enamel remineralization.	[142]/2017
Fluoride and sodium hexametaphosphate in toothpaste	In vivo/in vitro	TP having 1100 ppm F and 1100F + HMP1% and Pl.	TP containing HMP1% was more effective than TP containing 1100F in decreasing demineralization.	[143]/2015
Toothpaste Apadent Total Care medical nanohydroxyapatite	In vivo	Volunteers used Apadent Total Care toothpaste with nano-calcium hydroxyapatite.	Application of toothpaste with nanohydroxyapatite showed the improvement of all indices.	[144]/2016
Protective chlorhexidine varnish layer over resin-infiltrated proximal carious lesions	In vivo	The groups were as follows: in the test group infiltration + double layer of chlorhexidine varnish was used and in the control group only infiltration was used.	Results suggest application of chlorhexidine varnish layer on resin infiltration when surface had microcavitation.	[145]/2016
AgNO3 solution and FV	In vivo	The groups were as follows: (1) $AgNO_3$ solution (25%) + FV; (2) SDF (38%) + Pl V.	Results suggest application of AgNO3/NaF for management of ECC.	[146]/2015
Tooth Mousse		The groups were as follows: CPP-ACP (daily) and control.	CPP-ACP reduced *Streptococcus mutans* in test group.	[147]/2016
Fluoride rinse		The groups were as follows: sodium F + amine F; control.	Application of fluoride rinse helps prevent demineralization.	[148]/2015

primary dentition as a result of the application of 1% sodium fluoride twice per year. Fluoride foam has the same advantages and density as fluoride gel and releases the equivalent fluoride [153]. Fluoride exerts its anticaries effects by three different ways. In the first way, fluoride ion in dental tissues reinforces the fluorapatite deposition from the salivary phosphate and calcium ions. This insoluble deposition occupies the soluble salts including magnesium and carbonate lost during demineralization by the bacteria. This process makes the enamel more resistant to acid [9]. In the second way, caries becomes remineralized without the formation of the cavity using a similar process [9]. In the third way, fluoride ion has AM activity. At low concentrations, fluoride obstructs the construction of glycosyltransferase enzyme. Glycosyltransferase gets the glucose involved in the formation of extracellular polysaccharides and enhances the bacterial adhesion. The formation of extracellular polysaccharides is inhibited by limited bacterial metabolism during the meal time, which prevents the aggregation and maintenance of carbohydrates. Therefore, the

duration of the attack of caries is limited to the period of eating and after it. High concentrations of fluoride ions (12000 ppm) are directly toxic for some oral microorganisms like *SM*. Fluoride has a wide range of activities and has long stability in the oral cavity. It reduces the acid production at 1–10 ppm concentration; it is bacteriostatic at 250 ppm and bactericidal at 1000 ppm [9]. The iodine group is bactericidal and has a wide range of antibacterial activities and short-term stability in the mouth [9]. Many studies have documented the efficacy of fissure sealant treatment in reducing occlusal caries in permanent dentition in children and adults with a high risk of caries [36]. The population-based studies have confirmed the cost-effectiveness of fissure sealant and its long-term effects. Since most caries in the current population occurs in the pits and fissures, fissure sealant seems to be beneficial [150].

9.3. Silver Diamine Fluoride (SDF). Systematic reviews have recommended the application of SDF for termination or prevention of caries in children and adults and root caries in the aged people [155, 156]. This solution is used locally, and silver ions exert their antibacterial effects by breaking the bacterial membrane, denaturing the proteins, and preventing the DNA proliferation [157]. Silver and fluoride both have a key role in the termination of caries progress and sensitivity of tooth [158–161]. Silver reduces the demineralization speed and boosts the remineralization process [162].

9.4. Antimicrobial Agents. Numerous antimicrobial factors have been introduced to decrease the number of bacteria and disturb the biofilm structure. Dental decay is a biofilm associated disease which changes with regimen. Hence, changing the number of bacteria does not have a long-term effect on it. If a remarkable reduction does not occur in the consumption of fermentable carbohydrates, the microbiome in biofilm will adapt to the acidogenic environment and the uric acid produced by the cariogenic diets; thus, AM will have slight effect on the outcome of dental caries [9].

Principally, most antimicrobial agents used for prophylaxis contain a wide range of antimicrobials and provide a ground for the growth of opportunistic factors by eliminating the normal flora. Therefore, except for the consumers of fluoride toothpaste, all other chemical agents should not be used routinely in the daily schedule of the patients. These agents are used as an auxiliary aid when the routine prevention is not effective in individuals with a mental or physical disability, people with reduced salivary secretion, or cases with difficult mechanical removal of plaque such as conditions associated with orthodontic treatment, before and after oral surgeries, and frequent use of crowns [9]. Some antimicrobial agents along with their mechanism of effect are presented in Table 3.

10. Self-Care Methods for Caries Prevention

10.1. Reducing the Consumption of Fermentable Carbohydrates. The main reason for caries-induced dysbiosis is the overuse of fermentable carbohydrates [179]. The diet mechanism has significant effects on the impact of biofilm on dental caries. Frequent consumption of foods having sucrose changes the biofilm from a noncariogenic state to a cariogenic state. Established biofilm, which is repeatedly exposed to sucrose, quickly makes acids from it, thereby creating an acidic environment [22]. Dental caries is mostly caused by the frequency of sucrose consumption, not its amount [22]. The commensal bacteria use the sugar and make acid when a person has a low sugar diet; however, pH is quickly recovered by the mechanisms present in mouth. Frequent consumption of sugars disturbs the balance, and fully reciprocal acidogenic and aciduric strains appear in pathogenic amounts [180, 181]. WHO has seriously recommended restraining the intake of free sugars to <10% of the entire energy intake to prevent weight gain and dental caries [182]. This refers to the <50 g/day consumption of free sugars. Natural sugars such as sugars in honey and added monosaccharides to the foods are free sugars [182]. Cohort studies with quality evidence have reported 15% sugar as the moderate level. Other studies have also recommended the reduction of free sugars to 5% of total energy. Sugar consumption below 5% seems unlikely to cause any caries [183]. Diet with high amount of sugar causes the aggregation of acidogenic and acid-tolerant bacteria and protects them by increasing the production of EPS [27, 174]. Indirect evidence shows caries reduction by decreasing the intake of free sugars. For example, a significant decrease of caries during five years has been reported in the Iraqi children with reduced sugar intake due to the sanctions of the United Nations [184]. Starch as well as sucrose is known as a cariogenic agent. Starch's metabolism causes the long-term acidity in the pits and interdental spaces vulnerable to decay [180].

11. Oral Hygiene

The tooth surfaces free of biofilm are not decayed. Patients should regularly eliminate biofilm by brushing with fluoride-containing toothpaste and dental floss [9, 159]. The oral biofilm composition changes over time following oral hygiene by regular brushing twice a day, and oral microbiome is maintained in the healthy state [160]. The brushing does not remove oral bacteria totally but rather eliminates them from the tooth surface. A massive amount of them is removed from the mouth after swallowing and/or rinsing after brushing and flossing; however, an enough number of them stay for proliferation. Cleaning and exposing to oxygen may kill anaerobic organisms; however, no species is eliminated. Accurate mechanical tooth cleaning disrupts the dental biofilm and cleans tooth surface. While all bacteria that constitute established biofilm still do not exist, most of them are not able to bind to the clean tooth surface [9]. Brushing and flossing are advantageous in that they do not destroy the oral normal flora. Frequent mechanical removal of biofilm does not cause the risk of opportunist infection but rather changes the biofilm's composition. Patients with good oral hygiene have a high percentage of *S. mitis* or *S. sanguis* in their teeth biofilm and have a smaller amount of cariogenic bacteria than the more developed biofilm having a high

Table 3: Some antimicrobial agents and their mechanisms.

Antimicrobial agents	Combinations	Mechanisms	Ref
Antibiotics	Aminoglycosides	Inhibiting protein synthesis	[9, 163]
	Glycopeptides	Interfering with the construction of the cell wall	
	Penicillins	Interfering with the construction of the cell wall	
	Quinolones	Preventing DNA replication and transcription	
	Rifamycins	Inhibiting transcription	
	Tetracyclines	Inhibiting protein synthesis	
	Actinobolin	Obstructing protein synthesis	
AMEs*	Lysozyme	Catalyzing glycosidic bond hydrolysis in bacterial cell wall peptidoglycans	[9, 164, 165]
	Acylase	Quorum-quenching	
AMPs*	Natural	Pore construction in membrane Inhibition of metabolism	[19, 166]
	Synthetic AMPs	Pore construction in membrane Inhibition of metabolism	
Cationic compounds	Chitosan	Disruption of cell membrane	[9, 167]
	Chlorhexidine	Disruption of cell walls	
	Poly(ε-lysine)	Destroying the outer membrane	
	QACs*	Interference with enzymes	
Metal and metal oxides	Ag nanoparticles	Making oxidative stresses Disabling enzymes of bacteria Affecting the permeability of the cell membranes	[168–170]
	Cu nanoparticles	ROS* construction Lipid peroxidation in membranes	
	TiO_2 nanoparticles	ROS* construction Disrupting phosphorylation	
	ZnO nanoparticles	Making ROS* Making membrane more permeable	
Other noncationic compounds	Nitric oxide givers	Making nitrosative stresses Making oxidative stresses Disruption in signaling	[9, 13, 171]
	Triclosan	Disrupting synthesis of fatty acid	
Natural materials	Tea	Disruption of membrane Inhibiting salivary amylase activity	[26, 172, 173]
	Propolis	Interaction with bacterial membrane	
	Cranberry	Inhibition of biofilm formation	
Amino acids	Arginine	Keeping a well dental biofilm	[70, 118, 157, 174–177]
Antioxidants	Antioxidants	Disrupting proteins, decreasing bacterial EPS	[178]

*AMEs: antimicrobial enzymes; AMPs: antimicrobial peptides; QACs: quaternary ammonium compounds; ROS: reactive oxygen species.

amount of *S. mutans* [9]. Nevertheless, it should be emphasized that the former concepts of plaque removal or accurate control of another plaque are not considered for the management of caries. Proper oral hygiene is certainly important for biofilm control, but systemic review studies have shown that mechanical removal of biofilm alone, in the absence of fluoride, is not enough to manage caries [158].

