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REVIEW

Cariostatic Agents: From Silver Diamine Fluoride to Emerging Bioactive Compounds

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Abstract: Cariostatic agents are bioactive compounds that inhibit the progression of dental caries by promoting enamel and dentin remineralization while mitigating dentin hypersensitivity. This review conducted an extensive bibliographic search across specialized databases, including Web of Science, PubMed, Cochrane Library, and Scopus, to present a comprehensive and up-to-date analysis of the clinical applications of cariostatic agents. A critical appraisal of the available scientific evidence was performed to evaluate their efficacy and potential as adjunctive therapeutic strategies in caries management. Among the most well-documented agents, silver diamine fluoride (SDF) demonstrates superior efficacy in arresting active carious lesions and preventing lesion progression. Furthermore, emerging bioactive compounds, such as remineralizing peptides and phytochemicals, have exhibited promising anticariogenic properties, though their long-term clinical effectiveness remains under investigation. This review synthesizes key findings from recent research, underscoring the pivotal role of cariostatic agents in evidence-based caries prevention and management. The results highlight the necessity of integrating these agents into a minimally invasive and patient-centered approach, particularly for high-risk populations, to optimize long-term oral health outcomes.
Keywords: "cariostatics", "dental cariostatic", "anticariogenic", "caries"

Introduction

Caries is a disease that affects the teeth, caused by the fermentation of simple carbohydrates such as sucrose by bacteria present in the oral cavity, especially streptococci and lactobacilli.[1] These bacteria convert sugars into acids that demineralize tooth structure. Caries develops in a series of stages, starting from the surface of the tooth and advancing toward the interior of the tooth, bringing about demineralization and structural damage to dental tissues, which becomes irreversible once cavitation occurs.[2,3] The oral biofilm is the environment where the caries formation process takes place. This multiflora bacterial biofilm is constantly active due to changes in intraoral pH. Most of the tooth surface is kept free of bacteria due to contact with the tongue, mucosa, and food, however, in areas where there is continuous contact with the biofilm, bacteria can colonize these areas forming retentions that produce a dense film of bacteria known as dental plaque.[4]

Dental caries occurs when the microbiota of the biofilm, which is normally in equilibrium, becomes more acidogenic, aciduric, and cariogenic. This change can be caused by frequent consumption of sugars, which lowers the pH of dental plaque. The effect of this change may be clinically undetectable or present as a loss of minerals in the solid structures of the tooth, known as demineralization, which in advanced stages results in a visible carious lesion. In addition, caries can also develop without showing obvious outward signs.[5]

Concerning the above, dental caries is considered a disease caused by a combination of dietary and microbial factors, which requires the presence of a cariogenic biofilm and frequent exposure to fermentable carbohydrates (glucose, fructose, maltose, and sucrose) in the diet.[2,6] Among the microorganisms present in this infectious process are the

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group of Streptococci (*mutans, sobrinus, sanguis, salivarus, mitis, anginosus, gordinni, oralis), lactobacilli, veillonella, cocci, actinomyces viscosus*; the most common ones being.[3,7]

Globally, the number of dental caries cases in 2019 was estimated to be approximately 514 million, in the case of the prevalence of dental caries in primary dentition stood at 46.2%, based on a global sample of 80405 children.[8] These data demonstrate the importance of this disease in the global context and the constant search for new treatments. In addition, scientific evidence indicates that the global average prevalence of caries in primary dentition is 43%, and 134 of the 194 WHO (World Health Organization) Member States have prevalence figures above 40%.[9,10]

The most common way to detect dental caries is the visual and tactile clinical examination, which is complemented by radiographs, where radiographic examinations can give us a more accurate picture showing the changes in the enamel. At the same time, there are other diagnostic techniques that take advantage of the characteristics of carious lesions in dentin and enamel to detect them. Fluorescence: The enamel in the process of demineralization presents alterations in its structure. If they are exposed to fluorescent light, the teeth affected by caries respond differently from healthy teeth. A loss of minerals can be visualized, and by performing a quantification, we can make a diagnosis and treatment. Fluorescence uses two types of light sources, generally laser fluorescence and light fluorescence. Transillumination fiber optic (TIFO): This method uses a light emitted by a portable device that the dentist places on the outside of the tooth and observes how the light reflects inside. If there is any irregularity, such as a cavity or fracture, the light is deflected and can be easily detected because demineralization in affected teeth is observed something like shadows on the tooth, due to the alteration of its structure. Electrical conductance: This method is based on the alteration of the electrical conductance due to the demineralization of the tooth. It uses a probe that is placed on the surface of the tooth to measure the electrical conductivity. The carious areas, as they are filled with more saliva, present a higher potential, which facilitates its detection.[3,11,12]

The treatment of dental caries is varied and must be adapted to factors such as the patient's individual risk, the severity of the lesion and their level of collaboration. Current caries management strategies emphasize prevention, early detection and a diagnosis based on the evaluation of indicators and risk factors. In addition, minimally invasive dentistry approaches seek to preserve healthy tissue and maintain pulp vitality. In general terms, the therapeutic approach to teeth affected by caries is classified into preventive, noninvasive and minimally invasive treatments.[13,14]

In this work, we will describe cariostatic agents, substances that inhibit the development and progression of dental caries. These compounds act through various mechanisms, including remineralization of enamel, inhibition of demineralization and reduction of bacterial activity in dental plaque. Among them, fluoride is the most effective and widely used cariostatic agent in the prevention of caries, as it strengthens tooth enamel and reduces its solubility against acids produced by bacteria.[2,15]

Therefore, in view of the various treatments used in dental caries, the aim of this review is to provide an overview of recent cariostatic agents and their respective roles in caries prevention.

Materials and Methods

This study was developed in response to the need to obtain up information comprehensive overview of the available cariostatic agents, efficacy, and clinical relevance in caries prevention and management, so a bibliographic search was carried out for scientific articles published between January 2000 and August 2024 in databases such as: Web of Science, PubMed, Cochrane Library, and Scopus.

We used search strategy terms indexed in the MeSH (medical subject headings) keyword health descriptor, such as "cariostatics", "dental cariostatic", "anticariogenic" to identify relevant studies in the indicated databases. The inclusion criteria were information on cariostatic agents whose effects include remineralizing and antibacterial action and new or uncommon alternatives to the traditional ones, clinical trial articles, in vitro studies, and case reports. The exclusion criteria were studies that reported using agents such as fluoride varnish or fluoride gel used in pediatric dentistry, articles that did not report complete information, bibliographic reviews, short communications, and theses. Likewise, information from letters to the editor, congress abstracts, and non-peer-reviewed trial registries were not included.

Two independent reviewers performed the initial selection of articles based on titles and abstracts. In case of discrepancies, they were resolved through discussion and consensus. Subsequently, a thorough reading of the selected articles was carried out to determine their relevance and methodological quality. A thorough review and analysis of each article was carried out and relevant data were extracted from each of them, such as characteristics of the studies, interventions used, results, and conclusions.

Results and Discussion

Cariostatics

The use of cariostatic agents is one of several techniques for the preventive and non-invasive treatment of caries, which are substances that inhibit the progression of the disease, reduce sensitivity and may have antimicrobial action.[3,15–17] Among the cariostatic agents found, the studies analyzed are summarized in the Figure 1.

Table 1 describes each of the studies found on cariostatic agents. The studies are organized by agent type, study type, year of publication, objective, parameters evaluated, and most relevant outcomes.

