

Progress in the Study of the Cariogenic Effect of Epigallocatechin Gallate

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Abstract: Epigallocatechin gallate (EGCG), a compound rich in tea, has long been recognized for its diverse biological activities, including its remarkable antioxidant, anti-inflammatory, antibacterial, and anti-tumor properties. However, recent research has uncovered a new, promising application of EGCG: its role in the prevention of dental caries. This paper aims to comprehensively review the mechanisms underlying EGCG's involvement in caries development and progression, focusing on three key areas: its regulation of matrix metalloproteinases (MMPs), its inhibitory effects on *Streptococcus mutans*, and its promotion of dentin and enamel remineralization. Matrix metalloproteinases (MMPs) are a family of enzymes that play a crucial role in the degradation of extracellular matrix components. In the context of caries, MMPs are involved in the breakdown of tooth structure, facilitating the progression of the disease. EGCG has been shown to regulate MMP activity, thus potentially slowing down the destructive process associated with caries. By inhibiting MMPs, EGCG could help maintain the integrity of tooth structure and prevent further damage. Another significant aspect of EGCG's caries-preventive action is its inhibitory effect on *Streptococcus mutans*, a bacterium that plays a key role in caries development. *S. mutans* produces acids that erode tooth enamel, leading to caries formation. EGCG has been found to inhibit the growth of *S. mutans* and reduce its acid production, thereby reducing the risk of caries development. Lastly, EGCG promotes the remineralization of dentin and enamel. Remineralization is the process of depositing calcium and phosphate ions back into tooth structure, helping to repair damage caused by caries. EGCG has been shown to enhance this process, potentially leading to the reversal of early caries lesions and the restoration of tooth health.

Keywords: EGCG; Caries; MMPs; *Streptococcus Mutans*; Remineralization.

1. Introduction

Natural medicines have been favored by many scholars because of their non-toxic side effects and wide availability of materials, that studies on the anti-caries effects of natural medicines are increasing, while epigallocatechin gallate (EGCG) extracted from green tea is one of them. EGCG, a polyphenol monomers extracted from green tea, is the main component of green tea catechins, accounting for 59% of its total weight [1]. As a highly effective free radical scavenger and remineralizer, EGCG has a wide range of applications due to its low biotoxicity. An overview of the role of the EGCG in caries prevention and mechanisms is available.

2. Regulation of Matrix Metalloproteinases

The primary cariogenic proteases in saliva are called matrix metalloproteinases (MMPs), including members such as MMP-2 and MMP-9. MMPs. They have the ability to break down the extracellular matrix and remodel normal tissues and participate in the development of various diseases, including pulpitis, periodontal disease, dental caries, and tumors[2][3]. The study by Wu et al. found that the acid produced by cariogenic bacteria can cause dentin demineralization and release phosphorylated proteins, which in turn activate host MMPs to promote organics degradation. The acidic microenvironment after dentin demineralization alternates with the neutral microenvironment brought about by salivary buffer, greatly increasing the activity of MMPs, further degrading the exposed dentin matrix, and promoting the development of dental caries.[2]Therefore, controlling the

activity of MMPs is important for the development and prevention of caries.

EGCG can regulate the activity of MMPs through multiple pathways [4]. First, EGCG can directly inhibit the activity of MMPs by forming chelates with metal ions[5][6]. MMPs are a class of proteases that require the assistance of metal ions (e.g., zinc ions) in order to exert their biological activities, and the multiple phenolic hydroxyl groups in EGCG can directly form chelates with metal ions, thus competitively inhibiting the activity of MMPs. The degradation of MMPs-mediated collagen fibers further enhances dentin demineralization[5], whereas EGCG can reduce the degradation of the exposed collagen fiber after dentin deamination to achieve the objective of inhibiting the development of caries. In comparison with the artificial saliva control group, the EGCG-containing experimental group was able to observe a significant decrease in the expression level of the type I collagen carboxy-terminal peptide (ICTP), a specific substance produced in the process of MMPs-mediated degradation of mature type I collagen fibers. The results showed that EGCG could effectively reduce the degradation of collagen fibers during the progression of dentin caries, thus preventing further dentin caries[7].

EGCG can also affect the expression and activity of MMPs by regulating numerous signaling pathways, including AKT, ERK, and NF- κ B[8]. Park et al. found that EGCG could inhibit the abnormally active FAK, AKT and ERK signaling pathways by down-regulating the dose-dependent expression level of integrin β 1, thereby decreasing the expression levels of MMP-2 and MMP-9 [9].NF- κ B is an oxidative stress transcription factor involved in the regulation of a variety of important physiological processes, including

apoptosis, inflammation, and autoimmunity, and in the study of oral cancer, the NF- κ B signaling pathway was mainly involved in the inhibitory effect of EGCG on the overexpression of MMP-2 and MMP-9 [8].

In addition, EGCG can inhibit the activity of MMPs by suppressing ultraviolet B-induced MMP-1 expression and decreasing the ratio of MMP-1 to the tissue inhibitor of metalloproteinases under ultraviolet irradiation[10]. Kim HS, Jin et al. showed that EGCG also reduces the activity of MMPs by activating mitogen-activated protein kinase[11][12]. It is noteworthy that EGCG's modulatory effects on MMPs are dose-dependent while excessive or low doses may have different effects [13]. In the use of enzyme labeling assay to investigate the effect of different concentrations of EGCG on dentin-derived MMPs, researchers found that the inhibitory effect of EGCG on the activity of dentin-derived MMPs was concentration-dependent and that capacity was more pronounced than that of the positive CHX control group when the concentration reached 400 μ g/ml[5]. Therefore, when EGCG is used or studied, reasonable dose control is required to ensure optimum effect.

