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REVIEW ARTICLE

Clinical Applications of Catechin in Dentistry : A Review

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Abstract

Studies on plant and food phytochemistry and its potential benefits to human health are becoming the focus of the research community. Researchers are turning to alternatives drugs in treating human diseases using natural products from plants and foods. Polyphenols are one of the largest groups in the plant family and consist of many subgroups. One of them is catechin, which is generally acknowledged to be part of a compound in tea. Over the years, investigations have shown that catechin has anti-oxidant, anti-inflammatory and antibacterial properties. In dentistry, documented evidence have shown the use of catechin in treatment of dental caries, periodontal disease, pulp pathology, and oral cancer. Other crucial areas of research include advancements in dental material incorporated with catechin. This review article explores the current studies on the potential use of catechin in dentistry.

Keywords: Catechin, Dentistry, Dental Caries, Periodontal Disease, Oral Cancer

1. Introduction

The role of natural products in the pharmaceutical industry is undeniable. Prior to commercialization of drugs, people from ancient civilizations have used plant-based extracts to cure certain illnesses[1]. The Egyptians have documented the use of more than 1000 extracts derived from plants such as the oils from *Cedrus* species (cedar)[2] while Hippocrates has described the development of an anesthetic using the extract from *Atropa belladonna*[3]. The modernization and evolution in the fields of medicine and chemistry provide better insights to the mechanism of action of the natural products, thus providing a better platform for the researcher to find and develop products based on the extracts from plants.

The extracts of *Gingko biloba*, for example, have been used in various herbal medicinal products since it has been proven to have anti-oxidant and memory-enhancing effects[4,5]. In dentistry, the extract of propolis and miswak are added to toothpaste as studies have proven that these compounds have antibacterial effects[6,7] and promote gingival tissue health.

Another potential natural compound to be explored in dentistry is catechin. Catechin is a secondary plant metabolites, which is a flavonoid. It can be found in abundance in the human diet and plants, such as green tea, cocoa and beans. Chemically, catechin is featured as a compound with two benzene rings (Ring A and B) and a heterocyclic Ring C in between them. A hydroxyl group at position 3 of Ring C which leads to catechin also to be known as flavan-3-ol[8] (Figure 1). Catechin

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and epicatechin (EC), another derivative of flavan-3-ol with different chemical configurations, as a monomer can form an oligomer called proanthocyanidins (PAC)[9]. Esterification of this monomer with gallic acids produce epigallocatechin (EGC), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG)[10].

Over the years, reports from the *in vitro* and *in vivo* studies in the literature have proven the health benefits of catechin, mainly of its antioxidant and anti-inflammatory effects[11]. Both of these effects contribute to the potential usage of catechin in the treatment of certain illnesses. In cardiovascular disease, for example, catechin from red wine have platelet-inhibitory effects[12] while EGCG in green tea increases the blood level of nitric oxide (NO) and subsequently reduces vascular inflammation[13]. This, in turn, minimizes the individual risk of developing a cardiovascular-related disease such as hypertension and myocardial infarct. Owing to these facts, catechin has been increasingly used in foods and supplements for health purposes.

As a result of earlier studies on its biological properties, studies in the dental area have explored the potential application of catechin compounds. This review article aims to explore the current research on the usage of catechin and its derivatives in the field of dentistry.

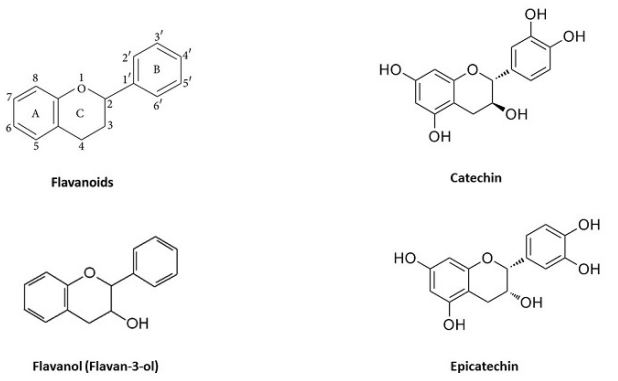

Figure 1. Chemical structure of flavonoids, flavanol, catechin, and epicatechin.

