Received: 16 September 2019 | Revised: 26 March 2020 | Accepted: 4 April 2020

DOI: 10.1002/jbm.a.36991

Society For Biomaterials

WILEY

REVIEW ARTICLE

Application of green tea extracts epigallocatechin-3-gallate in dental materials: Recent progress and perspectives

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Funding information
The Fundamental Research Funds for the Central Universities, Grant/Award Number: 2082604401239; Fundamental Research Funds for the Central Universities; National Natural Science Foundation of China, Grant/Award Number: 81870801

Abstract

Because of excellent biocompatibility, antioxidant activity, and anti-caries ability, epigallocatechin-3-gallate (EGCG) has been widely studied in the treatment of oral diseases, such as periodontal disease, oral cancer, and dental caries. To reach the site of the lesion or achieve sustained release, play the role of anti-caries, anti-inflammatory, or to maintain or improve the physical properties of the modified material, EGCG need to be cross-linked or embedded with dental adhesives, barrier membranes, bone replacement materials, tissue regeneration materials, and antimicrobial anti-caries materials to better prevent or treat oral diseases. This article reviews the applications of EGCG in oral materials, involving various areas of the oral cavity, reveals their excellent potential, and sees shortcomings in these research to promote the better development of EGCG applications in oral materials such as oral repair materials, bone tissue engineering materials and antibacterial and anti-caries materials.

KEYWORDS

dental materials, EGCG, green tea

1 | INTRODUCTION

Tea is one of the three major drinks in the world, second only to water (Babu & Liu, 2008). In East and Southeast Asia, tea is one of the most popular drinks. It is reported that drinking tea can reduce the risk of cardiovascular disease, dental caries, and other diseases, which has aroused people's great interest in it (Chowdhury, Sarkar, Chakraborti, Pramanik, & Chakraborti, 2016). From the dried tea leaves, there are 15 to 20% of proteins and 5 to 7% of carbohydrates, as well as aldehydes, alcohols, and some chemical elements, the most attractive of which are polyphenols (Chacko, Thambi, Kuttan, & Nishigaki, 2010). The polyphenols in tea are composed of epigallocatechin-3-gallate (EGCG) epigallocatechin (EGC) epicatechin-3-gallate (ECG), and epicatechin (EC), and their contents are different. The content of EGCG is the highest (about 50%) (Babu & Liu, 2008; McKay & Blumberg, 2002; Namal Senanayake, 2013). According to the study, EGCG, the most active component of green tea, is the primary provider of its health care and preventive function and can prevent cardiovascular disease, anti-tumor, anti-oxidation, and anti-virus (Babu, Sabitha, & Shyamaladevi, 2006; Crespy & Williamson, 2004; Namal Senanayake, 2013). EGCG contains a dihydropyran heterocycle (C ring) and two hydroxyl carbon on the benzene ring. Benzene ring A and benzene ring B, which have three hydroxyl groups. Many hydroxyl groups determine the anti-oxidant properties of EGCG, and it is also one of the chemical directions that people study. The structure of o-dihydroxycatechol in B ring and the unsaturated 4-oxo group in C ring may also improve the anti-oxidant activity, and the 2,3-double bond of dihydropyran may also be the site of accepting active oxide (Farkas, Jakus, & Heberger, 2004; Heim, Tagliaferro, & Bobilya, 2002).

In recent years, the development of materials science has advanced rapidly and has great potential in the clinical treatment of

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various diseases. Many studies have synthesized materials combined with EGCG and investigated their influence on the whole body. Such as multifunctional nanomaterials for tumor therapy (Jiang et al., 2019), polymer particles for antioxidant action (Seo et al., 2017), targeted nanoparticles for anti-atherosclerosis (Zhang et al., 2019), self-assembled nanogels for resistant breast cancer therapy (Ding, Liang, Min, Jiang, & Zhu, 2018), Co-delivery system of natural compounds and dual-target nanoparticles for improving in situ tumor models (Chu, Tsai, Ko, Wu, & Lin, 2019), dual-drug nanoparticles for the treatment of Alzheimer's disease (Cano et al., 2019), and so forth.

There also exist relevant reviews on the application of EGCG material in systemic aspects of research (Table 1) and their deficiencies.Simultaneously, the application of EGCG in oral materials has gradually become a hot topic, with many investigations studying on the influence of EGCG-related materials on bone tissue engineering, antibacterial and anti-caries functions in the oral cavity. Nevertheless, few literatures have focused on the trend in the development of these materials, and so far, there is a lack of a systematic review on the EGCG-related materials in the aspect of the oral cavity. For meeting the vast demand of oral materials engineering, this article reviews the application of EGCG in oral materials, revealing the shortcomings of previous research except for their merit, and sheds light on the future improvements and further exploration.

2 | MATERIALS AND EGCG

2.1 | EGCG in dental adhesives

Dental restoration is a conventional technology, in the process of which, the choice of restoration materials is of great importance, determining the success of the dental restoration. Dental bonding systems usually include dental adhesives and composite resins. A dental adhesive is usually used in order to improve the combination fastness of tooth tissue and restoration material, while the latter being the primary material of adhesive technology.

Since Buonocore first introduced acid corrosion technology, various resin-based adhesives have shown good prospects (Van Meerbeek et al., 2003). However, there exist two main problems: secondary caries and poor dentin-bond durability, which hinder its long-term clinical application (Brackett et al., 2011; Malhotra, Mala, & Acharya, 2011; Spagnuolo, Annunziata, & Rengo, 2004). To conquer these problems mentioned above, certain chemical synthetics such as Chlorhexidine (CHX) have been applied to the modification of adhesive materials, exerting specific positive effects (Deresinski, 2007). Nevertheless, bacterial resistance, the low biocompatibility and the adverse effects of chlorine on the mechanical properties of restoration materials over time have exposed the shortcomings of CHX, urging people to search for a new antimicrobial additive (Bagis, Baltacioglu, Ozcan, & Ustaomer, 2011; Lessa, Nogueira, Huck, Hebling, & Costa, 2010; Mankovskaia, Levesque, & Prakki, 2013).

