Polyphenols for Preventing Dental Erosion in Pre-clinical Studies with *in situ* Designs and Simulated Acid Attack

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ABSTRACT

Dental erosion is a chemical process characterized by acid dissolution of dental hard tissue, and its etiology is multifactorial. Dietary polyphenols can be a strategy for dental erosion management, collaborating to preserve dental tissues through resistance to biodegradation. This study describes a comprehensive review to interpret the effects of polyphenols on dental erosion of pre-clinical models with *in situ* designs and simulated acid attacks on enamel and dentin samples. We aim to evaluate evidence about Polyphenols' effects in the type of dental substrate, parameters of erosive cycling chosen in the *in situ* models, and the possible mechanisms involved. An evidence-based literature review was conducted using appropriate search strategies developed for main electronic databases (PubMed, Scopus, Web of Science, LILACS, EMBASE, LIVIVO, CINAHL, and DOSS) and gray literature (Google Scholar). The Joanna Briggs Institute checklist was used to evaluate the quality of the evidence. From a total of 1900 articles, 8 were selected for evidence synthesis, including 224 specimens treated with polyphenols and 224 control samples. Considering the studies included in this review, we could observe that polyphenols tend to promote a reduction in erosive and abrasive wear compared to control groups. However, as the few studies included have a high risk of bias with different methodologies and the estimated effect size is low, this conclusion should not be extrapolated to clinical reality.

Introduction

Erosive/tooth wear lesions represent a frequent clinical condition worldwide, with an average prevalence of 46.7 % [1]. These lesions may be even higher in older patients or patients with some risk factors [2], such as increased consumption of acidic foods and drinks, promoting erosive tooth wear [3]. Although erosive lesions are often associated with dietary habits, their multifactorial etiology raises their prevalence. Frequently, patients present an association of non-bacterial acidic attack, chewing, and brushing-induced abrasion [4].

Managing and preventing erosive/tooth wear lesions becomes very challenging for dentists. First, a detailed anamnesis is necessary to identify the causal factors of wear to eliminate or control them. In addition, treatment often becomes preventive to reduce wear progression [5]. For this, topical fluoridation is indicated. Fluorides such as amine fluoride, sodium fluoride, titanium tetrafluoride, or tin-containing fluoride products form a protective layer on dental hard tissues, mainly in enamel. Unfortunately, although there is evidence that these fluoride products reduce erosive and abrasive wear, it is essential to control the causal factors to prevent the progression of lesions [6]. However, the initial

enamel demineralization surface may be treated with topical use of remineralizing agents containing fluoride, calcium, and phosphate ions, achieving almost complete remineralization of the surface and a reorganization of the prismatic structure of the enamel [7], avoiding surface loss in the continuous demineralization-remineralization process.

One of the ongoing anti-erosion strategies investigated is dentin's biomodification with bioactive agents [8]. The investigated bioactive compounds increase or reinforce the mechanical properties of the collagen matrix. Bioactive compounds, termed collagen cross-linking agents, create covalent bonds and cross-links between collagen fibrils to maintain the demineralized organic matrix layer [8]. The collagen cross-linking agents can be synthesized or produced by nature without human intervention. Among the synthetic agents, glutaraldehyde and carbodiimide have shown promising outcomes [9, 10]. However, plants have been explored as an essential source of novel pharmacologically bioactive compounds derived directly or indirectly from plants. In addition to the improvement of properties of the collagen matrix, polyphenols interact with the acquired pellicle. Therefore, polyphenols increase acid-resistant proteins and release fewer calcium ions in the face of acid challenge, contributing more effectively to reducing dental erosion's effects clinically [5].

Natural extracts are a broad term that includes over 8000 polyphenolic compounds found in various plant species. Polyphenols are secondary metabolites of plants involved in their defense mechanism, and these compounds can result in numerous benefits for human health, including protection against the development and progression of chronic diseases such as cancer, cardiovascular disease, diabetes, and aging [11, 12]. Beyond that, these compounds can also benefit dentin, improving several characteristics such as its hardness, modulus of elasticity, tensile strength, adhesive strength, resistance to biodegradation, and reduction in demineralization [13–17]. In addition, their interaction with collagen results in highly stable bonds, hindering the degradation of dentin and increasing protection against erosion [8, 18].