2. Source of Catechin

Catechin can be found in our normal diet especially in fruits, vegetables, tea, and wine. Fruits such as plum, apple, peach, strawberry, and cherry are reported to have an abundance of catechin. The oligomeric form of catechin like proanthocyanidins is present in grape and berries mainly in their skins and seeds, while epicatechin is high in apple, cherry, and black grape.

In vegetables, catechin and its derivatives are highly found in grains and legumes compared to leafy vegetables. Catechin and procyanidins make up almost 70% of the total phenolic compound found in cranberry beans and lentils[14]. Pinta bean was reported to have high concentrations of catechin[15] while raw cranberry beans are enriched with both catechin and proanthocyanidins[16].

Also, several studies have shown that tea contains catechin. Green, black and oolong teas are reported to have a high level of catechin. Green tea comprises of 60 to 90% of total flavonoids while a lower percentage between 6 to 24% was found in black tea[17]. The bioactive components of tea include catechin, epicatechin, epigallocatechin (EGC), epigallocatechin gallate (EGCG) and epicatechin gallate (ECG)[18].

Catechin can also be found in wines, particularly the red ones. This is owing to the use of grapes in the wine-making industry. The quality of red wine, determined by its astringency and bitterness are attributed to the presence of proanthocyanidins, a polymeric form of catechin and epicatechin[19]. However, the phenolic structure of wines differs from each other, depending on the type of grapes, how they are grown, and also the techniques used during the winemaking process[20].

Besides tea and wines, cocoa also contains catechin and epicatechin. Both these compounds were isolated from both unroasted and roasted cocoa beans. Factors like high temperatures and alkalization of cocoa powder during the manufacturing process play a crucial role in this conversion[21]. Interestingly, dark chocolate, a product made from cocoa powder also has been reported to be rich in catechin and epicatechin[21,22].

3. Clinical Application of Catechin in Dentistry

Catechin and its derivatives possess antiinflammatory, antioxidant and antimicrobial effects which are beneficial for human health. These properties trigger the researchers to further investigate the potential application of catechin in dentistry. Numerous studies in the field of dentistry have indicated the beneficial

effects of catechin, mainly EGCG in the treatment of oral diseases. Tables 1 and 2 summarise the studies related to the use of catechin in dentistry.

3.1 Dental Caries

Tea contains an abundance of catechin. One of them is EGCG, which possesses strong bactericidal activity[23].

Table 1. Studies on the usage of catechin in dental caries, periodontal disease, and pulp pathology

Author	Year	Types of Study	Compound Investigated	Results/Conclusion
			Dental Caries	
Kawamura et al.	1989	*In vitro*	Green tea catechins	ECG and EGCG decreased the number and inhibited the growth of *Streptococcus mutans in vitro*
Ikigai et al.	1993	*In vitro*	EGCG, EC	EGCG caused leakage and damage to the Gram-positive bacterial membranes
Rasheed and Haider	1998	*In vitro*	Green and black tea extracts	Extracts of green tea inhibited the growth of *Escherichia coli, Streptococcus salivarius,* and *Streptococcus mutans.*
Hirasawa et al.	2006	*In vitro*	EGCG, EG	EGCG and EG inhibit sugar transport and acid secretion by interfering with membrane-bound enzymes, and acid-producing enzymes such as LDH
Xu et al.	2011	*In vitro*	EGCG	EGCG inhibits acid production and acid tolerance of *Streptococcus mutans in vitro*
Ferrazzano et al.	2011	Clinical study	Green tea	Significance reduces in colony count of *Streptococcus mutans* and *Lactobacili spp.*
Xu et al.	2012	*In vitro*	EGCG	EGCG inhibits cell adherence and biofilm formation via suppression of gtf B, C, and D gene expression
Tao et al.	2013	Clinical study	Tea polyphenol (chewing gum)	Lower DMFS increment over 24 months
Goyal et al.	2017	Clinical study	Green tea catechin	Significance reduction in *Streptococcus mutans* count in plaque as well as saliva for 1 to 2-week interval
			Periodontal Disease	
Sakanaka et al.	1996	*In vitro*	Green tea catechin	EGCG inhibited the growth and adherence of *Porphyromonas gingivalis* onto the buccal epithelial cells
Maruyama et al.	2011	*In-vivo*	Green tea catechin	Toothpaste containing green tea prevent periodontal inflammation by decreasing gingival oxidative stress and expression of pro-inflammatory cytokines
Asahi et al.	2014	*In vitro*	EGCG	EGCG destroys *Porphyromonas gingivalis* biofilm and inhibits biofilm formation
Schmuch et al	2015	*In vitro*	*Rumex acetosa L* (PAC enriched)	Reduced adhesion of *Porphyromonas gingivalis* to host cell in a dose-dependent manner to 90%
Fournier-Larente et al.	2016	*In vitro*	EGCG and green tea extract	Dose-dependent inhibition of *Porphyromonas gingivalis* to oral epithelial cell
Morin & Grenier	2016	*In vitro*	Green tea catechin	Decreased MMP secretion
Rayyan et al.	2018	Clinical study	Grape seed extract (PAC)	Significant reduction in gingival and plaque index after 6-month