Fluorinated Agents

Silver Diamine Fluoride (SDF)

It is the cariostatic par excellence, efficient, conservative and less invasive than other treatments. SDF compared to placebo or fluoride varnish seems to effectively prevent dental caries throughout the dentition.[24,36,37] The application of SDF according to various studies and protocols indicate that its application usually takes 10 to 240 seconds and an average time of 60 seconds.[38,39]

The use of SDF causes staining that discolors the teeth because SDF contains silver which oxidizes and causes a black stain in damaged tooth cavities. In a study, they propose a two-step protocol for the management of root caries using SDF by taking advantage of the discoloration. The method aims to make carious dentin more detectable by using the SDF in

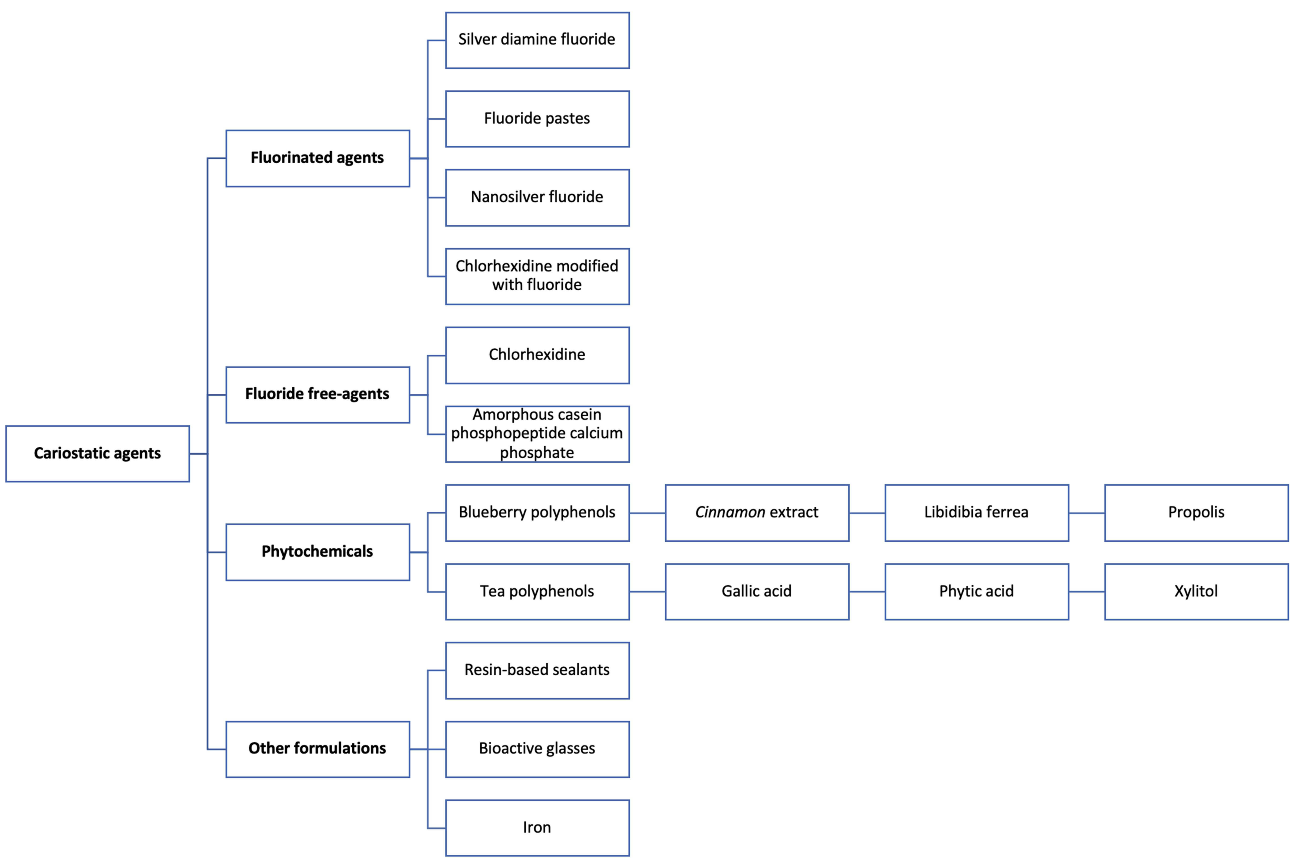

Figure 1 Classification of dental cariostatics.

Table 1 Summarizes the Studies Found on Cariostatic Agent

Agent Type	Author-Year/ Type of Study	Objective	Cariostatic Agent	Parameters Evaluated	Main Findings
FLUORINATED COMPOUNDS	Sajjan et al/ 2013[18] (RCT)	To evaluate and compare the effect of chlorhexidine varnish and fluoride varnish application on the number of Streptococcus mutans.	Chlorhexidine varnish	The study compared two varnishes, Cervitec and Duraphat, in 50 children aged 7–8 years to evaluate their effect on the reduction of *Streptococcus mutans* bacteria in dental plaque. The varnishes were applied to the molars and plaque samples were taken at baseline, at 5 and 10 days, and then at 1 and 3 months after initial application.	Cervitec® varnish showed a statistically significant reduction at the end of 1 month and at the end of 3 months ($P < 0.05$). Duraphat® varnish did not show a statistically significant difference in the reduction of *Streptococcus mutans* plaque count at the end of 1 month and at the third month ($P > 0.05$).
FLUORINATED COMPOUNDS	Randall et al/ 2015[19] (An in vitro study)	To compare the antimicrobial activity of different fluoride and herbal dentifrices and their individual components against Streptococcus mutans bacteria.	Fluoride compounds and herbs	An agar diffusion method using Mueller-Hinton agar was used. Wells were filled with 10 commercial fluoride or 6 herbal dentifrices, or with solutions of various fluoride compounds, sodium lauryl sulfate, sodium benzoate, chlorhexidine digluconate or triclosan. The diameters of the bacterial growth inhibition zones surrounding the wells were measured with a micrometer.	The antibacterial activities of the 6 herbal toothpastes varied, with Herbal Fresh being the strongest. Sodium lauryl sulfate showed strong antimicrobial activity against *Streptococcus mutans* at the levels used in toothpastes.
FLUORINATED COMPOUNDS	Vieira et al/ 2018[20] (An in vitro study)	To evaluate the remineralizing action of nanosilver fluoride (NSF) in incipient enamel caries.	Nano-silver fluoride	The deciduous enamel fragments were treated with sodium fluoride (NaF), NSF and deionized water, also placed in test tubes containing bacterial suspension and saliva. pH readings and quantification of microorganisms adhered to the dental enamel were determined.	Nanosilver fluoride had greater effectiveness compared to NaF in preventing pH decreases and adhesion of *Streptococcus mutans* to the enamel surface, with statistically significant differences ($p<0.001$).
FLUORINATED COMPOUNDS	Nagireddy et al/ 2019[21] (RCT)	To investigate the effectiveness of a new anticaries agent, nanosilver fluoride (NSF), to prevent and stop tooth decay in children.	Nano-silver fluoride	One hundred primary molars were randomly selected among 60 children aged 4 to 9 years, who were randomly divided into the NSF experimental group and the saline control group. The teeth were diagnosed and clinically treated by a masked examiner and followed at 7 days, 5 months, and 12 months by another calibrated examiner who was blinded to the type of treatment.	Seventy-eight percent of the carious teeth showed hard, arrested dentin at 7 days; after a 5-month analysis in the NSF group, 72.91% of the teeth showed arrested caries; and in the control group, only 34% of the teeth showed arrested caries. In the 12-month analysis in the NSF group, 65.21% of the teeth showed arrested caries, and in the control group, 28.88% of the teeth showed arrested caries.
	Silva et al/ 2019[22] (An in vitro study)	To evaluate the efficacy of nanosilver fluoride (NSF) in the remineralization process of dental enamel using optical coherence tomography (OCT).	Nano-silver fluoride	Caries lesions were induced in all samples by a pH cycling demineralization process for 14 days. Samples were randomly distributed into three groups: NSF, sodium fluoride (NaF) and negative control. OCT images were acquired at three different times: initial state (T0), post caries formation (T1) and post pH cycling (T2).	Nano-silver-fluoride (NSF) was shown to be as effective as sodium fluoride (NaF) in remineralizing tooth enamel. Nanosilver fluoride showed the best effect against caries compared to conventional fluoride treatments.

(*Continued*)

Table 1 (Continued).