Moving a drug from design to clinical trials takes 10 to 12 years on average. Based on that, the current evidence on the preventive effect of polyphenols on erosive and abrasive tooth wear heavily relies on pre-clinical studies. Unfortunately, randomized clinical trials involving erosive/tooth wear lesions are scarce and prominent for their lack of obtaining exact tooth wear measurements. Therefore, pre-clinical studies decide whether a bioactive compound is ready for clinical trials and involves extensive investigations using a vast range of bioactive compound concentrations that yield preliminary efficacy, toxicity, and safety information, mostly *in vitro* assays. Next, *in situ* investigations using intraoral devices bridge the information obtained from *in vitro* investigations using extracted teeth samples and provide relevant data that reflect what happens in the oral cavity because the samples are attached to an oral device [19]. In addition, *in situ* models offer the advantages of allowing control and isolating variables, such as erosive challenge, and permit the use of technologies to assess the target outcome: loss of tooth tissue. For these reasons, an evidence-based review is proposed on the protective effect of natural products against erosive and abrasive wear *in situ* because of the lack of published reviews on this topic and the need for studies that can synthesize and discuss the findings of the numerous articles that are published daily. Therefore, the obtained results can be relevant for increasing the knowledge of dental clinicians and also dietitians. Indeed, there is nowadays increasing attention on the development of therapeutic strategies for the prevention of tooth wear lesions. This review aimed to summarize the pre-clinical literature on the effect of different polyphenols on preventing erosive and abrasive wear in dentin and enamel.

Methods

Search strategy

The review process (registered on the International Prospective Register of Systematic Reviews, number CRD42021284869) was focused on the following strategy: P (population): enamel and dentin; I (intervention): polyphenols; C (control): water or placebo; O (outcome): reduction in erosive and/or abrasive tooth wear; T (type of study): *in situ* investigations.

PubMed, Scopus, Latin American and Caribbean Health Sciences (LILACS), EMBASE, Web of Science, LIVIVO, CINAHL, and Dentistry and Oral Sciences Source (DOSS) were searched on November 16, 2021. Furthermore, gray literature through Google Scholar was assessed to minimize selection and publication bias. In addition, a manual search was also performed through a complete analysis of the references from the eligible articles. The search strategies (**Table 1S**, Supporting Information) were developed through the advanced tool of each base using Boolean operators to enhance the search strategy through various combinations. Medical Subject Headings (MeSH), Descriptors in Health Sciences (DeCS), and Embase Subject Headings (Emtree) resources were used to select the search descriptors.

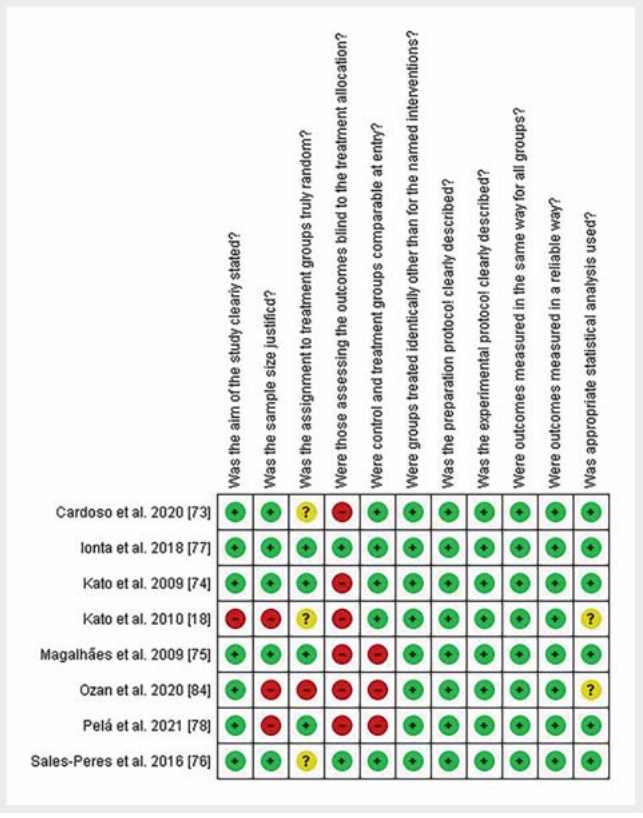
Inclusion and exclusion criteria

Selection criteria include experimental *in situ* investigations conducted with dental specimens from human or bovine origin attached to intraoral devices used by volunteers. These studies should have observed the effects of polyphenols on dental erosion and abrasion. There was no restriction on period, language, and publication status. However, the following articles were excluded: case reports, case series, observational studies, randomized controlled trials, controlled clinical trials, review articles, abstracts, interviews, editorials, or opinions.