EGCG is a polyphenol found in green tea, possessing multiple biological effects of inhibiting *Streptococcus mutans* and having other antibacterial activities (Demeule, Brossard, Page, Gingras, & Beliveau, 2000; Wu & Wei, 2002). Due to the advantages mentioned above, EGCG can be used as a promising antimicrobial agent to reduce the occurrence of secondary caries in resin restorations (Hannas, Pereira, Granjeiro, & Tjaderhane, 2007). An experiment demonstrated that dental adhesive incorporated with EGCG showed excellent antibacterial properties, and this is the first experiment to incorporate EGCG into dental adhesives as a modification (Du et al., 2012). After that, they modified glass ionomer cements (GIC) with EGCG, another adhesive material, which also proved that the application of EGCG increased the antibacterial and physical properties of GIC (Hu et al., 2013). An essential step in the development of secondary caries is the formation of acquired pellicle around enamel-restoration interface, which releases acidic by-products that destroy the dentin margin, causing further diffusion (Zarella et al., 2016). A recent experiment has shown that EGCG can positively influence the protein profile of acquired pellicle (AP), thus protecting periodontal tissue, reducing bacterial colonization, and having anti-caries effect (Pela et al., 2019).

Aside from the antibacterial properties, as a metal matrix proteases (MMPs) inhibitor, EGCG also plays a crucial role in improving the durability of the restoration materials (Costa, Passos, Neri, Mendonca, & Santiago, 2019). Contemporary restoration techniques rely on the bond between resin material and enamel or dentin. There is an area called mixed layer in the interface between resin material and tooth tissue where collagen fibers twine with polymer chains of resin material. Enzymes' degradation of the mixed layer mainly accounts for the shortening of restoration materials' life span (Mazzoni et al., 2015; Pashley et al., 2004; Scaffa et al., 2012). Hence, EGCG has been increasingly investigated in recent years in improving the bond durability. Prakki, A. et al. figured that EGCG could adsorb soluble peptides, inhibit the degradation of dentin matrix and increase the collagen link between adhesive and dentin (Prakki et al., 2018). Similarly, as metalloproteinase inhibitors, by contrast, CHX harms adhesive's adhesion strength, whereas EGCG did not (Costa et al., 2019). Furthermore, the addition of EGCG only reduced the solubility of the adhesive and had no adverse effect on other physicochemical properties of restoration materials such as water resolution/solubility, the degree of conversion, and the flexural strength (de Macedo et al., 2019; Neri et al., 2014). EGCG can not only be directly mixed with adhesive in the form of a solution but also mixed with it after being loaded by microparticles. Albuquerque, N. et al. produced poly (L-lactic acid) (PLGA) microparticle loaded with EGCG, demonstrating that the resin-dentin bond of the adhesive added with the microparticles was significantly higher than those of the control group after 12 months (Albuquerque et al., 2019). Similarly, the biocompatibility of the adhesive should be taken seriously. Beatriz M et al. evaluated the biological and mechanical performance of adhesive added with different concentration of EGCG and found that 0.5 and 1.0 wt% EGCG-doped adhesive system have less cytotoxicity (Lee, Lee, Lin, et al., 2016).

The color change is a clinical difficulty and may compromise the esthetics of composite resin. Previous studies have shown that EGCG

TABLE 1 summary on specific materials of EGCG in different applications

Application	Additive	Coating material	The specific material	Advantages	Reference
Dental adhesive	EGCG	Adhesive (AdperTM single bond 2)	A dental adhesive incorporated with EGCG	High antibacterial properties	(Du, Huang, Huang, Wang, & Zhang, 2012)
	EGCG	Glass ionomer cements	EGCG-containing glass ionomer cements	Enhancement of antibacterial and physical properties	(Hu et al., 2013)
	EGCG	BisGMA, TEDDMA	EGCG-treated experimental resins	Inhibition of bacterial colonization, protection of periodontal tissue, positive influence on AP	(Pela et al., 2019)
	EGCG	BisGMA, TEDGMA	Functionalized epigallocatechin gallate copolymer	Inhibition of the degradation of dentin matrix, increase of collagen link between adhesive and dentin	(Prakki et al., 2018)
	EGCG	Self-etch adhesive (Adper EASY one)	A methacrylate-based dental adhesive incorporated with EGCG	Almost no negative influence on physical properties but slight reduction of solubility	(Van Meerbeek et al., 2003)
	EGCG	Composite resin Filtek Z250	A self-etching adhesive incorporated with EGCG	Almost no negative influence on physical properties but slight reduction of solubility	(Mazzoni et al., 2015)
	EGCG	Poly(D-L lactide-co-glycolide) acid (PLGA) microparticles	Polymeric microparticles loaded with catechin of an adhesive system	Sustained release for more than 12 months	(Albuquerque et al., 2019)
	EGCG	Adhesive system single bond universal, composite resin Filtek bulk fill	Composite resin restorations treated with EGCG	No noticeable change of the color of dentin-resin	(Lopes et al., 2019)
Barrier membrane	EGCG, lovastatin	Chitosan membrane	The EGCG-CS-lovastatin membrane	Improvement of antibacterial activity and alkaline phosphatase activity, good biocompatibility	(Lee et al., 2016)
	EGCG	Collagen membrane	EGCG cross-linked collagen membranes	High anti-inflammatory effect	(Chu et al., 2016)
	EGCG, PEG	Collagen membrane	PEG and EGCG modified collagen-base membrane	Improvement of cell viability, suppression of expression of TNF-α	(Chu et al., 2017)
	EGCG, Nano-hydroxyapatite	Collagen membrane	Nanohydroxyapaptite coated EGCG cross-linked collagen membranes	Better osteogenic induction	(Chu, Deng, Man, & Qu, 2017)
Bone substitute material (natural polymer materials)	EGCG	Collagen bovine bone mineral (CBBM)	EGCG-soaked collagen bovine bone mineral	Better promotion of bone regeneration, reduction of extent of fibrosis	(Hong et al., 2015)
	EGCG	Gelatin in a solid form	Polyphenol-conjugated gelatin	Sustained release, promotion of differentiation to osteoblasts from D1 cells	(Honda et al., 2015)
	EGCG	Gelatin in a viscous liquid form	EGCG-modified gelatin	Suppression of bone resorption and orthodontic movement in mice	(Katsumata et al., 2018)
	EGCG	Gelatin heated by vacuum	EGCG-modified gelatin sponges treated by vacuum heating	Better osteogenic ability	(Honda et al., 2018)