Agent Type	Author-Year/ Type of Study	Objective	Cariostatic Agent	Parameters Evaluated	Main Findings
FLUORINATED COMPOUNDS	Ahmed et al/ 2019[23] (An in vitro study)	To analyze the antibacterial efficacy of nanosilver, chitosan and fluoride as ingredients in toothpastes against Streptococcus mutans strains and compare them with each other.	Nanosilver & Chitosan	Streptococcus mutans strain (MTCC 890) obtained from the Institute of Microbial Technology, Chandigarh, India was used. Three types of toothpastes were tested with nanosilver (Group 1), chitosan (Group 2) and fluoride (Group 3). Well diffusion method was used to determine the antimicrobial activity of the toothpastes. Saline solution was used as a control.	Toothpaste with nanosilver showed the highest antibacterial efficacy, followed by toothpastes with fluoride and chitosan.
FLUORINATED COMPOUNDS	Espíndola-Castro et al/ 2020[17] (An in vitro study)	To evaluate the dentin staining potential caused by nano-silver fluoride (NSF) in comparison with other cariostatic agents.	Nano-silver fluoride	Seventy-five human permanent molars extracted for therapeutic reasons were used, excluding teeth with caries, restorations or fractures. They were randomly assigned to five groups to apply different cariostatic agents according to the manufacturer's recommendations. Dentin color measurements were performed at three time points: at baseline, after two weeks and after four weeks, using a digital spectrophotometer.	The new nano-silver fluoride formulations (NSF 600 and 1500 ppm) resulted in the least color change ($\Delta E=1.02$ and 1.53) and dentin staining after four weeks ($\Delta L=-0.76$ and -1.2).
FLUORINATED COMPOUNDS	Sulyanto et al/ 2021[24] (An in vitro study)	To understand the mechanism of action of silver diamine fluoride (SDF) in the treatment of dental caries,	Silver diamine fluoride	Carious primary teeth were collected from patients at Boston Children's Hospital. Patients aged 3 to 10 years with carious lesions cavitated in primary teeth that were asymptomatic or showed signs of reversible pulpitis. Micro X-ray computed tomography (μXCT) was used to analyze the mineral density of the specimens.	SDF treatment of caries-affected primary teeth promotes pathological biomineralization by altering their physicochemical properties, occluding dentinal tubules and increasing the ume of tertiary dentin. These effects collectively contribute to the cariostatic activity of SDF.
FLUORINATED COMPOUNDS	Ammar et al/ 2022[25] (RCT)	To evaluate the antibacterial efficacy and impact on caries activity of two treatments, nanosilver fluoride (NSF) and silver diamine fluoride (SDF), in dental caries of primary teeth.	Silver diamine fluoride and Nanosilver fluoride	Fifty children aged 4 to 6 years with dentin caries (active caries corresponding to ICDAS code 5) in deciduous teeth were randomly assigned to treatment with NSF or SDF. Baseline assessment of *Streptococcus mutans* and lactobacilli counts as CFU/mL in caries lesions was performed, followed by application of the agents.	At the one-month follow-up appointment, both groups showed a significant decrease in baseline bacterial counts. There was significant difference in the reduction of *Streptococcus mutans* between NSF and SDF (21.3% and 10.5%, respectively, $p = 0.002$), while not in lactobacilli (13.9% and 6.0%, respectively, $p = 0.094$). In both groups, there was a significant reduction in the number of active caries from baseline.
FLUORINATED COMPOUNDS	Salem et al/ 2022[26] (RCT)	To increase the success rate of Hall's technique on carious primary molars by eradicating bacteria present in carious lesions using SDF (silver diamine	Silver diamine fluoride	A total of 159 children aged 4 to 8 years were randomly divided into three equal groups: Group I, application of the Hall technique; Group II, SDF with Hall technique; Group III, diode laser with Hall technique. The children were withdrawn at regular intervals for one year.	The use of SDF (silver diamine fluoride) or diode laser in combination with Hall's technique improved success rates in the treatment of caries in primary teeth.

(*Continued*)

Table 1 (Continued).

Agent Type	Author-Year/ Type of Study	Objective	Cariostatic Agent	Parameters Evaluated	Main Findings
PHYTOCHEMICALS	Tao et al/ 2013[27] (RCT)	To determine the cariostatic potential of a chewing gum containing tea polyphenol.	Tea Polyphenol	A total of 157 schoolchildren aged 8–9 years were randomly assigned into three groups. Two groups received gum with or without tea polyphenol. A third group did not receive gum. A single examiner assessed the caries status of all participants at baseline, 12 months and 24 months.	The mean increase in CPOD was 0.17 for the polyphenolic gum group, 0.60 for the control gum group, and 1.15 for the no gum group. Children who chewed gum containing tea polyphenols had a significantly lower mean increase in DMFS over the 24-month period than the other two groups ($p < 0.05$). The caries-free rate in the polyphenolic gum group was significantly higher than that of the other two groups ($p < 0.05$) after two years.
PHYTOCHEMICALS	Philip et al/ 2019[28] (An in vivo study)	To investigate the effect of cranberry extracts on saliva-derived polymicrobial biofilms.	Cranberry	Polymicrobial biofilms derived from saliva were taken were cultured for 96 h in a cariogenic environment and treated for 2 min every 12 h throughout the biofilm growth period with 500 µg/mL of cranberry extract or vehicle control. was evaluated with a quantitative real-time microarray PCR method.	Cranberry extracts affected significantly lower relative abundance of caries-associated *Streptococcus sobrinus* (fold change 0.004, P = 0.002) and *Prevotella denticola* (0.002, P < 0.001), and significantly higher relative abundance of health-associated *Streptococcus sanguinis* (fold change 90.715, P = 0.001).
PHYTOCHEMICALS	Chan et al/ 2020[29] (An in vitro study)	To investigate the preventive and therapeutic efficacy of sugar alcohols, xylitol and sorbitol, against *Streptococcus mutans* and *Candida albicans* biofilm formation.	Xylitol and sorbitol	Biofilm formation of individual and mixed species was evaluated in medium with different concentrations of xylitol, sorbitol with or without sucrose supplementation. Biofilm quantification methods such as crystal violet assay, XTT assay, CFU counting complemented with confocal and electron microscopy techniques were used.	In the absence of sucrose, xylitol and sorbitol significantly inhibit *Streptococcus mutans* biofilms. The presence of 1% sucrose reduces the efficacy of xylitol and sorbitol against both biofilms.
PHYTOCHEMICALS	Goyal et al/ 2020[14] (An in vitro study)	To investigate the effect of gallic acid, a natural polyphenol, in inhibiting the cariogenic activities of *Streptococcus mutans*.	Gallic acid	A strain of *Streptococcus mutans* was used and tests were performed to measure glucosyltransferase activity, minimum inhibitory concentration (MIC), adhesion to smooth surfaces, cell surface hydrophobicity and biofilm formation.	Gallic acid inhibited glycosyltransferase enzyme activity in *Streptococcus mutans*, crucial for sucrose metabolism, by 27–36%.
PHYTOCHEMICALS	Alshahrani et al/ 2020[30] (An in vitro study)	To investigate the effects of aqueous cinnamon extract on the inhibition of nicotine-induced *Streptococcus mutans* biofilm formation.	Cinnamon	A 24-h culture of Streptococcus mutansUA159 on microtiter plates was treated with varying concentrations of nicotine (0–32 mg/mL) in tryptic soy broth supplemented with 1% sucrose (TSBS) with or without a standardized concentration (2.5 mg/mL) of cinnamon water extract.	The presence of 2.5 mg/mL cinnamon water extract inhibits nicotine-induced Streptococcus mutans biofilm formation from 34 to 98% at different nicotine concentrations (0–32 mg/mL).
PHYTOCHEMICALS	Mala et al/ 2021[31] (An in vitro study)	To evaluate the effect of aqueous cinnamon extract on *Streptococcus mutans* biofilms exposed to nicotine.	Cinnamon	Different concentrations of nicotine (0–32 mg/mL) were used to treat microtiter plates with *Streptococcus mutans* culture. Cinnamon water extract (2.5 mg/mL) or no treatment was applied to the plates. For analysis, a spectrophotometer was used to analyze planktonic growth, total absorbance of growth and biofilm formation.	About 2.5 mg/mL cinnamon water significantly inhibits *Streptococcus mutans* biofilm (nicotine-induced) at various nicotine levels (0–32 mg/mL).

(*Continued*)

Table 1 (Continued).

