



Polyphenols in Dental Applications

Naji Kharouf, Youssef Haïkel, Vincent Ball

► To cite this version:

Naji Kharouf, Youssef Haïkel, Vincent Ball. Polyphenols in Dental Applications. Bioengineering, 2020, <10.3390/bioengineering7030072>. <hal-02931192>

HAL Id: hal-02931192

<https://hal.science/hal-02931192v1>

Submitted on 5 Sep 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Polyphenols in Dental Applications

Naji Kharouf ¹, Youssef Haikel ^{1,2} and Vincent Ball ^{1,2,*}

¹ Université de Strasbourg, Faculté de Chirurgie Dentaire, 8 rue Sainte Elisabeth, 67000 Strasbourg, France; vball@unistra.fr

² Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche 1121, 11 rue Humann, 67085 Strasbourg Cedex; vball@unistra.fr

* Correspondence: vball@unistra.fr; Tel.: +33-667-522-841

Received: date; Accepted: date; Published: date

Abstract: Background: Polyphenols are a broad class of molecules extracted from plants and having a large repertoire of biological activities. Biomimetic inspiration from the effect of tea or red wine on the surface of cups or glass lead to the emergence of versatile surface chemistry with polyphenols. Owing to their hydrogen bonding abilities, coordination chemistry with metallic cations and redox properties, polyphenols are able to interact, covalently or not, with a large repertoire of chemical moieties and can hence be used to modify the surface chemistry of almost all classes of materials. (2) Methods: The use of polyphenols to modify the surface properties of dental materials, mostly enamel and dentin to afford them with better adhesion to resins and improved biological properties, like antimicrobial activity has started more than 20 years ago, but no general overview has been written to our knowledge. (3) Results: The present review is aimed to show that molecules from all the major classes of polyphenolics allow for low cost improvements of dental materials and engineering of dental tissues.

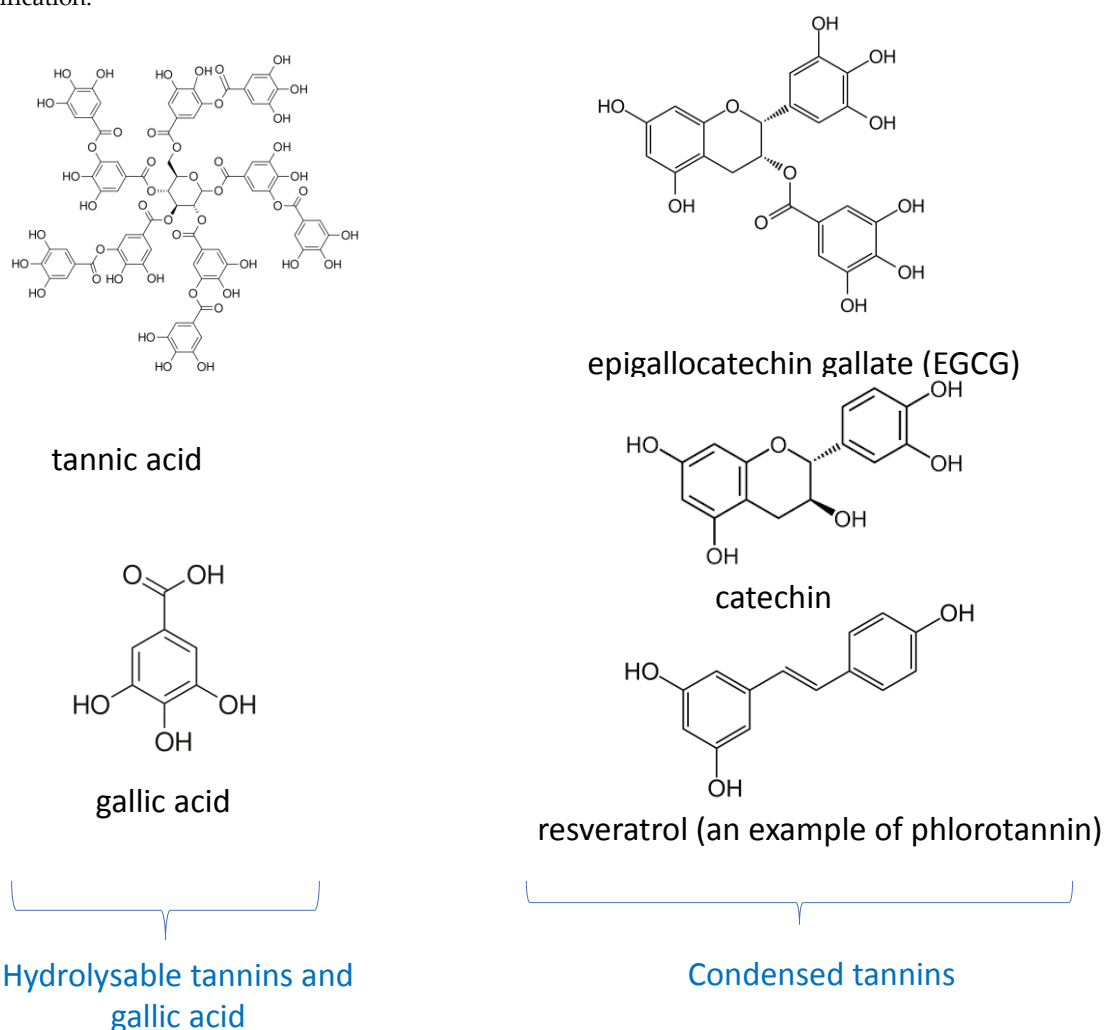
Keywords: polyphenols; interactions with collagen, dentin, enamel, dental resins; antibacterial activity

1. Introduction

The entry point for nutrients and food in the body is the oral cavity. Tea and some plants contain natural polyphenols [Pérez-Jiménez 2010]. Polyphenols are secondary metabolites defined by the presence of a minimal number of phenol groups [Handique 2002, Reitzer 2018]. Polyphenols play an interesting role in the oral cavity against many diseases, infections and oral cancers [Petti 2009]. This is because they have significant features such as antibacterial activities [Sánchez 2019], antioxidant effects [Fibach 2015] in the oral cavity. For these reasons, they are used in many dental applications. In this study, we focus on the most important polyphenols used in dental applications as tannic acid, catechin, resveratrol, gallic acid and epigallocatechin gallate (Figure 1).

In addition to their structure dependent properties, many polyphenols spontaneously adhere to the surface of almost all known materials [Sileika 2013] allowing to use them in a vast repertoire of materials functionalization strategies. Those possible post-functionalizations rely on the chemical versatility of polyphenols able to undergo acid-base reactions, oxidation processes, chemical reactivity with nucleophiles in the oxidized state, and also chemical coordination with metallic cations [Quideau 2011]. In particular polyphenols are able to interact with biological and synthetic macromolecules in either a non-covalent or covalent manner [Le Bourvellec 2012].

Figure 1. Chemical structure of the most important polyphenols used in dentistry according to their classification.



The purpose of this article is to review the literature in which polyphenols were used in dental treatments and engineering. Our literature review includes Pubmed which identify the articles with the following key search sentences: polyphenols from plants and drinking habits in dental caries, polyphenols in enamel, dentin, root canal and dental pulp treatments, polyphenols in dental adhesives and cements. At purpose, the review is not organized with respect to the different applications of polyphenols in the oral cavity but with respect to the big polyphenol families, each one having its chemical and biological specificities [Quideau 2011].

2. Condensed polyphenols

Dentin is the substance located under the enamel layer. It contains essentially hydroxyapatite crystals and a collagen matrix [Marshall 1997, Kharouf 2019]. Collagenase and different protease enzymes (Cysteine cathepsins and matrix metalloproteinases) have been reported to cut collagen chains and are responsible for collagen degradation [Osorio 2011, Toledano 2007]. The adhesion of an adhesive-resin material to dentin depends on the formation and the stability of a hybrid zone (zone where the resin infiltrates into the collagen fibrils of the dentin matrix) that forms a micromechanical interlocking between the resin and the dentin matrix [Mazzoni 2012]. Therefore, the stabilization of collagen in dentin and in the hybrid layer is possible by preventing the hydrolytic and enzymatic degradation catalyzed by the matrix metalloproteinases and the Cysteine cathepsins.

Proanthocyanidins are secondary class of non-hydrolysable plant metabolites used to pretreat dentin, to enhance its mechanical properties and to reduce the collagen digestion. Thus proanthocyanidins are a clinical agent for dentin bio-modification [Aguiar 2014, Vidal 2014]. The monomeric polyphenolic unit in proanthocyanidins interacts with collagen I to provide a stable interaction between the resin and dentin for 12 months. This stability of this interaction with time is due to a reduced biodegradation of the dentin matrix with low collagen digestion [Leme-Kraus 2017]. Tang et al [Tang 2013] showed that the use of 15 % “w/v” of grape seed extract (GSE), which contains proanthocyanidins, in contact with demineralized dentin protects the collagen matrix against degradation. They reported that using a solution with 15 % of GSE for 2 minutes treatment promotes the dentin remineralization rate and forms mostly hydroxyapatite crystals.

In addition, oligomeric proanthocyanidins enhance the elastic modulus of dentin, [Nam 2015, Phansalkar 2015].

Xu et al [Xu 2011] showed that a concentration of 31.25 µg/mL of epigallocatechin gallate from green tea (MIC) inhibits the glucosyltransferase activity of *S.mutans* and 15.6 µg/mL of the same molecule inhibits 90% of *S.mutans* biofilm formation.

Among tea polyphenols, (-)-epigallocatechin gallate (ECGC) binds to alpha-amylase, which is a salivary enzyme that catalyzes the breakdown of starch. ECGC could inhibit the activity of alpha-amylase by non-competitive inhibition. The antimicrobial activity of ECGC against *Aggregatibacter actinomycetemcomitans* was showed at concentrations higher than 0.5 mg/mL [Hara 2012].

In the study of Feng et al [Feng 2019], the most abundant polyphenols isolated from green tea were catechin and 1,4,6-tri-O-galloyl-βD-glucose. Catechin derivatives as galocatechin gallate (0.32 mM) and epigallocatechin gallate (0.31 mM) were able to inhibit *S.mutans* glucosyltransferases.

Melok et al [Melok 2018] showed that the use of 250 µg/mL of epigallocatechin-3-gallate- stearate which is an esterified derivative of epigallocatechin-3-gallate could completely inhibit *S.mutans* growth and biofilm formation. Using scanning electron microscopy, they evidenced, the antibacterial effect of epigallocatechin-3-gallate-stearate after four days of treatment (Figure 2).

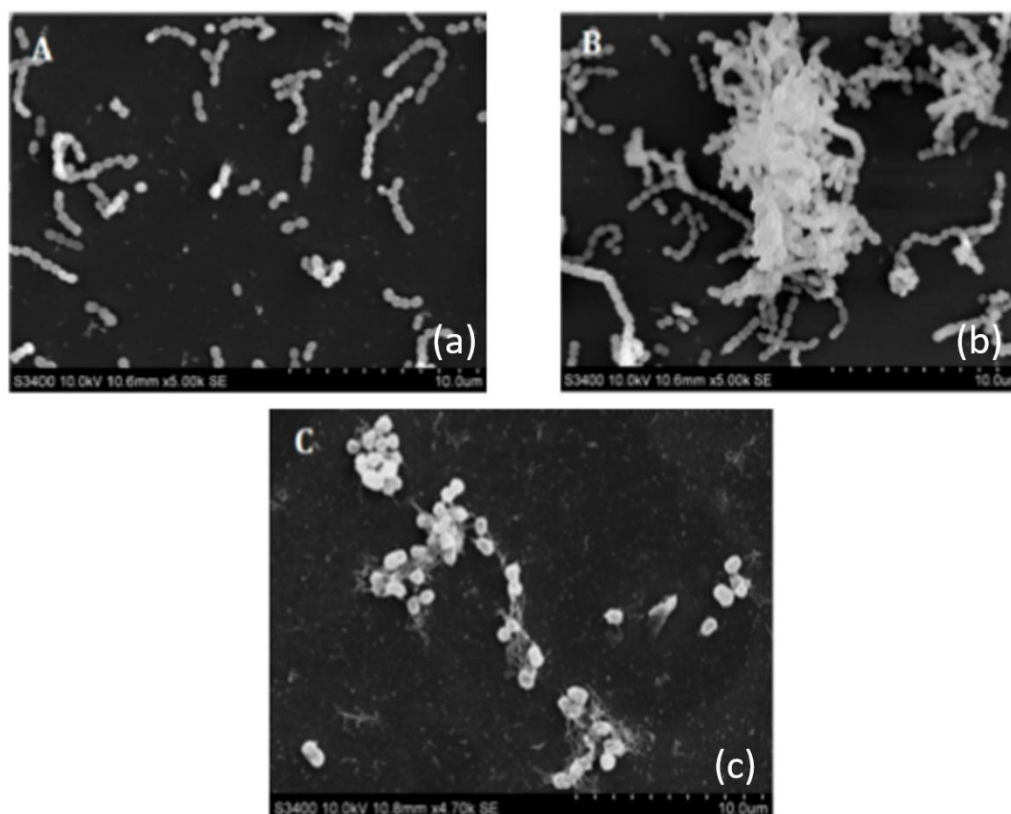


Figure 2. Scanning electron microscopy of *S.mutans*. (a) control; (b) Untreated *S.mutans* cells after 4 days; (c) *S.mutans* cells treated with 250 µg/mL of epigallocatechin-3-gallate-stearate after 4 days. Modified from Ref. [Melok 2018] with authorization.

A study on the resistance of enamel to dental abrasion was made using mammals' teeth [Lucas 2016]. Using a hardness test (Vickers indenter), it was shown that saliva containing polyphenol compounds (0.1 M epigallocatechin gallate) in contact with the enamel surfaces showed a greater resistance against abrasion than the enamel put in contact with saliva without added polyphenols.

The formation of cross-links in the collagen matrix provides cohesion and makes it more resistant to degradation [Bedran-Russo 2009].

Dental restorations require tooth surface preparation, this preparation creating a layer of dentinal debris called the "smear layer". Acid conditioners of dentin are recommended to achieve a clean dentin surface to subsequently provide the required bond strength [Zhang 2008, Kharouf 2019, Gu 2009].

A study [Liu 2015] reported that using 1% "w/w" of grape seed extract ((+)-catechin, (-)-catechin, (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechin gallate, (-)-epigallocatechin gallate, procyanidin B2 and a pCT-pCT dimer) for 1 min stabilizes the demineralized dentin and provides the cross-linked dentin-collagen complex.