(Continues)

TABLE 1 (Continued)

Application	Additive	Coating material	The specific material	Advantages	Reference
	EGCG	Gelatin sponge scaffold	EGCG-modified gelatin sponge scaffold based on stem cells	Enhancement of cell adhesion, promotion of calcium phosphate precipitation, better micro-environment for pluripotent progenitor cells	(Sasayama, Hara, Tanaka, Honda, & Baba, 2018)
Bone substitute material (synthetic polymer materials)	EGCG	PLLA nanofiber	EGCG-functionalized poly (L-lactic acid) (PLLA) nanofiber	Lower cytotoxicity, promotion of proliferation of bone marrow mesenchymal cells	(Madhurakkat Perikamana et al., 2019)
Bone substitute material (bioceramics)	EGCG	Alpha-tricalcium phosphate	Green tea catechin alpha-tricalcium phosphate combination	Sustained release, Promotion of osteogenesis	(Rodriguez et al., 2011)
	EGCG, duck's feet collagen	Nano-hydroxyapatite composite sponge	EGCG/duck's feet collagen/ hydroxyapatite (EGCG/DC/HAp) composite sponges	Enhancement of cell attaching to scaffold, promotion of osteogenesis	(Kook et al., 2018)
	EGCG,BMP-2	Biphasic calcium phosphate	ErhBMP-2-/EGCG-coated BCP bone substitute	Suppression of expression of NK-κB, sustained release, better biocompatibility	(Shin et al., 2014)
Bone substitute material (metal bone graft material)	EGCG	Titanium implant	EGCG coated titanium particles	Lower expression of TNF-α induced by Ti, high antioxidant activity	(Jin et al., 2011)
	EGCG	Gold nanoparticles	EGCG-functionalized gold nanoparticles	Sustained release, inhibition of MAPK pathway to reduce the production of ROS	(Zhu, Zhu, Yu, Wang, & Peng, 2019)
Dental pulp regeneration material	Epicatechin	Collagen scaffolds	Epicatechin cross-linked collagen scaffolds	Promotion of proliferation and differentiation of human dental pulp cells by regulation of ERK signaling pathways	(Lim et al., 2016)
	EGCG	Collagen scaffolds	EGCG cross-linked collagen scaffolds	Positive influence on collagen scaffolds about physical property	(Kwon et al., 2017)
Anti-caries substance	EGCG, chlorhexidine	Geltain	Gelatin containing EGCG and chlorhexidine	Suppression of MMPs, promotion of remineralization, inhibition of demineralization	(Kato, Leite, Hannas, & Buzalaf, 2010)
	EGCG	Geltain	Gelatin containing EGCG on the enamel surface	Increase of the AEP, enhancement of protection to enamel	(de Souza et al., 2017)
	EGCG	Adhesive resins	EGCG-containing adhesive resins	Enhancement of antibacterial and physical property	(Fialho et al., 2019)
	EGCG, Nano-hydroxyapatite	Mesoporous silica nanoparticles(MSN)	EGCG-encapsulated mesoporous silica nanoparticles (MSN)	Sustained release, inhibition of *S. mutans* biofilm, completed occluded dentin tubule	(Yu et al., 2017)

solution can change color because of pH changing, which cannot be restored by regulating pH (Mizooku, Yoshikawa, Tsuneyoshi, & Arakawa, 2003). Some researchers recognize that EGCG may cause the color change of prosthodontics materials. However, Lopes, R. G., et al.'s experiment prove that EGCG is not able to change the color of the dentin-resin interface in the immersion in beverages (Lopes et al., 2019).

In conclusion, more and more researches focus on the application of EGCG in prosthodontics materials which shows an excellent biological and mechanical performance, has excellent potential. Compared with free EGCG, release system may have a better performance because of the protection of premature degradation. The application of microparticles loaded with EGCG provides a new strategy for prosthetic dentistry. However, some question needs to be solved, such as the uncertain amount of EGCG release, the methodology and technology which need to be improved, and the interaction between these modified materials and dental pulp (Albuquerque et al., 2019; Hu et al., 2013). More clinical in vivo trials need to be carried out before EGCG can be applied to the patient's teeth.

2.2 | EGCG in barrier membrane

The ability of bone tissue regeneration is relatively weak after the bone defect, not only the healing time is long, but also the healing result is barely satisfactory. There are some problems in tooth implantation as the primary treatment for tooth loss, such as the loss of bone tissue, physiological bone resorption and other factors affect oral tissue regeneration after implantation. In severe cases, the implant cannot be combined with the alveolar bone, thus failing the implant operation (Petersen & Ogawa, 2005; Wang & Boyapati, 2006). Periodontitis is a process of chronic inflammation of periodontal support tissue mainly caused by local factors. Studies found that gingivitis could gradually develop into periodontitis, which is more common in people aged over 35 (Lee et al., 2016). Once affected periodontitis, when implants are implanted into the alveolus, the implants cannot be well combined with the alveolar bone because of the current condition of bone defect and poor bone healing ability, resulting in unsatisfactory implant surgery (de Pablo, Chapple, Buckley, & Dietrich, 2009).

We know that dental calculi and bacterial plaque on the root surface are the main factors causing periodontitis (Pihlstrom, Michalowicz, & Johnson, 2005). For traditional surgical treatments, these factors mentioned above were removed, but the subsequent repair process was only the result of the connection of epithelial tissue, resulting in the poor regeneration of connective tissue and cement. Therefore, the materials that researchers aim at should not only act as a barrier to prevent the proliferation and migration of epithelial cells, provide spaces for the adhesion and growth of osteoblasts, but also play a guiding role in the regeneration of bone tissue (Aljateeli et al., 2014; Becker et al., 1988; Caton, Nyman, & Zander, 1980). Hence, some biocompatible materials are used as membrane scaffolds to load some growth factors to promote the regeneration of new bone. In the mouse periodontitis model that LPS induce, EGCG can effectively inhibit the activation of COX-2 in osteoclasts and reduce the production of PEG2. Receptor activator of nuclear factor kappa B ligand (RANKL) of osteoclasts which promotes cell differentiation is also inhibited (Tominari et al., 2015). The pathogenesis of periodontitis, include many pathways and regulatory factors, in which macrophages are the main cause of inflammation. Tumor necrosis factor-α (TNF-α) is an important regulator of the inflammatory response which can promote the release of cytokine IL-1 β (Hajishengallis & Lamont, 2012). Lagha's study shows EGCG can inhibit the expression of NF- κ B pathway, the activation of Caspase-1 and the production of IL- β, all of which can enhance the activity of macrophages and aggravate the degree of inflammation (Lagha & Grenier, 2019; Lagha, Groeger, Meyle, & Grenier, 2018). Due to the excellent bacteriostat, anti-fibrosis (Nakamuta et al., 2005) and osteogenesis effects (Glowacki & Mizuno, 2008; Miyata, Taira, & Noishiki, 1992), some EGCG loaded barrier membranes for guided bone regeneration have emerged in recent years.