3. Inhibition of Streptococcus Mutans

EGCG can slow down the progression of caries by inhibiting the growth and adhesion of cariogenic bacteria, especially Streptococcus mutans. The pathogenic mechanisms of Streptococcus mutans are mainly strong acid production, the use of sugar metabolism, and adsorption on the tooth surface, in which bacteria are attached to the surface of the tooth is the basis of caries. The Glucosyl Transferase on the surface of Streptococcus mutans can synthesize insoluble dextran and water-soluble dextran by using sucrose that can mediate the adhesion of bacteria[14]. Lactate Dehydrogenase of Streptococcus mutans produces lactic acid through carbohydrate metabolism, that accumulates in dental plaque, making the plaque locally hyperacidic and leading to an enamel demineralization-remineralization imbalance, which is the direct cause of caries[15][16].

The main component of EGCG is ellagitannin, a natural polyphenolic compound, for its main chemical component can effectively inhibit the growth of Streptomyces mutans, thereby achieving an effect inhibiting the development of caries[7][17]. Some studies have shown that 6.25 mg/L of EGCG can significantly inhibit the growth and proliferation activity of Streptococcus mutans[18]. EGCG can significantly inhibit the growth and proliferation of Streptococcus mutans and inhibit the initial adhesion of extracellular polysaccharides to the tooth surface, biofilm formation, and plaque maturation by inhibiting the Glucosyl Transferase activity of bacteria[19]. This may be related to its own strong reducing properties, which inhibits its sugar metabolism by scavenging oxygen radicals, disrupting the metabolic balance of Streptococcus mutans and oxidizing it, thus making it underproductive and unable to reproduce normally due to insufficient production capacity in order to achieve antibacterial and anti-caries effect[14]. EGCG can also inhibit the activity of Lactate Dehydrogenase to inhibit acid production, thus affecting the development of caries. Liu's study showed that 62.5 mg/L EGCG solution inhibited acid production in 24 hours, which was better than 25 mg/L NaF solution. [20] The inhibition of bacterial glycolysis by EGCG was designed to reduce the adaptability of bacteria to acid and

inhibit acid production[21]. It has been suggested that the inhibitory effect of EGCG on bacterial acid production may be due to its biological effect on phosphopyruvate hydratase in the glycolytic pathway of Streptococcus mutans[22]. Moreover, The oral application of EGCG has not been shown to have harmful effects on experimental animals[23]. Some studies have shown that EGCG still has antimicrobial activity when incorporated into restorative materials,[24][25] which provides a new perspective for the development of dental restorative materials.

4. Effects on Demineralization and Remineralization of Dental Tissues

Dental hard tissues mainly consists of enamel, dentin, and osteoid, and their degree of mineralization directly affects the hardness and acid resistance of teeth. When dental hard tissues are exposed to an acidic environment such as acidosis and the acid etching treatment of bone restorations, the minerals within the hard tissue undergo dissolution, and calcium ions are removed from the teeth, resulting in tooth demineralization. Studies have shown that EGCG has the ability to promote the remineralization of dentin and enamel.

First, the main extract of EGCG, tannin, can react with calcium ions to form complexes that enter the deep carious tissues through dentin tubules to promote calcium ion deposition, guide the growth of partially dissolved crystals, and promote remineralization; therefore, EGCG can increase the surface hardness of demineralized dentin, prompt the closure of dentin tubule orifices, and thus accelerate the deposition of dentin surface mineralization and inhibit the continued demineralization of dentin. [17] Yu, H., et al. treated human isolated molar teeth with epigallocatechin-loaded nanohydroxyapatite/mesoporous silica biocomposite (EGCG@nHAp@MSN) powder samples and verified the remineralization ability of EGCG by the result of tubule sealing that is testing the fluid permeability of dentin tubules to reflect.

Secondly, EGCG can promote the deposition and crystallization of minerals in enamel and dentin, improve the hardness and acid resistance of teeth, and reduce the demineralization of teeth. Lin, Y. W., et al. remineralized demineralized enamel by placing a model of enamel demineralization within an EGCG solution using the pH cycling method and observed granular deposits on the surface of enamel using scanning electron microscopy, and the surface tended to flatten, which indicated that EGCG could promote the remineralization of enamel [26]. After dentin caries were made by the lactic acid demineralization system, they were put into EGCG solution to conduct remineralization experiments, and deposits were observed on the surface of dentin under a scanning electron microscope, which quantitatively demonstrated that EGCG could promote remineralization of demineralized dentin [5, [27][28].

Therefore, EGCG is able to inhibit the demineralization process of dentin and enamel and promote their remineralization by inducing the closure of dentin tubule orifices, promoting the deposition and crystallization of minerals in dentin and enamel, inhibiting the activity of MMPs, and reducing the degradation of collagen, thereby inhibiting the development of caries.

5. Summary

In summary, EGCG plays a significant role in the

progression and prevention of caries by regulating matrix metalloproteinases, inhibiting the action of cariogenic bacteria, and promoting the remineralization of dentin and enamel in various ways. Current research on the role and effects of EGCG in oral cavity-related conditions is still relatively limited, and in-depth studies are needed to reveal its specific mechanism and application value. It is hoped that this review will provide references and insight for further research on the aspects of EGCG in caries progression and prevention.

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