11.1. Fluoride Toothpaste. One of the main causes of caries reduction in developed countries is the extensive application of fluoride TP. Easy and extensive application, low cost, and cultural acceptance have turned fluoride toothpaste into an ideal method for the promotion of general health, and brushing twice a day using fluoride toothpaste has been recommended as a powerful preventive strategy [185].

11.2. Fluoride Supplements. Fluoride supplements are capable of decreasing dental caries by about 20–30% and apply to populations with no access to fluoridated water. These supplements, due to the risk of fluorosis, should be used cautiously and can be used in kids who are at high risk of dental caries and committed parents [153].

11.3. Fluoride Mouthwashes and Gels for Personal Use. Fluoride mouthwashes with 0.2 and 0.05% concentrations are available for daily and weekly use and have been reported to prevent caries by 26%. The fluoride gels for personal use are available as APF, neutral NaF, and stannous fluoride and have been found to reduce caries by 32% in communities with inadequate fluoridated water [36, 153].

11.4. Noncariogenic Sweeteners. Numerous studies have reported the caries-preventive effect for xylitol and to a lesser extent for sorbitol. Xylitol can decrease biofilm [186]. Xylitol is a five-carbon sweetener that has beneficial effects on oral health. Most clinical studies have shown that daily consumption of ≥5 g xylitol gum is efficacious in decreasing caries [187, 188]. Use of xylitol decreases the *SM* amount [189]. Different mechanisms that can reduce mutans are growth inhibition, plaque reduction, oral pH increase, reduction of sticky polysaccharides produced by mutants, and inhibition of stress proteins [48, 58, 60, 92, 98, 108, 186–190].

11.5. Strategies to Boost Saliva. Salivary secretion plays a pivotal role in preventing dysbiosis and maintaining oral health. In addition to the mechanical deletion and buffering capability of saliva, it has enzymes, GP, salts, immunoglobulins, and AM peptides which help with the biofilm stability and control [162]. Although there are clear salivary stimulants, salivary induction is difficult in practice. In patients who are still able to produce saliva, local methods like increasing water consumption and chewing gums and salivary alternatives regularly can enhance saliva making. The moisturizers and enzymes in the products can decrease the symptoms of patients with dry mouth and maintain healthy biofilm [4, 191, 192].

11.6. Prebiotics and Probiotics. Prebiotics are oligosaccharides and nutritional fibers which contribute to useful bacteria's growth while probiotics are defined as living microbes which have advantages for patients [155]. There are not many studies on prebiotics in dentistry, while there are more studies on Arg. Arg is an aminoacid that is found in saliva. The bacteria in healthy biofilm could use Arg through ADS. There is high activity of ADS in noncarious places rather than places with caries lesions [157, 193]. Moreover, studies [157, 194] have shown that adding Arg to fluoride TP can enhance the ADS activity, increase the pH, and help to make a healthy biofilm [157, 175, 193].

The analysis of clinical trials has shown the synergistic effect of arginine and fluoride on the primary caries [176]. Another interesting aspect of prebiotics is breastfeeding. Breast milk is rich in complex biotic oligosaccharides. Systemic studies have shown that breastfeeding in the first year has protective effects against ECC, and bottle-fed newborns had four times more caries than breastfed newborns [195, 196]. Recently, application of probiotics to fight harmful bacteria has increased [156]. Probiotics are dietary supplements that are principally consumed through fermented vegetables, dairy products, and bread. Additionally, there are different forms of these materials such as tablets, drops, and lozenges that have been commercialized. Their mechanism is not known completely. They have effects on biofilms directly and on the immune system [197]. Studies have concluded that therapeutic probiotics can especially reduce the number of *S. mutans* [198]. However, there are very few studies on the effect of oral microbiome composition. Moreover, an increase in nonmutans streptococci and a decrease in the count of *S. mutans*, *Fusobacterium*, and *Prevotella* have been reported after using a supplement for 12 weeks [199]. In contrast, another study has found that the use of lozenges containing *Lactobacillus rhamnosus* and *Brevibacillus brevis* has no significant effect on the oral microbiome in adults after 4 weeks. These conflicting results may be partly due to different molecular and sequencing technologies used in various studies. The results of these studies have shown a 33% reduction in caries in preschool children [200]. Nevertheless, there is insufficient evidence for their overall recommendation. Probiotic treatment for oral health is one of the highly advanced emerging concepts.

12. Conclusion

One of the basic aspects of general health is oral health. Oral diseases cause many problems for individuals and society. They are very common all over the world. While there are effective methods for and adequate information about the prevention of oral diseases, they are still one of the most prevalent health problems. The best strategy to fight caries is the use of a combination of community-based strategies, oral health professionals-based strategies, and self-care strategies. The most important strategies to fight against caries are paying attention to the oral health in macroeconomic policies of countries to create a healthy society, changing the attitude of dental professionals from a treatment-centered approach to a preventive approach, and empowering the individuals by enhancing their knowledge, attitude, and performance in line with maintaining and promoting their oral health.

13. Future Directions

Despite many attempts made to control caries, these efforts have not been effective in controlling caries. Further studies are suggested to identify the confounding factors of biofilm such as natural antimicrobial materials that, unlike antibiotics, do not cause bacterial resistance and are cheap and available to everyone. Moreover, more studies are required on probiotics and production of *S. mutans* strains that are not able to produce lactic acid by recombinant DNA technology or other bacteria that competitively eliminate the microbial cariogenic agents of the oral cavity and manufacture of slow-release devices for antimicrobials such as fluoride in the oral cavity and silver nanoparticle pins that prevent caries by releasing antimicrobial agents. Furthermore, we suggest conducting future studies on the production of caries vaccine to induce biologic defense against caries in the oral cavity and creation of protective layers on the tooth that act beyond the current sealants in terms of gear, duration, and caries prevention.

Abbreviations

AB: Antibacterial
ACP: Amorphous calcium phosphate
ADS: Arginine deiminase system

AM: Antimicrobials
AMEs: Antimicrobial enzymes
AMPs: Antimicrobial peptides
Arg: Arginine
ART-GIC: Atraumatic restorative treatment-high-viscosity glass-ionomer cement
B: Bifidobacterium
CE: Conventional oral health education
CHX: Chlorhexidine
CPP-ACP: Casein phosphate polypeptide-amorphous calcium phosphate
CR: Composite resin
CXT: Clinpro XT
Dl: Deciliters
E: Extracellular
ECC: Early childhood caries
EDI: Enamel decalcification index
EO: Essential oil
EPS: Extracellular polysaccharide production
F: Fluoride
J: Fuji IX GP FAST
FN: *Fusobacterium nucleatum*
FV: Fluoride varnish
G: Glucans
GI: Glass ionomer
GIS: Glass-ionomer sealant
GP: Glycoproteins
HE: Health education
ICDAS: International caries detection and assessment system
IPS: Intracellular polysaccharide production
IR: Infiltration resin
Irr: Irradiation
L: *Lactobacterium*
LA: Lactic acid
MB: Methylene blue
MIn: Motivational interviewing
MIPP: MI paste plus
MR: Mouth rinse
NP: Nanoparticles
P: *Prevotella*
PB: Clearfil Protect Bond
PBM: Photobiomodulation
PFS: Pit and fissure sealing
PG: *Porphyromonas gingivalis*
P.Int: *Prevotella intermedia*
Pl: Placebo
PRF: Preventive resin filling
PRG: Prereacted glass
QACs: Quaternary ammonium compounds
RA: Risk assessment
RBS: Resin-based sealants
Ref: Reference
ROS: Reactive oxygen species
RMGI: Resin-modified glass ionomer
S: *Streptococcus*
SDF: Silver diamine fluoride
SM: *Streptococcus mutans*
STB: Supervised tooth brushing
TB: Toothbrush
TP: Toothpaste
US: Ultrasonic scaler
V: Varnish
WHO: World Health Organization
WSLs: White spot lesions
Xy: Xylitol.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

The authors declare that this work was done by the authors named in this article. Mohammad Nima Motallaei, Mohsen Yazdanian, Hamid Tebyanian, Elahe Tahmasebi, Reza Ranjbar, and Alireza Yazdanian were involved in study design and data collection. Mohsen Yazdanian, Hamid Tebyanian, Elahe Tahmasebi, and Alexander Seifalian critically reviewed the data and wrote the review article.