Chitosan is a common biocompatible material. Besides its excellent mechanical properties, it can also hinder the process of periodontitis by inhibiting oral bacteria such as *Actinobacillus actinomycetemcomitan* and *Porphyromonas gingivalis* (Xu, Lei, Meng, Wang, & Song, 2012). Lee, B.S., et al. developed a functional chitosan membrane with grafted epigallocatechin −3-gallate and lovastatin, a three-layered structure with EGCG for the bactericidal effect on the outer layer and an intermediate layer loaded with lovastatin for control and sustained release. This material showed great properties in both in vivo and in vitro experiments, with significant effects on the improvement of antibacterial activity and alkaline phosphatase activity, and also showed excellent biocompatibility in the single wall defect of the Beagle's dog model. In general, it has a positive effect on the formation of new bone, and it is hoped that it can be used as a new material to guide tissue regeneration in the future (Lee, Lee, Lin, et al., 2016).

In addition to chitosan, collagen materials have been widely used in guided bone regeneration. From a clinical point of view, these materials have excellent biocompatibility, no need for secondary removal, and have the ability to promote wound healing, so they are often used as a barrier membrane in guided bone regeneration (Dahlin, Sennerby, Lekholm, Linde, & Nyman, 1989; Kostopoulos & Karring, 1994; Tonelli et al., 2011; Wang & Boyapati, 2006). The levels of inflammatory factors secreted by osteoblasts were regulated by crosslinking different concentrations of EGCG onto collagen. The EGCG-treated membrane still maintains the three-strand spiral structure and has better mechanical properties such as smoother surfaces and thickened collagen fibers than pure collagen. To sum up, the treatment of collagen membranes with appropriate concentrations of EGCG has an anti-inflammatory effect and improved cell proliferation, which supports their bone-preserving potential (Chu et al., 2016). However, pure collagen is also a foreign body which causes inflammation, leading to progressive bone absorption, while the addition of EGCG regulates the recruitment and polarization of macrophages and reduces the foreign body reaction (FBR) (Chu et al., 2018). Their study showed that the new EGCG modified collagen membrane

downregulates the secretion of proinflammatory factors and promotes the immune response to regeneration by modulating the recruitment of M2 macrophages (Chu et al., 2019). The expression of growth factor and related factors of osteogenic differentiation were improved, too. Generally speaking, the EGCG modified collagen membrane is an immunomodulatory membrane with excellent mechanical properties and has great potential in guided bone regeneration after implant surgery.

The EGCG-loaded collagen membrane cannot only act on but also induce the proliferation and differentiation of Schwann cells, a peripheral nerve sheath cell. It is of considerable significance to repair and guide the regeneration of nerve tissue (Chu, Deng, Cao, Man, & Qu, 2017). Nevertheless, the effect of EGCG on the cell viability of the two cells was not consistent. The cell viability of RSC96 cells was high with a concentration of 0.64% EGCG, which was proportional to the concentration in a particular range (Chu et al., 2016). On the contrary, the viability of osteoblasts was inhibited by the high concentration of EGCG (Chu et al., 2016). More researches are needed to explore the optimal concentration if the role of these two cells needs to be coordinated in oral tissue repair. To address this problem and improve the effect of biomaterials on cell viability, Chu, C. et al. consider that polyethylene glycol (PEG) as a nontoxic polymer with good biocompatibility, so they conducted surface modification of collagen membrane by PEG (Lampe, Bjugstad, & Mahoney, 2010; Mahoney & Anseth, 2006; Namba, Cole, Bjugstad, & Mahoney, 2009). The results showed that the PEG-modified EGCG cross-linked membrane improved cell viability and adhesion of osteoblasts even at high concentrations of EGCG, with the low release of tumor necrosis factor (Chu, Deng, Hou, et al., 2017). Meanwhile, mechanical properties require improvement and enhancement since the collagen membrane must remain in its structure for long enough time to prevent epithelial migration and proliferation during early wound healing. They modified the collagen membrane again in another way with nanohydroxyapaptite (nano-HA). Thanks to the excellent biocompatibility and bone inducing properties of nano-HA, the effect of nano-HA coated EGCG cross-linked collagen membranes (Table 1) on osteoblast differentiation was more significant and had better mechanical properties before the modification. In animal experiments, the membrane was the best one to promote bone healing compared with the unmodified (Chu, Deng, Man, & Qu, 2017). According to the above modification experiments, there exists great potential for the improvement of mechanical properties and biological activity of EGCG cross-linked collagen membrane by adding other biocompatible substances.

2.3 | Bone substitute material

Bone loss and bone regeneration involve many complex mechanisms, and the main problem to implant failure is an inflammatory reaction (Chen & Tuan, 2008). TNF-α is an essential inflammatory factor, which has a robust chemotactic effect on macrophages and osteoclasts, and one of the initiators of oxidative stress. In Maruyama's observation of gingival oxidative stress, 24 mice were treated with different doses of tea polyphenol toothpaste after inducing oral inflammation (Maruyama et al., 2011). There is a study that EGCG can activate a variety of cellular pathways, such as AMPK, cAMP, calcium, and other cellular antioxidant pathways. It is supposed to be noted that EGCG neutralizes the oxidation effect of reactive oxygen species (ROS) by upregulating the expression of NRF2 (Kim, Montana, Jang, Parpura, & Kim, 2013; Narotzki, Reznick, Aizenbud, & Levy, 2012). In addition, the promoting effect of EGCG on bone regeneration can reflect with the proliferation of osteoblasts. Osteoprotegerin, a kind of cytokines secreted by osteoblasts that can inhibit osteoclasts, is stimulated to express by EGCG (Sakai et al., 2017). From the observation about bone marrow mesenchymal stem cells (BMSCs) added with EGCG, Lin SY et al. found that BMP-2 had been detected, which enhanced de novo bone formation (Lin et al., 2019). The regeneration of periodontal ligament plays a vital role in bone regeneration, Liu J et al. found that EGCG can increase the mRNA expression of COL1, RUNX2, OPN, and OSX, all of which suggest the human periodontal ligament cells have a direction of osteogenic differentiation (Liu et al., 2019). EGCG is widely used in bone substitute materials because of its excellent osteogenesis, anti-inflammation, and biocompatibility. Several common bone substitute materials applied with EGCG are introduced below.

