MEDS Basic Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medbm.2024.020214
ISSN 2616-2091 Vol. 2 Num. 2

A Review of the Inhibitory Effect of Epigallocatechin Gallate on the Cariogenicity of Streptococcus Mutans

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Keywords: *Streptococcus mutans*; Epigallocatechin gallate; Biofilm; Dental caries; Oral microecology

Abstract: *Streptococcus mutans* (*S. mutans*) are currently recognized as the most important cariogenic bacteria. Their main cariogenic behaviors include adhesion, acid production and acid resistance, and inducing cariogenic transformation of oral microecology. *Streptococcus mutans* (*S. mutans*) colonize the oral cavity by adhering to the oral cavity and forming a biofilm, which produces acid and leads to the demineralization of teeth and the formation of cavities. The cariogenic transformation of oral microecology further promotes the formation of cariogenic biofilm and eventually leads to the occurrence of caries. Epigallocatechin gallate (EGCG) is one of the most abundant and important catechins in green tea. It is generally considered to have good antioxidant, anti-inflammatory and antibacterial properties. In vitro and in vivo studies have shown that EGCG can significantly inhibit the cariogenic ability of *S. mutans*, suggesting that EGCG has a broad application prospect in caries prevention. In addition to its ability to kill or inhibit S. mutans, EGCG inhibits *S. mutans* biofilm formation by promoting *S. mutans* cell aggregation, reducing *S. mutans* surface hydrophobicity, inhibiting the function of *S. mutans* surface protein and the formation of extracellular matrix. By inhibiting the activity and synthesis of lactate dehydrogenase and a series of related enzymes of *S. mutans*, EGCG can inhibit acid production and acid resistance. It can also inhibit cariogenic transformation of oral microecology. This article reviews the related research in recent years.

1. Introduction

Dental caries is a common chronic disease among Chinese residents. The incidence of dental caries in China is increasing year by year. Fluoride is commonly used in the prevention and treatment of dental caries. However, excessive intake of fluoride may lead to dental fluorosis and lead to enamel defects. Chlorhexidine is an antibacterial disinfectant commonly used in dental department. However, its anti-caries effect is not ideal, and it can cause hypersensitivity reactions and other problems. Effective and safer anti-caries drugs are needed in dental clinics.

Green tea is a popular beverage in the world. Its catechins are generally considered to have good antioxidant capacity, anti-inflammatory activity and antibacterial properties. epigallocatechin gallate (EGCG) not only contains the highest phenolic hydroxyl group of all catechins, but also is the most

abundant catechin in green tea, with stronger antioxidant activity and biological activity than other catechins[1]. EGCG not only does not cause cytotoxicity to odontoblast-like cells at high concentrations, but also inhibits the production of inflammatory mediators such as interleukin-1β induced by *S. mutans* and promoted the production of peroxiredoxin 1 in odontoblast-like cells, showing both non-proinflammatory and anti-inflammatory effects. In addition, EGCG has also been found to inhibit endogenous proteases in dentin and act as a collagen cross-linking agent to maintain collagen stability. These findings suggest that EGCG has the potential to be a clinical anti-caries agent.

In recent years, a number of studies have investigated the inhibitory effect of EGCG on the cariogenicity of *S. mutans*.

2. Streptococcus mutans-"dominant" cariogenic bacteria

Streptococcus mutans (S. *mutans*) are currently recognized as the most important cariogenic bacteria and play a key role in the formation of cariogenic biofilm. The cariogenic behaviors of *S. mutans* mainly include adhesion, acid production and acid resistance, and induction of cariogenic transformation of oral microecology.

2.1 Adhesion

Cariogenic biofilm is a microbial community composed of a variety of oral microorganisms and the extracellular polysaccharide (EPS) produced by them as the main component of the extracellular matrix. *Streptococcus mutans* (*S. mutans)* are the most common bacteria in cariogenic biofilms. They are involved in the construction of extracellular matrix and biofilm formation, which depends on the adhesion between *S. mutans* and the tooth surface.