Acknowledgments

The authors would like to acknowledge the useful comments given by colleagues at the Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran.

References

[1] J. A. Aas, B. J. Paster, L. N. Stokes, I. Olsen, and F. E. Dewhirst, "Defining the normal bacterial flora of the oral cavity," *Journal of Clinical Microbiology*, vol. 43, no. 11, pp. 5721–5732, 2005.

[2] E. Zaura, B. J. Keijser, S. M. Huse, and W. Crielaard, "Defining the healthy "core microbiome" of oral microbial communities," *BMC Microbiology*, vol. 9, no. 1, p. 259, 2009.

[3] J. Xiao, M. I. Klein, M. L. Falsetta et al., "The exopolysaccharide matrix modulates the interaction between 3D architecture and virulence of a mixed-species oral biofilm," *PLoS Pathogens*, vol. 8, no. 4, Article ID e1002623, 2012.

[4] P. D. Marsh, A. Moter, and D. A. Devine, "Dental plaque biofilms: communities, conflict and control," *Periodontology*, vol. 55, no. 1, pp. 16–35, 2000.

[5] G. N. Belibasakis, "Microbiological changes of the ageing oral cavity," *Archives of Oral Biology*, vol. 96, pp. 230–232, 2018.

[6] P. P. Hujoel and P. Lingström, "Nutrition, dental caries and periodontal disease: a narrative review," *Journal of Clinical Periodontology*, vol. 44, pp. S79–S84, 2017.

[7] R. Grigalauskiene, E. Slabsinskiene, and I. Vasiliauskiene, "Biological approach of dental caries management," *Stomatologija*, vol. 17, no. 4, pp. 107–112, 2015.

[8] M. Lof, M. M. Janus, and B. P. Krom, "Metabolic interactions between bacteria and fungi in commensal oral biofilms," *Journal of Fungi (Basel, Switzerland)*, vol. 3, 2017.

[9] A. V. Ritter and R. Walter, *Sturdevant's Art and Science of Operative Dentistry*, Elsevier, Amsterdam, Netherlands, 7th edition, 2018.

[10] C. J. Seneviratne, C. F. Zhang, and L. P. Samaranayake, "Dental plaque biofilm in oral health and disease," *The Chinese Journal of Dental Research: The Official Journal of the Scientific Section of the Chinese Stomatological Association (CSA)*, vol. 14, no. 2, pp. 87–94, 2011.

[11] N. Okahashi, M. Nakata, Y. Terao et al., "Pili of oral Streptococcus sanguinis bind to salivary amylase and promote the biofilm formation," *Microbial Pathogenesis*, vol. 50, no. 3-4, pp. 148–154, 2011.

[12] K. Hojo, S. Nagaoka, T. Ohshima, and N. Maeda, "Bacterial interactions in dental biofilm development," *Journal of Dental Research*, vol. 88, no. 11, pp. 982–990, 2009.

[13] M. G. Newman, H. Takei, P. R. Klokkevold, and F. A. Carranza, *Newman and Carranza's Clinical Periodontology E-Book*, Elsevier Health Sciences, Amsterdam, Netherlands, 2018.

[14] H. Seifi Kafshgari, M. Yazdanian, R. Ranjbar et al., "The effect of *Citrullus colocynthis* extracts on Streptococcus mutans, Candida albicans, normal gingival fibroblast and breast cancer cells," *Journal of Biological Research—Bollettino della Società Italiana di Biologia Sperimentale*, vol. 92, no. 1, p. 8201, 2019.

[15] L. S. G. Garcia, A. C. B. Delbem, J. P. Pessan et al., "Anticaries effect of toothpaste with nano-sized sodium hexametaphosphate," *Clinical Oral Investigations*, vol. 23, no. 9, pp. 3535–3542, 2019.

[16] S. A. Mosaddad, E. Tahmasebi, A. Yazdanian et al., "Oral microbial biofilms: an update," *European Journal of Clinical Microbiology & Infectious Diseases*, vol. 38, no. 11, pp. 2005–2019, 2019.

[17] S. Tamura, H. Yonezawa, M. Motegi et al., "Inhibiting effects of Streptococcus salivarius on competence-stimulating peptide-dependent biofilm formation by Streptococcus mutans," *Oral Microbiology and Immunology*, vol. 24, no. 2, pp. 152–161, 2009.

[18] E. M. Bik, C. D. Long, G. C. Armitage et al., "Bacterial diversity in the oral cavity of 10 healthy individuals," *The ISME Journal*, vol. 4, no. 8, pp. 962–974, 2010.

[19] X. Kuang, V. Chen, and X. Xu, "Novel approaches to the control of oral microbial biofilms," *BioMed Research International*, vol. 2018, Article ID 6498932, 13 pages, 2018.

[20] M. Zarco, T. Vess, and G. Ginsburg, "The oral microbiome in health and disease and the potential impact on personalized dental medicine," *Oral Diseases*, vol. 18, no. 2, pp. 109–120, 2012.

[21] J. Panezai, *Periodontal Medicine: Oral Inflammatory Conditions with Special Emphasis on Immunological Aspects*, Karolinska Institute, Solna, Sweden, 2018.

[22] N. Takahashi and B. Nyvad, "Ecological hypothesis of dentin and root caries," *Caries Research*, vol. 50, no. 4, pp. 422–431, 2016.

[23] T. Thurnheer and B. G. Belibasakis, "Streptococcus oralis maintains homeostasis in supragingival biofilms by antagonizing cariogenic pathogen Streptococcus mutans," *Molecular Oral Microbiology*, vol. 33, pp. 234–239, 2018.

[24] F. Bröseler, C. Tietmann, C. Bommer, T. Drechsel, M. Heinzel-Gutenbrunner, and S. Jepsen, "Randomised clinical trial investigating self-assembling peptide P11-4 in the treatment of early caries," *Clinical Oral Investigations*, vol. 24, no. 1, pp. 123–132, 2020.

[25] H.-C. Flemming, J. Wingender, U. Szewzyk, P. Steinberg, S. A. Rice, and S. Kjelleberg, "Biofilms: an emergent form of bacterial life," *Nature Reviews Microbiology*, vol. 14, no. 9, pp. 563–575, 2016.

[26] H. Koo, M. F. Hayacibara, B. D. Schobel et al., "Inhibition of Streptococcus mutans biofilm accumulation and polysaccharide production by apigenin and tt-farnesol," *Journal of Antimicrobial Chemotherapy*, vol. 52, no. 5, pp. 782–789, 2003.

[27] W. H. Bowen and H. Koo, "Biology of Streptococcus mutans-derived glucosyltransferases: role in extracellular matrix formation of cariogenic biofilms," *Caries Research*, vol. 45, no. 1, pp. 69–86, 2011.

[28] N. Rostami, R. C. Shields, S. A. Yassin et al., "A critical role for extracellular DNA in dental plaque formation," *Journal of Dental Research*, vol. 96, no. 2, pp. 208–216, 2017.

[29] M. I. Klein, G. Hwang, P. H. S. Santos, O. H. Campanella, and H. Koo, "Streptococcus mutans-derived extracellular matrix in cariogenic oral biofilms," *Frontiers in Cellular and Infection Microbiology*, vol. 5, p. 10, 2015.

[30] F. Zhu, H. Zhang, and H. Wu, "Glycosyltransferase-mediated sweet modification in oral streptococci," *Journal of Dental Research*, vol. 94, no. 5, pp. 659–665, 2015.

[31] L. Hobley, C. Harkins, C. E. MacPhee, and N. R. Stanley-Wall, "Giving structure to the biofilm matrix: an overview of individual strategies and emerging common themes," *FEMS Microbiology Reviews*, vol. 39, no. 5, pp. 649–669, 2015.

[32] J. L. Mark Welch, B. J. Rossetti, C. W. Rieken, F. E. Dewhirst, and G. G. Borisy, "Biogeography of a human oral microbiome at the micron scale," *Proceedings of the National Academy of Sciences*, vol. 113, no. 6, pp. E791–E800, 2016.

[33] A. Stacy, L. McNally, S. E. Darch, S. P. Brown, and M. Whiteley, "The biogeography of polymicrobial infection," *Nature Reviews Microbiology*, vol. 14, no. 2, pp. 93–105, 2016.

[34] A. M. Valm, "The structure of dental plaque microbial communities in the transition from health to dental caries and periodontal disease," *Journal of Molecular Biology*, vol. 431, no. 16, pp. 2957–2969, 2019.

[35] B. W. Peterson, Y. He, Y. Ren et al., "Viscoelasticity of biofilms and their recalcitrance to mechanical and chemical challenges," *FEMS Microbiology Reviews*, vol. 39, no. 2, pp. 234–245, 2015.

[36] S. Z. Mohebbi, *Early Childhood Caries and A Community Trial of Its Prevention in Tehran, Iran*, University of Helsinki, Helsinki, Finland, 2008.

[37] C. Frese, T. Wohlrab, L. Sheng et al., "Clinical management and prevention of dental caries in athletes: a four-year randomized controlled clinical trial," *Scientific Reports*, vol. 8, no. 1, Article ID 16991, 2018.