Epigallocatechin-3-gallate (ECGC) solutions with different concentrations (0.02, 0.1 and 0.5% w/v) were used in dentin pretreatment followed by etch-and-rinse adhesive [Santiago 2013]. The dentin treated with a concentration of 0.5% showed a lower bond strength for resins after one day than dentin treated with solutions at the other concentrations. In contrast, dentin treated with all the polyphenol concentrations preserves its bond strength values for resins during 6 months [Santiago 2013]. Accordingly, Singh et al [Singh 2017], reported that dentin treated with ECGC at 0.1% w/v preserves the bond strength for 6 months in an etch-and-rinse adhesive system. Contrarily, different concentrations of ECGC (0.02, 0.2 and 0.5% w/v) followed by two-step etch-and-rinse adhesive system hadn't preserved the bond strength for 1 year of storage in water [Fialho 2019]. These authors reported that the pretreatment with ECGC could reduce the nanoleakage of the resin-dentin interface in time hence reducing the bond strength values. Costa et al [Costa 2019] compared the effect of 0.1% of ECGC and 2% w/v of chlorhexidine as dentin pretreatment to a self-etch system. They demonstrated that the ECGC didn't affect the bond strength. The dentin having undergone chlorhexidine pretreatment showed lower values of bond strength after 24 h and 6 months of ageing in water. Another study compared the effect of 0.2 M ECGC and 0.2 M catechin as dentin pretreatment for 1 hour in self-etch and rinse-and-etch systems [Kalaiselvam 2018]. ECGC treated samples revealed a higher bond strength compared with catechin treated samples due maybe to the higher number of hydroxyl groups in ECGC (Figure 1), thus the ability to establish more hydrogen bond interactions.

ECGC was used as an antibacterial agent against *Enterococcus faecalis* (*E. faecalis*) biofilms which are associated with persistent root canal infections [Lee 2015]. The minimum inhibitory concentration of ECGC against *E. faecalis* was equal to 5 µg/mL. Lee et al. reported that a concentration of 500 µg/mL applied for 7 days completely eradicated the *E.faecalis* biofilm [Lee 2015].

ECGC enhances the bond strength of fiber post (a direct restorative dental material) bonded with adhesive-resin and cemented with dual-cure composite resin cement to intraradicular dentin which was treated with sodium hypochlorite. In this study a push-out test was used to evaluate the bond strength. The authors demonstrated that using an ECGC solution at 400 µg/mL for 1 min as the final irrigation in intraradicular dentin, treated with sodium hypochlorite, increased the push-out strength and bond stability of fiber post for a self-etching and an etch-and-rinse adhesive system [Yu 2017]. Accordingly, in the study of Pheenithicharoenkul et al [Pheenithicharoenkul 2016], the use of a 1 mg/mL ECGC solution (for 10 min) or ethylenediaminetetraacetic acid (EDTA) at 17% w/v (for 5 min) followed by ECGC (for 5 min) as the final canal irrigation, demonstrated a higher bond strength than

the use of EDTA alone or EDTA with sodium hypochlorite without ECGC in the final canal irrigation solution.

Methacrylate resin-based materials contain triethylene glycol dimethacrylate (TEGDMA) which induces the expression of cyclooxygenase-2. This TEGDMA-induced cyclooxygenase-2 plays a role in dental pulp diseases and pulpitis. The cyclooxygenase-2 activity could be suppressed in the presence of 10 and 15 $\mu\text{mol/L}$ of ECGC [Yang 2013].

Catechins, including epicatechin gallate and epigallocatechin gallate were used to reduce and inhibit the inflammatory factors which are found in inflamed pulp [Hirao 2010]. In the study of Hirao et al., two catechin concentrations were used (10 and 50 $\mu\text{g/mL}$) to show that this polyphenol didn't affect the viability of the human dental pulp fibroblast cells. Hence, catechins inhibited the effect of interleukins (IL-8 and -6), of monocyte-chemoattractant proteins and of prostaglandins which are receptors stimulating the pro-inflammatory mediators. Contrarily, high concentrations of epigallocatechin gallate (50 $\mu\text{g/mL}$) didn't inhibit the production of prostaglandins in pathogen-associated molecular patterns simulated human dental pulp fibroblasts. Therefore, catechin has an anti-inflammatory effect due to its activity on the inhibition of the cytokines and chemokines in human dental pulp fibroblasts modified with caries-related *S. mutans*, *S. sanguinis* and *S. salivarius*, and pathogen-associated molecular patterns. Accordingly, Nakanishi et al [Nakanishi 2010] showed the benefits of using epicatechin gallate (ECG) and epigallocatechin gallate (ECGC) to inhibit the expression of pro-inflammatory cytokines and adhesion molecules in human dental pulp cells.

Similarly, ECGC and ECG (dissolved at 20 and 50 $\mu\text{g/mL}$) reduced the up-regulated expression of vascular endothelial growth factors and cyclooxygenase-2 which are induced pro-inflammatory cytokines in dental pulp cells simulated with lipopolysaccharide (LPS), peptidoglycan (PG), interleukin-1b (IL-1b) or tumor necrosis factor- α (TNF- α) [Nakanishi 2015].

On the other hand, ECGC and ECG (10 mmol/L) didn't affect the dental pulp cells viability [Wang 2020]. Wang et al. also demonstrated that the anti-inflammatory activity of ECG and ECGC proceeds through the inhibition of the activity of nuclear factor-kappa B (NF- κB).

Kwon et al [Kwon 2017] compared the effects of two antibacterial agents and of two cross-linkers (ECGC and glutaraldehyde) on cell viability, odontogenic differentiation and proliferation of dental pulp cells, and antibacterial activity in collagen scaffolds. The results revealed that the cell viability is reduced in the presence of glutaraldehyde (0.1, 1, 10 and 100 $\mu\text{mol/L}$) compared with the presence of ECGC (0.1, 1, 10 and 100 $\mu\text{mol/L}$). In the presence of the highest ECGC concentrations (10- 100 $\mu\text{mol/L}$), the cell viability was nevertheless reduced. It was also concluded that ECGC didn't promote the odontogenic differentiation and proliferation by itself but facilitated these processes. The cross-linked collagen produced in the presence of ECGC showed a shorter setting time, a higher compressive strength and a rougher surface. Equal concentrations of ECGC and glutaraldehyde reduced the growth of *S. mutans*.

Lim et al [Lim 2016] reported that epicatechin (0.01, 0.05, or 0.1 mM) as a collagen cross-linker didn't affect the cell viability and induced a positive effect on the proliferation and differentiation of human dental pulp cells.

Reactive oxygen species (ROS) caused by pulp diseases and dental bleaching agents generate oxidative stress [Lee 2013]. Park et al [Park 2013] reported the effect of ECGC (5-50 μM) against nitric oxide-induced toxicity of human dental pulp cells which is driven by the ROS production. The Bcl-2 cell family contains anti- and pro-apoptotic proteins which are important moderators in regulating cell death. In this context, ECGC scavenges the ROS and regulates the expression of the Bcl-2 family preventing the nitric oxide-induced apoptosis.

Bonding the dental restoration to the structure of the tooth becomes a routine in dental practice and requires various properties such as a good sealing, high bonding strength to tooth surfaces, durability over time, low toxicity and low degradation rate [Frassetto 2016, Dutra-Correa 2018, Mishra 2018]. Various natural additives such as polyphenols were used and incorporated in dental biomaterials to provide bioactive properties.

Epigallocatechin-3-gallate (EGCG) is a polyphenol which has antibacterial and antioxidant activities [Hong 2015, de Assis 2015]. EGCG was incorporated in dental adhesive-resins for its inhibitory effects of matrix-metalloproteinases (MMPs) and cysteine cathepsins. Those proteins are major players in the degradation and perturbation of the resin-dentin interface [Neri 2014, Fonseca 2019]. EGCG was added to dental restorative composites to afford this material with an antibacterial activity [Mankovskaia 2013]. The addition of 700 $\mu\text{g/mL}$ of EGCG reduces the viability of *S.mutans*.

Another study showed that 200 $\mu\text{g/mL}$ and 300 $\mu\text{g/mL}$ of EGCG have an inhibitory effect on the growth of *S. mutans* (Figure 3) and increase the bond strength of the resin to dentin surface. EGCG also preserves the durability of the bond strength for six months [Du 2012].

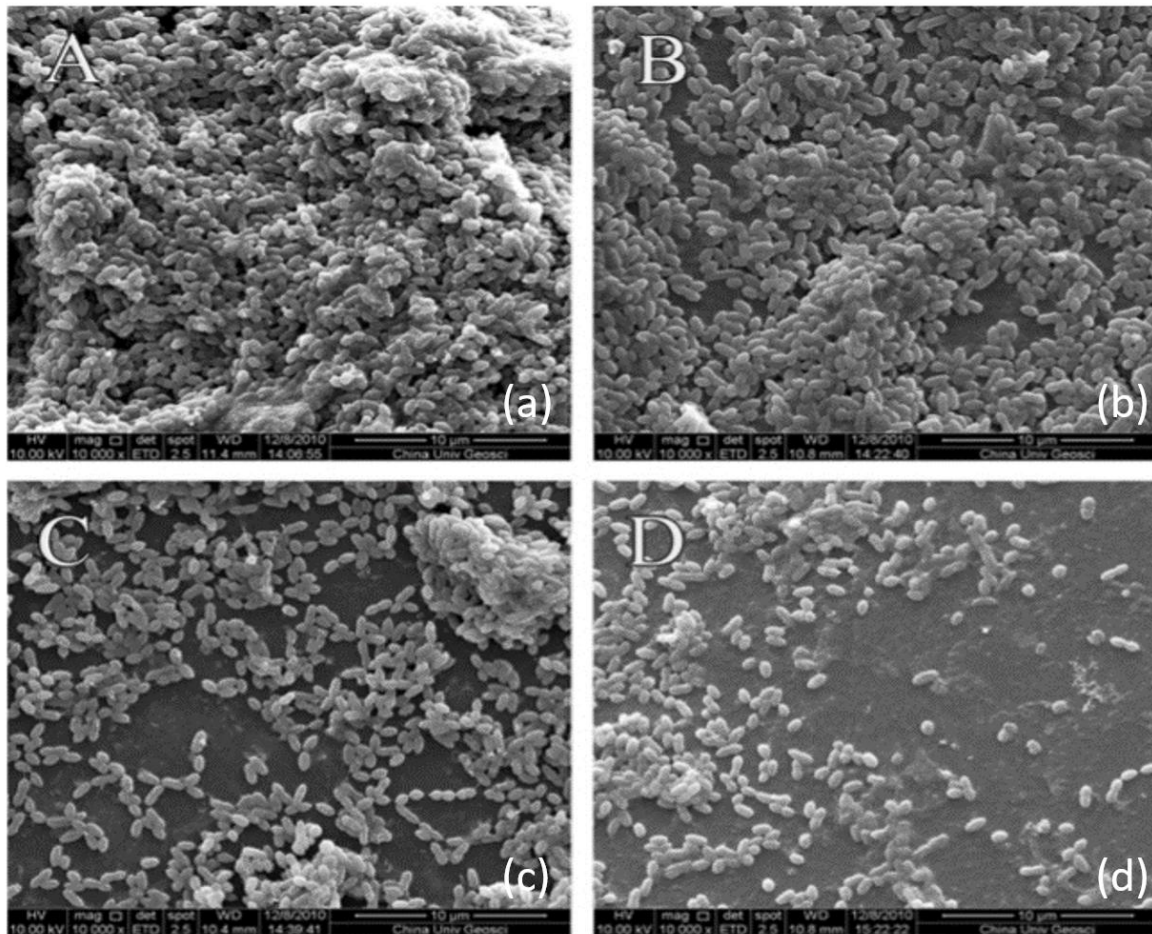


Figure 3. Scanning electron microscopy of *S.mutans* accumulation on specimens. (a) adhesive resin surface without EGCG; (b) ECGC 100 $\mu\text{g/mL}$; (c) ECGC 200 $\mu\text{g/mL}$, (d) ECGC 300 $\mu\text{g/mL}$. Biofilms accumulated on (c) and (d) were not compact after 24 h incubation. Modified from Ref. [Du 2012] with authorization.

At concentrations of 0.5 % and 1% (w/v), EGCG incorporated in an adhesive resin could increase the bond strength values and the longevity of adhesive-dentin bond for 6-12 months [de Macedo 2019, Albuquerque 2019]. In contrast to the previous investigation, the addition of 0.01 and 0.1 % (w/v) of EGCG to adhesive-resin compounds didn't affect the resin-dentin bond but could reduce the solubility of the adhesive-resin in water [Neri 2014]. Yu et al [Yu 2017] showed that EGCG, in addition to its antibacterial activity, increases the bond strength of root canal sealer to dentin. This result was obtained using a push-out test after a thermocycling procedure (5000 cycles).

The dental adhesive-resin incorporates many toxic compounds such as Bis-GMA, TEGDMA, and Bis-phenol A [Hanks 1991]. Fonseca et al [Fonseca 2019] demonstrated that the presence of 0.5-1 % (w/w)

of EGCG in the adhesive-resin could reduce the toxicity, reduce the solubility and the water sorption of this adhesive. These concentrations (0.5-1%) could maintain the hybrid layer and preserve the bond strength over time.

Glass ionomer cements were also blended with 0.1% (w/w) EGCG to improve their antibacterial activity and to increase their mechanical properties such as the flexural strength and the hardness [Hu 2013].

A comparison between three polyphenol solutions (at 50 g/L), quercetin, proanthocyanidins and baicalein, showed that the baicalein has the highest effect in the protection of the dentin matrix against collagenase digestion [Zheng 2014].

Three flavonoids (quercetin, genistein and baicalin) and phenamil -an osteoblast differentiation molecule- were used to test their cytotoxicity and their osteoblast differentiation activity on dental human cells [Kim 2013]. The used concentrations, ranging from 1 to 25 μ M, didn't alter the cell viability. Among the three tested polyphenols, phenamil had the strongest influence on alkaline phosphatase activity. In contrast, this *in vitro* study demonstrated that quercetin had a superior effect to phenamil in the osteogenic differentiation.

Mahmoud Hashemi et al [Mahmoud Hashemi 2018] evaluated the effect of adding 0.5 mg/mL of quercetin to simulated T cells extracted from pulpitis with high mobility group box 1 (HMGB1). They demonstrated that quercetin can decrease pro-inflammatory cytokines such as interleukin-6 and -1 β with blocking high mobility group box1 and inhibiting the mitogen activated protein kinase (MAPK) signaling pathway.

Luteolin (used at 35 μ mol/L) is a polyphenol from the flavonol family and was combined with phosphorylated pullulan to decrease the production of inflammatory cytokines [Yonehiro 2013]. It was reported that the combination of both compounds was less efficient than luteolin alone. This may be due to some strong interactions between both compounds reducing the concentration of available polyphenol.

ROS can be quenched by butein which is a plant polyphenol and one of the most active compounds of the *Rhus Verniciflua* plant found in east Asian countries [Lee 2013]. The study of Lee et al. demonstrated that butein quenches the ROS and suppresses the toxic effects of hydrogen peroxide which is used as a bleaching agent. The concentrations of butein (2.5-20 μ M) had no toxic effect on the dental pulp viability. The maximal heme oxygenase-1 protein expression and heme activity, which exhibit many cytoprotective effects and remove pro-oxidant heme molecules, were attained after 18 hours of butein exposure to human dental cells. Nuclear accumulation of nuclear factor-E2 caused by butein treatment increased the promoter activity of antioxidant response elements. Therefore, butein can prevent functional dental cell death and could be used as a protective agent in dental pulp diseases.