S. mutans adheres to teeth through two main pathways, sucralose independent adhesion and sucralose dependent adhesion: During the initial adhesion process, *S. mutans* adhere to the dental surface through a sucrose-independent pathway. The surface protein Pac interacts with salivary agglutinin in the acquired enamel pellicle, which mediates the low-affinity and rapid adhesion between *S. mutans* and the dental surface. The subsequent adhesion process is sucralose dependent. *S. mutans* use glucosyltransferases (GTFs) to convert sucrose into EPS such as glucan. EPS also binds to glucan-binding protein C, a surface-anchored protein of *S. mutans*, to promote adhesion. Sucrose-dependent adhesion mediates the high affinity and slow adhesion between *S. mutans* and the dental surface.

In addition, *S. mutans* can also release large amounts of extracellular DNA (eDNA) by regulating self-apoptosis through quorum sensing system and secreting membrane vesicle in a non-cell lysis manner during initial adhesion. Together with extracellular proteins, EPS and lipoteichoic acid produced by *S. mutans* during cell apoptosis and cell wall formation, these eDNA form a complex extracellular matrix. Extracellular matrix promotes the adhesion of *S. mutans* and other cariogenic microorganisms. It not only provides a three-dimensional scaffold for biofilm formation, but also shapes the cariogenic microenvironment that is conducive to the metabolism of *S. mutans*.

2.2 Acid production and acid resistance

After the mature and dense biofilm is formed, the bacteria in the biofilm produce organic acids such as lactic acid through lactate dehydrogenase (LDH). As by-products of fermented sugars, these organic acids are encapsulated by a large amount of extracellular matrix, which creates a local acidic microenvironment and leads to persistent lw pH, which eventually leads to demineralization and caries formation in tooth tissues.

This process is also closely related to the strong acid tolerance of *S. mutans*, which is related to F_1F_0-atpase and agmatine deiminase system (AgDS). F_1F_0-atpase is a multimeric enzyme composed of F_0 protein inserted in the membrane and a peripherally attached F_1 protein complex. It maintains the pH of the cytoplasm by removing protons from the cell, which not only maintains a stable acidic environment in the biofilm, but also promotes the survival of *S. mutans* in an acidic environment. AgDS converts agmatine to putrescine, ammonia and carbon dioxide, and the ammonia produced increases the cytoplasmic pH. In addition, ATP produced in this process can also be used for bacterial growth or proton efflux, thus maintaining the survival of *S. mutans* in an acidic environment and contributing to the formation of acid tolerance of *S. mutans*.[2].

2.3 Inducing the cariogenic transformation of oral microecology

Streptococcus mutans are not the only bacteria that causes caries. They interact with other oral microorganisms to cause the cariogenic transformation of oral microecology, which plays an important role in the occurrence and development of dental caries.

Most of the microorganisms living in the oral cavity are opportunistic pathogens. There are complex antagonistic and synergistic relationships among them. Under physiological conditions, some oral microorganisms, such as *Streptococcus gordonii* and *Streptococcus salivarius,* can inhibit the growth of *Streptococcus mutans* and other cariogenic bacteria by secreting bacteriocins and hydrogen peroxide, and *Streptococcus mutans* can secrete mutacin to fight against them, thus achieving a balance between commensal bacteria and cariogenic bacteria.

However, when the body ingests large amounts of carbohydrates such as sucrose, *S. mutans* can not only use sucrose to produce EPS, their GTFs can also combine with other cariogenic microorganisms such as Candida albicans, making other cariogenic microorganisms become producers of EPS, and the large amount of EPS produced in this process can promote the adhesion of other cariogenic microorganisms. Thus, the formation of cariogenic biofilm is greatly promoted.

In addition, Actinomycetes, *Streptococcus sobrinus* and some non-Streptococcus mutans group Streptococcus can also cooperate with *Streptococcus mutans* to produce acid. As *S. mutans* collaborates with other cariogenic microorganisms to produce EPS and acid, a highly acidic and hypoxic microenvironment is gradually established. Acid-nonresistant oral commensal bacteria are gradually inhibited, while acid-resistant cariogenic microorganisms dominate the microbial community and eventually lead to the formation of cariogenic biofilms.

Therefore, the development of dental caries is actually the result of the interaction between *S. mutans* and other cariogenic microorganisms, but *S. mutans* plays a key role in this process.