Agent Type	Author-Year/ Type of Study	Objective	Cariostatic Agent	Parameters Evaluated	Main Findings
PHYTOCHEMICALS	Passos et al/ 2021[32] (An in vitro study)	To evaluate the antimicrobial and anti-adherent activities of ethanolic extract, fractions and isolated compounds (gallic acid and ethyl gallate) from the fruit and seed of *Libidibia ferrea* against Streptococcus mutans.	Gallic acid and ethyl gallate	Biofilm formation inhibition, pH drop and proton permeability tests were performed with EELF, GA and EG, and the expression of GTF genes in biofilms was also evaluated. Compounds in the dichloromethane fraction were identified by GC-MS.	Ethanolic extract, gallic acid and ethyl gallate showed antimicrobial and antibiofilm activities, reduced the acidogenicity and aciduricity of *Streptococcus mutans*.
OTHER COMPOUNDS	Pukallus et al/ 2013.[33] (RCT)	To compare the effectiveness of 0.12% chlorhexidine gel and low-dose fluoride toothpaste in preventing early childhood caries (ECC) in a group of children.	Chlorhexidine	Participants were randomly assigned to receive (i) twice daily toothbrushing with toothpaste and once daily 0.12% CHX gel (n = 110) or (ii) twice daily toothbrushing with toothpaste alone (study controls) (n = 89).	At 24 months, the prevalence of caries was 5% (3/61) in CHX and 7% (4/58) in controls (P = 0.7).
OTHER COMPOUNDS	Lipták et al/ 2016.[34] (RCT)	To evaluate the effect: of a new chlorhexidine-fluoride varnish on streptococcus mutans counts.	chlorhexidine	The study group: 57 healthy school children (aged 7–14 years) who unteered after informed consent. A double-blind, split-mouth design was employed and 87 pairs of non-cavitated permanent molars were randomly assigned to treatment with chlorhexidine-fluoride varnish (CHX-F) or chlorhexidine-thymol varnish (CHX-T, Cervitec Plus) as an active control. The varnishes were applied topically at baseline and every six weeks during the 24-week study period.	At baseline, > 50% of occlusal fissures harbored high SM counts (≥ 105 CFU), but a significant decrease (P <0.05) was found after treatment with both varnishes. After 24 weeks, less than 5% exhibited high counts. There were no significant differences between varnishes at any time point.
OTHER COMPOUNDS	Rodriguez et al/ 2018[35] (An in vitro study)	To evaluate the ability of silver-containing bioactive glasses incorporated in toothpaste to reduce the incidence of dental caries.	Bioactive Glasses silver	Three types of glasses were created using the melt quenching technique. The amount of silver oxide (Ag_2O) in the mixtures was varied. The glasses were ground, sieved and characterized. Tests such as particle size analysis, X-ray diffraction and differential scanning calorimetry were performed. Bacterial strains were isolated from the oral cavity and exposed to the glasses to measure inhibition zones.	The Si-05 glass demonstrated better antibacterial performance compared to the other glasses, effectively inhibiting the growth of oral bacterial strains.

Abbreviation: RCT, A randomized controlled clinical trial.

a single appointment and leaving it to act for a few days, thus obtaining a blackish discoloration of the carious dentin. The SDF has two uses: as a caries detector and a caries counteractant, thus avoiding excessive tissue removal.[39]

An article published by Sulyanto RA, et al,[36] described the property of SDF to be a biomineralizer, the study described the application of SDF in *vivo* tests prior to planned extraction, in a total of 11 teeth that were segmented into groups as follows: patients without SDF, with an application of SDF once 2 minutes prior to extraction, application of SDF once three weeks prior to extraction, and application of SDF five times in a period of 2 years prior to planned extraction. The result showed that the teeth treated with SDF had an increase in mineral density in areas close to the lesion. Elements such as calcium, phosphorus and silver were also present. In addition, there was a correlation between the increased concentration of silver particles with greater mineralization in the external margins of the carious lesion in those teeth where the SDF was applied two minutes before, while there was greater mineralization in the subsurface area in those teeth treated with the product for weeks.[36]

Salem G.[26,] evaluated the efficacy of the Hall technique in conjunction with the application of SDF for the treatment of carious lesions in pediatric patients. The methodology of the study consisted of dividing patients aged 4 to 8 years into three equal groups; the first group underwent treatment with the Hall technique alone, the second group started treatment with the Hall technique in conjunction with SDF, and the third group underwent treatment with diode laser and the Hall technique. The results showed that the clinical efficacy rate of group two (96.2%) was superior to the others (group I 88.7% and group III 94.3%). The argumentation of the result was that the Hall technique cuts the nutrition of the bacteria that produce caries when the crown is sealed, however, these bacteria may have a nutritional supply of pulp fluid in the dentinal tubules, and this is where the initial application of SDF is used for the disinfection of carious lesions, producing with its cariostatic effect.[26]

A systematic review published by Zaffarano L, et al [40] analyzed the effect of SDF on cavitated primary molars. They found that SDF at 38% is effective in stopping cavitated lesions in primary molars with caries when applied once a year or twice a year.[40] With a similar objective, another research by Hafiz Z. et al,[41] raised the effectiveness of SDF in mixed and early dentition, compared to the common treatment, reaching the conclusion that the use of SDF proved to be more effective compared to sodium fluoride.

Fluoride Pastes

Research shows that the use of toothpastes with different fluoride concentrations has significant effects on the prevention of dental caries.[42] In the primary dentition, it has been observed that the use of a toothpaste with a concentration of 1500 ppm fluoride reduces the increase in caries compared to the use of toothpaste without fluoride. As for the permanent dentition of children and adolescents, it has been found that the use of toothpastes with fluoride concentrations between 1000 and 1250 ppm, as well as between 1450 and 1500 ppm, also decreases caries increment compared to the use of non-fluoride toothpaste.[43]

In a microbiological study, fluoride-containing toothpastes and herbal toothpaste products were compared against *Streptococcus mutans*. The results showed that fluoride-containing toothpastes demonstrated antimicrobial activity, plant-based toothpastes with fluoride did not show antimicrobial activity, of the pure fluoride solutions tested, stannous fluoride produced a growth inhibition of 24.3 mm for a 15% solution and 9.5 mm for a 2% solution, demonstrating the effectiveness of fluoride in dental caries.[19]

In a systematic review published by Walsh T, et al[43] evaluated the effects of toothpastes of different fluoride concentrations on the prevention of dental caries in children, adolescents and adults. The authors concluded that the higher the concentration of fluoride in toothpaste, the more effective it is. However, the concentration of fluoride must be balanced to avoid the risk of adverse effects such as dental fluorosis.

In another study they evaluated the mixture of 1450 ppm fluoride and 1.5% arginine in toothpaste, the results showed an efficacy in reducing the CPOD index (decayed, lost and filled in the permanent dentition) by 21% and CPOS (permanent decayed, lost and filled surfaces) by 19.6%, compared to the control toothpaste containing 1450 ppm fluoride. The results showed that the use of the fluoride and arginine mixture in the toothpaste-controlled cavity formation in populations with low to moderate caries risk. Regarding the reduction of carious process breakthroughs, the inactivity of the lesions was evaluated after 12 weeks of treatment. It was found that 14% of lesions were inactive after the use of toothpastes containing 1.5% arginine and 1450 ppm fluoride. Inactivation of carious lesions was observed more in enamel lesions than in dentin lesions.[44]

Nanosilver Fluoride (NSF)

The use of SDF has gained great popularity in recent years after its approval by the FDA (Food and Drug Administration) in 2014, as an effective agent to stop caries in children and adults. However, due to adverse effects such as: permanent unsightly black spot, possibility of soft tissue injury, and bad taste, patients often find its use unacceptable, especially for the treatment of anterior teeth. Therefore, modifications to this compound have been developed, such as nanosilver fluoride (NSF), which shows promising potential as a cariostatic agent with good antibacterial action and a lower tendency to cause dentin staining compared to SDF.[45,46] One such study published by Espíndola et al[24] evaluated the dentin staining potential of NSF at 600 and 1500 ppm in comparison with other cariostatic agents. The results showed that the use of these concentrations of NSF presented less dentin staining than commercial agents already available: 35% silver fluoride, 30% SDF and 38% SDF. The application of NSF could be an alternative to SDF since it does not compromise esthetics.[24]

Another study evaluated the efficacy of NSF as an agent to prevent and stop caries in children. The trial was performed on a total of 100 primary molars, both maxillary and mandibular, from a sample of 60 children aged 4 to 9 years, who were separated into an experimental group using NSF and a control group using saline solution. The teeth were diagnosed and clinically treated by a single anonymous examiner and followed up at 7 days, 5 months and 12 months by another calibrated examiner who was unaware of the type of treatment. To evaluate the caries index, ICDAS II criteria were used to determine lesion activity and caries diagnosis. The results indicated that 68% of the carious teeth showed hard dentin at 7 days; after 5 months in the NSF group, in 72.91% of the teeth showed arrested caries; and in the control group, only 34% of the teeth showed arrested caries. In the 12-month analysis in the NSF group, 65.21% of the teeth showed arrested caries, and in the control group, 28.88% of the teeth showed arrested caries. Therefore, it was concluded that NSF is a noninvasive cariostatic substance for the arrest and treatment of caries when applied directly on caries lesions in dentin.[21]

Ahmed, et al[23] developed a similar goal, they set out to examine the antibacterial efficacy of nanosilver, chitosan and fluoride in toothpastes against *Streptococcus mutans* strains and to compare their effects. In the study they administered nanosilver toothpastes to group 1, chitosan to group 2, and fluoride toothpastes to group 3. The results indicated that the nanosilver toothpaste showed the highest antibacterial efficacy against *Streptococcus mutans*, followed by the fluoride and chitosan toothpastes.