[38] A. H. Zhang and J. Li, "Evaluation of the efficacy of sodium fluoride dental protective agent combined with pit and fissure sealant in prevention of dental caries in preschool children," *Shanghai Journal of Stomatology*, vol. 28, no. 5, pp. 553–556, 2019.

[39] A. Al-Jobair, N. Al-Hammad, S. Alsadhan, and F. Salama, "Retention and caries-preventive effect of glass ionomer and resin-based sealants: an 18-month-randomized clinical trial," *Dental Materials Journal*, vol. 36, no. 5, pp. 654–661, 2017.

[40] J. Kalnina and R. Care, "Prevention of occlusal caries using a ozone, sealant and fluoride varnish in children," *Stomatologija*, vol. 18, no. 1, pp. 26–31, 2016.

[41] P. Milgrom, J. A. Horst, S. Ludwig et al., "Topical silver diamine fluoride for dental caries arrest in preschool

children: a randomized controlled trial and microbiological analysis of caries associated microbes and resistance gene expression," *Journal of Dentistry*, vol. 68, pp. 72–78, 2018.

[42] Y. J. Liu, Q. Chang, W. S. Rong, and X. L. Zhao, "Caries prevention effectiveness of aresin based sealant and a glass ionomer sealants: a report of 5-year-follow-up," *Chinese Journal of Stomatology*, vol. 53, no. 7, pp. 437–442, 2018.

[43] Y. Xu, Q. J. Wu, L. P. Luo, and S. Q. Jin, "Evaluation of the clinical effect of fluoride coating combined with pit and fissure sealing or preventive resin filling on prevention of first permanent molars caries," *Shanghai Journal of Stomatology*, vol. 27, no. 3, pp. 298–301, 2018.

[44] N. Pahumunto, S. Piwat, O. Chankanka, N. Akkarachaneeyakorn, K. Rangsitsathian, and R. Teanpaisan, "Reducing mutans streptococci and caries development by Lactobacillus paracasei SD1 in preschool children: a randomized placebo-controlled trial," *Acta Odontologica Scandinavica*, vol. 76, no. 5, pp. 331–337, 2018.

[45] P. Rechmann, S. Bekmezian, B. M. T. Rechmann et al., "MI varnish and MI paste plus in a caries prevention and remineralization study: a randomized controlled trial," *Clinical Oral Investigations*, vol. 22, no. 6, pp. 2229–2239, 2018.

[46] R. N. Cabral, J. Faber, S. A. M. Otero, L. A. Hilgert, and S. C. Leal, "Retention rates and caries-preventive effects of two different sealant materials: a randomised clinical trial," *Clinical Oral Investigations*, vol. 22, no. 9, pp. 3171–3177, 2018.

[47] I. G. Chestnutt, S. Hutchings, R. Playle et al., "Seal or Varnish? A randomised controlled trial to determine the relative cost and effectiveness of pit and fissure sealant and fluoride varnish in preventing dental decay," *Health Technology Assessment*, vol. 21, 2017.

[48] S. Watthanasaen, A. T. Merchant, S. Luengpailin, N. Chansamak, A. Pisek, and W. Pitiphat, "Xylitol-containing chewing gum for caries prevention in students with disabilities: a randomised trial," *Oral Health & Preventive Dentistry*, vol. 15, no. 6, pp. 519–527, 2017.

[49] D. D. Faustino-Silva, B. C. Colvara, E. Meyer, F. N. Hugo, R. K. Celeste, and J. B. Hilgert, "Motivational interviewing effects on caries prevention in children differ by income: a randomized cluster trial," *Community Dentistry and Oral Epidemiology*, vol. 47, no. 6, pp. 477–484, 2019.

[50] J. Lin and H. Yao, "Effects of pit and fissure sealant combined with fluorine protective paint on prevention of children caries aged 5–8 years old," *Shanghai Journal of Stomatology*, vol. 28, no. 4, pp. 384–387, 2019.

[51] L. Wu, X. Gao, E. C. M. Lo, S. M. Y. Ho, C. McGrath, and M. C. M. Wong, "Motivational interviewing to promote oral health in adolescents," *Journal of Adolescent Health*, vol. 61, no. 3, pp. 378–384, 2017.

[52] A. K. Alexandria, C. Nassur, C. B. C. Nóbrega et al., "Effect of TiF4 varnish on microbiological changes and caries prevention: in situ and in vivo models," *Clinical Oral Investigations*, vol. 23, no. 6, pp. 2583–2591, 2019.

[53] E. K. Salas-López, M. Pierdant-Pérez, J. F. Hernández-Sierra, F. Ruíz, P. Mandeville, and A. J. Pozos-Guillén, "Effect of silver nanoparticle-added pit and fissure sealant in the prevention of dental caries in children," *Journal of Clinical Pediatric Dentistry*, vol. 41, no. 1, pp. 48–52, 2017.

[54] W. Xin, K. C. M. Leung, E. C. M. Lo, M. Y. Mok, and M. H. Leung, "A randomized, double-blind, placebo-controlled clinical trial of fluoride varnish in preventing dental caries of Sjögren's syndrome patients," *BMC Oral Health*, vol. 16, no. 1, p. 102, 2016.

[55] H. Enerbäck, M. Möller, C. Nylén, C. Ödman Bresin, I. Östman Ros, and A. Westerlund, "Effects of orthodontic treatment and different fluoride regimens on numbers of cariogenic bacteria and caries risk: a randomized controlled trial," *European Journal of Orthodontics*, vol. 41, no. 1, pp. 59–66, 2019.

[56] L. Alsabek, Z. Al-Nerabieah, N. Bshara, and J. C. Comisi, "Retention and remineralization effect of moisture tolerant resin-based sealant and glass ionomer sealant on non-cavitated pit and fissure caries: randomized controlled clinical trial," *Journal of Dentistry*, vol. 86, pp. 69–74, 2019.

[57] H. R. Su, R. R. Yang, W. H. Qian, and J. M. Yu, "The effect of fluoride varnish Duraphat in preventing deciduous dental caries in preschool children," *Shanghai Journal of Stomatology*, vol. 28, no. 1, pp. 48–52, 2019.

[58] F. Cocco, G. Carta, M. G. Cagetti, L. Strohmenger, P. Lingström, and G. Campus, "The caries preventive effect of 1-year use of low-dose xylitol chewing gum. A randomized placebo-controlled clinical trial in high-caries-risk adults," *Clinical Oral Investigations*, vol. 21, no. 9, pp. 2733–2740, 2017.

[59] M. Muller-Bolla, F. Courson, L. Lupi-Pégurier et al., "Effectiveness of resin-based sealants with and without fluoride placed in a high caries risk population: multicentric 2-year randomized clinical trial," *Caries Research*, vol. 52, no. 4, pp. 312–322, 2018.

[60] E. Aluckal and A. Ankola, "Effectiveness of xylitol and polyol chewing gum on salivary streptococcus mutans in children: a randomized controlled trial," *Indian Journal of Dental Research*, vol. 29, no. 4, pp. 445–449, 2018.

[61] M. Memarpour, S. Dadaein, E. Fakhraei, and M. Vossoughi, "Comparison of oral health education and fluoride varnish to prevent early childhood caries: a randomized clinical trial," *Caries Research*, vol. 50, no. 5, pp. 433–442, 2016.

[62] C. R. Parkinson, A. T. Hara, M. Nehme, F. Lippert, and D. T. Zero, "A randomised clinical evaluation of a fluoride mouthrinse and dentifrice in an in situ caries model," *Journal of Dentistry*, vol. 70, pp. 59–66, 2018.

[63] M. Anderson, G. Dahllöf, F. C. Soares, and M. Grindefjord, "Impact of biannual treatment with fluoride varnish on tooth-surface-level caries progression in children aged 1–3 years," *Journal of Dentistry*, vol. 65, pp. 83–88, 2017.

[64] L. A. Hilgert, S. C. Leal, J. Mulder, N. H. J. Creugers, and J. E. Frencken, "Caries-preventive effect of supervised toothbrushing and sealants," *Journal of Dental Research*, vol. 94, no. 9, pp. 1218–1224, 2015.

[65] M. H. T. Fung, D. Duangthip, M. C. M. Wong, E. C. M. Lo, and C. H. Chu, "Randomized clinical trial of 12% and 38% silver diamine fluoride treatment," *Journal of Dental Research*, vol. 97, no. 2, pp. 171–178, 2018.

[66] M. Alkilzy, A. Tarabaih, R. M. Santamaria, and C. H. Splieth, "Self-assembling peptide P11-4 and fluoride for regenerating enamel," *Journal of Dental Research*, vol. 97, no. 2, pp. 148–154, 2018.

[67] S. Flamee, S. Gizani, C. Caroni, L. Papagiannoulis, and S. Twetman, "Effect of a chlorhexidine/thymol and a fluoride varnish on caries development in erupting permanent molars: a comparative study," *European Archives of Paediatric Dentistry*, vol. 16, no. 6, pp. 449–454, 2015.

[68] B. Charugundla, S. Anjum, and M. Mocherla, "Comparative effect of fluoride, essential oil and chlorhexidine mouth rinses on dental plaque and gingivitis in patients with and

without dental caries: a randomized controlled trial," *International Journal of Dental Hygiene*, vol. 13, no. 2, pp. 104–109, 2015.