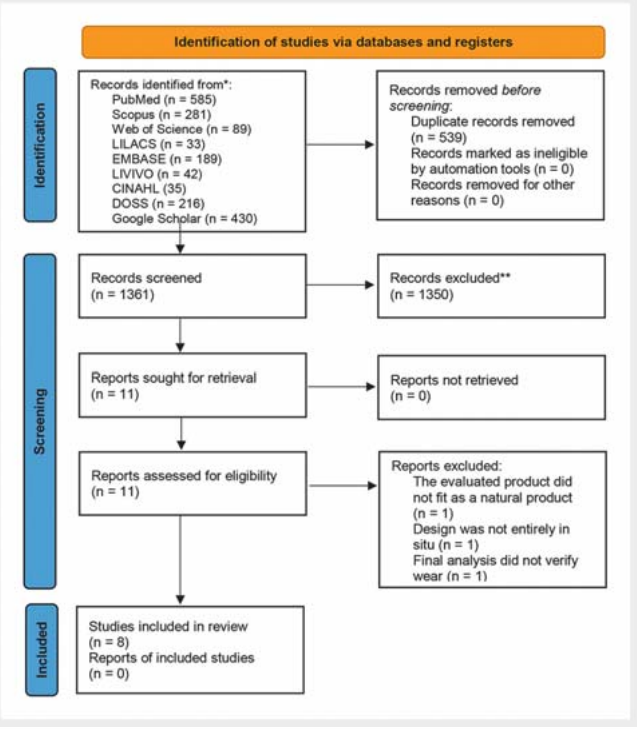
Study selection

The obtained records were exported to the app Rayyan (Rayyan Qatar Computing Research Institute, Doha, Qatar) [20], where duplicates were removed. Two researchers selected the studies independently (ICL and CSR) in two phases. Firstly, the titles and abstracts were systematically analyzed. Secondly, the preliminary eligible studies had their full texts obtained and evaluated to verify whether they fulfilled the eligibility criteria. Disagreements were resolved by two different reviewers (VFP and FWGC).

Two independent researchers (ICL and CSR) extracted data based on spreadsheets previously designed for this study. It included the following variables: title and authors of the paper, the number of participants, characteristics of erosive cycling, sample



▶ **Fig. 1** Risk of bias according to the author's judgment of each item evaluated.



▶ **Fig. 2** Flow diagram of study identification, screening, and inclusion process adapted from PRISMA.

characteristics, treatments used, methods for obtaining the results, wear values, and outcome. Two reviewers resolved disagreements with expertise in the present methodology (VFP and FWGC).

Two researchers independently (ICL and CSR) assessed each domain of the Joanna Briggs Institute Clinical Appraisal checklist for experimental studies to evaluate the potential risk of bias (RoB). Disagreements were resolved by two different reviewers (VFP and FWGC) [21]. This instrument consists of 11 items with responses corresponding to no (0) and yes (1). The sum of the items corresponds to the individual RoB of each item: was the aim of the study clearly stated? Was the sample size justified? Was the assignment to treatment groups truly random? Were those assessing the outcomes blind to the treatment allocation? Were control and treatment groups comparable at entry? Were groups treated identically other than for the named interventions? Was the preparation protocol clearly described? Was the experimental protocol clearly described? Were outcomes measured in the same way for all groups? Were outcomes measured reliably? Was appropriate statistical analysis used? (▶ **Fig. 1**)

The search strategy retrieved 1900 articles. After excluding duplicates, 1361 articles were evaluated by title and abstract to select those relevant for a full review of the article. Among these, 11 studies had their full text read to assess whether they met the inclusion criteria, as shown in the study flowchart adapted from PRISMA [22] (▶ **Fig. 2**). A total of 8 articles were selected for evidence synthesis (▶ **Table 1**), including 224 specimens treated with polyphenols and 224 control samples.

Polyphenols and treatment approaches

Polyphenols are a group of natural bioactive compounds abundant in our feeding, mainly in fruits, vegetables, and cereals [12] (▶ **Fig. 3**). As the entry point of food into the human body is the oral cavity, polyphenols play a significant role in many oral diseases and conditions [23]. Some studies demonstrate that this occurs both because of the antioxidant effect and antibacterial activities of polyphenols and their role as "processing cofactors" to improve the mechanical and functional properties of biomaterials [24–26]. The classification of polyphenols into different groups considers the number of phenol rings present and the structural elements that bind these rings to one another. Some classes are phenolic acids, flavonoids, stilbenes, and lignans [27]. Polyphenols' properties, characteristics, and effects depend on their structure and chemical versatility, as they can undergo acid-base reactions, oxidation processes, chemical reactivity, and chemical coordination [28].

Camellia sinensis

Camellia sinensis, a well-known tea plant, is native to mainland China and South and Southeast Asia but is currently cultivated worldwide, including in tropical and subtropical climates. It is a plant of the Theaceae family with flowers, thus being of the genus Camellia. It is an evergreen shrub or small tree with a strong taproot and is often kept under two meters when cultivated for its

▶ **Table 1** Characteristics of the included studies.

Study	Country	*n*	Specimen origin	Intervention	Control	Analysis methods	Financing source	Outcome (Tooth loss)
Cardoso et al. 2020 [73]	Brazil	8	Bovine dentin	PA (pH 7) PA (pH 3)	No treatment CHX	Contact profilometry	Scholarship	Reduced
Ionta et al. 2018 [77]	Brazil	16	Bovine enamel	Palm oil Palm oil + $SnCl_2$/NaF/AmF	Water $SnCl_2$/NaF/AmF	Contact profilometry	Scholarship	Reduced
Kato et al. 2009 [74]	Brazil	10	Bovine dentin	Green tea	Water	Contact profilometry	Scholarship	Reduced
Kato et al. 2010 [18]	Brazil	10	Bovine dentin	EGCG 10 µM EGCG 400 µM	Gel placebo CHX NaF	Contact profilometry	Scholarship	Reduced
Magalhães et al. 2009 [75]	Brazil	12	Bovine dentin	Green tea	Water CHX SnF/AmF	Microhardness	Scholarship	Reduced
Ozan et al. 2020 [79]	Turkey	10	Human dentin	Green tea Black tea	Water NaF CHX CHX + NaF	Contact profilometry	Scholarship	Increased
Pelá et al. 2021 [78]	Brazil	15	Bovine enamel	CaneCPI	Water $SnCl_2$/NaF/AmF	Contact profilometry	Scholarship	Reduced
Sales-Peres et al. 2016 [76]	Brazil	10	Human enamel and dentin	Euclea Natalensis	No treatment		Scholarship	Reduced