3. The inhibitory effect of EGCG on the cariogenic activity of Streptococcus mutans and the underlying mechanism

3.1 Bactericidal mechanism of EGCG

EGCG has a significant inhibitory effect on the cellular activity of *Streptococcus mutans*. EGCG not only significantly inhibited the growth of planktonic *S. mutans*, but also showed a significant bactericidal effect on the bacteria in the biofilm. EGCG inhibits the cell activity of *S. mutans* mainly by changing the membrane potential of *S. mutans* and destroying the bacterial cell wall and membrane:

3.1.1 Changing the membrane potential of *Streptococcus mutans*

Membrane potential plays an important role in regulating *S. mutans* cell metabolism, cell division, pH homeostasis, and membrane transport. The protein regulatory effect of EGCG may affect the

activity of ion transporters on the cell surface of *S. mutans*, leading to cell membrane hyperpolarization. The hyperpolarization of cell membrane changes the normal membrane potential of S. mutans, and then inhibits the cell activity of *S. mutans* [3].

3.1.2 Damaging the cell wall and membrane of S. *mutans*

EGCG may directly bind to the peptidoglycan layer and interfere with its structure through hydrogen bonding, leading to the rupture of the pentapeptide cross-bridges and degradation of the peptidoglycan layer, resulting in the rupture of the bacterial cell body [4]. Moreover, EGCG may cause irreversible damage to the cell membrane of *S. mutans* by acting on some components of the cell membrane and causing membrane rupture and cytoplasmic leakage at high concentrations, thereby inhibiting the cell activity of *S. mutans*[5].

3.2 Inhibiting the biofilm formation of S. *mutans*

Several studies[3, 5-7] have demonstrated that EGCG has a significant inhibitory effect on *S. mutans* biofilm formation. EGCG may inhibit the biofilm formation of *S. mutans* by inhibiting the surface protein function and extracellular matrix formation of *S. mutans*:

3.2.1 Promoting S. *mutans* cell aggregation

EGCG could significantly promote planktonic *S. mutans* cell aggregation, thereby reducing bacterial adhesion and inhibiting biofilm formation[1].

3.2.2 Reducing the surface hydrophobicity of *Streptococcus mutans*

Bacterial cell surface hydrophobicity is one of the mechanisms by which bacteria attach to different hard surfaces. EGCG at a low concentration can reduce the surface hydrophobicity of *S. mutans* and block hydrogen bond formation without affecting the cell activity of *S. mutans*, possibly by binding to hydrophobic components of bacterial cell surface, thereby inhibiting its attachment to different hard surfaces[5].

3.2.3 Inhibiting the function of surface proteins of S. *mutans*

3.2.3.1 Inhibiting the function of amyloid fibril forming proteins

Amyloid fibers exist on the surface of *Streptococcus mutans* cells, which can promote adhesion and protect eDNA from degradation, suggesting that are the key structures for biofilm formation and integrity[8]. As an inhibitor of amyloid fibers, EGCG may reduce the formation of amyloid fibers by inhibiting the Pac and WapA proteins, thereby inhibiting the adhesion of *S. mutans* and the construction of biofilm formation related structures [9].

3.2.3.2 Inhibiting the function of biofilm regulation related proteins

It has been confirmed that the *brpA* gene plays an important role in regulating biofilm formation. The membrane-associated protein BrpA expressed by *brpA* gene plays an important role in regulating cell division, biofilm formation and maturation of *S. mutans*. In addition, the *brpA* gene is also associated with acid resistance and oxidative stress protection of *S. mutans*. Lack of *brpA* gene leads to defective biofilm formation, decreased acid resistance and increased sensitivity to oxidative stress in *S. mutans*. SCHNEIDER-RAYMAN et al. conducted Real Time-qPCR analysis and found that the expression of *brpA* gene in *S. mutans* was significantly down-regulated under EGCG treatment. In

addition, EGCG also significantly down-regulated the expression of *nox* and *sodA* genes involved in oxidative stress protection[3]. These results indicated that EGCG could not only aggravate the oxidative stress of S. mutans by inhibiting the expression of stress-related genes, but also interfere with the function of biofilm regulatory proteins by down-regulating the expression of biofilm regulatory genes. Thus, the biofilm formation of *S. mutans* is significantly inhibited.