Pulp Pathology				
Nakanishi et al.	2010	*In vitro*	EGCG, ECG	EGCG & ECG significantly reduced expression of IL-6 and IL-8 in dental pulp cell exposed to Lipopolysaccharide and Peptidoglycan
Hirao et al	2010	*In vitro*	Tea catechin	Catechin, ECG and EGCG inhibit up-regulated expressions of IL-8 or PGE2 in Streptococci or PAMP-stimulated Human dental pulp fibroblast
Nakanishi et al.	2015	*In vitro*	Catechin	Catechin inhibits expression of VEGF and COX-2 in HDPC treated with PAMPS and IL-1b
Lee et al.	2015	*In vitro*	EGCG	EGCG inhibited the growth and eradicated the biofilm produced by *Enterococcus faecalis* by inducing the formation of hydroxyl radicals and down-regulate the bacterial genes.
Lim et al.	2016	*In vitro*	Epicatechin	Epicatechin promotes proliferation and differentiation of HDPCs which regulated by ERK signaling pathway
Katu et al	2016	*In vitro*	Extracts of *Uncaria gambir*	1% concentration of Uncaria gambir extract inhibited the growth of *Enterococcus faecalis* within 24 hours of contact time.
Herrera et al	2016	*In vitro*	Extracts of *Uncaria tormentosa*	2% of the extract of Uncaria tormentosa in gel form used as endodontic irrigants in infected root canal reduced the bacterial load of *Enterococcus faecalis* and maintain its activity up to 7 days.
Kulakowski et al.	2017	*In vitro*	Oligomeric PAC	Increased the expression of key biomineralization and odontogenic differentiation regulators, including RUNX2, BMP2, OCN, and DSPP
Kwon et al	2017	*In vitro*	EGCG	EGCG promoted the proliferation and differentiation of human dental pulp cells cultured in collagen scaffolds and increased the surface roughness and compressive strength of the collagen
Ismiyatin et al.	2019	*In vivo*	EGCG	EGCG suppressed the expression of Toll-like receptor 4, prostaglandin E2 and transient receptor potential vanilloid 1 associated with pulpal inflammation in rat models.

Table 2. Studies on the usage of catechin in dental restorative and oral cancer

Author	Year	Types of Study	Compound Investigated	Results/Conclusion
Dental Restorative				
Al-Ammar et al.	2009	*In vitro*	PAC	PAC extracted from grape seed acts as a crosslinker and improved bond strength toward dentine
Kato et al.	2010	*In vivo*	EGCG	The wear of bovine dentin blocks placed on a palatal device was significantly reduced after treatment with EGCG gel, an MMP inhibitor.
Fang et al.	2012	*In vitro*	PAC	Transient proanthocyanidin preconditioning improved resin-dentine bond without compromising curing behavior of tested adhesives
Castellan et al.	2012	*In vitro*	PAC	Pretreatment of the dentine with PAC extracted from grape and cocoa seed improved and stabilized the elasticity of the collagen matrices through the formation of exogenous crosslinkage.
Pallan et al.	2012	*In vitro*	EGCG	The incorporation of EGCG did not change the degree of conversion and water sorption of the resin monomer.
Kato et al.	2012	*In vitro*	EGCG	EGCG gel significantly reduced the concentration of hydroxyproline which is associated with the degradation of collagen and demineralized organic matrix in dentine, suggesting the protease inhibitory effects of EGCG
Liu et al.	2013	*In vitro*	PAC	PAC can effectively cross-link collagen and improve dentin collagen's biological stability in time periods as short as 10 s