* PA= proanthocyanidin; CHX= chlorhexidine; EGCG= epigalocatequin-3-galato; CaneCPI= sugarcane cystatin

leaves, as this plant species is the raw material for many Chinese teas. The leaves are treated differently to obtain distinct oxidation levels and, thus, produce diverse teas, such as white tea, green tea, oolong, and black tea [29].

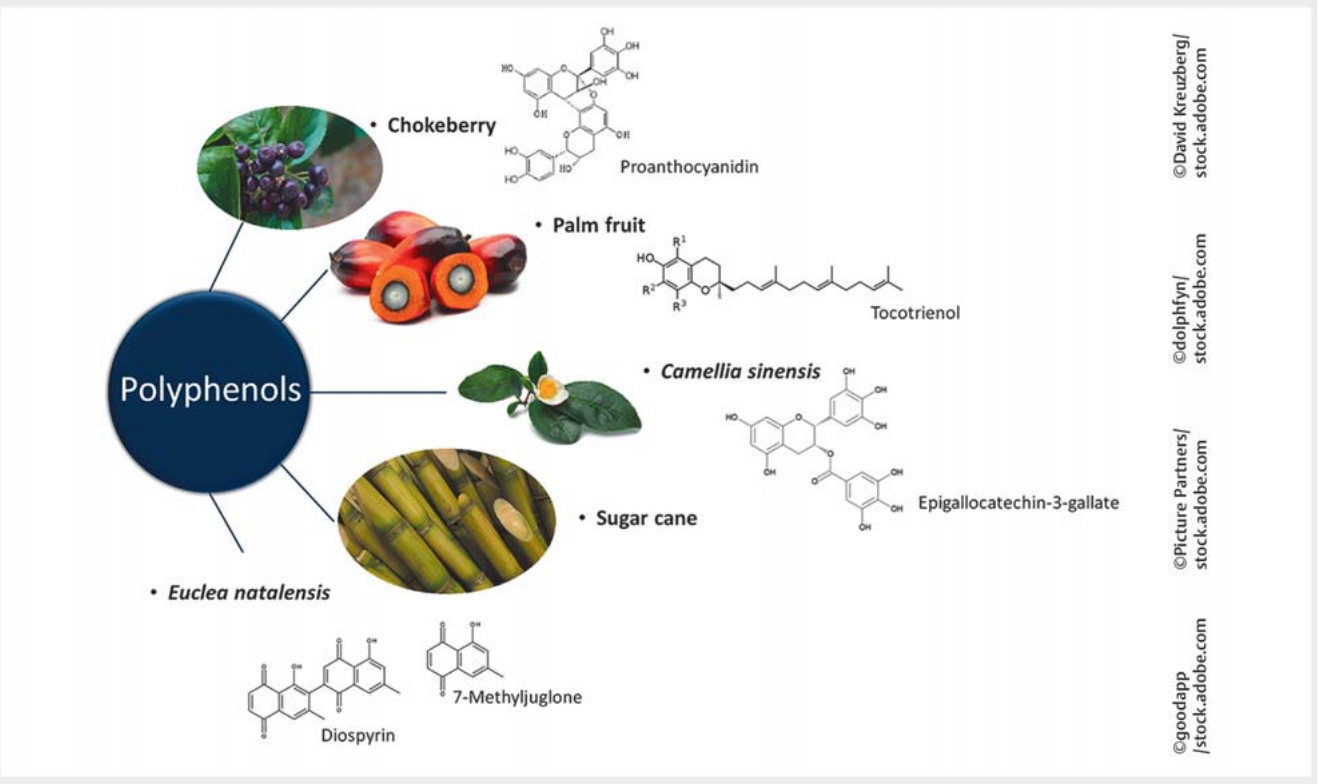
Teas from the Camellia sinensis plant contain about 4000 bioactive compounds, only a third of which are polyphenols [30]. Polyphenols are believed to be responsible for the health benefits traditionally attributed to green tea [31]. Among the polyphenols, the most active and abundant catechin in green tea is epigallocatechin-3-gallate (EGCG), but epicatechin gallate (ECG), epicatechin (EC), and epigallocatechin (EGC) are also in great abundance. Black tea contains the same catechins in lower concentrations [32], and all of them (black tea, green tea, and oolong) are sources of vitamin C.