[69] L. Wu, K. Geng, and Q. Gao, "Effects of different anti-caries agents on microhardness and superficial microstructure of irradiated permanent dentin: an in vitro study," *BMC Oral Health*, vol. 19, no. 1, p. 113, 2019.

[70] Y. Xue, Q. Lu, Y. Tian, X. Zhou, L. Cheng, and B. Ren, "Effect of toothpaste containing arginine on dental plaque-A randomized controlled in situ study," *Journal of Dentistry*, vol. 67, pp. 88–93, 2017.

[71] L. Lipták, K. Szabó, G. Nagy, S. Márton, and M. Madléna, "Microbiological changes and caries-preventive effect of an innovative varnish containing chlorhexidine in orthodontic patients," *Caries Research*, vol. 52, no. 4, pp. 272–278, 2018.

[72] N. Megalaa, K. Thirumurugan, G. Kayalvizhi et al., "A comparative evaluation of the anticaries efficacy of herbal extracts (Tulsi and Black myrobalans) and sodium fluoride as mouthrinses in children: a randomized controlled trial," *Indian Journal of Dental Research*, vol. 29, no. 6, pp. 760–767, 2018.

[73] B. Latifi-Xhemajli, A. Begzati, J. Veronneau, T. Kutllovci, and A. Rexhepi, "Effectiveness of fluoride varnish four times a year in preventing caries in the primary dentition: a 2 year randomized controlled trial," *Community Dental Health*, vol. 36, no. 2, pp. 190–194, 2019.

[74] C. Anauate-Netto, L. Borelli Neto, R. Amore, V. Di Hipólito, and P. H. P. D'Alpino, "Caries progression in non-cavitated fissures after infiltrant application: a 3-year follow-up of a randomized controlled clinical trial," *Journal of Applied Oral Science*, vol. 25, no. 4, pp. 442–454, 2017.

[75] R. Mariño, F. Traub, P. Lekfuangfu, and K. Niyomsilp, "Cost-effectiveness analysis of a school-based dental caries prevention program using fluoridated milk in Bangkok, Thailand," *BMC Oral Health*, vol. 18, no. 1, p. 24, 2018.

[76] S. Ntaoutidou, A. Arhakis, K. Tolidis, and N. Kotsanos, "Clinical evaluation of a surface pre-reacted glass (S-PRG) filler-containing dental sealant placed with a self-etching primer/adhesive," *European Archives of Paediatric Dentistry*, vol. 19, no. 6, pp. 431–437, 2018.

[77] S. León, K. González, F. N. Hugo, K. Gambetta-Tessini, and R. A. Giacaman, "High fluoride dentifrice for preventing and arresting root caries in community-dwelling older adults: a randomized controlled clinical trial," *Journal of Dentistry*, vol. 86, pp. 110–117, 2019.

[78] P. Muñoz-Millán, C. Zaror, G. Espinoza-Espinoza et al., "Effectiveness of fluoride varnish in preventing early childhood caries in rural areas without access to fluoridated drinking water: a randomized control trial," *Community Dentistry and Oral Epidemiology*, vol. 46, no. 1, pp. 63–69, 2018.

[79] B. C. Colvara, D. D. Faustino-Silva, E. Meyer, F. N. Hugo, J. B. Hilgert, and R. K. Celeste, "Motivational interviewing in preventing early childhood caries in primary healthcare: a community-based randomized cluster trial," *The Journal of Pediatrics*, vol. 201, pp. 190–195, 2018.

[80] S. Khatri, K. Madan, S. Srinivasan, and S. Acharya, "Retention of moisture-tolerant fluoride-releasing sealant and amorphous calcium phosphate-containing sealant in 6–9-year-old children: a randomized controlled trial," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 37, no. 1, pp. 92–98, 2019.

[81] U. M. Sköld, "Approximal caries increment in relation to baseline approximal caries prevalence among adolescents in Sweden with and without a school-based fluoride varnish programme," *Community Dental Health*, vol. 33, no. 4, pp. 281–285, 2016.

[82] D. Duangthip, M. C. M. Wong, C. H. Chu, and E. C. M. Lo, "Caries arrest by topical fluorides in preschool children: 30-month results," *Journal of Dentistry*, vol. 70, pp. 74–79, 2018.

[83] G. K. M. Muhoozi, P. Atukunda, A. B. Skaare et al., "Effects of nutrition and hygiene education on oral health and growth among toddlers in rural Uganda: follow-up of a cluster-randomised controlled trial," *Tropical Medicine & International Health*, vol. 23, no. 4, pp. 391–404, 2018.

[84] B. T. Amaechi, H. Kasundra, L. O. Okoye, P. L. Tran, and T. W. Reid, "Comparative efficacy in preventing plaque formation around pit and fissure sealants: a clinical trial," *The Journal of Contemporary Dental Practice*, vol. 20, no. 5, pp. 531–536, 2019.

[85] D. F. Nóbrega, C. E. Fernández, A. A. Del Bel Cury, L. M. A. Tenuta, and J. A. Cury, "Frequency of fluoride dentifrice use and caries lesions inhibition and repair," *Caries Research*, vol. 50, no. 2, pp. 133–140, 2016.

[86] I. M. Makeeva, M. A. Polyakova, V. Y. Doroshina, A. Y. Turkina, K. S. Babina, and M. G. Arakelyan, "Comparative effectiveness of therapeutic toothpastes with fluoride and hydroxyapatite," *Stomatologiya*, vol. 97, no. 5, pp. 34–40, 2018.

[87] M. Koopaie, M. Fatahzadeh, S. Jahangir, and R. Bakhtiari, "Comparison of the effect of regular and probiotic cake (Bacillus coagulans) on salivary pH and Streptococcus mutans count," *Dental and Medical Problems*, vol. 56, no. 1, pp. 33–38, 2019.

[88] C. Erbe, V. Klees, F. Braunbeck et al., "Comparative assessment of plaque removal and motivation between a manual toothbrush and an interactive power toothbrush in adolescents with fixed orthodontic appliances: a single-center, examiner-blind randomized controlled trial," *American Journal of Orthodontics and Dentofacial Orthopedics*, vol. 155, no. 4, pp. 462–472, 2019.

[89] J. Villavicencio, L. M. Villegas, M. C. Arango, S. Arias, and F. Triana, "Effects of a food enriched with probiotics on Streptococcus mutans and Lactobacillus spp. salivary counts in preschool children: a cluster randomized trial. Journal of applied oral science," *Revista FOB*, vol. 26, Article ID e20170318, 2018.

[90] M. M. Ammari, R. C. Jorge, I. P. R. Souza, and V. M. Soviero, "Efficacy of resin infiltration of proximal caries in primary molars: 1-year follow-up of a split-mouth randomized controlled clinical trial," *Clinical Oral Investigations*, vol. 22, no. 3, pp. 1355–1362, 2018.

[91] E. Haznedaroglu, S. Guner, C. Duman, and A. A. Mentes, "48-month randomized controlled trial of caries prevention effect of a one-time application of glass ionomer sealant versus resin sealant," *Dental Materials Journal*, vol. 35, no. 3, pp. 532–538, 2016.

[92] E. Ghasemi, R. Mazaheri, and A. Tahmourespour, "Effect of probiotic yogurt and xylitol-containing chewing gums on salivary S. mutans count," *Journal of Clinical Pediatric Dentistry*, vol. 41, no. 4, pp. 257–263, 2017.

[93] M. Smitha, S. T. Paul, T. Nagaraj, A. R. Khan, and K. Rinu, "Comparison and clinical evaluation of two pit and fissure sealants on permanent mandibular first molars: an in vivo study," *The Journal of Contemporary Dental Practice*, vol. 20, no. 10, pp. 1151–1158, 2019.

[94] C. Gómez, R. Abellán, and J. C. Palma, "Efficacy of photodynamic therapy vs ultrasonic scaler for preventing

gingival inflammation and white spot lesions during orthodontic treatment," *Photodiagnosis and Photodynamic Therapy*, vol. 24, pp. 377–383, 2018.

[95] M. K. Keller, B. J. Klausen, and S. Twetman, "Fluoride varnish or fluoride mouth rinse? A comparative study of two school-based programs," *Community Dental Health*, vol. 33, no. 1, pp. 23–26, 2016.

[96] G. Rodríguez, B. Ruiz, S. Faleiros et al., "Probiotic compared with standard milk for high-caries children," *Journal of Dental Research*, vol. 95, no. 4, pp. 402–407, 2016.

[97] A. E. Paek, Y. Li, Z. Wang et al., "Caries outcome following an intensive fluoride varnish treatment regimen for children at high risk for early childhood caries," *International Journal of Paediatric Dentistry*, vol. 28, no. 3, pp. 291–299, 2018.

[98] G. Falony, S. Honkala, R. Runnel et al., "Long-term effect of erythritol on dental caries development during childhood: a posttreatment survival analysis," *Caries Research*, vol. 50, no. 6, pp. 579–588, 2016.

[99] A. Quaranta, O. Marchisio, O. D'Isidoro, A. M. Genovesi, and U. Covani, "Single-blind randomized clinical trial on the efficacy of an interdental cleaning device in orthodontic patients," *Minerva Stomatologica*, vol. 67, no. 4, pp. 141–147, 2018.