NSF and SDF were compared in terms of antibacterial effect and their action against caries, evaluated *Streptococcus mutans* and lactobacilli count as CFU/mL of carious lesions, followed by the application of cariostatic agents. After one-month, microbiological samples were collected, and lesion activity was reevaluated. Demonstrating that the short-term antibacterial efficacy of NSF was like that of SDF. In both groups there was a significant reduction in *Streptococcus mutans*, and lactobacilli counts in active dentin caries, and two-thirds of the lesions became inactive with no difference between the two interventions. This is evidence that further research is needed to substantiate the long-term efficacy of NSF and its suitability for clinical use in the treatment of caries.[47]

In a study, they compared the antibacterial effect between NSF and SDF, and how they act in the process against dental caries in deciduous teeth. Evaluating the count of *Streptococcus mutans* and lactobacilli as CFU/mL in carious lesions, followed by the application of the agents. After one-month, microbiological samples were collected, and lesion activity was reevaluated. Demonstrating that the short-term antibacterial efficacy of NSF was like that of SDF. In both groups there was a significant reduction in *Streptococcus mutans*, and lactobacilli counts in active dentin caries, and two-thirds of lesions became inactive with no difference between the two interventions. Further research is needed to substantiate the long-term efficacy of NSF and its suitability for clinical use in the treatment of caries.[25]

Another study published by Vieira Costa E Silva et al[20] tested the remineralizing action of PNF on incipient enamel caries and its action on acid production and *Streptococcus mutans* adhesion. To achieve this, they treated enamel fragments with sodium fluoride (NaF), NSF and deionized water. They performed microhardness imaging, fluorescence spectroscopy and optical coherence tomography on each sample before chemical caries induction, after caries induction and after 14 days of pH cycling. Treated enamel fragments were also placed in test tubes containing bacterial suspension and saliva. pH readings and quantification of microorganisms attached to the tooth enamel were determined. Based on the results, it was shown that NSF may be more effective than conventional fluorides in the treatment of incipient caries lesions due to its remineralizing and antibacterial effect.[20]

They have also evaluated the impact of NSF on tooth enamel remineralization using optical coherence tomography. Samples were subjected to a pH demineralization cycle for two weeks and divided into three groups: one with nanosilver fluoride, one with sodium fluoride and a control group. Optical coherence tomography images were taken at three stages: initial, after caries formation and after the pH cycle. Enamel surface integrity was observed, and tissue ume loss was measured after pH cycling. After analyzing the data, they found differences in light propagation between the samples. At the stage after caries formation, the dentin-enamel junction could not be visualized, possibly due to increased light scattering in demineralized enamel. The nanosilver fluoride and sodium fluoride groups showed similar behaviors, while the control group presented a lower extinction coefficient. Therefore, NSF proved to be more effective against caries compared to conventional fluoride treatments.[22]

On the other hand, in a systematic review they analyzed the clinical applications and the antimicrobial potential of silver-containing formulations in the arrest of dentin caries. The results showed that in *vivo*, there is contradictory evidence of the antimicrobial efficacy of SDF on a wide range of microbial taxa present in the decayed dentin of primary and permanent teeth. In addition, there is insufficient evidence on the application of AgNP fluoride (silver nanoparticles) as an effective microbicide against cariogens in dentin lesions. In the in vitro assay, good evidence was found for the microbicidal efficacy of silver diamine fluoride on cariogenic microorganisms. Also, good in vitro evidence of silver nanoparticles (AgNPs) as a useful microbicide against adhesion, growth and subsequent biofilm formation of *Streptococcus mutans* was observed. Concluding that the in vitro evidence positions this compound as a potential antimicrobial against the predominant cariogenic flora, particularly of dentin lesions. However, it should be mentioned that post-treatment clinical data are scarce. NSF has promising anticariogenic properties, but has limitations such as gingival irritation, metallic taste and stability problems. Factors such as exposure to light, temperature variations and prolonged storage can degrade the solution and reduce its effectiveness. Proper storage and handling are essential to maintain its stability and effectiveness.[48]

Chlorhexidine Modified with Fluoride

Chlorhexidine, a potent broad-spectrum antimicrobial, has found multiple applications in restorative dentistry. Its ability to kill a wide variety of microorganisms, including bacteria, fungi and some viruses, makes it a valuable ally in preventing infections and promoting oral health. In addition to its antimicrobial action, chlorhexidine has been shown to improve the adhesion of restorative materials to the tooth by inhibiting metalloproteinases, enzymes that degrade the bond between the two. Its versatility is enhanced by the availability of different formulations, which allows its use to be adapted to various clinical situations.[49]

In a study, they tested a new chlorhexidine-fluoride varnish on *Streptococcus mutans* levels and laser fluorescence (LF) readings in permanent molar fissures. The study was conducted with 57 healthy schoolchildren aged 7 to 14 years and randomly assigned to two treatment groups: one with chlorhexidine-fluoride varnish (CHX-F) and one with chlorhexidine-thymol varnish (CHX-T). The varnishes were applied at baseline and every six weeks for 24 weeks. They regularly evaluated *Streptococcus mutans* levels and laser fluorescence readings. The results showed that both varnishes significantly reduced *Streptococcus mutans* levels after four applications over 24 weeks, with a decrease in high counts at baseline. Laser fluorescence readings also decreased in both groups compared to baseline. In conclusion, there was no significant difference between the two varnishes in the suppression of *Streptococcus mutans*, and both showed a reduction in laser fluorescence readings. However, longer-term studies are needed to confirm their preventive effect on dental caries, mentioning that no adverse effects were reported.[34]

Fluoride-Free Agents

Chlorhexidine and Associates

Research in the relentless search for anticariogenic agents that prevent dental caries led researchers to evaluate fluoride-free substances as a method to control caries and promote tissue remineralization. Among these fluoride-free agents we find compounds such as: Chlorhexidine, xylitol, and casein phosphopeptide phosphate.[50,51]

Pukallus M, et al[33] compared the efficacy of 0.12% chlorhexidine gel and 30.4% fluoride toothpaste in the prevention of caries in children during early childhood from birth to 24 months. The study participants were randomly assigned into two groups: one group that performed tooth brushing twice daily with toothpaste and once daily with chlorhexidine gel and the other control group that only brushed twice daily with toothpaste. The primary outcome measured was the incidence of caries, and the secondary outcome was the percentage of children with *Streptococcus mutans*. At 24 months, the prevalence of caries was found to be 5% in the group using chlorhexidine gel and 7% in the control group. No significant differences were observed between the groups in the percentage of children with *Streptococcus mutans*, which was 54% in the chlorhexidine gel group and 53% in the control group. In addition, only 20% of the participants applied the chlorhexidine gel once a day, and 80% used it less than once a day. The results of the study indicated that toothbrushing with fluoride toothpaste, either with or without the application of 0.12% chlorhexidine gel, reduced the incidence of caries in early childhood children from 23% to 5–7%. However, no significant differences were observed in the prevalence of caries or in the percentage of children with *Streptococcus mutans*. between the two groups. It is suggested that the lack of effect of chlorhexidine could be due to low compliance in its application by the participants.[33]

An in vivo study compared the effect of two compounds, 1% chlorhexidine varnish plus 1% thymol, and a 5% sodium fluoride varnish on *Streptococcus mutans* counts in the dental plaque of children. The varnishes were applied to the pits and fissures of permanent mandibular first molars. The results showed a significant reduction in counts with chlorhexidine varnish after 1 and 3 months. However, fluoride varnish did not show a significant reduction.[18]

A systematic review collected the current state of evidence on the antiplaque, antigingivitis and cariostatic properties of mouthwashes based on systematic reviews from the last six years. The following results were found: 129 studies evaluated mouth rinses with different active agents, such as chlorhexidine, essential oils, cetylpyridinium chloride, delmopinol and fluoride. Mouthrinses with chlorhexidine and essential oils showed strong evidence of efficacy as antiplaque and anti-gingivitis agents, with significant reductions in plaque and gingivitis indices. Fluoride mouthrinses showed a cariostatic effect, especially in children and adolescents, but the quality of evidence was low. Mouthrinses with cetylpyridinium chloride, delmopinol, and amine/tin fluoride had minor or nonsignificant effects on plaque and gingivitis prevention.[52]