Dental adhesive-resins were also modified with quercetin which is an amphiphilic antioxidant. The addition of 500 μ g/mL quercetin to dental adhesive could give an antibacterial effect and preserve its bond strength by inhibiting the collagenase activity [Yang 2017].

Gotti et al [Gotti 2015] analyzed the effect of the addition of 5 % (w/w) quercetin to a two-step etch-and-rinse, two-step self-etch and one step self-etch adhesive system on bond strength durability to dentin surfaces after two storage periods in water (24 h and 6 months). They demonstrated a negative effect on the bond strength of these adhesives after 24 h. In contrast, for a 6 months storage period, the two-step etch-and-rinse and the two-step self-etch adhesive systems incorporating quercetin increased the bond strength, whilst the one step self-etch adhesive incorporated with quercetin maintained the bond strength durability.

3. Phlorotannins

Resveratrol inhibits interleukin (IL-8 and -6) and suppresses the c-Jun N-terminal Kinase (JNK) signaling pathway in dental pulp cells simulated by tumor necrosis factor α (TNF α). TNF α is one of the cytokines that initiates the natural inflammatory response in the dental pulp. In contrast,

resveratrol didn't inhibit the degradation of I κ B α nor the phosphorylation and nuclear translocation of p65 NF- κ B in TNF α treatments. The results of this study allowed to hypothesize that resveratrol can be beneficial to decrease pulpal damage during the severe phase of inflammation in vital pulp [Wang 2019].

Another study reported that using resveratrol at a concentration up to 50 μ M had no toxic effect on dental pulp stem cells [Geng 2017]. Resveratrol raises the activity of Sirtuin 1 (stress-activated nicotinamide adenine dinucleotide-dependent protein deacetylase) which is a mediator of the immune and defense genes in human dental pulp cells [Lee 2011]. Resveratrol (at 5 μ mol/L) activates the function of Sirtuin 1 which can promote the osteogenic differentiation of dental pulp stem cells in inflammation micro environment through Wnt/ β -catenin signal [Feng 2016].

Resveratrol was added to adhesive-resin materials to promote the biocompatibility of these adhesive-resins, and to reduce the oxidative stress of L929 mouse fibroblast cells without decreasing the bond strength to dentin [Atalayin 2015, Atalayin 2019].

Osteoclasts and osteoblasts play an important role in orthodontic tooth movements. These movements could produce complications such as root resorption. Liu et al [Liu 2020] used two doses of resveratrol (5 mg/kg/day and 10 mg/kg/day) to evaluate its effect on the orthodontic tooth movement and root resorption. This study, performed on rats, demonstrated that resveratrol could inhibit tooth movement during orthodontic treatment and reduce the rate of root resorption during orthodontic therapy as described in (Figure 4). This investigation also showed that resveratrol promotes the osteoblastic activity and reduces the osteoclastic activity during orthodontic therapy. Therefore, resveratrol application during orthodontic therapy could be used as a novel approach to prevent undesired tooth movement (anchorage or relapse).

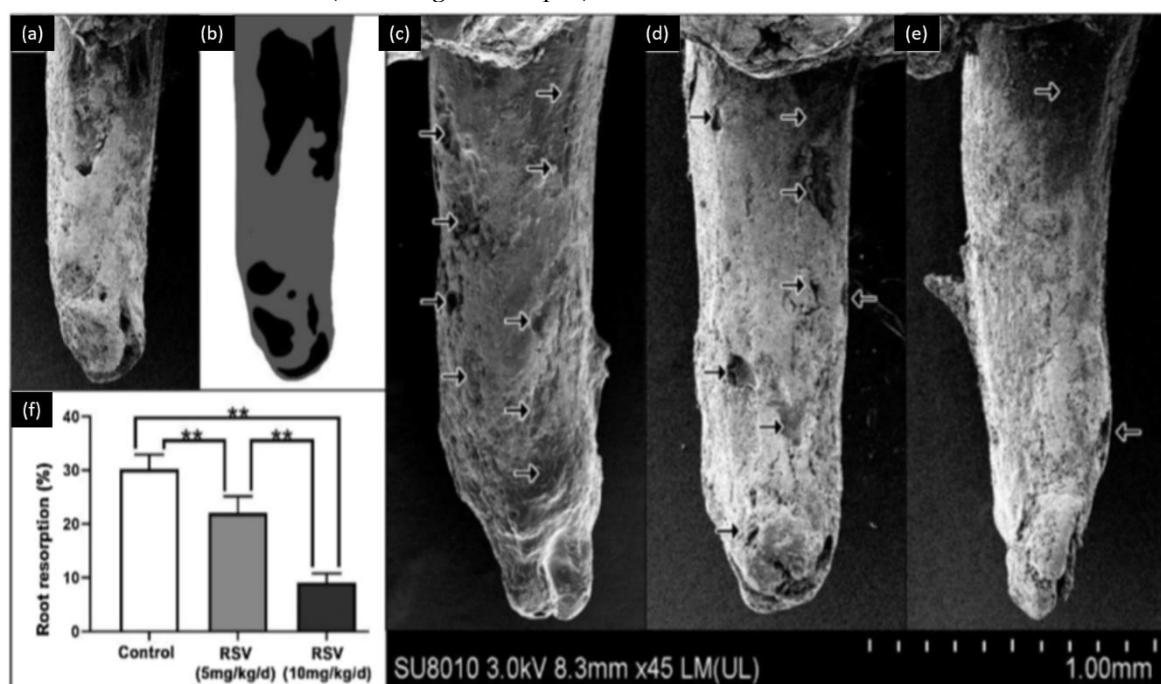


Figure 4. Observation of root resorption. A. SEM image of the tooth, B. Root resorption area (black) and the total surface area (grey), C. Representative SEM pictures of the control group, D. 5mg/kg/d resveratrol group, E. 10mg/kg/d resveratrol group, F. The resorption ratio of the three groups were calculated by dividing the surface of black area by the grey area. (* $p < 0.05$, ** $p < 0.01$, $N = 6$). Modified from Ref. [Liu 2020] with authorization.

Tooth development may be perturbed during exposure to high energy radiations. Barbosa et al [Barbosa 2016] used resveratrol, as a radioprotector, on rats to analyze its effect. Each rat received 100 mg/kg of resveratrol. Barbosa et al concluded that this dose of resveratrol had no radioprotective effect on the dental tooth structure.

4. Hydrolysable tannins and gallic acid

Four dentin bio-modifiers extracted from different plants were compared such as hydrolysable tannins from Aroeira, condensed tannins from grape seed with cardol and cardanol from cashew nut shell liquid. The results demonstrated that the four groups achieved cross-linking in dentin matrix after 1 min of treatment and the best bio-modifiers were cardol and cardanol [Moreira 2017].

Tannic acid forms stable cross-links with exposed collagen fibrils allowing to increase the resistance against their degradation process [Mukai 1998]. Bedran-Russo et al [Bedran-Russo 2009] reported that solutions containing 10% and 20% (w/v) of tannic acid could increase the stiffness of demineralized dentin and reduce the enzymatic degradation of collagen most probably due to hydrogen bonds between the biopolymer and TA.

A successful dental root canal treatment depends on various factors such as proper cleaning, and tridimensional filling of the root canal system. The removal of the smear layer and the disinfection of the root canal system is of prime importance during the endodontic therapy [Mancino 2019, Haapasalo 2014].

Bitter [Bitter 1989] analyzed the effect of using hydrogen peroxide and sodium hypochlorite followed by a solution containing 25% (w/v) of tannic acid as the final irrigation solution in dental root canal. This study showed that using tannic acid in the final irrigation fluid revealed a smoother and cleaner pulp chamber surface compared with hydrogen peroxide and sodium hypochlorite treatment without tannic acid as final irrigation solution.

Bitter [Bitter 1989] showed that using a 25% (w/v) solution of tannic acid in contact for 60 s removed the smear layer without broadening the orifice of dentinal tubules, and removed partially the organic material of the dentinal tubules.

It was reported that the dentin treated with tannic acid had an improved resistance to collagenase degradation [Bitter 1990]. In contrast, another study demonstrated that the application of solutions containing 15, 20 and 25% (w/v) of tannic acid on dentin surfaces for 5, 10 or 15 min couldn't totally remove the smear layer owing to the astringent action of tannic acid. They reported that tannic acid itself attached to collagen by means of hydrogen bonds [Sabbak 1998]. Different concentrations of tannic acid (2, 5, 10, 15, 20 and 25 % (w/v)) were applied on dentin surfaces for different times (15, 30 and 60s) [Takahashi 1993]. These researchers reported that a low concentration of tannic acid (2 or 5% (w/v)) applied for 60 s could remove the smear layer, leaving the orifices of dentinal tubules occluded. The dentinal surface that was treated with 20 % or 25 % (w/v) of tannic acid for 15s revealed incomplete removal of the smear layer and exposure of some of the dentinal tubules. Accordingly, Bitter [82] tested the permeability of methylene blue in 62 dentinal cavities treated with solutions containing 25% (w/v) of tannic acid for 15 s. Their results showed that 48 over 62 cavities did not allow for the penetration of methylene blue into the dentinal tubules.

A glass ionomer was blended with 1.5 %, 5% and 10% (w/w) tannin-fluoride preparation; the 1.5% preparation increased the bond strength of glass ionomer to dentin after one day. The bond strength of glass ionomer modified with tannin-fluoride preparation didn't reveal a significant difference after one month [Yamaga 1993].

Tannic acid incorporated in polycarboxylate cement, as well zinc fluoride enhances the resistance of dentinal collagen to collagenase and proteolytic enzymes [Okamoto 1990].

The structure of enamel is an essential portion of the tooth substance which is exposed in the oral cavity. It is the hardest and most mineralized tissue of the body [Hu 2007, Lacruz 2017]. Salivary pellicles composed of adsorbed macromolecular compounds delivered from saliva, blood, gingival fluids, *bacteria*, molecules and particles from the diet [Hannig 2014], *Streptococcus mutans* (*S. mutans*) and other oral bacteria adhere on the surface of enamel. All these substances and particles demineralize this surface resulting in the formation of dental caries [Babaeekhou 2020, Kolahi 2009, Veloz 2019].

Gallic acid, present in various food and plants can inhibit the enamel demineralization and can enhance the remineralization of the demineralized enamel. Thus gallic acid is a promising agent for

enamel remineralization and caries treatments [Zhang 2015, Huang 2012]. Gallic acid was also used to re-mineralize the early carious enamel, to increase the surface microhardness and simultaneously to reduce the wear resistance of enamel [Gao 2009].

The dentin fluid flow is the main cause of dentin hypersensitivity, which was reduced by using gallic acid/ Fe^{+3} complexes (Aqueous solutions of FeCl_3 (1.2×10^{-3} M) and gallic acid (0.47×10^{-3} M)), which performed for four repeated treatments each lasting over 60 s [Oh 2018]. This kind of catechol-iron complex is able to deposit on the surface of all known materials [Ejima 2013]. Oh et al [Oh 2018] showed that the pyrogallol group of gallic acid binds to dentin and Fe^{+3} ions create stable crosslinked complexes in an aqueous environment. Their scanning electron microscopy observations showed that dentin treated with gallic acid/ Fe^{+3} complexes create tight bridge like connections between adjacent peritubular dentin, which resulted in less outward flow. Another complex which is fluoride-tannin acid-lanthanum-apatite was used to reduce the dentinal hypersensitivity [Mukai 1998]. The surfaces of the treated samples were completely covered with fine spherical compounds, and the dentinal tubules were occluded with materials (Figure 5).

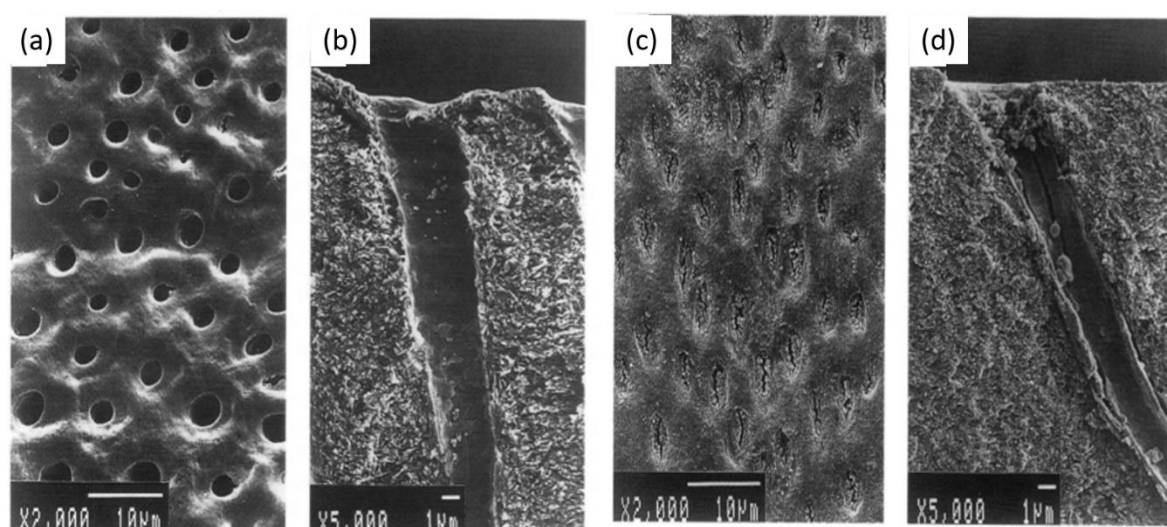


Figure 5. (a, b). Scanning electron micrographs of dentin hypersensitivity, (c, d). Scanning electron micrographs of dentin treated with fluoride-tannin acid-lanthanum-apatite. Modified from Ref. [Mukai 1998] with authorization.

Three different antioxidants (solutions containing 10% gallic acid, 10% tannic acid and 10% ascorbic acid “w/v”) were used to irrigate the root canal and to evaluate the infiltration of resin sealer in dentinal tubules [Christopher 2016]. The application of gallic acid for 10 min showed the best penetration of resin sealer into dentinal tubules, maybe due to the presence of three vicinal hydroxyl groups in its structure (Figure 1). In addition, gallic acid is a very active phenolic acid with a high free radical scavenging activity [Christopher 2016].

Gallic acid improved its inhibitory effect on matrix metalloproteinases and cysteine cathepsins to improve the durability of bond strength [Vidal 2014]. In contrast, it reduced the mechanical properties of adhesive-resin such as biaxial flexural strength and hardness values [Oguz Ahmet 2019].

Apacaries gel is a material containing polyphenols from mangosteen extracts and papain as an enzyme [Juntavee 2014]. This gel, including polyphenolic compounds, such as gallic acid, which have antibacterial effects, could play an interesting role in the removal of various tissues.