Hu et al.	2013	*In vitro*	EGCG	Increased in flexural strength and surface microhardness of GIC incorporated with EGCG, with no interference towards the fluoride ion released by the material.
Manskovia et al.	2013	*In vitro*	EGCG	The resin containing EGCG inhibited the growth of *Streptococcus mutans*
Liu et al.	2014	*In vitro*	PAC	PAC biomodification effects in inhibiting proteolytic activity on demineralize dentine matrix
Zarella et al.	2016	*In vitro*	EGCG	EGCG non-cytotoxic toward dentine cell and retained antiproteolytic activity after extraction from a dental copolymer
Pheenithicharoenkul & Panichuttra	2016	*In vitro*	EGCG	Final irrigation with EGCG after 17% EDTA increases the push-out and the bond strength of an epoxy resin sealant
Oral Cancer				
Masuda et al	2002	*In vitro*	EGCG	EGCG inhibited VEGF promoter activity and cellular production of VEGF via inhibiting activation of Stat3 and NF-kappa B in head and neck and breast carcinoma cell lines.
Hastak et al	2003	*In vitro*	EGCG	EGCG induced stabilization of p53 and down-regulated the activity of NF-kappa B causing apoptosis of carcinoma cells.
Hsu et al.,	2005	*In vitro*	EGCG	P21WAF involved in EGCG induced growth arrest of OSC cell which may facilitate caspase-3-mediated apoptosis
Mohan et al.	2007	*In vitro*	Tea polyphenol	Tea polyphenol transduced apoptosis signal via generation of reactive oxygen species (ROS) and reduced in the BCL-2/BAX ratio
Leong et al	2009	*In vitro & in vivo*	Green tea extract	Green tea extracts inhibited cancer cell migration and VEGF and MMP9 gene expression.
Tsao et al	2009	Clinical study	Green tea extract	Administration of green tea extract over a period of 12 weeks improved the clinical outcome of patients with high risk oral premalignant lesions.
Koh et al.	2011	*In vitro & in vivo*	EGCG	EGCG inhibits HGF-induced tumor growth and invasion in oral cancer cell through suppression of HGF/c-Met signaling pathway.
Chen et al	2011	*In vitro*	EGCG	EGCG inhibited the invasion, migration, motility, and adhesion of oral squamous cell carcinoma cells.
Hwang et al.	2013	*In vitro & in vivo*	EGCG	EGCG inhibits cancer invasion by disrupting functional invadopodia formation
Lee et al	2013	*In vitro*	EGCG	EGCG inhibited the self-renewal capacity of head and neck squamous carcinoma stem cells
Tao et al.	2014	*In vitro*	EGCG	EGCG induces mitochondrial ROS and dysfunction causing apoptosis
Tao et al.	2015	*In vitro*	EGCG	EGCG induces differential mitochondrial dysfunction and oxidative stress in normal vs cancer cells, and it is related to differential modulation of SIRT3 and its downstream targets.
Lee et al.	2015	*In vitro*	EGCG	EGCG attenuates cell proliferation of oral cancer cell by upregulating BTG2 expression via p38 and ERK pathway

Based on this knowledge, numerous studies have been conducted to investigate the effectiveness of catechin as an anti-cariogenic agent, with mainly targeting the cariogenic bacteria *Streptococcus mutans* and *Streptococcus sobrinus*[24,25].

It is found that catechin from the tea extract can damage the gram-positive bacterial cell membrane by binding directly to its lipid bilayer. However, it is less efficacious against gram-negative bacteria due to the presence of the negatively charged lipopolysaccharides (LPS) on its outer membrane[26].

Virulence factor consists of protein metabolites produced by the bacteria which enables it to invade and cause damage to the host[27]. *Streptococcus*

mutans, for example produces glucosyltransferase (GTF), one of the virulence factors that leads to the production of intracellular polysaccharides (IPS) and extracellular polysaccharides (EPS). EPS helps in initial adherence of *Streptococcus mutans* and other oral bacteria on the tooth surface and forms mature dental plaque biofilm[28,29]. Apart from GTF, other virulence factors produced by *Streptococcus mutans* include the membrane-bound F1-F0 ATPase system and the enzyme enolase and lactate dehydrogenase[30].