2.3.1 | Natural bone substitute material

Collagen bovine bone mineral (CBBM) is a natural polymer material that has been widely used in bone regeneration. Ji-Youn Hong et al. found that the immediate transplantation of CBBM soaked in EGCG into the extraction sockets with a periapical lesion could reduce the extent of fibrosis and better promote bone regeneration than pure CBBM, which means that the combination of EGCG and CBBM can be used as a candidate biomaterial for the healing of extraction sockets (Hong et al., 2015).

Although many studies on EGCG have been conducted in osteogenesis, the absence of an excellent drug delivery system leads to high concentrations of EGCG that inhibit osteogenesis (Jin, Wu, Xu, Zheng, & Zhao, 2014; Wei et al., 2011). As a degradation product of collagen, gelatin has good biocompatibility and belongs to natural polymer materials. The mechanical properties of gelatin are not very good compared with collagen, so it is generally modified to obtain better physicochemical properties. Yoshitomo Honda et al. cross-linked EGCG and gelatin to produce epigallocatechin-3-gallate-conjugated gelatin (EGCG/gel), which has remarkable osteogenic ability compared to uncross-linked gelatin. It promotes the migration and adhesion of mesenchymal stem cells D1cells, making them differentiate into osteoblasts within 14 days, which provides a locally controlled release of polyphenols for bone therapy (Honda et al., 2015). Apart from the solid forms mentioned above, their team also gave a single local injection of EGCG modified gelatin in forms of a viscous liquid, demonstrating that this material reduced bone resorption, and orthodontic movement in mice. Compared with previous multiple injections, EGCG-GL prolongs the release of EGCG and inhibits osteoclastogenesis by enhancing

antioxidant enzymes to inhibit intracellular ROS signaling (Honda et al., 2018). To further improve the mechanical properties and osteogenic ability of the above materials, Satoshi Sasayama et al. also vacuum heated the EGCG modified gels (Katsumata et al., 2018). The results show that vacuum-heated gelatin sponge modified with EGCG (vh EGCG -GS) has an excellent osteogenic effect compared with a pure vacuum-heated gelatin sponge (vhGS). The osteogenic ability of vacuum-heated gelatin sponge modified with EGCG (vh EGCG-GS) is superior to that of autogenous bone graft and becomes the gold standard for repairing the bone defect (Katsumata et al., 2018; Li et al., 2016). Nevertheless, whether this chemical modification method is suitable for the scaffold preparations based on stem cells to regenerate bone tissue is unclear. To explore this issue, Satoshi Sasayama et al. demonstrate that vhEGCG-GS enhances cell adhesion, promotes calcium phosphate precipitation, provides a better microenvironment for pluripotent progenitor cells, and induces superior bone formation in vivo. Thus, it is hopefully expected to be a scaffold for bone regeneration in maxillofacial defects (Sasayama et al., 2018). At the same time, the problem is how the composition of EGCG and gel should be controlled to obtain better bone quality. With vhEGCG-GS containing the same amount of EGCG but different amounts of gelatin, Eiki Hara et al. found that increased gelatin content in vhEGCG-GS promoted bone formation but produced porous bone. Besides, the tissue density decreased, and the maximum mineral matrix ratio increased. Conversely, vhEGCG-GS containing a small amount of gelatin form a mature collagen matrix in the regenerated bone. All these results indicate that the presence of vhEGCG-GS affects the osteogenic ability and quality of regenerated bone, providing valuable insights for the preparation of new bone replacement materials (Hara, Honda, Suzuki, Tanaka, & Matsumoto, 2018).

While the above series of step-by-step, in-depth studies reveal the tremendous osteogenic potential of EGCG-gelatin, more studies are required to regulate the clinical use of this material, for example, the optimal dose of EGCG has not been determined. Furthermore, the specific release amount of EGCG in this material has not been determined due to the presence of impurities. Moreover, for stem cell-based bone regeneration scaffold materials, the optimal amount of seeding cells for different cell types incorporated on this gel sponge needs to be determined. There should also be more research further to investigate the bone quality of the regenerated bone.

2.3.2 | Synthetic polymer bone substitute material

Polymer bone graft consists of nature polymer bone graft and synthetic polymer bone graft. The natural polymer bone graft sources very extensive, mainly including chitosan, collagen, geltain. The natural polymer bone graft establishes good degradability, biocompatibility, and modifiability. However, it faces the drawbacks about low mechanical properties, deposition caused by macrophages (Ravi & Chaikof, 2010; Zhu & Marchant, 2011). Synthetic polymer bone graft mainly includes PLLA, PLA, PLGA, all of whose safety to the human body, the Food and Drug Administration (FDA) admits. Synthetic polymer bone graft can be designed for a particular pore size and have the function of sustained release when drug coating (Sheikh et al., 2016). It is the lack of proper drug delivery system that limits the development of EGCG, which is a promising therapeutic potential in curing osteoporosis, periodontitis, and other inflammatory osteolysis diseases. To overcome the limitation of EGCG, Sajeesh et al. functionalized a poly (L-lactic acid) (PLLA) nanofiber with EGCG through oxidative polymerization and cation-mediated self-assembly. To reduce cytotoxicity and simplify the process, they abandoned nano-drug-delivery-system. The results show that PLLA nanofiber does not perform well in promoting the proliferation of bone marrow mesenchymal cells, but also inhabiting the activity of RAW2.64.7 osteoclasts. Moreover, the scaffold coating EGCG can provide a proper environment for osteoblast (Madhurakkat Perikamana et al., 2019). Compared with the scaffold, not coating EGCG, nanofiber coating EGCG significantly suppress inflammation. As a new way of bonding, the coating may contribute to the application of EGCG and synthetic polymer bone graft.