Enamel is mostly composed of mineral, approximately 96% in weight. Gallic acid (GA) was previously used to enhance the remineralization of demineralized enamel [Zhang 2015, Huang 2012]. Gallic acid (4 g/L) was used in the formation of hydroxyapatite (HAP) [Tang 2015]. It was shown that gallic acid participates in hydroxyapatite formation, limits the crystal growth mainly along the [002] direction and changes the crystal morphology and size. GA-HAP crystals were smaller than the HAP

crystals obtained in the absence of polyphenol. The crystal morphology was observed by scanning electron microscopy (Figure 6). It was found that GA-HAP had an urchin-like shape, while loose needle-like crystals were found in HAP formed without additive.

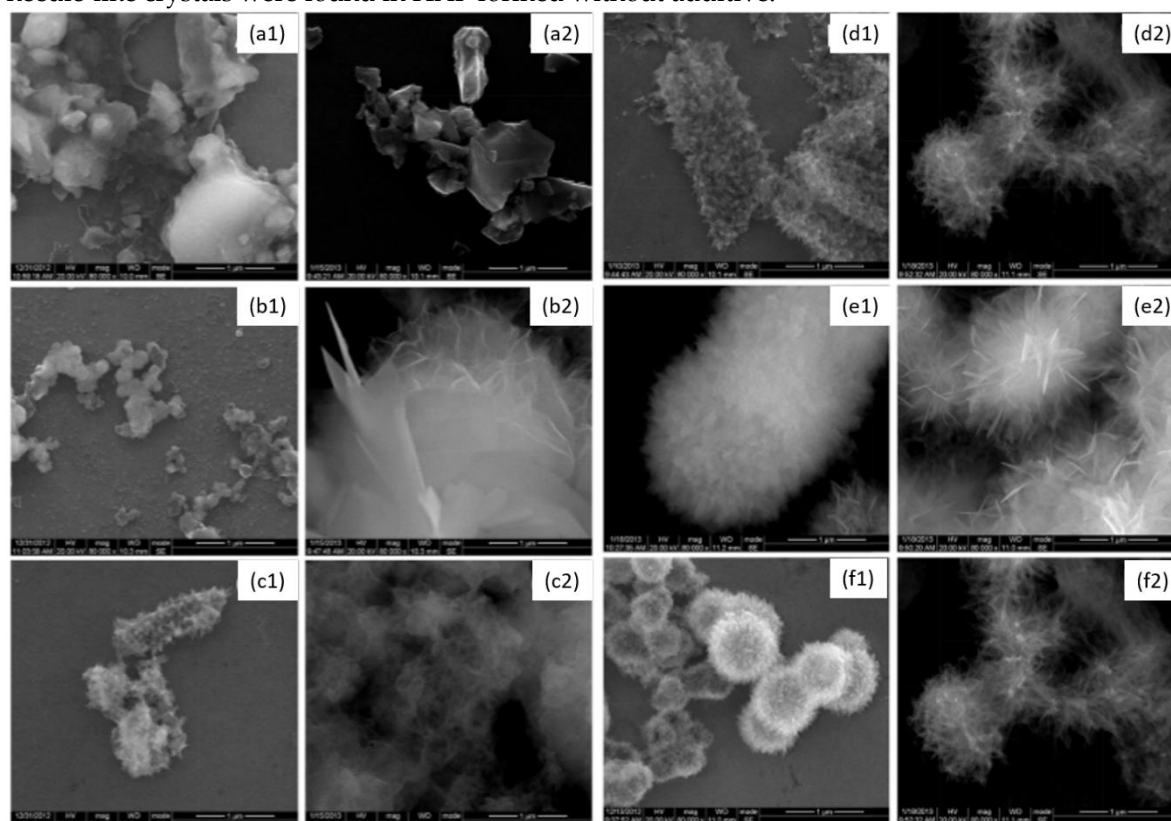


Figure 6. Morphology of hydroxyapatite (1) and hydroxyapatite + gallic acid (2) crystals at different times; (a)=3 h, (b)=12 h, (c)=24 h, (d)=3 days, (e)=7 days, (f)=14 days at 80000X magnification. Modified from Ref. [Tang 2015] with authorization.

Accordingly, the same authors [Tang 2015] investigated the morphology and the size changes of crystals as function of the GA concentration (0.05 to 4 g/L). They reported that increasing the concentration in GA reduced the crystal size from 40 to 25 nm.

5. Polyphenol mixtures

The oral cavity contains around 750 kinds of bacteria in dental plaques. These bacteria are responsible for dental diseases such as dental caries [Li 2019]. Dental caries have been considered to be the most polymicrobial diseases in the oral cavity [Cheng 2015]. Oral Streptococci, especially *Streptococcus mutans* (*S. mutans*) have been implicated and considered as the main cause and the most cariogenic agent of dental caries in humans [Melok 2018, Babaeekhou 2020]. These bacteria excrete carbohydrates like glucose and sucrose metabolized in organic acids by glucosyltransferases and generate stable biofilms which affect the mineralized dental surfaces [Kolahi 2009, Veloz 2019]. Several studies analyzed the effects of different food components, drinks and plants containing polyphenol groups in order to prevent the dental decay [Cheng 2015, Slobodníková 2016]. For instance, tea and cranberry are very rich in polyphenols [Daglia 2011].

Tea is the most popular drink in the world including black, green and oolong teas which are produced from the plant *Camellia sinensis* [Friedman 2007]. Tea is rich in polyphenols which have antifungal activities, antibacterial and antioxidant activities, and inhibitory effects on some oral pathogenic microorganisms and oral bacteria such as *S. mutans* [Li 2019, Okubo 1991, Signoretto 2006, Ferrazzano 2009]. Green tea is an unfermented product mostly containing catechins. Fermented tea (black tea) and

semi fermented tea (oolong tea) contains (catechins, theaflavins, polymeric thearubigins), catechins and theaflavins, respectively [Friedman 2007].

The anticariogenic effects of 10 % tea polyphenol (10 g of green tea polyphenol extract in 100 mL of dimethyl sulfoxide), 0.05% (w/v) fluoride, 0.2% (w/v) chlorhexidine, and 1:1 solution of 0.2% (w/v) chlorhexidine and 0.05% (w/v) fluoride combined were analyzed [Jazaeri 2015]. This study showed that all the groups had an anticariogenic effect compared with saline, whilst the anticariogenic effect of fluoride-chlorhexidine combined was the highest among those groups.

Ferrazzano et al [Ferrazzano 2011] compared in an *in vivo* study the antibacterial effect of tea polyphenol mouthwash (1.6 g of pulverized *Camellia sinensis* leaves was suspended in 40 mL of distilled water at 100°C for 3 minutes) and placebo mouthwash against *mutans streptococci* and lactobacilli. Forty milliliters of each mouthwash were used 3 times/day for 7 days. The results showed a significant lowering of the levels of *mutans streptococci* (60 %) and a significant lowering of levels of lactobacilli (42.4 %) using green tea mouthwash compared with the subjects using placebo mouth-rinse.

Hambire et al [Hambire 2015] compared the effect of 0.5% (w/v) solution of green tea extracted mouthwash with a commercial 0.2% chlorhexidine gluconate mouthwash and 0.05% sodium fluoride mouthwash on the plaque, gingival status, oral hygiene status, and salivary pH. The study was conducted for a period of two weeks on children. The results showed that green tea mouthwash plays an important positive role on the criteria tested and no known side effects that are found with the others mouthwashes tested. Lee et al [Lee 2004] showed that chewing green and black tea leaves resulted in higher levels of catechin and teaflavins in the oral cavity than holding tea leaves. Another study demonstrated that tea polyphenols extracted from green and black teas showed, at 1-10 mM concentrations, a potent (teaflavin) or a moderate (catechin and epicatechin) effect against glucosyltransferase from *S.mutans* [Hattori 1990].

Green tea polyphenols ((+)-catechin (2.9%), (-)-epicatechin (6.8%), (+)-gallocatechin (12.8%), (-)-epigallocatechin (16.5%), (-)-epicatechin gallate (6.6%), (-)-gallocatechin gallate (8.5%), and (-)-epigallocatechin gallate (21.3%) with other compounds such as caffeine (9.9%), sugars (5.1 %), amino acids and peptides (2.7%), ash (0.3%), and moisture were added at different concentrations (0.1-0.5 % (w/v)) to diet or water drinking in rats [Sakanaka 1992]. The results showed that the caries activity was reduced by adding tea polyphenols to the diet. Forty percent of dental caries lesions reduction was observed after a diet containing 0.1 % (w/v) tea polyphenols as well as no toxic effects were observed on rats.

Oolong tea is mostly consumed in China and Taiwan [Goenka 2013]. An *in vitro* study demonstrated that Oolong tea polyphenols (monomeric and polymeric polyphenols, caffeine, and other components) could be used as antibacterial agents and are able to reduce glucan synthesis by inhibiting the glucosyltransferase activity of *S. mutans* [Matsumoto 2003]. Accordingly, several studies performed on rats demonstrated that the polymeric polyphenols in oolong tea are the main compounds which reduce the dental plaque and prevent caries development. The mechanism consists again in the inhibition of glycosyltransferases of *S. mutans* and *Streptococcus sobrinus* [Ooshima 1998, Ooshima 1993]. The same authors reported that performing mouthrinse with 0.5 mg/mL of oolong tea extracts in 0.2 % ethanol solutions before and after each meal and before sleeping during four days could reduce the plaque deposition on human teeth [Ooshima 1994].

The prevention of dental caries and antibacterial activities of polyphenols in other drinks as cacao, wine, coffee and barley coffee were studied [Signoretto 2010, Ferrazzano 2009]. Barley coffee contains fluorid, zinc ions and phenolic compounds, and has an antibacterial effect on *S.mutans* by changing the hydrophobicity of bacterial cell walls and hence the adhesive capacity of bacteria on hydroxyapatite [Papetti 2007]. Accordingly, Stauder et al [Stauder 2010] demonstrated the *in vitro* antibacterial and the *in vitro* antiadhesive effects of barley coffee against *S. mutans* biofilms and expressed the opinion that the addition of Barley coffee compounds to oral health care materials could prevent the *S. mutans*-induced lesions *in vivo*. They showed that Barley coffee contains low molecular mass polyphenols, zinc and fluoride ions and, above all, a high molecular mass melanoidin. After 24h,

Barley coffee and the high molecular mass melanoidin fraction had an inhibitory effect (ranging from 82 to 93 %), whilst the low molecular mass caused a biofilm reduction of only 36 %.

An *in vivo* study [Signoretto 2010] compared the effect of coffee, wine and water consumption on the microbial population of dental supra- and subgingival plaque by the separation of PCR-amplified fragments using the denaturing gradient gel electrophoresis technique. This study showed that the coffee (five cups a day “30 to 40 mL each”) and red wine consumers (couple of glasses a day “200 mL each”) had lower intensity bands observed in supra- and subgingival plaque than water consumers. An *in vivo* study [Signoretto 2006] demonstrated that less biofilms developed on the teeth of consumers drinking higher volumes of wine, tea and/or coffee.

Wine is one of the alcoholic drinks which is the most frequently consumed by humans. It contains numerous biologically active compounds which have beneficial effects for the human health [Daglia 2007]. In contrast, several studies showed that wine can alter the tooth color and the long contact duration of this alcoholic beverage with its low pH could promote dental erosion [Chikte 2005, Borges 2014]. Red and white wines contain some organic acids and polyphenols; these organic acids such as tartaric, citric, succinic, malic, lactic, and acetic acids could be responsible for the antibacterial activity against *S. mutans*. Conversely, wine polyphenols-catechin and tannin-didn't affect the microorganisms [Daglia 2007].

Wine has strong antibacterial activity against *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum*. Hence, the identified active compounds in wine could be used in the prevention and the treatment of periodontal diseases [Sánchez 2019]. Resveratrol, flavonols, tannins and gallic acid are the most represented polyphenols in red wine; these polyphenols and anthocyanins which are present in red wine could have the capacity to inhibit bacterial growth in the oral cavity [Di Lorenzo 2016].

Several studies analyzed the antibacterial effect of many plants rich in polyphenol compounds which can be used to prevent dental caries. Hop Bract is a plant that contains a high molecular weight polyphenol which can inhibit the adherence of the *S. mutans* and 80% of their glucosyltransferase activity at smaller concentrations than the polyphenols extracted from tea [Tagashira 1997]. A recent *in vivo* study demonstrated that the use of 0.1% of Hop Bract polyphenol based mouthrinse (1 min, five times per day) reduces 25.4 % of the dental plaque growth over 3 days without teeth discoloration [Shinada 2007]. *Salvadora Persica* is a plant containing phenolic, flavonoid, tannins and alkaloids [Kholkhali 2010]. The methanolic extracts from this plant contain some polyphenols such as Chrysin-8-c- β -D-glucopyranoside, gallic acid and ferulic acid. Its concentration (20 mg/mL) showed high antibacterial activity *in vitro* against *S. aureus* and *Streptococcus sp.* and mostly nearest or more than the antibacterial activity of the ampicillin [Khalil 2019].

Tymus Lamiaceae comprises over 200 species. The essential oils of four *Tymus* species contain thymol, and polyphenolic compounds such as phenolic acids, labiate tannins and flavonoids. They displayed antibacterial activities against *S. mutans*. This study noted that the polyphenols of *Tymus vulgaris* (one of the four species studied) do not have an antibacterial effect but can reduce the initial bacterial colonization on dental enamel *in situ* [Schött 2017]. Yamamoto and Ogawa [Yamamoto 2002] studied the role of *Perilla frutescens* seed that contain various polyphenols such as luteolin, quercetin, gallic acid and epigallocatechin gallate against different oral bacteria. They observed that the presence of a hydroxyl group at the 3' position in the flavonoid group of quercetin confers an antibacterial role and prevents the occurrence of dental caries.

The antioxidant and antibacterial effects of the polyphenols compounds contained in *Paullina Cupana* (caffeine, epicatechin and catechin) [Yamaguti-Sasaki 2007], *Oenothera biennis* Matsumoto-Nakano 2011], *Sida urens* L. (Malvaceae) [Konaté 2013], *Cistus incanus* Herbal (flavonols, glycosylated flavonol, catechin, gallic acid) [Wittpahl 2015], *Ziziphus jujuba* (quercitrin, catechin, gallic acid) [Damiano 2017] and *Trachyspermum ammi* (Ajwain) [Dadpe 2018] showed that these plants could be used to inhibit activities of *S. mutans*, thus in the prevention of dental caries.

Candida albicans (*C. albicans*) is a colonizer of dental caries in children and adults. It has an important role in caries evolution due to the production of some organic acids and dietary sugars in the dental

plaque [Klinke 2009]. Polyphenols of green tea (1.25 $\mu\text{g/mL}$) and *Padma Hepaten* (0.16 $\mu\text{g/mL}$) can inhibit the growth of *C. albicans* by 88% and prevent biofilm formation for orthodontic patients [Farkash 2018].