According to a literature review with meta-analysis, consuming three or more cups of green or black tea daily brings a 21% lower risk of stroke [33]. Furthermore, the low risk of developing cardiovascular disease and stroke was associated with high consumption of green tea [34]. Previous studies in animal and cell culture models suggest that EGCG from green tea may inhibit several targets associated with the progression of Alzheimer's disease [35–37]. In addition to systemic benefits, green tea can prevent tooth caries. Camellia sinensis leaves have an abundance of fluoride, but the oral health benefits of tea are not limited to this component [38]. Polyphenols inhibit the growth of cariogenic bacteria and the adherence of these bacteria to tooth surfaces, reducing the formation of dental plaque by 30 to 43% [39–42].

Euclea natalensis

Euclea natalensis is a small to medium-sized tree common in sub-Saharan Africa from the botanical family Ebenaceae. This plant has dark green leaves and wavy edges, with small glands on the surfaces. It thrives under different conditions and habitats, growing from arid rocky shrubs to dune shrubs, open grasslands, woodlands, forests, forest margins, riverbanks, savannah, and swamps, from sea level to 1200 m. Depending on the external environment, it can become stunted and measure less than one meter in size, but under favorable conditions, it can reach about 12 and 18 m in height [43].

In safety analyses with different cell lines, it was observed that cell toxicity of Euclea natalensis is low or absent. Therefore, it is commonly used as a healing medium by some South African ethnic groups such as the Zulus, Tsongas, and Xhosas. The root is applied to the skin to treat injuries and is drunk as an infusion to cure abdominal pain and parasitic infections such as ancylostomiasis. Furthermore, an infusion is used from the shoots and bark of the plant to treat complications such as chest pain, bronchitis, and



▶ **Fig. 3** Sources of natural products.
Chokeberry: © David Kreuzberg/stock.adobe.com.
Palm fruit: © dolphfyn/stock.adobe.com.
Camellia sinensis: © Picture Partners/stock. adobe.com.
Sugar cane: © goodapp/stock.adobe.com.

asthma. Also, the powdered root is applied to reduce toothaches and headaches [43, 44].

The chemical constituents of Euclea natalensis involve some belonging to the class of naphthoquinones. Diospirin, 8-hydroxydiospirin isodiopyrin, and neodiospirin were previously isolated from roots, and compounds isolated from the plant include 7-methyljuglone, euclanone, galpinone, mamegakinone, natalenone, and shinanolone [45–48]. Therefore, extracts from various areas of the plant are produced, and all have a broad antibacterial effect. In a previous study, the water and acetone extracts of the roots of E. natalensis were analyzed, and it was observed that both extracts inhibited the growth of Staphylococcus aureus and other bacillus [49]. Also, the ethanolic shoot extract reduced the bacterial load in mice infected with Mycobacterium tuberculosis in an *in vivo* mice model [50].

Palm fruit

The palm is a monocotyledonous plant of the genus Elaeis. This genus includes Elaeis oleifera from South America and Elaeis guineensis from West Africa, the most used species in commercial plantations [51]. The fruit of the oil palm forms a compact bunch and is a drupe, which contains a single seed. The fruit wall or pericarp is divided into three layers: exocarp or shell; mesocarp, which is usually edible; and endocarp, which is the thickest part surrounding the seeds or endosperm. Palm oil is obtained from the mesocarp of the palm fruit, mainly from the African oil palm Elaeis guineensis [52]. While the mesocarp produces palm oil, which is edible and used in the food industry, the kernel produces palm kernel oil, which is widely used in the oleochemical industry.

The world's largest palm oil producers come from Southeast Asia, especially Malaysia, and Indonesia. This oil has been widely used in the food industry for over 5000 years and is the most produced edible vegetable oil worldwide. Palm oil has replaced other cooking oils as it is cleaner, more stable, and does not contain trans fats, which can contribute to clogged arteries. Thus, palm oil is included in the manufacture of margarine and is used as an ingredient in various prepared foods [53].

The constitution of palm oil can be divided into two groups. First, about 50% of the oil consists of saturated fatty acid derivatives such as partial glycerides, phosphatides, esters, and sterols. Second, its composition includes compounds chemically unrelated to fatty acids, such as hydrocarbons, aliphatic alcohols, free sterols, tocopherols, pigments, and residual metals [54]. In addition, palm oil is rich in vitamin K and dietary magnesium and is the highest natural source of tocotrienol and carotenoids. The human body uses carotenoids like vitamin A. Furthermore, carotenoids improve immune function and cardiovascular health and play a significant role as biological antioxidants. As such, no vegetable oil has such a unique natural combination of phytonutrients and antioxidants as palm oil [55].