2.3.3 | Bioceramic bone substitute material

The resorption of peri-implant alveolar bone that tooth loosen and periodontitis induce the destruction of alveolar bone and the loss of papilla, which is responsible for subsequent implant failure (Chow & Wang, 2010; Edens, Khaled, & Napenas, 2016). Much effect has been attached to bone substitutes in clinical to prevent or treat the loss of bone that the resorption induces. Conventional bone substitutes include autogenous bone graft, allografts, and alloplastic bone substitutes. The effect of autogenous bone graft has the best biocompatibility, but it is difficult to obtain. Compared to autogenous bone graft, allografts is much easier to obtain, whereas the occurrence of immune rejection blocks the development of it (Hollister, 2005). Much effect has been made to invent alloplastic bone substitutes and improve osteogenesis and biocompatibility of alloplastic bone substitutes to avoid the drawbacks about autogenous bone graft or allografts mentioned above. In alloplastic bone substitutes, bioceramics raise significant interests due to its excellent performance in mechanical properties and osteoconductivity (Bohner, Galea, & Doebelin, 2012). However, the limitation of bioceramics is the low osteoinductivity because of poor antioxidation and the lack of effect of stimulating cytokines. According to epidemiologic observation, tea is reported to reduce the risk of osteoporosis and increase bone mineral density. EGCG, the main active compound of tea, is considered to perform brilliant in antioxidation and osteoinductivity (Morinobu et al., 2008). To investigate the effect of osteoinductivity in vivo, in a groundbreaking way, Reena Rodriguez used alpha-tricalcium phosphate (α-TCP), a bioactive and degradable bioceramic (Table 1), to adsorb EGCG, and demonstrated that it is the porous structure of α-TCP that achieve uniform distribution of the EGCG. According to their report, EGCG-α-TCP shows an excellent performance in guided bone regeneration in rat skull defect model.

Moreover, the released EGCG was detected for 14 days continuously, which indicated the sustained release ability of

α-TCP(Rodriguez et al., 2011). Yeon Ji Kook fabricated EGCG/duck's feet collagen/hydroxyapatite (EGCG/DC/HAp) composite sponges. They made bone marrow mesenchymal stem cells migrate to the composite sponge and implanted the composite sponge on a full-thickness the subcutaneous region of athymic nude mice. A high number of BMSCs was found to be a round shape or osteoblastic-like morphology and surrounded the composite sponge. In RT-PCR analysis, bone-specific genes such as *OCN* and *RUNX-2* were detected after 21 days of cell culture. Their result indicated the potential of EGCG/DC/Hap sponges to regenerate bone (Kook et al., 2018). Biphasic calcium phosphate (BCP), which is made of hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), has a similar structure with natural bone. To inhabit the peri-implant inflammation and promote the proliferation and differentiation of osteoblast, Y-S Shin et al. attached BCP coating ErhBMP-2 and EGCG to the titanium membrane of dental implants in dogs (Table 1). BCP coating ErhBMP-2 and EGCG showed an excellent performance in inhibiting the RANKL pathway and enhancing the osteogenic potential (Bae, Kim, Kim, Yun, & Kim, 2010; Shin et al., 2014). However, just as Y-S Shin et al. worry about, few study focus on how to feature out quantification when drug release. Much attention is supposed to pay to the phenomenon of "local overdose." Recently, the nanotechnology has much promoted the development of a drug delivery system and a sustained release system. Some researchers have reported the application of nano-bioceramic (Bolelli et al., 2015; Raza, Sulong, Muhamad, Akhtar, & Rajabi, 2015). Nanoparticles have a better capacity of releasing drug, which may bring a future for the application of bioceramic and EGCG.

2.3.4 | Metal bone substitute material

It is the high mechanical of metal bone graft material that renders an excellent performance for use load-bearing conditions. To imitate the function of bone trabeculae, metal bone graft material is made to process a unique porous structure, in which living bone tissue proliferate, and migrate in vivo (Fujibayashi et al., 2001; Nishiguchi et al., 1999). Due to its excellent biocompatibility, titanium metal can use as osteoconductive material after unique chemical and thermal treatments (Fujibayashi, Neo, Kim, Kokubo, & Nakamura, 2004). However, some reports pointed out that titanium particulate and debris improve the release of TNF-α, which induce the proliferation and migration of osteoclast. Over-stimulation of osteoclast causes osteolysis and bone loosening that has a great relationship to implant failure (Kaufman, Alabre, Rubash, & Shanbhag, 2008; Merkel et al., 1999). Some studies demonstrate that EGCG performs well in osteogenesis and anti-oxidation, and researchers attach much great attention to the application of material with EGCG (Cho et al., 2013). According to Jin et al.'s experiment, they found EGCG to downregulate the JNK/AP-1 and NF-κ B pathways, which reduce the production of TNF-α in vitro as well as in vivo. Jin considers that EGCG can inhibit the proliferation and migration of osteoclast Ti-induced (Jin et al., 2011). In their experiment, the intraperitoneal injection may lead to low bioavailability of EGCG. Low bioavailability and the short half-life is the main obstacle to reduce the therapeutic effect of EGCG. Nanoparticles are supposed to improve the bioavailability of EGCG and enhance the interaction between EGCG and metal bone material. In the treatment of periodontitis, Dentist often focuses on reducing excessive bone resorption and inhibit inflammation as nano-carrier gold nanoparticles have some advantages of low toxicity, large surface area, excessive loading of the drug. Recently, gold nanoparticle was found that it could inhibit RANKL and reduce ROS levels in BMMs, which hint gold nanoparticles may serve as an excellent osteoconductive material. Zhu et al. demonstrated that the nanoparticle was well engulfed and releasing EGCG had performed well in inhabiting MAPK of osteoclast, which may lead to the production of ROS. Nanoparticle-based delivery does not only give a new direction for treating postmenopausal osteoporosis, rheumatoid arthritis, periodontitis, and inflammatory osteolysis, but also establish the potential of nano-metal bone graft material (Zhu et al., 2019). Nevertheless, chemical approaches coupling nanoparticles and EGCG may increase potential cytotoxicity. Some reports put out the view of EGCG coating, a form of easy physical adsorption to probably take the place of chemical approach and reduce the cytotoxicity further (Madhurakkat Perikamana et al., 2019).