Farkash et al. [Farkash 2018] used scanning electron microscopy to observe the reduction in cell number and the morphology changes of *C. albicans* in the untreated group, in the group treated with green tea polyphenols and in the group treated with green tea polyphenols and *Padma Hepaten*. The group treated with both plant polyphenols may affect *C. albicans* morphology that contains more yeast shaped cells and less hyphal cells (Figure 7).

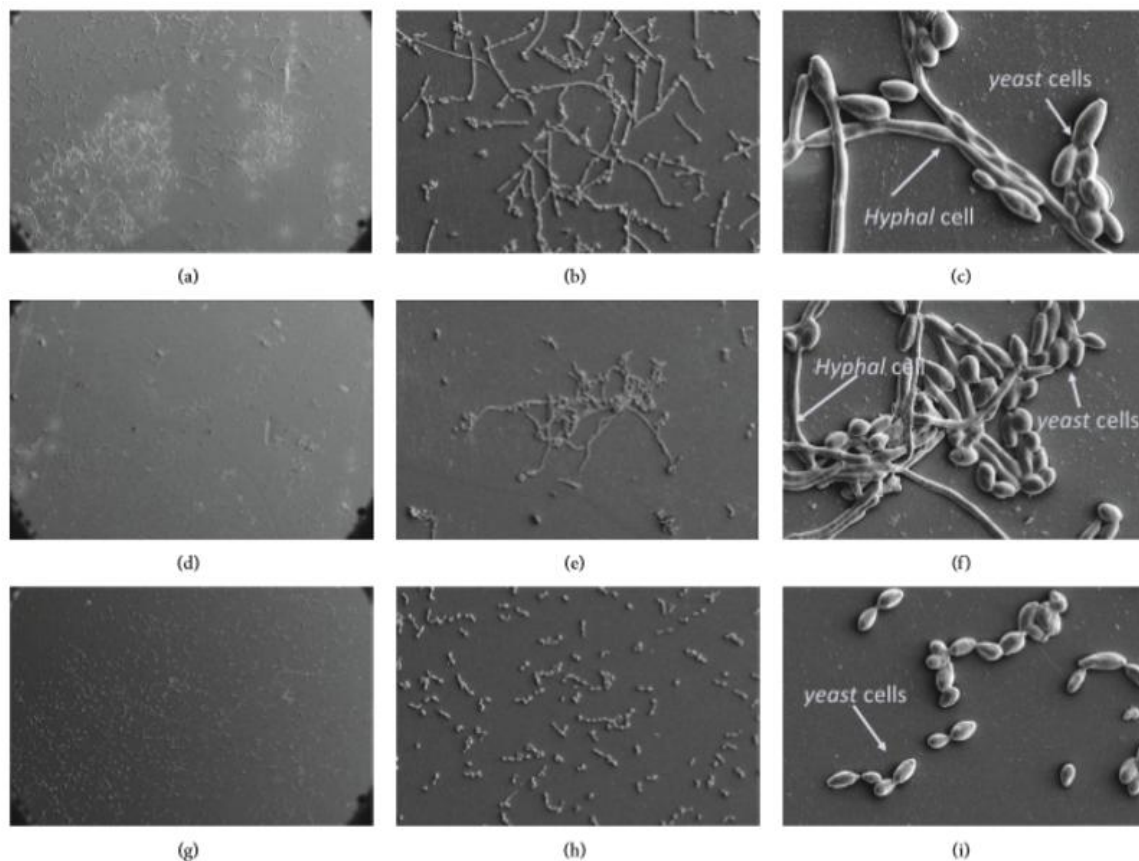


Figure 7. Morphology of the biofilm on orthodontic polyvinyl chloride using scanning electron microscopy at 200x, 1000x and 5000x magnifications, respectively. (a, b, c) untreated group, (d, e, f) green tea polyphenols, (g, h, i) green tea and *Padma Hepaten* polyphenols. Modified from Ref. [Farkash 2018] with authorization.

Accordingly, a recent study [Farkash 2019] showed the ability of the polyphenols in green tea and *Padma Hepaten* in the inhibition of the caries-inducing properties of *S. mutans* and *C. albicans*.

Thymus capitatus (TC) and *Citrus limon var. pompia* showed antimicrobial capacity against *S. mutans*; but only TC was effective as a fungicidal compound against *C. albicans* able to kill 70% of them. TC is hence a promising plant to prevent caries lesions [Pinna 2019].

Polyphenol-rich cranberry could inhibit the cariogenic factors of *S. mutans*-*C. albicans* biofilms by reducing its acidogenicity and metabolic activity [Philip 2019].

Poly (methyl methacrylate) (PMMA) is a denture based material that was blended with Curcumin, a polyphenol with potent biological effects. The results of Alawan et al. showed that 50 $\mu\text{g/mL}$ of curcumin reduces the adhesion of *C. albicans* biofilms on dental materials [Alalwan 2017].

Polyphenols contained in tea such as tannins, catechin and caffeine as well as fluoride containing compounds contribute to increase its resistance against acid solutions [Yu 1995].

Green tea polyphenols (TP) mixed with nano-sized calcium phosphate particles (TP-CaP) were used in enamel caries lesions [He 2015]. Various TP concentrations (0, 1.2, 12, 18, and 27 mg/mL) were used in the crystal syntheses. The highest concentration (12-27 mg/mL) changed the structure and the crystal

size from micro-sized plates with porous faces to nano-sized globular particles. The results of this study also showed that adding tea polyphenols to calcium phosphate particles provide an antibacterial effect and enhance the remineralization process. Therefore, this TP-CaP composites could be a promising additive in toothpastes.

Some polyphenols extracted from many plants as *Thymus* species demonstrated an anti-adherent activity against oral bacteria on the enamel surfaces [Schött 2017]. An *in vitro* study on enamel surface using an antioxidant rich-apple (essentially quercetin, epicatechin, procyanidin B2, vitamin C, phloretin and chlorogenic acid) against *S. mutans* biofilms showed that its polyphenolic compounds decreased the demineralization rate of enamel which is produced by *S. mutans* biofilms [Giacaman 2014].

A polyphenol containing mouth rinse bath is recommended for its ability to reduce bacterial colonization and adherence on the surface of enamel [Hannig 2008, Hannig 2011, Hannig 2009].

Quercetin and resveratrol or a mixture of both were also used for dentin pretreatment to promote and stabilize the resin-dentin bond [Porto 2018]. Different concentrations were used (100, 250, 500, or 1,000 µg/mL) for 60 s followed by a two-step etch-and-rinse adhesive. The adhesion measurements were made after immersion in water for 1 day and four months, and revealed that the resveratrol and the 1:1 resveratrol-quercetin mixture had the best performance after 4 months. Resveratrol pretreatment showed lower bond strength values than quercetin after 1 day, due probably to its variety of antioxidative mechanisms. Therefore, the polyphenols used in this study demonstrated a protective effect on the dentin collagen matrix [Porto 2018].

Galla Chinensis compounds are polyphenols exhibiting an antioxidant and antibacterial activity [Guo 2012]. Their study compared the effect of 4000 mg/L of *Galla Chinensis* extract with deionized water or a remineralizing solution on the subsurface root lesions and erosive root lesions. They demonstrated that the *Galla Chinensis* extract enhances the remineralization of root lesions (Figure 8) more than deionized water or a remineralizing solution containing 1.5 mmol/L CaCl₂, 0.9 mmol/L KH₂PO₄, 130 mmol/L KCl, 1 mmol/L NaN₃ and 20 mmol/L Hepes buffer. The *Galla Chinensis* extract also inhibits the activity of collagenase and protects the collagen fibers against enzymatic degradation [Guo 2012].

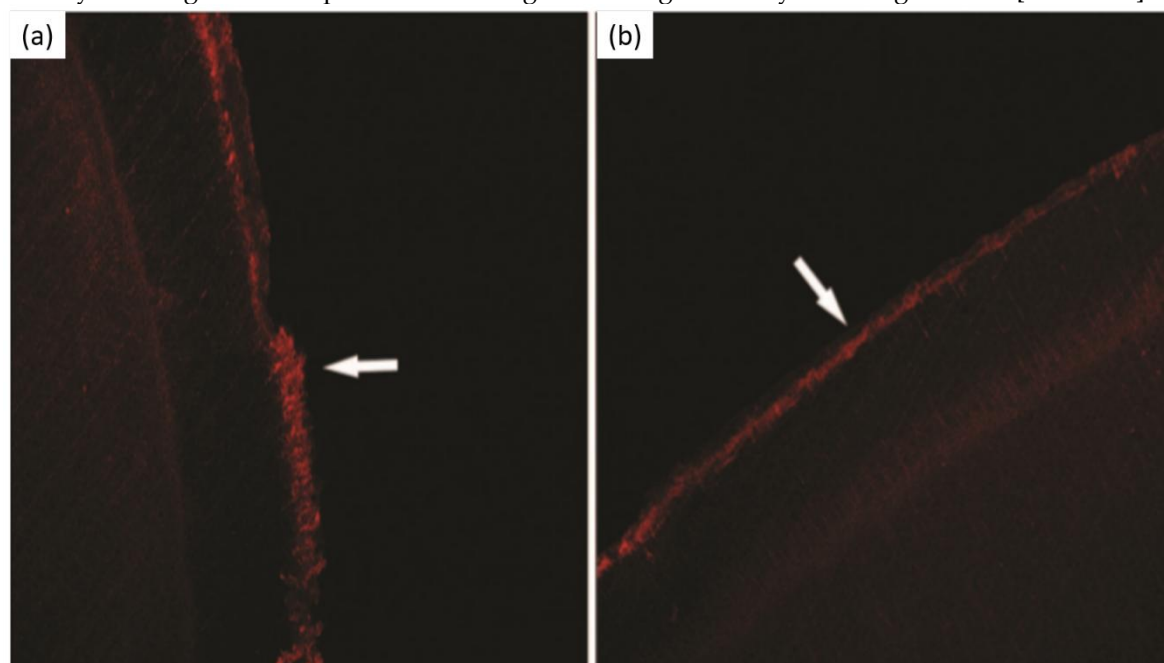


Figure 8. Laser scanning confocal microscopy micrographs. (a) Subsurface lesion, (b) Subsurface lesion after *Galla Chinensis* extract treatment. Modified from Ref. [Guo 2012] with authorization.

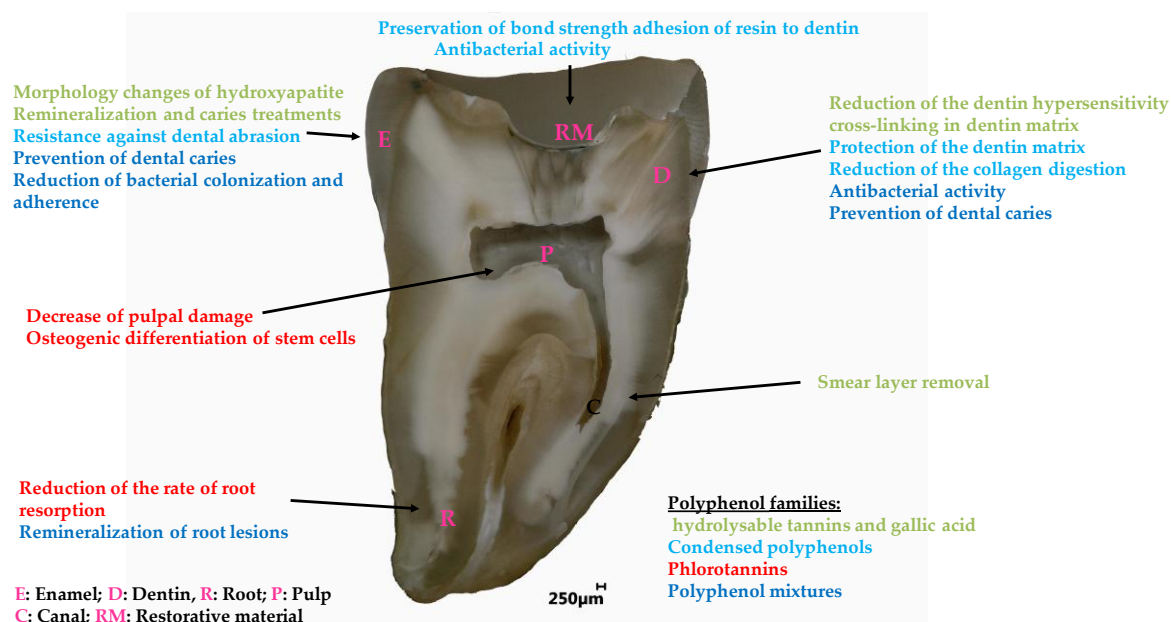
Biodegradable chitosan chips containing propolis was used in the treatment of vital pulpotomy [Balata 2018]. The study of Balata et al. compared the effect of propolis polyphenols (caffeic acid,

quercetin, rutin and chrysin) and formocresol (the gold standard dressing agent in pulpotomy) in the inflammatory response and hard tissue formation. They demonstrated that the propolis samples induced mild or no inflammation compared with formocresol samples. Thus formulation of propolis extract as chitosan biodegradable chips (3% propolis, 1.8% chitosan, 0.2% hydroxypropyl methyl cellulose, 5% propylene glycol) can be used in pulpotomy and in the infected periodontal pockets. These results may be due to the anti-inflammatory activity of propolis which is rich in polyphenols that inhibit the lipoxigenase pathway of arachidonic acid.

Finally, we can conclude that many natural agents present in many habit drinks and plants could prevent dental caries by killing and reducing the amount of bacteria, removing the dental plaque or inhibiting the adherence of bacteria and biofilms on the dental surfaces.

6. Future Perspectives and Concluding Remark

Polyphenolics whatever their classification as condensed polyphenols, phlorotannins, hydrolysable tannins or mixtures thereof allow to easily modify the surface properties of dentin, mainly through interactions with collagen, and enamel affording them with better adhesive properties and antibacterial activity against a broad range of microorganisms present in the proximity of the teeth. All these properties are summarized in Scheme 1.



Scheme 1: Overview of the applications of polyphenols in the engineering of dental materials.

Future investigations will aim to better understand, and master the use of polyphenols in dental remineralization processes as they are also able to interact with phosphates.

Even if the literature describing the use of polyphenols in dental material engineering is vast, as seen in this review, it seems important to develop combinatorial approaches to select the best possible candidates for a required application.