Sugarcane

Sugarcane is a plant of the group of tall perennial grass species of the genus Saccharum, native to the tropical climate of southern Asia and Melanesia. This plant mainly produces sugar and ethanol, a renewable fuel that partially replaces petroleum derivatives. However, a limiting factor in sugarcane productivity is its susceptibility to fungal diseases, which require fungicides and pesticides that increase costs and can lead to environmental problems. The production of cysteine protease inhibitor phytocystatins contributes to the development of sugarcane fields that are more resistant to pathogens and, consequently, a reduction in the chemical products used [56].

Phytocystatins are reversible inhibitors of cysteine proteases and are naturally found in several plants, mainly in angiosperms such as rice, corn, soy, orange, and sugarcane [56–58]. Phytocystatins regulate the activity of endogenous plant proteases involved in their development beyond playing a defense role in response to exogenous peptidases of herbivorous insects, pathogens, and nematodes [57, 59]. There are currently six cystatins derived from sugarcane and produced recombinantly: CaneCPI-1, CaneCPI-2, CaneCPI-3, CaneCPI-4, CaneCPI-5, and Cane-CPI-6 [58, 59].

Recombinant canacistatin 4 (CaneCPI-4) inhibits human cathepsins B and L. Furthermore, this cystatin has shown potential for therapeutic medical applications as it significantly reduced the invasiveness of breast cancer cells, inhibited melanoma growth, and decreased *in vitro* and *in vivo* angiogenesis and tumor metastasis [60, 61]. In dental applications, studies have shown that CaneCPI-5 has strong interaction and adhesion to dental enamel, which is reflected in protection against erosive wear. Also, CaneCPI-5 interacts with the acquired pellicle, increasing acid-resistant proteins and releasing fewer calcium ions in the face of acid challenge, minimizing the effects of dental erosion [62, 63].

Proanthocyanidins

Flavonoids are a class of polyphenols, some of which can polymerize to form tannins. Tannins are secondary plant metabolites that can be hydrolyzed or condensed [64]. Among the condensed polyphenols, we have proanthocyanidins, also known as condensed tannins. Proanthocyanidins are made from the polymerization between catechin and epicatechin [65] and are present in flowers, nuts, fruits, bark, and seeds as a defense against stresses and pathogens. The best sources with a predominant content of proanthocyanidins are berry fruits, such as lingonberry, cranberry, black elderberry, black chokeberry, blackcurrant, and blueberry, with the highest content per fresh weight in chokeberries [66–68].

Proanthocyanidins can provide astringency, viscosity, flavor, aroma, and color. They can be applied as food additives to increase microbial, oxidative, and thermal stability. In addition, they have several beneficial effects on human health, such as antioxidant, antitumor, immunostimulant, antibacterial, antiviral, anticarcinogenic, anti-inflammatory, and antiallergic properties [69]. In dentistry, cranberry proanthocyanidins demonstrated the ability to inhibit periodontopathogenic virulence factors and modulate the activities of the cells that make up the periodontium [70]. Previous studies showed that proanthocyanidin extracted from grape seed applied to dental substrates is an antiproteolytic agent and collagen crosslinker. Thus, by inactivating proteinases and increasing the resistance of collagen fibrils to degradation, it is presented as an effective strategy to control the progression of dentine wear and minimize the aging of the adhesive interface [9, 71, 72].

Discussion and Future Perspectives

Regarding erosion on dentin substrates, Cardoso et al. 2020 [73] performed two wear evaluations, one after treatment with proanthocyanidin (pH 3) and one after treatment with proanthocyanidin (pH 7). Kato et al. 2009 [74] tested epigalocatequin-3-galato (EGCG) after an immediate erosion test. Kato et al. 2010 [18] tested EGCG as a natural product at two different concentrations, and Magalhães et al. 2009 [75] performed erosion in addition to the green tea extract treatment. Sales-Peres et al. 2016 [76] performed a wear analysis on human dentin treated with 10% *Euclea Natalensis*. Pooled data from these studies demonstrate that polyphenols reduce erosive wear compared to their respective controls. However, there was significant heterogeneity between studies.

In the field of erosion and abrasion on dentin substrates, Kato et al. 2009 [74] tested EGCG after an erosion test with immediate abrasion, and after 30 minutes of abrasion. Magalhães et al. 2009 [75] and Sales-Peres et al. 2016 [76] performed erosion combined with abrasion. These investigations show that polyphenols reduced erosive-abrasive wear compared to their respective controls.

Only three studies performed wear analysis on enamel: Ionta et al. 2018 [77], who evaluated erosion only and erosion combined with abrasion, including palm oil treatment with and without a combination of tin, Pelá et al. 2021 [78], and Sales-Peres et al. 2016 [76]. In the erosion and abrasion on enamel substrates, the use of polyphenols did not bring significant clinical benefit, but in erosion on enamel substrates, the use of polyphenols reduced the erosive wear.