2.4 | EGCG in dental pulp regeneration

Tissue engineering strategies in vitro or in vivo mainly aim at using a scaffold material to give a supply for cell delivery and proliferation. The intact preservation of scaffold materials can maximize their support for cells. Bacteria and the fragile structure of the scaffold itself may lead to the undesirable preservation effect of the scaffold (Costa, Naranjo, Londono, & Badylak, 2017). EGCG may contribute to protecting the material from bacterial interference and enhancing the physical properties of the material.

Pulp necrosis is a common clinical problem. In previous studies, pulp necrosis was treated with apical induction or Regenerative pulp therapy based on blood clots, but the efficacy and predictability of these methods are controversial (Iwaya, Ikawa, & Kubota, 2001; Petrino, Boda, Shambarger, Bowles, & McClanahan, 2010; Tierney et al., 2009). With the development of biotechnology, the regeneration of dental pulp-dentin complex using the concept of tissue engineering has gradually appeared. Collagen is a nontoxic and biocompatible material, composing almost 90% organic matrix of dentin. It has better access to the complex root canal system due to its ability to be made into hydrogel form (Park, Li, Hwang, Huh, & Min, 2013). However, because collagen degrades quickly, the crosslinking agent should be added to improve the physicochemical property of the collagen scaffold. Compared with other crosslink agents, epicatechin has nontoxic properties and better biological properties (Nakanishi et al., 2010). Eun-Su LIM et al. explored the effect of Epicatechin on human dental pulp cells on collagen scaffolds as a crosslinking agent and found that ECN promoted human dental pulp cells (hDPCs) proliferation and differentiation by regulating differentiation through ERK signaling pathways. At the same time, the change of scaffold mechanical strength is related to cell proliferation and differentiation. Therefore, ECN therapy

might be used as a way to regenerate dentin pulp complexes (Lim et al., 2016). Young-Sun Kwon, MS et al. also confirmed this view again, they found that EGCG, as an antibacterial crosslinking agent, promoted the proliferation and differentiation of hDPCs cultured in collagen scaffolds. EGCG itself does not increase the proliferation and adhesion of human dental pulp cells but changes the mechanical properties of collagen scaffolds by shortening the gel conversion time, more conducive to cell adhesion and proliferation, and increasing surface strength (Kwon et al., 2017). Studies have shown that EGCG down-regulates the expression of inflammatory pathways in human dental pulp cells, such as NF-κ B and I-κ B-α. Yang et al. demonstrated that in maxillary mesenchymal cells and human dental pulp cells, EGCG can reduce the expression of inflammatory response TEGDMA-induced of COX-2 pathway by inhibiting the phosphorylation of extracellular signal-regulated kinase 1/2 (Yang et al., 2013).

There are few relevant studies on the effects of EGCG on hDPCs, thus, further studies are expected to identify EGCG promotes the proliferation and differentiation of human pulp cells and promote tissue engineering-based regenerative pulp therapy.

2.5 | EGCG in anti-caries materials

The antibacterial effect of tea can be traced back to the observation of McNaught, a major in the British Army Medical Corps, on the prevention from the infection *Salmonella typhi* and *Brucella melitensis* of brewed black tea a 100 years ago (Taylor, Hamilton-Miller, & Stapleton, 2005). Caries occurs first in bacteria adhering to the surface of the tooth, while bacteria form a film composed of a glucan. The biofilm containing bacteria and production of bacteria is also known as dental plaque, which results in the occurrence of caries. There are some convincing reports that EGCG may act as a preventer to interfere with the process for bacterial adhesion to enamel, reduce the activity of glucosyltransferase and amylase and inhibit bacterial proliferation in dental plaque (Taylor et al., 2005). Hare K et al. demonstrated that the activity of α-amylase was inhibited by EGCG, which indicate that EGCG is capable of inhibiting the caries formation by blocking the source of energy (Hara et al., 2012). Xu X et al. found that EGCG inhibits the growth of both *S. mutans* planktonic and biofilm cultures. Moreover, at the transcriptional and enzymatic levels, various cariogenic virulence factors of *S. mutans* was reduced, which put down acidogenicity and compromised stress tolerance (especially acid tolerance) (Xu, Zhou, & Wu, 2011). Toward the influence of dentin, Oliveira-Reis's experiment shows that EGCG can reduce the expression of MMPs and keep the maintenance of collagen stability (Oliveira-Reis et al., 2019). In addition, EGCG is considered to have potential in improving the microbial community and immune system after interaction with *L. salivarius* WB21 against *S. mutans* (Higuchi et al., 2019).

Dental caries is a chronic disease induced by biofilms bacteria accumulating and products of bacteria, often affecting tooth defect, periodontitis, and food impaction (Narotzki et al., 2012). Conventional bactericide substances have the limitation about drug resistance, tooth staining, instability, and cytotoxicity (Raut & Angus, 2010; Shen et al., 2016). For instance, CHX has been demonstrated that its cytotoxic effect on pulp cells, as well as drug resistance, which is supposed to be paid attention to (Lessa et al., 2010). Compared with conventional bactericide substance, EGCG, as a natural compound extracted from green tea, establish a better capacity of biocompatibility and antimicrobial properties (Narotzki et al., 2012). It is reported that drinking green tea may reduce the risk of dental caries in humans and laboratory animals (Wu & Wei, 2002). The protection of teeth by EGCG mainly contain inhibiting the formation of biofilm, suppressing the expression of MMPs, and the influence of de/remineralization processes in dentin (Narotzki et al., 2012). As we know, the toothpaste and mouthwash, which both contains EGCG, have a particular curative effect for preventing from dental caries, even some researches show that a toothpaste containing EGCG is helpful to prevent periodontal inflammation with its excellent antimicrobial properties (Maruyama et al., 2011). In order to explore the mechanism between EGCG and dentin, Baruch et al. attached gel containing EGCG and chlorhexidine to the surface of dentin. They found that the presence of deposition of particles inside the dentin tubules suggested that the dentin tubules were blocked entirely by gel, indicating the excellent performance for inhabiting dentin erosion (Kato et al., 2010). Similarly, Cinta et al. smeared the gel containing EGCG to the enamel surface. Interestingly, they found that EGCG can enhance the formation of AEP and acid-resistant organic layer on the enamel surface made of proteins (de Souza et al., 2017). These experiments indicate that the protection of EGCG for teeth is worth being more attentive. However, they ignored that not only do gel provide the local release, but also sustained release for EGCG to treat teeth. Because of the limitation of instability and less bioavailable, more attention is paid to sustained release (Li et al., 2018).