Author Contributions: Conceptualization, N.K. and V.B.; methodology, N.K. and V.B.; resources, N.K. and V.B.; data curation, Y.H. and V.B.; writing—original draft preparation, N.K. and V.B.; writing—review and editing, N.K. and V.B.; visualization, Y.H. and V.B.; supervision, V.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pérez-Jiménez, J.; Neveu, V.; Vos, F.; Scalbert, A. Identification of the 100 richest dietary sources of polyphenols: an application of the Phenol-Explorer database. *Eur J Clin Nutr* **2010**, *64 Suppl 3*, S112–120.
2. Handique, J.G.; Baruah, J.B. Polyphenolic compounds: an overview. *Reactive and Functional Polymers* **2002**, *52*, 163–188.
3. Reitzer, F.; Allais, M.; Ball, V.; Meyer, F. Polyphenols at interfaces. *Adv Colloid Interface Sci* **2018**, *257*, 31–41.
4. Petti, S.; Scully, C. Polyphenols, oral health and disease: A review. *J Dent* **2009**, *37*, 413–423.
5. Sánchez, M.C.; Ribeiro-Vidal, H.; Esteban-Fernández, A.; Bartolomé, B.; Figuero, E.; Moreno-Arribas, M.V.; Sanz, M.; Herrera, D. Antimicrobial activity of red wine and oenological extracts against periodontal pathogens in a validated oral biofilm model. *BMC Complement Altern Med* **2019**, *19*, art. 145.
6. Fibach, E.; Ginsburg, I. The Antioxidant Effect of Fermented Papaya Preparation in the Oral Cavity. *Phytother Res* **2015**, *29*, 1317–1322.
7. Sileika, T.S.; Barrett, D.G.; Zhang, R.; Lau, K.H.A.; Messersmith, P.B. Colorless multifunctional coatings inspired by polyphenols found in tea, chocolate, and wine. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 10766–10770.
8. Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. Plant polyphenols: chemical properties, biological activities, and synthesis. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 586–621.
9. Le Bourvellec, C.; Renard, C.M.G.C. Interactions between polyphenols and macromolecules: quantification methods and mechanisms. *Crit Rev Food Sci Nutr* **2012**, *52*, 213–248.
10. Marshall, G.W.; Marshall, S.J.; Kinney, J.H.; Balooch, M. The dentin substrate: structure and properties related to bonding. *J Dent* **1997**, *25*, 441–458.
11. Kharouf, N.; Rapp, G.; Mancino, D.; Hemmerlé, J.; Haikel, Y.; Reitzer, F. Effect of etching the coronal dentin with the rubbing technique on the microtensile bond strength of a universal adhesive system. *Dent Med Probl* **2019**, *56*, 343–348.
12. Osorio, R.; Yamauti, M.; Osorio, E.; Ruiz-Requena, M.E.; Pashley, D.; Tay, F.; Toledano, M. Effect of dentin etching and chlorhexidine application on metalloproteinase-mediated collagen degradation. *Eur. J. Oral Sci.* **2011**, *119*, 79–85.
13. Toledano, M.; Osorio, R.; Osorio, E.; Aguilera, F.S.; Yamauti, M.; Pashley, D.H.; Tay, F. Effect of bacterial collagenase on resin-dentin bonds degradation. *J Mater Sci Mater Med* **2007**, *18*, 2355–2361.
14. Mazzoni, A.; Nascimento, F.D.; Carrilho, M.; Tersariol, I.; Papa, V.; Tjäderhane, L.; Di Lenarda, R.; Tay, F.R.; Pashley, D.H.; Breschi, L. MMP activity in the hybrid layer detected with in situ zymography. *J. Dent. Res.* **2012**, *91*, 467–472.
15. Aguiar, T.R.; Vidal, C.M.P.; Phansalkar, R.S.; Todorova, I.; Napolitano, J.G.; McAlpine, J.B.; Chen, S.N.; Pauli, G.F.; Bedran-Russo, A.K. Dentin biomodification potential depends on polyphenol source. *J. Dent. Res.* **2014**, *93*, 417–422.
16. Vidal, C.M.P.; Leme, A.A.; Aguiar, T.R.; Phansalkar, R.; Nam, J.-W.; Bisson, J.; McAlpine, J.B.; Chen, S.-N.; Pauli, G.F.; Bedran-Russo, A. Mimicking the hierarchical functions of dentin collagen cross-links with plant derived phenols and phenolic acids. *Langmuir* **2014**, *30*, 14887–14893.
17. Leme-Kraus, A.A.; Aydin, B.; Vidal, C.M.P.; Phansalkar, R.M.; Nam, J.W.; McAlpine, J.; Pauli, G.F.; Chen, S.; Bedran-Russo, A.K. Biostability of the Proanthocyanidins-Dentin Complex and Adhesion Studies. *J. Dent. Res.* **2017**, *96*, 406–412.
18. Tang, C.; Fang, M.; Liu, R.; Dou, Q.; Chai, Z.; Xiao, Y.; Chen, J. The role of grape seed extract in the remineralization of demineralized dentine: micromorphological and physical analyses.

Arch. Oral Biol. **2013**, *58*, 1769–1776.

19. Nam, J.-W.; Phansalkar, R.S.; Lankin, D.C.; Bisson, J.; McAlpine, J.B.; Leme, A.A.; Vidal, C.M.P.; Ramirez, B.; Niemitz, M.; Bedran-Russo, A.; et al. Subtle Chemical Shifts Explain the NMR Fingerprints of Oligomeric Proanthocyanidins with High Dentin Biomodification Potency. *J. Org. Chem.* **2015**, *80*, 7495–7507.
20. Phansalkar, R.S.; Nam, J.-W.; Chen, S.-N.; McAlpine, J.B.; Napolitano, J.G.; Leme, A.; Vidal, C.M.P.; Aguiar, T.; Bedran-Russo, A.K.; Pauli, G.F. A galloylated dimeric proanthocyanidin from grape seed exhibits dentin biomodification potential. *Fitoterapia* **2015**, *101*, 169–178.
21. Xu, X.; Zhou, X.D.; Wu, C.D. The tea catechin epigallocatechin gallate suppresses cariogenic virulence factors of *Streptococcus mutans*. *Antimicrob. Agents Chemother.* **2011**, *55*, 1229–1236.
22. Hara, K.; Ohara, M.; Hayashi, I.; Hino, T.; Nishimura, R.; Iwasaki, Y.; Ogawa, T.; Ohyama, Y.; Sugiyama, M.; Amano, H. The green tea polyphenol (-)-epigallocatechin gallate precipitates salivary proteins including alpha-amylase: biochemical implications for oral health. *Eur. J. Oral Sci.* **2012**, *120*, 132–139.
23. Feng, L.; Yan, Q.; Zhang, B.; Tian, X.; Wang, C.; Yu, Z.; Cui, J.; Guo, D.; Ma, X.; James, T.D. Ratiometric fluorescent probe for sensing *Streptococcus mutans* glucosyltransferase, a key factor in the formation of dental caries. *Chem. Commun. (Camb.)* **2019**, *55*, 3548–3551.
24. Melok, A.L.; Lee, L.H.; Mohamed Yussof, S.A.; Chu, T. Green Tea Polyphenol Epigallocatechin-3-Gallate-Stearate Inhibits the Growth of *Streptococcus mutans*: A Promising New Approach in Caries Prevention. *Dent J (Basel)* **2018**, *6*, art. 38;
25. Lucas, P.W.; Wagner, M.; Al-Fadhalah, K.; Almusallam, A.S.; Michael, S.; Thai, L.A.; Strait, D.S.; Swain, M.V.; van Casteren, A.; Renno, W.M.; et al. Dental abrasion as a cutting process. *Interface Focus* **2016**, *6*, art. 20160008.
26. Bedran-Russo, A.K.B.; Yoo, K.J.; Ema, K.C.; Pashley, D.H. Mechanical properties of tannic-acid-treated dentin matrix. *J. Dent. Res.* **2009**, *88*, 807–811.
27. Zhang, L.; Huang, L.; Xiong, Y.; Fang, M.; Chen, J.-H.; Ferrari, M. Effect of post-space treatment on retention of fiber posts in different root regions using two self-etching systems. *Eur. J. Oral Sci.* **2008**, *116*, 280–286.
28. Kharouf, N.; Mancino, D.; Naji-Amrani, A.; Eid, A.; Haikel, Y.; Hemmerle, J. Effectiveness of Etching by Three Acids on the Morphological and Chemical Features of Dentin Tissue. *J Contemp Dent Pract* **2019**, *20*, 915–919.
29. Gu, X.-H.; Mao, C.-Y.; Liang, C.; Wang, H.-M.; Kern, M. Does endodontic post space irrigation affect smear layer removal and bonding effectiveness? *Eur. J. Oral Sci.* **2009**, *117*, 597–603.
30. Liu, Y.; Bai, X.; Li, S.; Liu, Y.; Keightley, A.; Wang, Y. Molecular weight and galloylation affect grape seed extract constituents' ability to cross-link dentin collagen in clinically relevant time. *Dent Mater* **2015**, *31*, 814–821.
31. Santiago, S.L.; Osorio, R.; Neri, J.R.; Carvalho, R.M.; Toledano, M. Effect of the flavonoid epigallocatechin-3-gallate on resin-dentin bond strength. *J Adhes Dent* **2013**, *15*, 535–540.
32. Singh, P.; Nagpal, R.; Singh, U.P. Effect of dentin biomodifiers on the immediate and long-term bond strengths of a simplified etch and rinse adhesive to dentin. *Restor Dent Endod* **2017**, *42*, 188–199.
33. Fialho, M.P.N.; Hass, V.; Nogueira, R.P.; França, F.M.G.; Turssi, C.P.; Basting, R.T.; Amaral, F.L.B. Effect of epigallocatechin-3-gallate solutions on bond durability at the adhesive interface in caries-affected dentin. *J Mech Behav Biomed Mater* **2019**, *91*, 398–405.
34. Costa, C.A.G. de; Passos, V.F.; Neri, J.R.; Mendonça, J.S.; Santiago, S.L. Effect of Metalloproteinase Inhibitors on Bond Strength of a Self-etching Adhesive on Erosively Demineralized Dentin. *J Adhes Dent* **2019**, *21*, 337–344.
35. Kalaiselvam, R.; Ganesh, A.; Rajan, M.; Kandaswamy, D. Evaluation of bioflavonoids on the immediate and delayed microtensile bond strength of self-etch and total-etch adhesive systems to sound dentin. *Indian J Dent Res* **2018**, *29*, 133–136.
36. Lee, P.; Tan, K.S. Effects of Epigallocatechin gallate against *Enterococcus faecalis* biofilm and

virulence. *Arch. Oral Biol.* **2015**, *60*, 393–399.

37. Yu, H.-H.; Zhang, L.; Xu, S.; Li, F.; Yu, F.; Liu, Z.-Y.; Huang, L.; Chen, J.-H. Effects of Epigallocatechin-3-gallate (EGCG) on the bond strength of fiber posts to Sodium hypochlorite (NaOCl) treated intraradicular dentin. *Sci Rep* **2017**, *7*, art. 4235.
38. Pheenithicharoenkul, S.; Panichuttra, A. Epigallocatechin-3-gallate increased the push out bond strength of an epoxy resin sealer to root dentin. *Dent Mater J* **2016**, *35*, 888–892.
39. Yang, W.-H.; Deng, Y.-T.; Kuo, M.Y.-P.; Liu, C.-M.; Chang, H.-H.; Chang, J.Z.-C. Epigallocatechin-3-gallate blocks triethylene glycol dimethacrylate-induced cyclooxygenase-2 expression by suppressing extracellular signal-regulated kinase in human dental pulp and embryonic palatal mesenchymal cells. *J Endod* **2013**, *39*, 1407–1412.
40. Hirao, K.; Yumoto, H.; Nakanishi, T.; Mukai, K.; Takahashi, K.; Takegawa, D.; Matsuo, T. Tea catechins reduce inflammatory reactions via mitogen-activated protein kinase pathways in toll-like receptor 2 ligand-stimulated dental pulp cells. *Life Sci.* **2010**, *86*, 654–660.
41. Nakanishi, T.; Mukai, K.; Yumoto, H.; Hirao, K.; Hosokawa, Y.; Matsuo, T. Anti-inflammatory effect of catechin on cultured human dental pulp cells affected by bacteria-derived factors. *Eur. J. Oral Sci.* **2010**, *118*, 145–150.
42. Nakanishi, T.; Mukai, K.; Hosokawa, Y.; Takegawa, D.; Matsuo, T. Catechins inhibit vascular endothelial growth factor production and cyclooxygenase-2 expression in human dental pulp cells. *Int Endod J* **2015**, *48*, 277–282.
43. Wang, F.; Han, Y.; Xi, S.; Lu, Y. Catechins reduce inflammation in lipopolysaccharide-stimulated dental pulp cells by inhibiting activation of the NF- κ B pathway. *Oral Dis* **2020**, *26*, 815–821.
44. Kwon, Y.-S.; Kim, H.-J.; Hwang, Y.-C.; Rosa, V.; Yu, M.-K.; Min, K.-S. Effects of Epigallocatechin Gallate, an Antibacterial Cross-linking Agent, on Proliferation and Differentiation of Human Dental Pulp Cells Cultured in Collagen Scaffolds. *J Endod* **2017**, *43*, 289–296.
45. Lim, E.; Lim, M.-J.; Min, K.-S.; Kwon, Y.-S.; Hwang, Y.-C.; Yu, M.-K.; Hong, C.-U.; Lee, K.-W. Effects of epicatechin, a crosslinking agent, on human dental pulp cells cultured in collagen scaffolds. *J Appl Oral Sci* **2016**, *24*, 76–84.
46. Lee, D.-S.; Li, B.; Kim, K.-S.; Jeong, G.-S.; Kim, E.-C.; Kim, Y.-C. Butein protects human dental pulp cells from hydrogen peroxide-induced oxidative toxicity via Nrf2 pathway-dependent heme oxygenase-1 expressions. *Toxicol In Vitro* **2013**, *27*, 874–881.
47. Park, S.Y.; Jeong, Y.J.; Kim, S.H.; Jung, J.Y.; Kim, W.J. Epigallocatechin gallate protects against nitric oxide-induced apoptosis via scavenging ROS and modulating the Bcl-2 family in human dental pulp cells. *J Toxicol Sci* **2013**, *38*, 371–378.
48. Frassetto, A.; Breschi, L.; Turco, G.; Marchesi, G.; Di Lenarda, R.; Tay, F.R.; Pashley, D.H.; Cadenaro, M. Mechanisms of degradation of the hybrid layer in adhesive dentistry and therapeutic agents to improve bond durability--A literature review. *Dent Mater* **2016**, *32*, e41–53.
49. Dutra-Correa, M.; Leite, A.A.B.V.; de Cara, S.P.H.M.; Diniz, I.M.A.; Marques, M.M.; Suffredini, I.B.; Fernandes, M.S.; Toma, S.H.; Araki, K.; Medeiros, I.S. Antibacterial effects and cytotoxicity of an adhesive containing low concentration of silver nanoparticles. *J Dent* **2018**, *77*, 66–71.
50. Mishra, P.; Jaiswal, S.; Nikhil, V.; Gupta, S.; Jha, P.; Raj, S. Evaluation of marginal sealing ability of self-adhesive flowable composite resin in Class II composite restoration: An in vitro study. *J Conserv Dent* **2018**, *21*, 363–368.
51. Hong, J.-Y.; Yon, J.; Lee, J.-S.; Lee, I.-K.; Yang, C.; Kim, M.-S.; Choi, S.-H.; Jung, U.-W. Effects of epigallocatechin-3-gallate on the healing of extraction sockets with a periapical lesion: A pilot study in dogs. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2015**, *103*, 727–734.
52. de Assis, J.S.; Lima, R.A.; Marques Lima, J.P.; Azevedo Rodrigues, L.K.; Santiago, S.L. Effect of epigallocatechin-3-gallate application for remaining carious dentin disinfection. *J Conserv Dent*

2015, 18, 51–55, doi:10.4103/0972-0707.148896.