EGCG hampers the effects of the virulence factors produced by *Streptococcus mutans* at both transcriptional and enzymatic levels, leading to reduced acidogenicity and stress tolerance of the bacteria[31]. EGCG also inhibits the action of the membrane-bound ATPase and lactate dehydrogenase (LDH) enzymes, affecting the sugar transport and acid secretion of the bacteria[32]. In addition, EGCG can suppress the GTF expression in *Streptococcus mutans*, therefore, inhibiting the cell adherence ability of *Streptococcus mutans* and reduce its biofilm production[33]. Other forms of catechin like proanthocyanidins (PAC) in cranberry extract was also found to cause a reduction in the biofilms formation and subsequently minimizes the risk of caries development both *in vitro* and *in vivo* studies[34].

Clinical studies also proved the efficacy of catechin-rich products in the prevention of dental caries. The use of a tea-based[35] and catechin[36] mouth rinse showed a remarkable reduction in the number of *Streptococcus mutans* and *Lactobacilli ssp*. colony respectively. While the incorporation of green tea extract in chewing gum reduced the DMFS (decayed, missing, and filled surfaces) score[37].

3.2 Periodontal Disease

Periodontitis is the disease of the tooth-supporting tissue, which involves inflammation and sometimes infection of the gingiva, periodontal ligament, and alveolar bone[38]. The ability of catechin to exert an effect on the periodontal pathogen will be beneficial in preventing the occurence and treating periodontal disease. The majority of the studies available have investigated the effects of catechin, mainly in the form of EGCG on *Porphyromonas gingivalis*- the principle reason in the development of chronic and aggressive periodontitis.

Porphyromonas gingivalis produces a variety of virulence factors that can penetrate the gingiva and cause tissue destruction, which includes gingipains, FimA fimbriae, HtrA protease, and lipid A phosphatase[39]. The most potent amongst these are the gingipains, which produce fibrillin that helps the bacteria to directly bind and adhere to the extracellular matrix proteins of the host[40].

Studies on the effects of catechins towards *Porphyromonas gingivalis* showed that EGCG extracted from green tea suppress the growth and prevent the adherence of the bacteria to the epithelial cells[41,42], mainly due to the action of the gallic acids within the phenolic compound of the EGCG[41]. Catechin[43] and proanthocyanidins[44] on the other hand, inhibit the production of gingipains which leads to the inability of *Porphyromonas gingivalis* to attach and invade the host. EGCG can also destroy the biofilms established by the bacteria[42] and inhibit the gene expression of the virulence factor produced by *Porphyromonas gingivalis*, mainly on the genes that involve in host colonization, tissue destruction, and heme acquisition[43].

Besides these, catechins have been reported to exhibit potential synergistic effects with conventional antibiotics directed against *Porphyromonas gingivalis*, specifically metronidazole[43].

Apart from studies related to *Porphyromonas gingivalis* , researchers also have investigated the effects of catechins on matrix metalloproteinases (MMPs). MMPs, released by the inflamed connective tissue in the periodontium cause destruction of the gingival collagen and periodontal ligament, and alveolar bone resorption[45]. EGCG was found to be able to reduce the secretion of MMPs released by the inflamed periodontal tissue[46], which in turn limits the progression of the disease itself.

Clinically, the researcher has incorporated catechin in topical agents used in the management of periodontal disease. Incorporation of catechin in dentifrice, from the green tea extract has reduced the periodontal inflammation[47] while catechin from the grape seed extract, applied in a gel form into the periodontal pocket resulted in improvement of the

plaque and gingival index. However, it did not effect the periodontal pocket depth significantly[48].

3.3 Pulp Pathology

When caries invades deeper into dentine and closer to the pulp, dental pulp cells start to produce pro-inflammatory cytokines and inflammatory cells. This, in turn, will cause pain as the pulp tissue undergoes some inflammatory changes. Catechin is known to posses anti-inflammatory properties which would be beneficial in reducing and treating symptoms that arise from pulpal inflammation.

EGCG and ECG from the tea extracts also have the ability in reducing the expression of pro-inflammatory mediators such as interleukin 1(IL-1) and interleukin 8 (IL-8) found in inflamed pulp[49–51]. *In vivo* study on animal model also showed the inhibitory effects of EGCG towards pain conduction that occurs during pulpal inflammation by inhibiting the production of prostaglandin E2 (PG-E2) and the subsequent release of transient receptor potential vanilloid (TRPV1) and substance P[52].