Some reports show that the addition of EGCG can enhance the anti-caries ability of adhesive resins, and the sustained release prolongs the antimicrobial period (Fialho et al., 2019). Nanoparticles, a potential approach to sustained release drug, often serve as a drug delivery system. Jian et al. fabricated a form of mesoporous silica nanoparticles (MSN) encapsulating EGCG to occlude the dentin tubules and resist bacteria-induce acid. Their nano-biomaterial shows an excellent performance in protecting dentin, and EGCG release can be detected more than 96 hr, which enhance the inhabitation of *S. mutans* biofilm (Yu et al., 2017). These results suggest that a better drug delivery system may be a prospect for EGCG to be a better bactericide substance.

2.6 | Elimination of halitosis

Halitosis refers to the unpleasant gas emitted from the mouth. It is a common disease in the oral and will bring some social anxiety to patients (Bicak, 2018). The main source of halitosis is the volatile sulfur-containing compounds (VSCs), produced by some bacteria, such as hydrogen sulfide, methyl mercaptan and so on, as well as some volatile aromatic compounds such as indole also playing a role in causing

odor (Tsuruta et al., 2017). Halitosis is caused by bacteria in the mouth. A proper way to treat halitosis is to inhibit oral anaerobes in the mouth. EGCG has a good bactericidal effect and the ability to regulate oral microbiota. In the EGCG immersion experiment of *Solobacterium moorei*, which can produce VSCs and cause halitosis by Morin, it was found that EGCG could target the cell membrane of *S. moorei* under an electron microscope. And prevent its adhesion to oral epithelial cells (Morin et al., 2015). EGCG can specifically inhibit the gene expression of specific oral anaerobic bacteria and inhibit the gene encoding L-methionine-α-diamino- γ-mercapto methane-lyase of *Lactobacillus*, *Streptococcus mutans*, and so on (Xu, Zhou, & Wu, 2010). In previous literature, EGCG has also been shown to inhibit the bacterial β-galactosidase gene. Additionally, in the regulation of the oral microbial environment, EGCG can inhibit the growth, acid production, metabolism, and glycosyltransferase of bacteria. By inhibiting the activity of the lactic acid enzyme in the oral cavity and increasing the pH level of the oral cavity, it can inhibit the growth of bacteria (Higuchi et al., 2019). All the above prove that the mechanism of EGCG for the elimination of halitosis is single and different. Because of the good inhibitory effect of EGCG on oral bacteria and satisfying therapeutic effect on halitosis, EGCG has been added to some chewing gum and toothpaste (Zeng, Wu, & Pika, 2010).

3 | CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, more and more researches focus on the application of EGCG in restoration materials which shows excellent biological and mechanical performance, providing a new understanding of the resin-based dental materials with therapeutic goals, and may open a new era for oral restoration. Compared with free EGCG, the release system may have a better performance because of the protection of EGCG premature degradation. Thus, the application of microparticles loaded with EGCG provides a new strategy for restoration technology. Due to the excellent antibiosis, anti-fibrosis, and osteogenesis effects, some EGCG loaded membranes for guided bone regeneration have emerged in recent years. The EGCG modified collagen membrane is an immunomodulatory membrane with excellent mechanical properties and has excellent potential in guiding bone regeneration after implant surgery. EGCG can inhibit the expression of TNF-α, inhibit the activity of osteoclasts, and reduce the damage caused by ROS to reduce the inflammatory response of the barrier membrane.

Meanwhile, EGCG can well reduce the oxidation induced by bone substitute materials. According to some studies, the osteogenesis of EGCG is mainly reflected in the inhibition of osteoclasts and the promotion of osteoblast proliferation. Additionally, ECN promotes human dental pulp cells (hDPCs) proliferation and differentiation by regulating differentiation through ERK signaling pathways and promoting the mechanical properties of collagen. Moreover, EGCG has the ability to reduce dental caries and halitosis by inhibiting bacterial reproduction and plaque growth.

However, there remain problems that need to be solved, such as the uncertain amount of EGCG release in microparticles, the methodology, which requires further investigations and the pulpal response of the modified materials. More in vivo trials need to be carried out before EGCG can be applied clinically into the patients' teeth. While series of in-depth studies reveal the tremendous osteogenic potential of EGCG- gelatin, more studies are required to regulate the clinical use of this material, for example, the optimal dose of EGCG has not been determined. In addition, the specific release amount of EGCG in this material has not been determined due to the presence of impurities. Moreover, for stem cell-based bone regeneration scaffold materials, the optimal amount of seeding cells for different cell types incorporated on this gel sponge needs to be determined. There are few relevant studies on the effects of EGCG on hDPCs; thus, further studies are expected to identify EGCG promotes the proliferation and differentiation of human pulp cells and promote tissue engineering-based regenerative pulp therapy. The instability of EGCG in the oral environment hinders its efficacy, and a growing number of materials aim to slow the release of EGCG, allowing it to remain at a sufficient concentration in the oral environment for a long time. However, studies have shown that excessive EGCG has certain cytotoxicity and can induce apoptosis of cells. Hence, more attention should be paid to the phenomenon of "local overdose." The emergence of nanomaterials may provide a more suitable carrier for local release. If the above concerns can be further and deeper investigated and solved well, EGCG will show excellent clinical potential in dental materials.

ACKNOWLEDGMENTS

National Natural Science Foundation of China (No. 81870801) and The Fundamental Research Funds for the Central Universities (No. 2082604401239).

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How to cite this article: Liao S, Tang Y, Chu C, et al. Application of green tea extracts epigallocatechin-3-gallate in dental materials: Recent progress and perspectives. *J Biomed Mater Res*. 2020;1–14. https://doi.org/10.1002/jbm.a.36991