53. Neri, J.R.; Yamauti, M.; Feitosa, V.P.; Pires, A.P.M.; Araújo, R.D.S.; Santiago, S.L. Physicochemical properties of a methacrylate-based dental adhesive incorporated with epigallocatechin-3-gallate. *Braz Dent J* **2014**, 25, 528–531.
54. Fonseca, B.M.; Barcellos, D.C.; Silva, T.M. da; Borges, A.L.S.; Cavalcanti, B. das N.; Prakki, A.; Oliveira, H.P.M. de; Gonçalves, S.E. de P. Mechanical-physicochemical properties and biocompatibility of catechin-incorporated adhesive resins. *J Appl Oral Sci* **2019**, 27, e20180111.
55. Mankovskaia, A.; Lévesque, C.M.; Prakki, A. Catechin-incorporated dental copolymers inhibit growth of *Streptococcus mutans*. *J Appl Oral Sci* **2013**, 21, 203–207.
56. Du, X.; Huang, X.; Huang, C.; Wang, Y.; Zhang, Y. Epigallocatechin-3-gallate (EGCG) enhances the therapeutic activity of a dental adhesive. *J Dent* **2012**, 40, 485–492.
57. de Macedo, F.A.A.; Souza, N.O.; Lemos, M.V.S.; De-Paula, D.M.; Santiago, S.L.; Feitosa, V.P. Dentin bonding and physicochemical properties of adhesives incorporated with epigallocatechin-3-gallate. *Odontology* **2019**, 107, 23–28.
58. Albuquerque, N.; Neri, J.R.; Lemos, M.; Yamauti, M.; de Sousa, F.; Santiago, S.L. Effect of Polymeric Microparticles Loaded With Catechin on the Physicochemical Properties of an Adhesive System. *Oper Dent* **2019**, 44, E202–E211.
59. Yu, H.H.; Zhang, L.; Yu, F.; Zhou, H.; Shen, L.J.; Chen, J.H. [Effects of epigallocatechin-3-gallate modification on the bonding stability of an etch-and-rinse adhesive to intraradicular dentin]. *Zhonghua Kou Qiang Yi Xue Za Zhi* **2017**, 52, 114–119.
60. Hanks, C.T.; Strawn, S.E.; Wataha, J.C.; Craig, R.G. Cytotoxic effects of resin components on cultured mammalian fibroblasts. *J. Dent. Res.* **1991**, 70, 1450–1455.
61. Hu, J.; Du, X.; Huang, C.; Fu, D.; Ouyang, X.; Wang, Y. Antibacterial and physical properties of EGCG-containing glass ionomer cements. *J Dent* **2013**, 41, 927–934.
62. Zheng, K.; Wu, S.; Chen, B.; Liao, W.; Li, Y. [Effect of baicalein and quercetin on enzymatic resistance of dentin collagen]. *Zhonghua Kou Qiang Yi Xue Za Zhi* **2014**, 49, 667–671.
63. Kim, J.-G.; Son, K.M.; Park, H.C.; Zhu, T.; Kwon, J.H.; Yang, H.-C. Stimulating effects of quercetin and phenamil on differentiation of human dental pulp cells. *Eur. J. Oral Sci.* **2013**, 121, 559–565.
64. Mahmoud Hashemi, A.; Solahaye Kahnamouii, S.; Aghajani, H.; Frozannia, K.; Pournasrollah, A.; Sadegh, R.; Esmaeeli, H.; Ghadimi, Y.; Razmpa, E. Quercetin Decreases Th17 Production by Down-Regulation of MAPK- TLR4 Signaling Pathway on T Cells in Dental Pulpitis. *J Dent (Shiraz)* **2018**, 19, 259–264.
65. Yonehiro, J.; Yoshida, Y.; Yamashita, A.; Yoshizawa, S.; Ohta, K.; Kamata, N.; Okihara, T.; Nishimura, F. Flavonol-containing phosphorylated pullulan may attenuate pulp inflammation. *Int Endod J* **2013**, 46, 119–127.
66. Yang, H.; Li, K.; Yan, H.; Liu, S.; Wang, Y.; Huang, C. High-performance therapeutic quercetin-doped adhesive for adhesive-dentin interfaces. *Sci Rep* **2017**, 7, art. 8189.
67. Gotti, V.B.; Feitosa, V.P.; Sauro, S.; Correr-Sobrinho, L.; Leal, F.B.; Stansbury, J.W.; Correr, A.B. Effect of antioxidants on the dentin interface bond stability of adhesives exposed to hydrolytic degradation. *J Adhes Dent* **2015**, 17, 35–44.
68. Wang, F.-M.; Hu, Z.; Liu, X.; Feng, J.Q.; Augsburg, R.A.; Gutmann, J.L.; Glickman, G.N. Resveratrol represses tumor necrosis factor α /c-Jun N-terminal kinase signaling via autophagy in human dental pulp stem cells. *Arch. Oral Biol.* **2019**, 97, 116–121.
69. Geng, Y.-W.; Zhang, Z.; Liu, M.-Y.; Hu, W.-P. Differentiation of human dental pulp stem cells into neuronal by resveratrol. *Cell Biol. Int.* **2017**, 41, 1391–1398.
70. Lee, S.-I.; Min, K.-S.; Bae, W.-J.; Lee, Y.-M.; Lee, S.-Y.; Lee, E.-S.; Kim, E.-C. Role of SIRT1 in heat stress- and lipopolysaccharide-induced immune and defense gene expression in human dental pulp cells. *J Endod* **2011**, 37, 1525–1530.
71. Feng, G.; Zheng, K.; Song, D.; Xu, K.; Huang, D.; Zhang, Y.; Cao, P.; Shen, S.; Zhang, J.; Feng, X.; et al. SIRT1 was involved in TNF- α -promoted osteogenic differentiation of human DPSCs

through Wnt/ β -catenin signal. *In Vitro Cell. Dev. Biol. Anim.* **2016**, *52*, 1001–1011.

72. Atalayin, C.; Armagan, G.; Konyalioglu, S.; Kemaloglu, H.; Tezel, H.; Ergucu, Z.; Keser, A.; Dagci, T.; Onal, B. The protective effect of resveratrol against dentin bonding agents-induced cytotoxicity. *Dent Mater J* **2015**, *34*, 766–773.
73. Atalayin, C.; Tezel, H.; Ergucu, Z.; Unlu, N.; Armagan, G.; Dagci, T.; Kose, T. The improvement of biocompatibility of adhesives : The effects of resveratrol on biocompatibility and dentin micro-tensile bond strengths of self-etch adhesives. *Clin Oral Investig* **2019**, *23*, 3213–3218.
74. Liu, X.-C.; Wang, X.-X.; Zhang, L.-N.; Yang, F.; Nie, F.-J.; Zhang, J. Inhibitory effects of resveratrol on orthodontic tooth movement and associated root resorption in rats. *Arch. Oral Biol.* **2020**, *111*, art. 104642.
75. Barbosa, G.L. de R.; Pimenta, L.A.; Almeida, S.M. de Micro-CT evaluation of the radioprotective effect of resveratrol on the mandibular incisors of irradiated rats. *Braz Oral Res* **2016**, *30*.
76. Moreira, M.A.; Souza, N.O.; Sousa, R.S.; Freitas, D.Q.; Lemos, M.V.; De Paula, D.M.; Maia, F.J.N.; Lomonaco, D.; Mazzetto, S.E.; Feitosa, V.P. Efficacy of new natural biomodification agents from Anacardiaceae extracts on dentin collagen cross-linking. *Dent Mater* **2017**, *33*, 1103–1109.
77. Mukai, Y.; Tomiyama, K.; Okada, S.; Mukai, K.; Negishi, H.; Fujihara, T.; Teranaka, T. Dentinal tubule occlusion with lanthanum fluoride and powdered apatite glass ceramics in vitro. *Dent Mater J* **1998**, *17*, 253–263.
78. Mancino, D.; Kharouf, N.; Hemmerlé, J.; Haïkel, Y. Microscopic and Chemical Assessments of the Filling Ability in Oval-Shaped Root Canals Using Two Different Carrier-Based Filling Techniques. *Eur J Dent* **2019**, *13*, 166–171.
79. Haapasalo, M.; Shen, Y.; Wang, Z.; Gao, Y. Irrigation in endodontics. *Br Dent J* **2014**, *216*, 299–303.
80. Bitter, N.C. A 25% tannic acid solution as a root canal irrigant cleanser: a scanning electron microscope study. *Oral Surg. Oral Med. Oral Pathol.* **1989**, *67*, 333–337.
81. Bitter, N.C. Tannic acid for smear layer removal: pilot study with scanning electron microscope. *J Prosthet Dent* **1989**, *61*, 503–507.
82. Bitter, N.C. The effect of 25% tannic acid on prepared dentin: a scanning electron microscope-methylene blue dye study. *J Prosthet Dent* **1990**, *64*, 12–16.
83. Sabbak, S.A.; Hassanin, M.B. A scanning electron microscopic study of tooth surface changes induced by tannic acid. *J Prosthet Dent* **1998**, *79*, 169–174.
84. Takahashi, H.; Okamoto, Y.; Fujinaka, S.; Shintani, H. A pilot study of exposure of the smear layer to tannic acid solutions. *J Prosthet Dent* **1993**, *70*, 261–263.
85. Yamaga, M.; Koide, T.; Hieda, T. Adhesiveness of glass ionomer cement containing tannin-fluoride preparation (HY agent) to dentin--an evaluation of adding various ratios of HY agent and combination with application diammine silver fluoride. *Dent Mater J* **1993**, *12*, 36–44.
86. Okamoto, Y.; Shintani, H.; Yamaki, M. A medicated polycarboxylate cement to prevent complications in composite resin therapy. *J Prosthet Dent* **1990**, *63*, 37–40.
87. Hu, J.C.-C.; Chun, Y.-H.P.; Al Hazzazzi, T.; Simmer, J.P. Enamel formation and amelogenesis imperfecta. *Cells Tissues Organs (Print)* **2007**, *186*, 78–85.
88. Lacruz, R.S.; Habelitz, S.; Wright, J.T.; Paine, M.L. Dental enamel formation and implications for oral health and diseases. *Physiol. Rev.* **2017**, *97*, 939–993.
89. Hannig, M.; Hannig, C. The pellicle and erosion. *Monogr Oral Sci* **2014**, *25*, 206–214.
90. Babaeekhou, L.; Ghane, M. Antimicrobial activity of ginger on cariogenic bacteria: molecular networking and molecular docking analyses. *J. Biomol. Struct. Dyn.* **2020**, 1–12.
91. Kolahi, J.; Fazilati, M.; Kadivar, M. Towards tooth friendly soft drinks. *Med. Hypotheses* **2009**, *73*, 524–525.
92. Veloz, J.J.; Alvear, M.; Salazar, L.A. Antimicrobial and Antibiofilm Activity against

- Streptococcus mutans of Individual and Mixtures of the Main Polyphenolic Compounds Found in Chilean Propolis. *Biomed Res Int* **2019**, 2019, 7602343.
93. Zhang, J.; Huang, X.; Huang, S.; Deng, M.; Xie, X.; Liu, M.; Liu, H.; Zhou, X.; Li, J.; Ten Cate, J.M. Changes in composition and enamel demineralization inhibition activities of gallic acid at different pH values. *Acta Odontol. Scand.* **2015**, 73, 595–601.
 94. Huang, X.-L.; Liu, M.-D.; Li, J.-Y.; Zhou, X.-D.; ten Cate, J.M. Chemical composition of Galla chinensis extract and the effect of its main component(s) on the prevention of enamel demineralization in vitro. *Int J Oral Sci* **2012**, 4, 146–151.
 95. Gao, S.S.; Qian, L.M.; Huang, S.B.; Yu, H.Y. Effect of gallic acid on the wear behavior of early carious enamel. *Biomed Mater* **2009**, 4, 034101.
 96. Oh, S.; Gu, Y.; Perinpanayagam, H.; Yoo, Y.-J.; Lee, Y.; Kim, R.K.; Chang, S.W.; Lee, J.; Zhu, Q.; Kum, K.Y. Dentinal tubule sealing effects of 532-nm diode-pumped solid-state laser, gallic acid/Fe³⁺ complex, and three commercial dentin desensitizers. *Lasers Med Sci* **2018**, 33, 1237–1244.
 97. Ejima, H.; Richardson, J.J.; Liang, K.; Best, J.P.; van Koeverden, M.P.; Such, G.K.; Cui, J.; Caruso, F. One-step assembly of coordination complexes for versatile film and particle engineering. *Science* **2013**, 341, 154–157.
 98. Christopher, S.R.; Mathai, V.; Nair, R.S.; Angelo, J.M.C. The effect of three different antioxidants on the dentinal tubular penetration of Resilon and Real Seal SE on sodium hypochlorite-treated root canal dentin: An in vitro study. *J Conserv Dent* **2016**, 19, 161–165.
 99. Oguz Ahmet, B.S.; Sayin Ozel, G.; Mutluay, M.M.; Tezvergil Mutluay, A. Effect of gallic acid addition on some mechanical properties of self-adhesive resin cements. *Braz Oral Res* **2019**, 33, e053.
 100. Juntavee, A.; Peerapattana, J.; Ratanathongkam, A.; Nualkaew, N.; Chatchiwiwattana, S.; Treesuwan, P. The Antibacterial Effects of Apacaries Gel on Streptococcus mutans: An in vitro Study. *Int J Clin Pediatr Dent* **2014**, 7, 77–81.
 101. Tang, B.; Yuan, H.; Cheng, L.; Zhou, X.; Huang, X.; Li, J. Effects of gallic acid on the morphology and growth of hydroxyapatite crystals. *Arch. Oral Biol.* **2015**, 60, 167–173.
 102. Tang, B.; Yuan, H.; Cheng, L.; Zhou, X.; Huang, X.; Li, J. Control of hydroxyapatite crystal growth by gallic acid. *Dent Mater J* **2015**, 34, 108–113.
 103. Li, Y.; Jiang, X.; Hao, J.; Zhang, Y.; Huang, R. Tea polyphenols: application in the control of oral microorganism infectious diseases. *Arch. Oral Biol.* **2019**, 102, 74–82.
 104. Cheng, L.; Li, J.; He, L.; Zhou, X. Natural products and caries prevention. *Caries Res.* **2015**, 49 Suppl 1, 38–45.
 105. Slobodníková, L.; Fialová, S.; Rendeková, K.; Kováč, J.; Mučaji, P. Antibiofilm Activity of Plant Polyphenols. *Molecules* **2016**, art. 21.
 106. Daglia, M.; Papetti, A.; Mascherpa, D.; Grisoli, P.; Giusto, G.; Lingström, P.; Pratten, J.; Signoretto, C.; Spratt, D.A.; Wilson, M.; et al. Plant and fungal food components with potential activity on the development of microbial oral diseases. *J. Biomed. Biotechnol.* **2011**, 2011, art. 274578.
 107. Friedman, M. Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. *Mol Nutr Food Res* **2007**, 51, 116–134.
 108. Okubo, S.; Toda, M.; Hara, Y.; Shimamura, T. [Antifungal and fungicidal activities of tea extract and catechin against Trichophyton]. *Nippon Saikingaku Zasshi* **1991**, 46, 509–514.
 109. Signoretto, C.; Burlacchini, G.; Bianchi, F.; Cavalleri, G.; Canepari, P. Differences in microbiological composition of saliva and dental plaque in subjects with different drinking habits. *New Microbiol.* **2006**, 29, 293–302.
 110. Ferrazzano, G.F.; Amato, I.; Ingenito, A.; De Natale, A.; Pollio, A. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). *Fitoterapia* **2009**, 80, 255–262.
 111. Jazaeri, M.; Pakdek, F.; Rezaei-Soufi, L.; Abdolsamadi, H.; Rafieian, N. Cariostatic effect of green tea in comparison with common anticariogenic agents: an in vitro study. *J Dent Res Dent*

Clin Dent Prospects **2015**, 9, 44–48.