The protective effect of polyphenols on tooth wear remains unclear, mainly because of the plethora of natural bioactive compounds. This review provides insights into natural compounds intended as anti-erosive agents, mostly collagen cross-linking agents. Here, we have investigated the most updated evidence based on preclinical *in situ* methodology. Eight studies were included from 1900 initially obtained from electronic search. Seven studies concluded that natural extracts significantly reduced tooth wear [18, 73–78], while one showed that their use had no beneficial or harmful effects [79]. It is worth noting that variability in the evaluated extracts and treatment times between the studies makes a precise assessment of this aspect difficult. Overall, this review showed that using natural extracts presents statistically significant differences in the reduction of erosive-abrasive tooth wear.

EGCG is a polyphenol in green tea and one of the most studied natural extracts in dentistry. In our review, it was the most tested product among the included studies, present in four of the eight studies. The high interest in this extract is due to its chemical structure. Studies have shown that catechins with the galoyl radi-

cal are more effective in reducing collagen biodegradation [80]. This effect is due to the formation of cross-links in dentin. In addition, EGCG has proven inhibitory activity against matrix metalloproteinases [81] and antibacterial activity against cariogenic and periodontal bacteria [82–84]. Thus, they can inhibit the biofilm formation of bacteria that cause periodontal diseases and periodontal pockets and may act as a treatment or prevention of the disease [84].

Except for the work by Ozan et al. 2020 [79], which employed human dentin, the included studies that examined the EGCG [18, 74, 75, 79] underwent erosive cycling with Coca-Cola four times per day for five minutes. Only Magalhães et al. 2009 [75] and Kato et al. 2009 [74] performed abrasive cycling with an electric toothbrush, and as a treatment, EGCG was analyzed at different concentrations and application times. Kato et al. 2009 [74] and Magalhães et al. 2009 [75] performed the treatment 4×/day for 1 min, Ozan et al. 2020 [79] applied the EGCG 2×/day for 1 min, and Kato et al. 2010 [18] did a single application at the beginning for 1 min. The results were obtained with contact profilometry, except for the study by Ozan et al. 2020 [79], which used microhardness. Coincidentally, this was the only study that did not obtain a positive result from using natural products to control erosive and abrasive wear [79]. Possibly, this finding may be related to the method of obtaining the results since hardness measurements are not very relevant when surface losses occur. Either work with an erosion model that can promote surface loss accurately measured by a profilometer or with initial erosion models, which can be more accurately assessed by surface hardness.

With a similar mechanism of action to EGCG, the proanthocyanidins have also been extensively analyzed in previous studies and are polyphenols found in various vegetables, fruits, and plants [65]. This compound has antibacterial, anti-inflammatory, anti-allergic, and antioxidant characteristics and also interacts with collagen by forming covalent bonds with proteins, ionic bonds, hydrogen bonds, and hydrophobic interactions [85–88]. Because of these interactions, they can increase collagen synthesis and keep it intact. Despite many positive characteristics, both EGCG and proanthocyanidins still demonstrated a preventive capacity against erosive wear [18, 73–75]. Cardoso et al. 2020 [73] performed the treatment with one application per day of proanthocyanidin 10 % pH 7 or pH 3 for 5 min and evaluated with contact profilometry after 5 days of cycling with Coca-Cola 3×/day for 5 min and observed that proanthocyanidin pH 7 showed significantly lower wear values.

Many plant species are used for medicinal purposes, especially in populations with less access to pharmaceutical products. For example, *Euclea Natalensis* is the main plant used for oral hygiene by the indigenous African population, as it has antibacterial properties [89]. Few studies have evaluated its mechanism of action on the tooth, but it is probably due to the presence of naphthoquinones in its root since this compound has fungicidal, antibacterial, insecticidal, phytotoxic, cytostatic, and anti-cariogenic properties [90]. One of the included studies evaluated this plant as a single application treatment before cycling with Coca-Cola 4×/day for 5 min and abrasion 4×/day for 30 s with a soft toothbrush (after 30 min of erosion), and it was observed with contact profilometry that it could be a great alternative to prevent erosive wear [76].

Another plant derivative analyzed for its preventive effect on erosion was the sugarcane-derived cystatin, CaneCPI-5. After treatment with 4×/day applications for 1 min of CaneCPI-5, this protein has been shown to have strong binding strength to hydroxyapatite and, in addition, inhibition of enamel erosion *in vitro* and *in situ* after cycling with citric acid immersion 4×/day for 90 s and abrasion 2×/day for 15 s with an electric toothbrush (after 30 min of erosion) [78, 91].

Several natural oils, such as olive and safflower, have been researched for their potential dental applications. Among the natural oils, there is palm oil, which is popular in African and Brazilian cuisines and is produced from the fruit of the palm tree. Olive oil has already demonstrated the ability to prevent erosive wear but with less potential than fluoride products [92, 93]. Furthermore, in previous *in vitro* and *in situ* studies, palm oil has been shown to reduce erosive demineralization more than fluoride products and four other vegetable oils, which suggests that it would be an excellent approach for controlling erosive lesions [77, 94]. In the *in situ* study included in our review, this oil was analyzed alone and associated with SnCl2/NaF/AmF in two daily applications for 1 min. Cycling was performed with citric acid immersion 4×/day for 2 min and abrasion 2×/day for 15 s with an electric toothbrush (after erosion), and contact profilometry data showed that palm oil associated or not to Sn significantly reduced enamel wear [77].