Moreover, EGCG also suppresses the growth of *Enterococcus faecalis*, a potent bacteria that commonly results in root canal infections[53]. *In vitro* studies using extracts from *Uncaria tomentosa*[54] and *Uncaria gambir*[55] showed that the extracts of both plants managed to suppress the growth of *Enterococcus faecalis*. Extracts of *Uncaria tomentosa,* used in a gel form produced similar antibacterial activity as compared to chlorhexidine when tested against *Enterococcus faecalis* in the infected root dentine. Interestingly, the substantivity of the antibacterial effects were longer compared to the sodium hypochlorite (NaOCl)[54].

Regenerative endodontic has emerged as one of the methods that has been reviewed and suggested to replace the conventional apexification procedure. Advancement in tissue engineering technology opens more opportunities and options in the regeneration of the pulp-dentine complexes. The use of stem cells, scaffolds, and suitable growth factors have been reported in the literature as part of the mechanism to induce regeneration of the dentine and pulp tissue.

The study on epicatechin and EGCG[56] found that it can establish a cross-linkage with the collagen from the collagen scaffolds. This mechanism, which is regulated by the extracellular signal-regulated kinase (ERK) signaling pathway, provides a strong platform for the differentiation and proliferation of the pulp cells[57]. EGCG enhanced the strength and surface roughness of the collagen scaffolds besides showing the antibacterial activity against *Streptococcus mutans, Fusobacterium nucleatum,* and *Enterococcus faecalis*[56]. All of these desirable effects will improve the environment of the collagen scaffolds that is suitable for pulp cell's attachment, differentiation, and growth.

Proanthocyanidins, on the other hand, enhanced the differentiation of the pulp cells and promoted dentinogenesis and biomineralisation[58] which in turn stimulated the growth of the dentine-pulp complex as part of regenerative endodontic therapy.

3.4 Dental Restorative Material

The adhesive system in a dental restorative material creates a solid and durable bond between resin and tooth structure. The bond, known as a hybrid layer, consists of embedded collagen fibrils of the dentine matrix in the adhesive resin. Despite the strong bond of the resin onto the dentine, it tends to deplete over time because of the degradation of collagen fibrils by the oral environment both chemically and mechanically[59], which consequently leads to the failure of the restoration.

Exogenous cross-linking agents such as formaldehyde and glutaraldehyde can contribute in modifying the structure of collagen fibrils and improve degradation resistance. However, these agents have shortcomings in terms of cytotoxicity, ill-matched mechanical properties, and poor long-term stability[60]. Hence, a natural cross-linking agent such as proanthocyanidins from the catechin subunit is a useful alternative due to its biocompatibility to biological tissue and its health-promoting effect.

Proanthocyanidins were reported to have the ability to form a cross-linkage with the collagen fibrils of the dentine and therefore improved the tensile strength and stability of dentine matrix mainly at the hybrid layer interface[61–63]. In addition, the application of proanthocyanidins-rich agents improved the quality of the hybrid layer in terms of susceptibility towards enzymatic degradation and water absorption, which

in turn reduced the material creep rupture and fatigue over time[64]. Besides that, the proanthocyanidins-rich agent also exhibited an inhibitory effect against proteases that is responsible for the degradation of the material[65].

The potential usage of EGCG has also been vastly investigated in the dental restorative field. An *in vitro* study was conducted looking into the effects of EGCG that has been incorporated as part of the glass ionomer cement (GIC) particle. Although the antibacterial effects were minimal compared to the control, EGCG improved the mechanical property of GIC and did not interfere with the fluoride released by the material[66].

The incorporation of EGCG extracts as a copolymer in composite resin showed that it did not affect the polymerization of the resin monomer[67] and has the ability to inhibit the enzymatic degradation of the material[68,69] and growth of *Streptococcus mutans*[70]. This, in turn, improves the long-term durability of the material. It is believed that the inhibitory effects against enzymatic degradation are due to the fact that ECGC carries a strong inhibition against MMPs[71]. The action against MMPs have also triggered researchers to investigate the potential development of an anti-erosive gel[72] which will benefit the patient with severe reflux disease.

A similar concept of MMPs inhibition by EGCG also has been investigated in the development of endodontic sealers. Good sealing and bonding abilities are crucial requirements for an endodontic sealer. The resin-based sealer has been used for decades to meet these demanding criteria. However, root canal irrigation with ethylenediaminetetraacetic acid (EDTA) and sodium hypochlorite before the obturation procedure can lead to collagen degradation, which usually stems from host-derived proteases MMPs[73]. The degradation of collagen will affect the covalent bond between the epoxy resin sealer and the root dentine. EGCG has been hypothesized to prevent the action of MMPs in root dentine thus increase the bond of the sealer to the root dentine[74].