112. Ferrazzano, G.F.; Roberto, L.; Amato, I.; Cantile, T.; Sangianantoni, G.; Ingenito, A. Antimicrobial properties of green tea extract against cariogenic microflora: an in vivo study. *J Med Food* **2011**, 14, 907–911.
113. Hambire, C.U.; Jawade, R.; Patil, A.; Wani, V.R.; Kulkarni, A.A.; Nehete, P.B. Comparing the antiplaque efficacy of 0.5% Camellia sinensis extract, 0.05% sodium fluoride, and 0.2% chlorhexidine gluconate mouthwash in children. *J Int Soc Prev Community Dent* **2015**, 5, 218–226.
114. Lee, M.-J.; Lambert, J.D.; Prabhu, S.; Meng, X.; Lu, H.; Maliakal, P.; Ho, C.-T.; Yang, C.S. Delivery of tea polyphenols to the oral cavity by green tea leaves and black tea extract. *Cancer Epidemiol. Biomarkers Prev.* **2004**, 13, 132–137.
115. Hattori, M.; Kusumoto, I.T.; Namba, T.; Ishigami, T.; Hara, Y. Effect of tea polyphenols on glucan synthesis by glucosyltransferase from Streptococcus mutans. *Chem. Pharm. Bull.* **1990**, 38, 717–720.
116. Sakanaka, S.; Shimura, N.; Aizawa, M.; Kim, M.; Yamamoto, T. Preventive Effect of Green Tea Polyphenols against Dental Caries in Conventional Rats. *Biosci. Biotechnol. Biochem.* **1992**, 56, 592–594.
117. Goenka, P.; Sarawgi, A.; Karun, V.; Nigam, A.G.; Dutta, S.; Marwah, N. Camellia sinensis (Tea): Implications and role in preventing dental decay. *Pharmacogn Rev* **2013**, 7, 152–156.
118. Matsumoto, M.; Hamada, S.; Ooshima, T. Molecular analysis of the inhibitory effects of oolong tea polyphenols on glucan-binding domain of recombinant glucosyltransferases from Streptococcus mutans MT8148. *FEMS Microbiol. Lett.* **2003**, 228, 73–80.
119. Ooshima, T.; Minami, T.; Matsumoto, M.; Fujiwara, T.; Sobue, S.; Hamada, S. Comparison of the cariostatic effects between regimens to administer oolong tea polyphenols in SPF rats. *Caries Res.* **1998**, 32, 75–80.
120. Ooshima, T.; Minami, T.; Aono, W.; Izumitani, A.; Sobue, S.; Fujiwara, T.; Kawabata, S.; Hamada, S. Oolong tea polyphenols inhibit experimental dental caries in SPF rats infected with mutans streptococci. *Caries Res.* **1993**, 27, 124–129.
121. Ooshima, T.; Minami, T.; Aono, W.; Tamura, Y.; Hamada, S. Reduction of dental plaque deposition in humans by oolong tea extract. *Caries Res.* **1994**, 28, 146–149.
122. Signoretto, C.; Bianchi, F.; Burlacchini, G.; Sivieri, F.; Spratt, D.; Canepari, P. Drinking habits are associated with changes in the dental plaque microbial community. *J. Clin. Microbiol.* **2010**, 48, 347–356.
123. Ferrazzano, G.F.; Amato, I.; Ingenito, A.; De Natale, A.; Pollio, A. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). *Fitoterapia* **2009**, 80, 255–262.
124. Papetti, A.; Pruzzo, C.; Daglia, M.; Grisoli, P.; Bacciaglia, A.; Repetto, B.; Dacarro, C.; Gazzani, G. Effect of barley coffee on the adhesive properties of oral streptococci. *J. Agric. Food Chem.* **2007**, 55, 278–284.
125. Stauder, M.; Papetti, A.; Daglia, M.; Vezzulli, L.; Gazzani, G.; Varaldo, P.E.; Pruzzo, C. Inhibitory activity by barley coffee components towards Streptococcus mutans biofilm. *Curr. Microbiol.* **2010**, 61, 417–421.
126. Daglia, M.; Papetti, A.; Grisoli, P.; Aceti, C.; Dacarro, C.; Gazzani, G. Antibacterial activity of red and white wine against oral streptococci. *J. Agric. Food Chem.* **2007**, 55, 5038–5042.
127. Chikte, U.M.E.; Naidoo, S.; Kolze, T.J. v W.; Grobler, S.R. Patterns of tooth surface loss among winemakers. *SADJ* **2005**, 60, 370–374.
128. Borges, A.; Caneppele, T.; Luz, M.; Pucci, C.; Torres, C. Color stability of resin used for caries infiltration after exposure to different staining solutions. *Oper Dent* **2014**, 39, 433–440.
129. Di Lorenzo, A.; Bloise, N.; Meneghini, S.; Sureda, A.; Tenore, G.C.; Visai, L.; Arciola, C.R.; Daglia, M. Effect of Winemaking on the Composition of Red Wine as a Source of Polyphenols for Anti-Infective Biomaterials. *Materials (Basel)* **2016**, art. 9.
130. Tagashira, M.; Uchiyama, K.; Yoshimura, T.; Shirota, M.; Uemitsu, N. Inhibition by hop bract

- polyphenols of cellular adherence and water-insoluble glucan synthesis of mutans streptococci. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 332–335.
131. Shinada, K.; Tagashira, M.; Watanabe, H.; Sopapornamorn, P.; Kanayama, A.; Kanda, T.; Ikeda, M.; Kawaguchi, Y. Hop bract polyphenols reduced three-day dental plaque regrowth. *J. Dent. Res.* **2007**, *86*, 848–851.
 132. Kholkhali, W.; Ilias, F.; Traore, B.; Bekkara, F.A.; Bekhechi, C. *Salvadora persica*: A rich medicinal plant of polyphenols and alkaloids with biological activity. *Natural Products: An Indian Journal* **2010**, *6*, 136–142.
 133. Khalil, M.A.; El-Sabbagh, M.S.; El Naggat, E.B.; El-Erian, R.H. Antibacterial activity of *Salvadora persica* against oral pathogenic bacterial isolates. *Niger J Clin Pract* **2019**, *22*, 1378–1387.
 134. Schött, G.; Liesegang, S.; Gaunitz, F.; Gleß, A.; Basche, S.; Hannig, C.; Speer, K. The chemical composition of the pharmacologically active *Thymus* species, its antibacterial activity against *Streptococcus mutans* and the antiadherent effects of *T. vulgaris* on the bacterial colonization of the in situ pellicle. *Fitoterapia* **2017**, *121*, 118–128.
 135. Yamamoto, H.; Ogawa, T. Antimicrobial activity of perilla seed polyphenols against oral pathogenic bacteria. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 921–924.
 136. Yamaguti-Sasaki, E.; Ito, L.A.; Canteli, V.C.D.; Ushirobira, T.M.A.; Ueda-Nakamura, T.; Dias Filho, B.P.; Nakamura, C.V.; de Mello, J.C.P. Antioxidant capacity and in vitro prevention of dental plaque formation by extracts and condensed tannins of *Paullinia cupana*. *Molecules* **2007**, *12*, 1950–1963.
 137. Matsumoto-Nakano, M.; Nagayama, K.; Kitagori, H.; Fujita, K.; Inagaki, S.; Takashima, Y.; Tamesada, M.; Kawabata, S.; Ooshima, T. Inhibitory effects of *Oenothera biennis* (evening primrose) seed extract on *Streptococcus mutans* and *S. mutans*-induced dental caries in rats. *Caries Res.* **2011**, *45*, 56–63.
 138. Konaté, K.; Zerbo, P.; Ouédraogo, M.; Dibala, C.I.; Adama, H.; Sytar, O.; Brestic, M.; Barro, N. Anti-nociceptive properties in rodents and the possibility of using polyphenol-rich fractions from *sida urens* L. (Malvaceae) against of dental caries bacteria. *Ann. Clin. Microbiol. Antimicrob.* **2013**, *12*, 14.
 139. Wittpahl, G.; Kölling-Speer, I.; Basche, S.; Herrmann, E.; Hannig, M.; Speer, K.; Hannig, C. The Polyphenolic Composition of *Cistus incanus* Herbal Tea and Its Antibacterial and Anti-adherent Activity against *Streptococcus mutans*. *Planta Med.* **2015**, *81*, 1727–1735.
 140. Damiano, S.; Forino, M.; De, A.; Vitali, L.A.; Lupidi, G.; Taglialatela-Scafati, O. Antioxidant and antibiofilm activities of secondary metabolites from *Ziziphus jujuba* leaves used for infusion preparation. *Food Chem* **2017**, *230*, 24–29.
 141. Dadpe, M.V.; Dhore, S.V.; Dahake, P.T.; Kale, Y.J.; Kendre, S.B.; Siddiqui, A.G. Evaluation of antimicrobial efficacy of *Trachyspermum ammi* (Ajwain) oil and chlorhexidine against oral bacteria: An in vitro study. *J Indian Soc Pedod Prev Dent* **2018**, *36*, 357–363.
 142. Klinke, T.; Kneist, S.; de Soet, J.J.; Kuhlisch, E.; Mauersberger, S.; Forster, A.; Klimm, W. Acid production by oral strains of *Candida albicans* and lactobacilli. *Caries Res.* **2009**, *43*, 83–91.
 143. Farkash, Y.; Feldman, M.; Ginsburg, I.; Steinberg, D.; Shalish, M. Green Tea Polyphenols and Padma Hepaten Inhibit *Candida albicans* Biofilm Formation. *Evid Based Complement Alternat Med* **2018**, *2018*, 1690747.
 144. Farkash, Y.; Feldman, M.; Ginsburg, I.; Steinberg, D.; Shalish, M. Polyphenols Inhibit *Candida albicans* and *Streptococcus mutans* Biofilm Formation. *Dent J (Basel)* **2019**, *7*, art. 42.
 145. Pinna, R.; Filigheddu, E.; Juliani, C.; Palmieri, A.; Manconi, M.; D'hallewin, G.; Petretto, G.; Maioli, M.; Caddeo, C.; Manca, M.L.; et al. Antimicrobial Effect of *Thymus capitatus* and *Citrus limon* var. *pompia* as Raw Extracts and Nanovesicles. *Pharmaceutics* **2019**, *11*, art. 234.
 146. Philip, N.; Leishman, S.J.; Bandara, H.; Walsh, L.J. Polyphenol-Rich Cranberry Extracts Modulate Virulence of *Streptococcus mutans*-*Candida albicans* Biofilms Implicated in the Pathogenesis of Early Childhood Caries. *Pediatr Dent* **2019**, *41*, 56–62.

147. Alalwan, H.; Rajendran, R.; Lappin, D.F.; Combet, E.; Shahzad, M.; Robertson, D.; Nile, C.J.; Williams, C.; Ramage, G. The Anti-Adhesive Effect of Curcumin on *Candida albicans* Biofilms on Denture Materials. *Front Microbiol* **2017**, *8*, 659.
148. Yu, H.; Oho, T.; Xu, L.X. Effects of several tea components on acid resistance of human tooth enamel. *J Dent* **1995**, *23*, 101–105.
149. He, L.; Deng, D.; Zhou, X.; Cheng, L.; ten Cate, J.M.; Li, J.; Li, X.; Crielaard, W. Novel tea polyphenol-modified calcium phosphate nanoparticle and its remineralization potential. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2015**, *103*, 1525–1531.
150. Giacaman, R.A.; Contzen, M.P.; Yuri, J.A.; Muñoz-Sandoval, C. Anticaries effect of an antioxidant-rich apple concentrate on enamel in an experimental biofilm-demineralization model. *J. Appl. Microbiol.* **2014**, *117*, 846–853.
151. Hannig, C.; Spitzmüller, B.; Knausenberger, S.; Hoth-Hannig, W.; Hellwig, E.; Hannig, M. Detection and activity of peroxidase in the in situ formed enamel pellicle. *Arch. Oral Biol.* **2008**, *53*, 849–858.
152. Hannig, C.; Spitzmüller, B.; Hoth-Hannig, W.; Hannig, M. Targeted immobilisation of lysozyme in the enamel pellicle from different solutions. *Clin Oral Investig* **2011**, *15*, 65–73.
153. Hannig, C.; Sorg, J.; Spitzmüller, B.; Hannig, M.; Al-Ahmad, A. Polyphenolic beverages reduce initial bacterial adherence to enamel in situ. *J Dent* **2009**, *37*, 560–566.
154. Porto, I.C.C.M.; Nascimento, T.G.; Oliveira, J.M.S.; Freitas, P.H.; Haimeur, A.; França, R. Use of polyphenols as a strategy to prevent bond degradation in the dentin-resin interface. *Eur. J. Oral Sci.* **2018**, *126*, 146–158.
155. Guo, B.; Que, K.-H.; Jing Yang, null; Wang, B.; Liang, Q.-Q.; Xie, H.-H. Effect of *Galla chinensis* on the remineralization of two bovine root lesions morphous in vitro. *Int J Oral Sci* **2012**, *4*, 152–156.
156. Balata, G.F.; Abdelhady, M.I.S.; Mahmoud, G.M.; Matar, M.A.; Abd El-Latif, A.N. Formulation of Saudi Propolis into Biodegradable Chitosan Chips for Vital Pulpotomy. *Curr Drug Deliv* **2018**, *15*, 97–109.