Similarly, a systematic review proposed as the objective of the study to evaluate the effects of oral formulations containing chlorhexidine, such as toothpastes, mouthwashes, varnishes, gels, chewing gums and sprays, in the prevention of dental caries in children and adolescents. They included in the study eight trials that evaluated chlorhexidine varnishes and gels on primary or permanent teeth in children. The results showed no clear advantage of chlorhexidine over placebo or no treatment in caries prevention. The quality of evidence was considered very low overall. The trials did not report side effects, pain, quality of life, patient satisfaction or costs. Therefore, the review concludes that the evidence from trials of chlorhexidine varnishes and gels neither supports nor refutes the effectiveness of chlorhexidine in the prevention of dental caries in children and adolescents. In addition, no trials were found on other chlorhexidine products, such as sprays, toothpastes, chewing gums or mouthwashes. It is suggested that it is. Therefore, more high-quality research is needed, especially in relation to primary and permanent dentition, as well as other oral products containing chlorhexidine.[53]

Several studies have evaluated non-fluoride agents, and among these a systematic review evaluated the use of non-fluoride agents in the prevention of dental caries in children, considering randomized controlled clinical trials in patients who received non-fluoride agents for caries control. This investigation evaluated chemical agents such as: arginine, amorphous casein phosphopeptide phosphate (CPP-ACP), chlorhexidine, triclosan, and xylitol. The xylitol was a useful adjunct for caries control in infants, chlorhexidine and CPP-ACP may be more effective than placebo in the treatment of caries in the primary dentition, but their efficacy is questionable compared to fluoride.[54]

Amorphous Casein Phosphopeptide Calcium Phosphate

It is a remineralization system composed of two phases: multiphosphorylated casein phosphopeptides (CPP) and amorphous calcium phosphate (ACP). CPP is a milk-derived protein that is part of the salivary proteins and can stabilize calcium in saliva. When CPP and ACP are mixed, it raises the levels of calcium in the plaque fluid, inhibiting demineralization and favoring remineralization of the incipient lesion by precipitation of the ions released.[50,51] The amorphous calcium phosphopeptide casein phosphate casein phosphopeptide known as (CPP-ACP) is a phosphoprotein with the ability to release calcium and phosphate ions into the oral environment that promote remineralization.[55–57]

CPP-ACP is released into saliva and dental plaque, providing calcium, phosphate and fluoride ions that inhibit demineralization and promote remineralization of tooth enamel. It can act by inhibiting bacterial adhesion, as a buffer, disrupting biofilm and as a bacteriostatic or bactericide. CPP-ACP is a natural and safe anticariogenic agent that may enhance enamel remineralization and possibly have a beneficial effect on dental plaque ecology.[58]

Several studies have evaluated the remineralizing efficacy of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) compared to other cariostatic agents, such as silver diamine fluoride (SDF). A recent clinical study assessed the effectiveness of CPP-ACP, SDF/potassium iodide (SDF/KI), and sodium fluoride with functionalized tricalcium phosphate (NaF/fTCP) in artificial enamel lesions. The results indicated that, after 30 days of treatment, SDF/KI significantly reduced the area and volume of demineralized lesions compared to CPP-ACP and NaF/fTCP, demonstrating superior remineralization potential.[59] Similarly, an in vitro study compared the remineralization efficacy of SDF, CPP-ACP, CPP-ACFP, and fluoride-containing and fluoride-free toothpastes. The findings revealed that SDF exhibited the highest remineralization capacity, followed by CPP-ACFP and CPP-ACP, suggesting that while CPP-ACP is effective, SDF may provide superior benefits for enamel remineralization.[60] A systematic review and meta-analysis investigated the remineralization potential and caries preventive efficacy of combined CPP-ACP/bioactive glass/xylitol/ozone and topical fluoride (TF) therapy versus monotherapy with topical fluoride alone. The results showed that the combination of CPP-ACP, xylitol, ozone, bioactive glass and fluoride showed a higher remineralization and caries prevention capacity compared to fluoride monotherapy. These results suggest that combination therapy may be a more effective option for caries prevention in clinical dental practice.[61] Another systematic review and meta-analysis aimed to perform a meta-evaluation of calcium-based caries preventive agents. The study showed that calcium-based caries preventive agents, such as amorphous calcium phosphate and casein phosphopeptide (CPP-ACP/CPP-ACF), demonstrated a significant reduction in caries incidence. In addition, compared to other preventive methods, such as fissure sealants and fluorides, calcium-based agents showed comparable or even superior results.[62] Although CPP-ACP has demonstrated effective remineralizing properties, some clinical limitations remain. A randomized clinical trial found no statistically significant differences between the application of CPP-ACFP paste and a placebo in the remineralization of post-orthodontic white spot lesions over a 12-week period, suggesting that its clinical efficacy still requires further validation.[63] Furthermore, evidence on its synergistic effect with fluoride continues to be studied, highlighting the need for high-quality controlled clinical trials to establish definitive recommendations for clinical practice.[64,65]

CPP-ACP is widely recognized for its ability to promote enamel remineralization and reduce dentin hypersensitivity. However, its efficacy may not surpass that of agents such as SDF in certain clinical applications. The selection of the most appropriate cariostatic agent should be based on an individualized patient assessment, considering factors such as caries risk, lesion severity, treatment adherence and cost. In this context, SDF has been established as a highly effective option, particularly for arresting active carious lesions in high-risk populations. Future research should focus on long-term clinical trials directly comparing these agents and assessing their effectiveness in different clinical scenarios. Optimizing new formulations and combining remineralizing agents may represent a promising approach to improving caries prevention and management strategies.[55–57,65]

Natural Phytochemicals

In recent years, there has been a great deal of interest in the anticariogenic properties of various natural products. These products are especially valued for their ability to inhibit cariogenic virulence properties and bacterial adhesion, without adversely affecting the oral microbiome, and can inhibit demineralization and promoting remineralization.[66] Phytochemicals have enormous potential as coadjuvant therapeutic agents in the prevention and control of cariogenic bacteria, thus contributing to the fight against dental caries.[67,68] Despite the potential of natural compounds with anticariogenic properties, their application in oral hygiene products for the control of dental caries faces several challenges. These include: the need to develop stable and effective formulations, the rigorous evaluation of possible toxic effects, the scarcity of human clinical studies confirming the efficacy of phytochemicals (most research has focused on in vitro models) and the high costs associated with the extraction and purification of these compounds.[68–72]

Among the studies that have investigated this antimicrobial activity are:

Polyphenols

Polyphenols are bioactive compounds found in plant foods and are classified into flavonoids (flavonols, flavones, flavanones, isoflavones, catechins, chalcones, and anthocyanins) and non-flavonoid molecules (phenolic acids, hydroxycinnamic acids, lignans, stilbenes, and tannins). These compounds have been the subject of increasing interest in recent years for their role in health protection, nutrition and their high antioxidant capacity, contributing significantly to the prevention of various diseases.[73,74]

Polyphenols (Blueberry)

The effects of the polyphenolic components of blueberry (*Vaccinium macrocarpon*) act on oral bacteria, especially the A-type proanthocyanidins and flavonols, inhibit the acidogenicity, aciduricity, glucan synthesis and hydrophobicity of bacteria, without being bactericidal. Bioactive compounds in blueberries and anthocyanins have great potential to be developed as adjuvant agents against caries.[27] However, the cariostatic effects of blueberry have been demonstrated mainly in laboratory studies and clinical trials are needed to evaluate the proposed cariostatic effects.[28]

Polyphenols (Cranberry)

Cranberry extracts were evaluated with saliva-derived polymicrobial biofilms in terms of: Biofilm biomass, acidogenicity, exopolysaccharide (VEP)/microbial umes, colony forming units (CFU) and the relative abundance of specific bacteria associated with caries. For the study, saliva-derived polymicrobial biofilms were cultured for 96 hours in a cariogenic environment and treated for 2 minutes every 12 hours throughout the biofilm growth period with the 500 μg/mL cranberry extract. Results indicated that the cranberry-treated biofilms showed significant decreases in biomass (38% reduction), acidogenicity (44% reduction), VEP/microbial ume ratios, and CFU counts (51% reduction). In addition, cranberry extracts produced significantly lower relative abundance of caries-associated *Streptococcus sobrinus* and *Prevotella denticola*, and significantly higher relative abundance of good health-associated *Streptococcus sanguinis. Thus, cranberry extract reduced biofilm biomass, acidogenicity*, VEP/microbial umes, CFU counts, and modulated a beneficial microbial ecological shift in saliva-derived polymicrobial biofilms.[75]