[100] F. Perrini, L. Lombardo, A. Arreghini, S. Medori, and G. Siciliani, "Caries prevention during orthodontic treatment: in-vivo assessment of high-fluoride varnish to prevent white spot lesions," *American Journal of Orthodontics and Dentofacial Orthopedics*, vol. 149, no. 2, pp. 238–243, 2016.

[101] N. Abreu-Placeres, L. E. Garrido, I. C. Jáquez, and L. E. Féliz-Matos, "Does applying fluoride varnish every three months better prevent caries lesions in erupting first permanent molars? A randomised clinical trial," *Oral Health & Preventive Dentistry*, vol. 17, no. 6, pp. 541–546, 2019.

[102] C. Kirschneck, J.-J. Christl, C. Reicheneder, and P. Proff, "Efficacy of fluoride varnish for preventing white spot lesions and gingivitis during orthodontic treatment with fixed appliances-a prospective randomized controlled trial," *Clinical Oral Investigations*, vol. 20, no. 9, pp. 2371–2378, 2016.

[103] S. Yadav, V. Sachdev, M. Malik, and R. Chopra, "Effect of three different compositions of topical fluoride varnishes with and without prior oral prophylaxis on Streptococcus mutans count in biofilm samples of children aged 2–8 years: a randomized controlled trial," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 37, no. 3, pp. 286–291, 2019.

[104] R. J. Hegde and S. Kamath, "Comparison of the Streptococcus mutans and Lactobacillus colony count changes in saliva following chlorhexidine (0.12%) mouth rinse, combination mouth rinse, and green tea extract (0.5%) mouth rinse in children," *Journal of the Indian Society of Pedodontics and Preventive Dentistry*, vol. 35, no. 2, pp. 150–155, 2017.

[105] A. Narayan, S. Satyaprasad, S. Anandraj, S. Ananda, P. Kamath, and S. Nandan, "Comparison of efficacy of three chemotherapeutic agents on Streptococcus mutans count in plaque and saliva: a randomized controlled triple blind study," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 35, no. 2, pp. 174–180, 2017.

[106] R. Patil, P. Dastoor, and M. Unde, "Comparative evaluation of antimicrobial effectiveness of probiotic milk and fluoride mouthrinse on salivary Streptococcus mutans counts and plaque scores in children—an in vivo experimental study," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 37, no. 4, pp. 378–382, 2019.

[107] D. Duangthip, C. H. Chu, and E. C. M. Lo, "A randomized clinical trial on arresting dentine caries in preschool children by topical fluorides-18 month results," *Journal of Dentistry*, vol. 44, pp. 57–63, 2016.

[108] D. L. Chi, G. Zegarra, E. C. Vasquez Huerta et al., "Milk sweetened with xylitol: a proof-of-principle caries prevention randomized clinical trial," *Journal of Dentistry for Children (Chicago, Ill.)*, vol. 83, no. 3, pp. 152–160, 2016.

[109] T. Hedayati-Hajikand, U. Lundberg, C. Eldh, and S. Twetman, "Effect of probiotic chewing tablets on early childhood caries - a randomized controlled trial," *BMC Oral Health*, vol. 15, no. 1, p. 112, 2015.

[110] C. H. Kau, J. Wang, A. Palombini, N. Abou-Kheir, and T. Christou, "Effect of fluoride dentifrices on white spot lesions during orthodontic treatment: a randomized trial," *The Angle Orthodontist*, vol. 89, no. 3, pp. 365–371, 2019.

[111] M. Kavitha, G. Prathima, G. Kayalvizhi, A. Sanguida, G. Ezhumalai, and V. Ramesh, "Evaluation of Streptococcus mutans serotypes e, f, and k in saliva samples of 6–12-year-old school children before and after a short-term daily intake of the probiotic lozenge," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 37, no. 1, pp. 67–74, 2019.

[112] C. F. Pinto, S. B. Berger, V. Cavalli et al., "In situ antimicrobial activity and inhibition of secondary caries of self-etching adhesives containing an antibacterial agent and/or fluoride," *American Journal of Dentistry*, vol. 28, no. 3, pp. 167–173, 2015.

[113] R. Hegde and J. Thakkar, "Comparative evaluation of the effects of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) and xylitol-containing chewing gum on salivary flow rate, pH and buffering capacity in children: an in vivo study," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 35, no. 4, pp. 332–337, 2017.

[114] S. M. Bagher, F. M. Hegazi, M. Finkelman et al., "Radiographic effectiveness of resin infiltration in arresting incipient proximal enamel lesions in primary molars," *Pediatric Dentistry*, vol. 40, no. 3, pp. 195–200, 2018.

[115] R. A. Jordan, A. Schulte, A. C. Bockelbrink et al., "Caries-preventive effect of salt fluoridation in preschool children in the Gambia: a prospective, controlled, interventional study," *Caries Research*, vol. 51, no. 6, pp. 596–604, 2018.

[116] S. K. Patil, M. Fatangare, R. G. Jadhav, G. R. Shinde, S. S. Pawar, and M. D. Kathariya, "Caries preventive effect of sodium fluoride varnish on deciduous dentition: a clinical trial," *The Journal of Contemporary Dental Practice*, vol. 18, no. 12, pp. 1190–1193, 2017.

[117] J. Homoki, G. Gyémánt, P. Balogh et al., "Sour cherry extract inhibits human salivary α-amylase and growth of Streptococcus mutans (a pilot clinical study)," *Food & Function*, vol. 9, no. 7, pp. 4008–4016, 2018.

[118] A. Y. Sanchez, C. L. de Oliveira, T. C. Negrini et al., "In situ effect of arginine-containing dentifrice on plaque composition and on enamel demineralization under distinct cariogenic conditions," *Caries Research*, vol. 52, no. 6, pp. 588–597, 2018.

[119] L. Nemeth, M. Groselj, A. Golez, A. Arhar, I. Frangez, and K. Cankar, "The impact of photobiomodulation of major salivary glands on caries risk," *Lasers in Medical Science*, vol. 35, no. 1, pp. 193–203, 2020.

[120] S. Dahal, A. Shrestha, and T. Bhagat, "Effectiveness of herbal mouthwash among visually impaired residential school students," *Journal of Nepal Medical Association*, vol. 56, no. 212, pp. 728–734, 2018.

[121] S. Y. Zhang, H. Dong, and M. Yu, "The effects of different interventions on 12-year-old children's permanent teeth caries and filling rate in Shanghai Jiading district," *Shanghai Journal of Stomatology*, vol. 24, no. 3, pp. 341–344, 2015.

[122] M. C. Peters, A. R. Hopkins Jr., and Q. Yu, "Resin infiltration: an effective adjunct strategy for managing high caries risk-A within-person randomized controlled clinical trial," *Journal of Dentistry*, vol. 79, pp. 24–30, 2018.

[123] N. M. Alamoudi, E. S. Almabadi, E. A. El Ashiry, and D. A. El Derwi, "Effect of probiotic Lactobacillus reuteri on salivary cariogenic bacterial counts among groups of preschool children in Jeddah, Saudi Arabia: a randomized clinical trial," *Journal of Clinical Pediatric Dentistry*, vol. 42, no. 5, pp. 331–338, 2018.

[124] S. Joshi, M. Sandhu, H. P. S. Sogi, S. Garg, and A. Dhindsa, "Split-mouth randomised clinical trial on the efficacy of GIC sealant on occlusal surfaces of primary second molar," *Oral Health & Preventive Dentistry*, vol. 17, no. 1, pp. 17–24, 2019.

[125] E. M. R. Neto, L. A. R. Valadas, P. L. D. Lobo et al., "Dose-response evaluation of propolis dental varnish in children: a randomized control study," *Recent Patents on Biotechnology*, vol. 14, no. 1, pp. 41–48, 2020.

[126] H. Meyer-Lueckel, A. Balbach, C. Schikowsky, K. Bitter, and S. Paris, "Pragmatic RCT on the efficacy of proximal caries infiltration," *Journal of Dental Research*, vol. 95, no. 5, pp. 531–536, 2016.

[127] A. Mishra, R. K. Pandey, and N. Manickam, "Antibacterial effect and physical properties of chitosan and chlorhexidine-cetrimide-modified glass ionomer cements," *Journal of the Indian Society of Pedodontics and Preventive Dentistry*, vol. 35, no. 1, pp. 28–33, 2017.

[128] C. P. C. Sim, J. Wee, Y. Xu, Y.-B. Cheung, Y.-L. Soong, and D. J. Manton, "Anti-caries effect of CPP-ACP in irradiated nasopharyngeal carcinoma patients," *Clinical Oral Investigations*, vol. 19, no. 5, pp. 1005–1011, 2015.

[129] S. M. Hammad and M. Knösel, "Efficacy of a new sealant to prevent white spot lesions during fixed orthodontic treatment," *Journal of Orofacial Orthopedics/Fortschritte der Kieferorthopädie*, vol. 77, no. 6, pp. 439–445, 2016.

[130] J. S. Joshi, N. M. Roshan, B. Sakeenabi, P. Poornima, N. B. Nagaveni, and V. V. Subbareddy, "Inhibition of residual cariogenic bacteria in atraumatic restorative treatment by chlorhexidine: disinfection or incorporation," *Pediatric Dentistry*, vol. 39, no. 4, pp. 308–312, 2017.