3.5 Oral Cancer

The antioxidant and anti-inflammatory properties of catechin suggest that catechin can play an essential role in the prevention and treatment of cancer. Catechin, mainly EGCG in green tea has been extensively studied as a potential chemopreventive and therapeutic agent of oral cancer.

Literature has reported the antitumor effects of EGCG by preventing the early stages of cancer development[75], hindering tumor cell proliferation[76,77] and preventing the metastasis of cancer[78,79]. These effects are due to the ability of the extract to interfere with the cancer cell activity at the molecular level.

EGCG suppresses the expression of mRNA and transcription of transporter genes that is involved in the self-renewal ability (stemness) of the head and neck cancer stem cells[75,80]. Besides that, EGCG directly blocks the tumor signaling pathways regulated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[81]. Other pathways that are affected include the epidermal growth factor receptors (EGFR)[82], activator protein-1 (AP1) and signal transducers and activators of transcription (STATs)[83]. The angiogenesis ability of the cancer cells are also affected by inhibiting the expression of vascular endothelial growth factor (VEGF) and MMP9 genes[83].

Hsu, et al. explained that catechin could induce cell cycle arrest by up-regulating the cyclin-dependent kinase inhibitor p21[WAF1 76]. Besides that, Lee et al. in their study had concluded that EGCG enhanced the expression of BTG2 gene that arrests cell cycle at the G1 phase and depreciated cell proliferation via p38 mitogen-activated protein kinase (MAPK) signal pathway[77]. They also highlighted the ability of EGCG in inducing apoptotic cell death via inactivation of protein kinase B (AKT)[84] and alteration of the Bcl-2/bax ratio[85].

EGCG also has been reported to show selective inhibitory activity against oral cancer cells. The study has shown that it induced the formation of mitochondrial ROS leading to the dysfunction of the organelle and subsequently resulted in early cell apoptosis[86]. At the same time, EGCG also acts as an antioxidant in healthy cells and protects the cell from damage. This selective effect is related to the differential modulation of NAD-dependent deacetylase sirtuin-3 (SIRT3) and its downstream targets[87].

In addition, Hsu et al. described the selective induction of cancer cell apoptosis by EGCG involving the expression of p57, a cyclin-dependent kinase and

apoptosis inhibitor[76]. Lacking the p57 gene expression will lead to caspase-3 activation and cell apoptosis. They postulated that EGCG has the ability to selectively induce and increase the production of p57 in normal cells, leading to the survival pathway but induced the pro-apoptosis pathway in cancer cells.

Aside from hindering tumor cell proliferation, evidence showed that EGCG has a potential effect on the prevention of metastasis of cancer. Hwang et al. discovered that the administration of EGCG into an in vitro 3-D culture system of oral squamous cell carcinoma (OSCC) cells led to the inhibition of the cells' growth and suppressed the activation of the invadopodia protein that is responsible for the invasion of the cancer cells[78]. Chen and his colleagues in another study also proved the ability of EGCG in causing complete inhibition of the growth and invasion of OSCC cells, this time by reducing the expression of matrix metalloproteinase-2 and urokinase-type plasminogen activator[79].

Clinically, EGCG has been shown to suppress oral premalignant lesion, blocking the angiogenesis stimulation towards the dysplastic epithelial cells[88]. Moreover, the synergistic application of green tea and anticancer drugs have shown promising results. The application of EGCG enhanced the effects of the anticancer drugs[89,90], where a study found that it not only reduced the weight of the tumor formed by the human cancer stem cells[80], but it also inhibits the stemness ability and viability of the cells[75].

All of these findings and a better understanding of the molecular effects of EGCG towards cancer cells provide a new perspective on the direction of future cancer therapy. The use of catechin-based products can be an alternative option in prolonging the survival rate of cancer patients.

4. Conclusion

Catechin and its derivatives possess biological properties that have a promising potential in the field of dental caries, periodontal disease, pulpal pathology, dental restorative materials, and oral cancer research. However, most of the studies conducted were laboratory-based. Thus, more future *in vivo* studies is required to validate its use in the clinical setting.

5. Conflict of interest

The authors deny any conflict of interest regarding the review article.

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