Others Polyphenols (Grape, Cherry)

A systematic review published by Garcia N, et al[76] synthesized information from the literature to discover if there is any inhibitory effect of grape seed, cranberry and sour cherry on dental biofilm, and any anticariogenic effect. The results showed that only three types of berries had a reported anticariogenic effect: grape seed extract, cranberry and tart cherry. Grape seed extract was associated with increased remineralization of tooth enamel and dentin. Cranberry extracts positively influenced cariogenic dental biofilm by decreasing biofilm biomass and bio ume and increasing biofilm pH. Grape seed extract and cranberries or their active compounds could represent an alternative for the management of caries.[76] A systematic review was conducted on the effects of grape seed and cranberry extracts on *Streptococcus mutans* activity. The results obtained indicate that these extracts, rich in proanthocyanidins, exert an inhibitory effect on the growth of this bacterium and the formation of biofilms, also reducing the expression of virulence factors such as glycosyltransferases. These findings suggest that flavonoids present in these foods could be a promising strategy to prevent bacterial colonization and, consequently, decrease the risk of developing dental caries.[27]

Polyphenols (Tea)

Green, black, and oolong tea polyphenols have demonstrated cariostatic actions by inhibiting the bacteria and biochemical processes that drive caries. Different tea varieties provide distinct polyphenolic profiles: green tea (unfermented) is rich in catechins such as epigallocatechin-3-gallate (EGCG), epicatechin gallate (ECG), epigallocatechin (EGC), and epicatechin (EC). Black tea (fully fermented) contains polyphenolic oxidation products like theaflavins and thearubigins, derived from catechins, which have their own biological activities. Key compounds like EGCG (from green tea) and theaflavins (from black tea) can hinder bacterial growth, biofilm formation, and acid production, thereby potentially slowing the progression of existing carious lesions.[30–32,77–79] Clinical trials support that tea polyphenols significantly reduce cariogenic organisms in vivo and can be an effective adjunct to oral hygiene for caries-prone individuals.[30,79,80] A clinical trial examined the impact of a chewing gum enriched with tea polyphenols on the prevention of dental caries. The study focused on evaluating the ability of this gum to prevent tooth decay compared to a gum that did not contain tea polyphenols and a group that did not chew gum. The results revealed that the children who chewed the gum with tea polyphenols experienced a decrease in caries count over the 24-month period compared to the other two groups. The caries-free rate in the group that chewed the gum with polyphenols was significantly higher than in the other two groups after two years. These results suggest that oral use of tea polyphenols may have an inhibitory effect on dental caries. Tea polyphenols may possess caries-preventive properties as well as anti-inflammatory, antioxidant and antimicrobial effects.[81] However, these natural agents are not without limitations – issues like tooth staining, taste, and somewhat lower efficacy compared to gold-standard treatments must be considered. With their low toxicity and multifaceted oral health benefits, tea polyphenols hold promise as a natural means to help inhibit caries progression, especially in patients seeking alternatives or supplements to conventional antimicrobial rinses.[31]

Cinnamon Extract

Cinnamon (Cinnamomum spp). is a natural source of bioactive compounds with antimicrobial properties, most notably cinnamaldehyde and eugenol. These compounds have demonstrated activity against oral pathogens, including Streptococcus mutans, Lactobacillus casei, Candida albicans, Enterococcus faecalis, and Porphyromonas gingivalis. In vitro studies indicate that cinnamon essential oil (EO) and extracts can significantly reduce bacterial and fungal biofilm formation, with particular interest in the prevention of dental caries, periodontal disease, and the treatment of endodontic infections and oral candidiasis. Cinnamon EO has demonstrated bactericidal activity comparable to conventional agents such as chlorhexidine and sodium hypochlorite, suggesting its potential as an endodontic irrigant or additive in mouthwashes and toothpastes. Furthermore, its inhibitory action on Solobacterium moorei suggests applications in the control of halitosis. However, the variability in the composition of the extracts and the potential hypersensitivity to certain compounds require additional clinical studies to confirm its safety and efficacy in the dental context.[82–84]

The cariostatic effects of cinnamon aqueous extract were evaluated by an in vitro study on nicotine-induced *Streptococcus mutans* biofilm formation, a spectrophotometer was used to determine the absorbance of total growth and planktonic growth. The results showed that nicotine-induced *Streptococcus mutans* biofilm formation is reduced from 34 to 98% in the presence of 2.5 mg/mL aqueous cinnamon extract. This provides further evidence for the biofilm inhibitory properties of aqueous cinnamon extract and reconfirms the deleterious effects of nicotine.[82] Another article aimed to evaluate the use of cinnamon aqueous extract on *Streptococcus mutans* biofilms exposed to nicotine. For this, *Streptococcus mutans* was cultured in microtitre plates with different concentrations of nicotine and treated with cinnamon aqueous extract or without treatment. Planktonic growth, total growth absorbance and biofilm formation were measured with a spectrophotometer. Cinnamon aqueous extract significantly inhibited *Streptococcus mutans* biofilm at various nicotine concentrations, especially at 8, 16 and 32 mg/mL. It also reduced the total and planktonic growth of *Streptococcus mutans*, thus, the aqueous extract of cinnamon has a powerful inhibitory effect on the growth of *Streptococcus* mutans.[83]

Emerging clinical studies suggest that cinnamon based formulations may have cariostatic effects in vivo, particularly in inhibiting *Streptococcus mutans*. Various formulations have been evaluated, however, most available studies are in vitro or short-term, limiting the extrapolation of results to the real-life oral environment, where factors such as saliva composition and biofilm complexity can influence treatment efficacy.[29,84–88] Cinnamon-based agents represent a promising alternative for caries prevention and oral biofilm reduction, especially for patient's intolerant to chlorhexidine. However, further clinical studies are required to determine their long-term efficacy, optimize their formulation, and establish protocols for their use in dentistry.

Gallic Acid

Gallic acid, also called 3,4,5-trihydroxybenzoic acid, is a natural secondary metabolite found in various fruits, plants and nuts.[89] The effect of gallic acid was evaluated on *Streptococcus mutans* by parameters such as glucosyltransferase activity, growth, adhesion, hydrophobicity, biofilm formation and acid production. The results of the study showed that gallic acid inhibited the activity of glucosyltransferase, a key enzyme in sucrose metabolism by *Streptococcus mutans*, by 27–36%. Gallic acid inhibited *Streptococcus mutans* growth by 50% and reduced biofilm formation by 40%, hydrophobicity by 60% and acid production by 36% by *Streptococcus mutans* under in vitro culture conditions. Fluorescence microscopy revealed that in the absence of gallic acid the cells were present as aggregates, whereas in the presence of gallic acid they were well segregated due to inhibition of biofilm formation. Therefore, the present findings suggest that gallic acid has cariostatic activity against *Streptococcus mutans*, which may have a potential application in the prevention of dental caries.[14]

Libidibia ferrea, also known as “Pau Ferro” or “Jucá”, is a leguminous plant native to northern and northeastern Brazil. It is used in traditional medicine as an antifungal, antimicrobial and anti-inflammatory. In the Amazon region, it is used as an antimicrobial mouthwash and to heal oral wounds. The objectives were to evaluate the effect of Libidibia ferrea extracts and their components (ethyl gallate and gallic acid) on the formation, adhesion and viability of *Streptococcus mutans* biofilms. For this, different concentrations of the extracts and components were used to treat *Streptococcus* mutans biofilms for 1, 3 and 5 days. Biomass, metabolic activity, expression of genes related to biofilm formation and acid production, and the composition of the extracellular matrix of the biofilms were measured. The results evidenced that gallic acid was shown to have a significant effect on the reduction of biomass, metabolic activity, gene expression and acid production of *Streptococcus mutans* biofilms. It was also observed to alter the composition of the extracellular matrix, decreasing polysaccharide and protein levels. These results suggest that gallic acid may have potential for preventing or treating dental caries by inhibiting the growth and activity of *Streptococcus mutans* biofilms.[90]

Phytic Acid

Phytic acid, also known as inositol hexaphosphate or IP6, is a natural antioxidant that regulates metabolic processes in many plants. Found in some cereals, oilseeds, nuts, legumes and tubers, it is often extracted with aqueous acids.[91] The properties and possible applications of phytic acid (IP6) in dentistry were studied showing that it can be useful as a cariostatic, anti-plaque, anti-calculus, cementing, and remineralizing agent. Phytic acid can inhibit plaque formation and enamel dissolution by forming a mono-molecular layer on the hydroxyapatite surface. It can also interact with starch, proteins and salivary enzymes, affecting carbohydrate metabolism and bacterial adhesion. Several oral care products containing phytic acid have been developed to take advantage of its cariostatic, anti-plaque and anti-calcifying effects.[92]