[131] M. M. Alabdullah, A. Nabawia, M. A. Ajaj, and H. Saltaji, "Effect of fluoride-releasing resin composite in white spot lesions prevention: a single-centre, split-mouth, randomized controlled trial," *European Journal of Orthodontics*, vol. 39, no. 6, pp. 634–640, 2017.

[132] M. Malinowski, K. J. Toumba, S. M. Strafford, and M. S. Duggal, "The effect on dental enamel of the frequency of consumption of fluoridated milk with a cariogenic challenge in situ," *Journal of Dentistry*, vol. 70, pp. 87–91, 2018.

[133] R. Shetty, S. Shetty, S. Janardhanan, S. Shetty, S. Shetty, and K. Raj, "Comparative evaluation of effect of use of toothbrush with paste and munident on levels of Streptococcus mutans and gingival health in children: an in vivo study," *Journal of Indian Society of Pedodontics and Preventive Dentistry*, vol. 35, no. 2, pp. 162–166, 2017.

[134] O. B. Al-Batayneh, E. I. Bani Hmood, and S. N. Al-Khateeb, "Assessment of the effects of a fluoride dentifrice and GC Tooth Mousse on early caries lesions in primary anterior teeth using quantitative light-induced fluorescence: a randomised clinical trial," *European Archives of Paediatric Dentistry*, vol. 21, no. 1, pp. 85–93, 2020.

[135] S. Yassaei and M. N. Motallaei, "The effect of the Er:YAG laser and MI paste plus on the treatment of white spot lesions," *Journal of Lasers in Medical Sciences*, vol. 11, no. 1, pp. 50–55, 2020.

[136] S. Gizani, G. Petsi, S. Twetman, C. Caroni, M. Makou, and L. Papagianoulis, "Effect of the probiotic bacteriumLactobacillus reuterion white spot lesion development in orthodontic patients," *The European Journal of Orthodontics*, vol. 38, no. 1, pp. 85–89, 2016.

[137] A. Kumar Jena, S. Pal Singh, and A. Kumar Utreja, "Efficacy of resin-modified glass ionomer cement varnish in the prevention of white spot lesions during comprehensive orthodontic treatment: a split-mouth study," *Journal of Orthodontics*, vol. 42, no. 3, pp. 200–207, 2015.

[138] M. D. Ferrer, A. López-López, T. Nicolescu et al., "A pilot study to assess oral colonization and pH buffering by the probiotic Streptococcus dentisani under different dosing regimes," *Odontology*, vol. 108, no. 2, pp. 180–187, 2020.

[139] M. Anderson, G. Dahllöf, S. Twetman, L. Jansson, A.-C. Bergenlid, and M. Grindefjord, "Effectiveness of early preventive intervention with semiannual fluoride varnish application in toddlers living in high-risk areas: a stratified cluster-randomized controlled trial," *Caries Research*, vol. 50, no. 1, pp. 17–23, 2016.

[140] E. Esenlik, E. Uzer Çelik, and E. Bolat, "Efficacy of a casein phosphopeptide amorphous calcium phosphate (CPP-ACP) paste in preventing white spot lesions in patients with fixed orthodontic appliances: a prospective clinical trial," *European Journal of Paediatric Dentistry*, vol. 17, no. 4, pp. 274–280, 2016.

[141] A. Nishad, N. Sreesan, J. Joy, L. Lakshmanan, J. Thomas, and V. Anjali, "Impact of mouthwashes on antibacterial activity of subjects with fixed orthodontic appliances: a randomized clinical trial," *The Journal of Contemporary Dental Practice*, vol. 18, no. 12, pp. 1112–1116, 2017.

[142] L. P. Comar, B. M. Souza, J. Martins, M. G. Santos, M. A. R. Buzalaf, and A. C. Magalhães, "Response of carious enamel to TiF 4 varnish treatment under diverse cariogenic activities in situ," *Journal of Dentistry*, vol. 63, pp. 81–84, 2017.

[143] D. M. da Camara, J. P. Pessan, T. M. Francati, J. A. Santos Souza, M. Danelon, and A. C. B. Delbem, "Synergistic effect of fluoride and sodium hexametaphosphate in toothpaste on enamel demineralization in situ," *Journal of Dentistry*, vol. 43, no. 10, pp. 1249–1254, 2015.

[144] I. M. Makeeva, M. A. Polyakova, O. E. Avdeenko, Y. O. Paramonov, S. A. Kondrat'ev, and A. A. Pilyagina, "Effect of long term application of toothpaste Apadent total care medical nano-hydroxyapatite," *Stomatologiya*, vol. 95, no. 4, pp. 34–36, 2016.

[145] P. Rai, R. K. Pandey, and R. Khanna, "Effect of a protective chlorhexidine varnish layer over resin-infiltrated proximal carious lesions in primary teeth," *Pediatric Dentistry*, vol. 38, no. 4, pp. 40–45, 2016.

[146] C.-H. Chu, S. S. Gao, S. K. Li, M. C. Wong, and E. C. Lo, "The effectiveness of the biannual application of silver nitrate solution followed by sodium fluoride varnish in arresting early childhood caries in preschool children: study protocol for a randomised controlled trial," *Trials*, vol. 16, no. 1, p. 426, 2015.

[147] A. N. Fadl, M. M. ElTekeya, K. L. Dowidar, N. Mokhles, and M. M. El Tantawi, "Effect of tooth mousse on Streptococcus

mutans in the plaque of high caries-risk preschool children: a triple-blind, randomized clinical trial," *Pediatric Dentistry*, vol. 38, no. 4, pp. 300–304, 2016.

[148] N. C. W. Kaaij, M. H. Veen, M. A. E. Kaaij, and J. M. Cate, "A prospective, randomized placebo-controlled clinical trial on the effects of a fluoride rinse on white spot lesion development and bleeding in orthodontic patients," *European Journal of Oral Sciences*, vol. 123, no. 3, pp. 186–193, 2015.

[149] R. A. Bagramian, F. Garcia-Godoy, and A. R. Volpe, "The global increase in dental caries. A pending public health crisis," *American Journal of Dentistry*, vol. 22, no. 1, pp. 3–8, 2009.

[150] W. M. Thomson, "Dental caries experience in older people over time: what can the large cohort studies tell us?" *British Dental Journal*, vol. 196, no. 2, pp. 89–92, 2004.

[151] O. Fejerskov and E. Kidd, *Dental Caries: The Disease and its Clinical Management*, John Wiley & Sons, Hoboken, NJ, USA, 2009.

[152] O. Norderyd and Å. Wahlin, *Impact of Risk-Based Prevention on Public Oral Health. Risk Assessment in Oral Health:*, Springer, Berlin, Germany, 2020.

[153] S. Khazaei, M. S. Firouzei, S. Sadeghpour et al., "Edentulism and tooth loss in Iran: SEPAHAN systematic review," *International Journal of Preventive Medicine*, vol. 3, no. Suppl1, pp. S42–7, 2012.

[154] I. Polzer, M. Schimmel, F. Müller, and R. Biffar, "Edentulism as part of the general health problems of elderly adults," *International Dental Journal*, vol. 60, no. 3, pp. 143–155, 2010.

[155] M. E. Sanders, "Probiotics: definition, sources, selection, and uses," *Clinical Infectious Diseases*, vol. 46, no. s2, pp. S58–S61, 2008.

[156] S. Twetman, "Prevention of dental caries as a non-communicable disease," *European Journal of Oral Sciences*, vol. 126, no. S1, pp. 19–25, 2018.

[157] M. M. Nascimento, C. Browngardt, X. Xiaohui, V. Klepac-Ceraj, B. J. Paster, and R. A. Burne, "The effect of arginine on oral biofilm communities," *Molecular Oral Microbiology*, vol. 29, no. 1, pp. 45–54, 2014.

[158] E. Figuero, D. F. Nóbrega, M. García-Gargallo, L. M. A. Tenuta, D. Herrera, and J. C. Carvalho, "Mechanical and chemical plaque control in the simultaneous management of gingivitis and caries: a systematic review," *Journal of Clinical Periodontology*, vol. 44, pp. S116–S134, 2017.

[159] A. Mira, A. Simon-Soro, and M. A. Curtis, "Role of microbial communities in the pathogenesis of periodontal diseases and caries," *Journal of Clinical Periodontology*, vol. 44, pp. S23–S38, 2017.

[160] V. N. Stone and P. Xu, "Targeted antimicrobial therapy in the microbiome era," *Molecular Oral Microbiology*, vol. 32, no. 6, pp. 446–454, 2017.

[161] M. Yazdanian, A. Rahmani, E. Tahmasebi, H. Tebyanian, A. Yazdanian, and S. A. Mosaddad, "Current and advanced nanomaterials in dentistry as regeneration agents: an update," *Mini-Reviews in Medicinal Chemistry*, vol. 21, no. 7, pp. 899–918, 2021.

[162] B. T. Rosier, P. D. Marsh, and A. Mira, "Resilience of the oral microbiota in health: mechanisms that prevent dysbiosis," *Journal of Dental Research*, vol. 97, no. 4, pp. 371–380, 2018.