According to the present study, natural extracts proved to be an excellent alternative treatment to reduce erosive-abrasive wear. However, the present results must be interpreted in view of the differences concerning the mechanisms of action. In dentin, the protection effect is provided by increasing mechanical properties and reducing collagen digestion through cross-linking in the collagen matrix, providing cohesion and making it more resistant to degradation. In enamel, the formation of the acquired enamel film is important in the mechanism of protection against erosion. Thus, some products can modulate the composition and ultrastructure of the film, making it more resistant and protecting the enamel surface from direct contact with acids, reducing wear.

The study by Kato et al. 2010 [18] presented a high risk of publication bias with a strong tendency to bias the results in favor of polyphenols. With the complete reading of this study and the analysis of the risk of bias, systematic errors and topics that were not adequately described were identified, which may have compromised the internal validity of its results. For example, the purpose of the study was not clearly defined; the sample size was not justified; the randomization for allocation of specimens to groups was not described as it was performed; the researcher who evaluated the outcomes was not blinded to the allocation of treatments, and the statistical analysis used was non-parametric.

The included studies have some limitations that deserve to be discussed. Among them, the researcher who performed the analyses were blinded in only two studies, Ionta et al. 2018 [77] and Sales-Peres et al. 2016 [76]. In three studies, Kato et al. 2010 [18], Pelá et al. 2021 [78], and Ozan et al. 2020 [79], there was no justification for the sample size used. In three studies, Pelá et al. 2021 [78], Ozan et al. 2020 [79], and Magalhães et al. 2009 [75], an initial standardization of the specimens allocated to the experimental groups was not performed. Ozan et al. 2020 [79] did not perform randomization of the allocation of specimens to

groups, and another three studies, Kato et al. 2010 [18], Sales-Peres et al. 2016 [76], and Cardoso et al. 2020 [73], mentioned that randomization was performed but did not describe how it was done.

Given the developmental and innovative nature commonly observed in primary *in vitro* and *in situ* studies, different materials and substrates were observed among the included studies in this comprehensive review. The diversity of natural extracts tested is an aspect that should be carefully considered, as they present different molecular geometries that determine their antioxidant and anti-inflammatory effects, among others. In addition to these changes, some compounds may be more hydrophilic, while others may be more hydrophobic [95]. Thus, considering that dentin has an organic matrix and water in its composition and enamel is composed of an inorganic matrix, these variations in hydrophilicity can affect the interaction of extracts with different dental substrates. Therefore, these facts may contribute to poor results on the human enamel tissue.

The protocols for simulating the erosive-abrasive challenges and the application of treatments differ regarding the compound used and the time of action, which can be a source of methodological heterogeneity. In this scenario, there is currently limited evidence on the benefit of enamel concerning erosive-abrasive tooth because of the reduced number of studies that analyzed this condition, the small sample size in each study group, and the insufficient data for a meta-analysis. Thus, it is encouraged to conduct new primary investigations with larger samples based on sample size calculation, allocating samples in groups in a random way, and more homogeneous methodologies, which will allow a more precise analysis and increase the power of the results.

In summary, the current evidence from this literature review highlights that data from *in situ* studies do not allow a definitive conclusion of its clinical applicability. Although it is not possible to evaluate erosive-abrasive wear clinically for methodological reasons, it is interesting to conduct well-designed clinical trials with a long-term follow-up that can investigate such polyphenols in the form of mouthwash or dentifrice incorporated by them, observing some signs and clinical symptoms that indicate progression or control of wear. Therefore, considering the studies included in this review, it could observe that polyphenols tend to promote a reduction in erosive and abrasive wear compared to control groups, but as the few studies included have a high risk of bias with different methodologies, and the estimated effect size is low, this conclusion should not be extrapolated to clinical reality.

Contributors' Statement

Data collection: I. C. Leal; C. S. Rabelo; M. A. S. Melo; P. G. B. Silva; F. W. G. Costa; V. F. Passos; design of the study: I. C. Leal; M. A. S. Melo; P. G. B. Silva; F. W. G. Costa; V. F. Passos; statistical analysis: P. G. B. Silva; F. W. G. Costa; V. F. Passos; analysis and interpretation of the data: I. C. Leal; C. S. Rabelo; M. A. S. Melo; P. G. B. Silva; F. W. G. Costa; V. F. Passos; drafting the manuscript: I. C. Leal; C. S. Rabelo; M. A. S. Melo; P. G. B. Silva; F. W. G. Costa; V. F. Passos; critical revision of the manuscript: M. C. I. C. Leal; C. S. Rabelo; M. A. S. Melo; P. G. B. Silva; F. W. G. Costa; V. F. Passos.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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