In an experimental study, Parkinson et al[93] investigated the synergistic effect of fluoride and IP6 on the remineralization of tooth enamel. When comparing different concentrations of IP6, the authors found no evidence that this compound, nor zinc, potentiated or diminished the action of fluoride in the prevention of caries under the conditions of the model used.[93]

In a study by Creeth et al[94] the effect of a toothpaste with IP6 and sodium fluoride on erosive enamel lesions was evaluated. The results indicated that this dental combination could promote remineralization. However, the investigation also revealed that the incorporation of IP6 reduced the absorption of fluoride, an essential mineral for this repair process.[94]

Propolis

Propolis is a resinous substance that bees produce naturally by combining plant exu s with enzymes, wax and pollen.[95] Honeybees make propolis from plant resins that they collect and combine with their own wax and secretions. This substance, also known as “bee glue”, has been appreciated for its therapeutic properties since ancient times. Its Greek name, which means “defense of the city”, refers to its protective role in the beehive.[96] Its color can vary widely, from shades of red and green to light and dark browns. In addition, its consistency can be very diverse, ranging from solid and firm to malleable and rubbery.[97]

Propolis has several applications including the reduction of dental plaque accumulation. The use of propolis and a diet rich in polyphenols can be a useful strategy to improve oral health and prevent systemic diseases. Propolis can be used as a natural agent in dentistry and oral health, as well as a supplement and functional food. A diet rich in polyphenols can prevent cariogenic bacteria and reduce the inflammatory process.[35]

An in vitro study evaluated the efficacy of Brazilian red propolis-based mouth rinses, with and without fluoride, in the fight against bacteria and oral biofilms, as well as their potential toxicity to cells. The results obtained showed that the red propolis rinses presented antibacterial and antibiofilm activity comparable to that of chlorhexidine, a reference oral antiseptic. In addition, the addition of fluoride to red propolis did not significantly increase its efficacy.[98]

Studies show that propolis has a beneficial effect on oral health by significantly reducing the formation of plaque and gingivitis. This action is attributed to its ability to inhibit the growth of bacteria such as *Streptococcus mutans*, the main cause of these conditions. In addition, propolis decreases the diversity of oral flora, contributing to a healthier oral environment. Taken together, these findings indicate that propolis products can consistently improve oral hygiene and periodontal condition.[99–102]

Xylitol

Xylitol is a polyol that occurs in the form of white crystals and is found naturally in various plants, such as plums, strawberries, and pumpkins, and is used as a substitute for sugar.[103,104] A scientific study has shown that xylitol and sorbitol, sweeteners commonly used in oral hygiene products, can help prevent the formation of biofilms that cause cavities and oral candidiasis. These sweeteners interfere with the growth of the bacteria and fungi responsible for these infections. However, research also revealed that sugar consumption can cancel out the beneficial effects of these sweeteners. Therefore, limiting sugar consumption and using products with xylitol and sorbitol could be an effective strategy to improve oral health.[105]

A systematic review evaluated the evidence on the anticariogenic effect of xylitol compared to topical fluoride. The results suggest a possible additive effect of xylitol, but the high risk of bias in the included studies limits the generalizability of the findings. Xylitol exerts an anticariogenic effect by both passive (replacement of fermentable sugars) and active (inhibition of bacterial adherence) mechanisms. However, the current evidence does not allow us to discern the relative contribution of each of these mechanisms.[106]

The Cochrane systematic review, entitled "Xylitol products for caries prevention in children and adults", aimed to analyze the efficacy of various xylitol products compared with placebo or no treatment in the prevention of caries in children and adults. They collected data on increased dental caries, quality of life, cost, and side effects. They micro titrated and found some low-quality evidence suggesting that fluoride and xylitol toothpaste may be more effective than fluoride-only toothpaste in preventing caries in children's permanent teeth and that no adverse effects were associated with such toothpastes. The remaining evidence found is of low to very low quality and is not sufficient to determine whether any other xylitol product can prevent caries in infants, older children, or adults.[107]

Other Formulations

Iron

Iron is an essential element of several metabolic processes in humans, including DNA synthesis, electron transport and oxygen transport. Unlike other minerals, iron levels in the human body are controlled solely by absorption.[108,109]

A systematic review evaluated the existing scientific evidence on the impact of iron-based products on the prevention of dental caries. The results obtained suggest that the combination of iron and sucrose (present in many iron drops) could reduce the occurrence of caries. Additionally, it was found that iron can decrease tooth mineral loss (demineralization) and changes in tooth hardness, especially when exposed to acidic or caries-promoting foods. However, due to the wide variety of compounds and additives present in commercial iron drops, it is difficult to generalize and state with certainty that all of them have the same effect.[110]

Resin-Based Sealants

For decades, dental sealants have been used as a protective barrier against cavities that often appear in pits and fissures of the teeth. Resin dental sealants act as a physical barrier that protects the pits and fissures of the occlusal surfaces from the buildup of bacterial plaque and exposure to acids that can cause cavities.[111] Applying the sealant involves cleaning the tooth surface, followed by acid etching with phosphoric acid to create a rough surface that improves the sealant's adhesion. The liquid resin is then applied and polymerizes, forming an acid-resistant protective layer.[112]

The cariostatic effect of hydrophilic and hydrophobic resin-based sealants (SBR) was evaluated in primary and/or permanent teeth with a minimum follow-up period of 3 months. The results showed no statistically significant differences in retention and cariostatic effect between the two types of sealants, with or without bonding agent, after 3, 6 and 12 months of follow-up. Hydrophilic SBRs may be a viable alternative to hydrophobic SBRs, especially in cases where complete isolation cannot be achieved. No difference in occlusal caries prevention was found between the two types of sealants.[113]

Numerous studies and reviews confirm that sealants markedly reduce caries incidence and can arrest early lesions. At the same time, the effectiveness of resin sealants can be limited by practical factors: Retention problems remain the chief cause of sealant failure, prompting the development of hydrophilic sealants to improve success in less-than-ideal conditions – with generally encouraging but varied outcomes so far. Therefore, resin-based sealants are a proven cariostatic intervention that work through enamel bonding, biofilm inhibition, and enhanced remineralization, but achieving their full benefits requires attention to their limitations (proper placement, maintenance, and material selection for the clinical environment).[111,113–115]

Bioactive Glasses

Bioactive glasses are materials that can interact with the biological environment to elicit a specific response, such as the formation of a hydroxyapatite coating that binds to tissue.[116] Bioactive glass is a calcium phosphosilicate cement that has been shown to alleviate dental hypersensitivity by producing deposition of hydroxyapatite on the dentin surface.[117]

A study explores a series of bioactive glasses enriched with silver oxide, which are integrated into toothpastes with the aim of reducing the occurrence of caries and dental lesions. Three types of glasses, each with different proportions of silver oxide, were presented and examined in terms of particle size, structure, glass transition temperature, solubility, ion release and antibacterial properties. In addition, their ability to remineralize the dental enamel of lamb molars that had undergone an in vitro demineralization process was evaluated. The results concluded that bioactive glasses with silver oxide could be potential candi s for use as anticaries components in toothpastes, as they combine remineralization and antibacterial properties.[118]

Conclusions

This review reaffirms that fluoride-based agents remain the gold standard for caries prevention, with robust scientific evidence supporting their efficacy in inhibiting lesion formation and promoting enamel remineralization. While alternative cariostatic agents, including phytochemicals and bioactive compounds, exhibit promising properties, the current body of evidence is insufficient to warrant their replacement of fluoride-based therapies. However, some of these agents may exert a synergistic effect, enhancing fluoride's remineralizing and antimicrobial properties. The clinical effectiveness of any cariostatic strategy is contingent upon multiple factors, including application frequency, concentration, physicochemical stability, and patient-specific variables such as caries risk and oral hygiene practices. Among emerging alternatives, silver diamine fluoride remains the most widely endorsed non-invasive intervention due to its superior cariostatic and caries-arresting capabilities, underpinned by extensive clinical validation. Further high-quality, long-term clinical trials are required to substantiate the efficacy of bioactive compounds as viable adjuncts or alternatives to fluoride in caries management and prevention.

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Disclosure

The authors declare no competing interests in this work.

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