[163] D. Campoccia, L. Montanaro, and C. R. Arciola, "A review of the biomaterials technologies for infection-resistant surfaces," *Biomaterials*, vol. 34, pp. 8533–8554, 2013.

[164] M. Cloutier, D. Mantovani, and F. Rosei, "Antibacterial coatings: challenges, perspectives, and opportunities," *Trends in Biotechnology*, vol. 33, no. 11, pp. 637–652, 2015.

[165] D. G. Moussa and C. Aparicio, "Targeting the oral plaque microbiome with immobilized anti-biofilm peptides at tooth-restoration interfaces," *PLoS One*, vol. 15, no. 7, Article ID e0235283, 2020.

[166] S. M. d. F. Lima, G. M. de Pádua, M. G. d. C. Sousa, M. d. S. Freire, O. L. Franco, and T. M. B. Rezende, "Antimicrobial peptide-based treatment for endodontic infections—biotechnological innovation in endodontics," *Biotechnology Advances*, vol. 33, no. 1, pp. 203–213, 2015.

[167] A. Jain, L. S. Duvvuri, S. Farah, N. Beyth, A. J. Domb, and W. Khan, "Antimicrobial polymers," *Advanced Healthcare Materials*, vol. 3, no. 12, pp. 1969–1985, 2014.

[168] G. C. Padovani, V. P. Feitosa, S. Sauro et al., "Advances in dental materials through nanotechnology: facts, perspectives and toxicological aspects," *Trends in Biotechnology*, vol. 33, no. 11, pp. 621–636, 2015.

[169] F. Paladini, M. Pollini, A. Sannino, and L. Ambrosio, "Metal-based antibacterial substrates for biomedical applications," *Biomacromolecules*, vol. 16, no. 7, pp. 1873–1885, 2015.

[170] S. Yassaei, A. Nasr, H. Zandi, and M. N. Motallaei, "Comparison of antibacterial effects of orthodontic composites containing different nanoparticles on Streptococcus mutans at different times," *Dental Press Journal of Orthodontics*, vol. 25, no. 2, pp. 52–60, 2020.

[171] A. B. Seabra, G. Z. Justo, and P. S. Haddad, "State of the art, challenges and perspectives in the design of nitric oxide-releasing polymeric nanomaterials for biomedical applications," *Biotechnology Advances*, vol. 33, no. 6, pp. 1370–1379, 2015.

[172] K. Feghali, M. Feldman, V. D. La, J. Santos, and D. Grenier, "Cranberry proanthocyanidins: natural weapons against periodontal diseases," *Journal of Agricultural and Food Chemistry*, vol. 60, no. 23, pp. 5728–5735, 2012.

[173] P. W. Taylor, J. M. T. Hamilton-Miller, and P. D. Stapleton, "Antimicrobial properties of green tea catechins," *Food Science Technology Bulletin: Functional Foods*, vol. 2, no. 7, pp. 71–81, 2005.

[174] W. H. Bowen, R. A. Burne, H. Wu, and H. Koo, "Oral biofilms: pathogens, matrix, and polymicrobial interactions in microenvironments," *Trends in Microbiology*, vol. 26, no. 3, pp. 229–242, 2018.

[175] J. E. Koopman, M. A. Hoogenkamp, M. J. Buijs et al., "Changes in the oral ecosystem induced by the use of 8% arginine toothpaste," *Archives of Oral Biology*, vol. 73, pp. 79–87, 2017.

[176] J. Li, Z. Huang, L. Mei, G. Li, and H. Li, "Anti-caries effect of arginine-containing formulations in vivo: a systematic review and meta-analysis," *Caries Research*, vol. 49, no. 6, pp. 606–617, 2015.

[177] X. Huang, K. Zhang, M. Deng et al., "Effect of arginine on the growth and biofilm formation of oral bacteria," *Archives of Oral Biology*, vol. 82, pp. 256–262, 2017.

[178] F. J. Xu, K. G. Neoh, and E. T. Kang, "Bioactive surfaces and biomaterials via atom transfer radical polymerization," *Progress in Polymer Science*, vol. 34, no. 8, pp. 719–761, 2009.

[179] N. B. Pitts, D. T. Zero, P. D. Marsh et al., "Dental caries," *Nature Reviews Disease Primers*, vol. 3, no. 1, Article ID 17030, 2017.

[180] R. Giacaman, "Sugars and beyond. The role of sugars and the other nutrients and their potential impact on caries," *Oral Diseases*, vol. 24, no. 7, pp. 1185–1197, 2018.

[181] D. Head, D. A. Devine, and P. D. Marsh, "In silico modelling to differentiate the contribution of sugar frequency versus total amount in driving biofilm dysbiosis in dental caries," *Scientific Reports*, vol. 7, no. 1, Article ID 17413, 2017.

[182] World Health Organization, *Guideline: Sugars Intake for Adults and Children*, World Health Organization, Geneva, Switzerland, 2015.

[183] P. Moynihan, "Sugars and dental caries: evidence for setting a recommended threshold for intake," *Advances in Nutrition*, vol. 7, no. 1, pp. 149–156, 2016.

[184] H. Jamel, A. Plasschaert, and A. Sheiham, "Dental caries experience and availability of sugars in Iraqi children before and after the United Nations sanctions," *International Dental Journal*, vol. 54, no. 1, pp. 21–25, 2004.

[185] B. I. Truman, B. F. Gooch, I. Sulemana et al., "Reviews of evidence on interventions to prevent dental caries, oral and pharyngeal cancers, and sports-related craniofacial injuries," *American Journal of Preventive Medicine*, vol. 23, no. 1 Suppl, pp. 21–54, 2002.

[186] E. Söderling, M. ElSalhy, E. Honkala et al., "Effects of short-term xylitol gum chewing on the oral microbiome," *Clinical Oral Investigations*, vol. 19, no. 2, pp. 237–244, 2015.

[187] G. Campus, M. G. Cagetti, S. Sale et al., "Six months of high-dose xylitol in high-risk caries subjects-a 2-year randomised, clinical trial," *Clinical Oral Investigations*, vol. 17, no. 3, pp. 785–791, 2013.

[188] K. K. Mäkinen, "Sugar alcohol sweeteners as alternatives to sugar with special consideration of xylitol," *Medical Principles and Practice*, vol. 20, no. 4, pp. 303–320, 2011.

[189] E. M. Söderling, "Xylitol, mutans streptococci, and dental plaque," *Advances in Dental Research*, vol. 21, no. 1, pp. 74–78, 2009.

[190] M. Hrimech, D. Mayrand, D. Grenier, and L. Trahan, "Xylitol disturbs protein synthesis, including the expression of HSP-70 and HSP-60, in Streptococcus mutans," *Oral Microbiology and Immunology*, vol. 15, no. 4, pp. 249–257, 2000.

[191] S. Furness, H. V. Worthington, G. Bryan, S. Birchenough, and R. McMillan, "Interventions for the management of dry mouth: topical therapies," *The Cochrane Database of Systematic Reviews*, vol. 12, Article ID CD008934, 2011.

[192] P. D. Marsh and D. A. Devine, "How is the development of dental biofilms influenced by the host?" *Journal of Clinical Periodontology*, vol. 38, no. s11, pp. 28–35, 2011.

[193] M. M. Nascimento, Y. Liu, R. Kalra et al., "Oral arginine metabolism may decrease the risk for dental caries in children," *Journal of Dental Research*, vol. 92, no. 7, pp. 604–608, 2013.

[194] X. Zheng, J. He, L. Wang et al., "Ecological effect of arginine on oral microbiota," *Scientific Reports*, vol. 7, no. 1, p. 7206, 2017.

[195] W. M. Avila, I. A. Pordeus, S. M. Paiva, and C. Martins, "Breast feeding as risk factors for dental caries: a systematic review and meta-analysis," *PLoS One*, vol. 10, no. 11, Article ID e0142922, 2015.

[196] R. Tham, G. Bowatte, S. Dharmage et al., "Breastfeeding and the risk of dental caries: a systematic review and meta-analysis," *Acta Paediatrica*, vol. 104, no. 467, pp. 62–84, 2015.

[197] G. Reid, J. A. Younes, H. C. Van der Mei, G. B. Gloor, R. Knight, and H. J. Busscher, "Microbiota restoration: natural and supplemented recovery of human microbial communities," *Nature Reviews Microbiology*, vol. 9, no. 1, pp. 27–38, 2011.

[198] D. Gruner, S. Paris, and F. Schwendicke, "Probiotics for managing caries and periodontitis: systematic review and meta-analysis," *Journal of Dentistry*, vol. 48, pp. 16–25, 2016.

[199] N. Romani Vestman, T. Chen, P. Lif Holgerson, C. Ohman, and I. Johansson, "Oral microbiota shift after 12-week supplementation with Lactobacillus reuteri DSM 17938 and PTA 5289; a randomized control trial," *PLoS One*, vol. 10, no. 5, Article ID e0125812, 2015.

[200] M. R. Jørgensen, G. Castiblanco, S. Twetman, and M. K. Keller, "Prevention of caries with probiotic bacteria during early childhood. Promising but inconsistent findings," *American Journal of Dentistry*, vol. 29, no. 3, pp. 127–131, 2016.