3.2.4 Inhibiting the formation of extracellular matrix

3.2.4.1 Inhibiting the production of extracellular polysaccharides

EGCG not only inhibited the synthesis of GTFs and fructosyltransferase by down-regulating the expression of *gtfB*, *gtfC*, *gtfD* and *ftf genes* in *S. mutans* biofilms at the transcriptional level[3, 7, 10], but also inhibited the activity of glucosyltransferase at the enzymatic level, thereby reducing the production of extracellular polysaccharides such as glucans[6, 10].This not only inhibited the sucrose-dependent adhesion of *S. mutans*, but also hindered the construction of extracellular matrix, thereby inhibiting the biofilm formation.

The binding ability of EGCG to *S. mutans* glucosyltransferase was analyzed by molecular docking. It was found that EGCG could bind to glutamate 515 and tryptophan 517 in glucosyltransferase, two amino acid residues associated with catalytic function and receptor binding, respectively. These results suggest that EGCG inhibits the EPS production and cell adhesion of *S. mutans* by inhibiting its catalytic activity and its binding ability with *S. mutans*[6]. Notably, the concentration of EGCG that significantly decreased EPS production was smaller than that that significantly decreased *gtf* gene expression in *S. mutans*, indicating that the enzymatic activity of glycosyltransferase is more sensitive to EGCG than the gene expression[10].

3.2.4.2 Inhibiting the eDNA production

As an important component of the quorum-sensing system of *Streptococcus mutans*, *luxS* gene plays an important role in the regulation of biofilm formation, acid production and acid resistance of *Streptococcus mutans*. The *luxS* gene is also closely related to the *ftf* gene, *brpA* gene and *ComDE* gene, and the deficiency of *luxS* gene results in the significant down- regulation of the expression of these genes. The *ComDE* gene is an important part of the ComDE two-component signal transduction system. The ComD and ComE proteins encoded by *ComDE* gene can regulate the autolysis to release eDNA in the biofilm environment of high cell density.

EGCG can significantly down-regulate the expression of *luxS* [3], which not only affects the physiological activities of *S. mutans* such as acid production, acid resistance and EPS synthesis, but also inhibits the function of the ComDE two-component signal transduction system and eDNA production, thereby inhibiting the synthesis of extracellular matrix.

3.2.4.3 Inhibiting the function of two-component signal transduction system

The VicRK two-component signal transduction system can regulate the expression of *gtfB*, *gtfC* and other genes by sensing the changes of the external environment, which plays an important role in the formation of biofilm. In addition, the VicRK two-component signal transduction system also plays an important role in the regulation of *S. mutans* cell wall synthesis and degradation, and stress tolerance such as acid resistance, osmotic pressure and oxidative stress. The VicRK system also regulates the quorum-sensing of *S. mutans* by regulating the ComDE two-component signal transduction system and the transcription of mutacin gene [11].

EGCG significantly down-regulates the expression of *vicR* gene in *S. mutans*[3]. This may not only inhibit the cell viability and EPS production of *S. mutans*, but also affect the quorum-sensing system

of *S. mutans*, thereby inhibiting the extracellular matrix construction and biofilm formation of *S. mutans*.S

3.3 Inhibiting the acid production and acid resistance of S. *mutans*

The acid resistance and acid production of *S. mutans* can synergistically promote the cariogenic transformation of oral microecology, which plays an important role in the formation of cariogenic biofilm. EGCG can significantly inhibit both acid production and acid resistance of *S. mutans* [1, 10]. In addition, EGCG also has a certain buffering ability, which can strengthen the neutralization effect of saliva on pH reduction, and play a positive role in maintaining a relatively neutral oral environment. Its main mechanisms of action are as follows:

3.3.1 Inhibiting the acid production by *Streptococcus mutans*

EGCG inhibits acid production of *S. mutans* mainly by inhibiting the activity and synthesis of LDH, the activity of sugar transport related enzymes and the synthesis of enolase.

3.3.1.1 Inhibiting the activity and synthesis of LDH

EGCG not only inhibits the activity of lactate dehydrogenase in *S. mutans* at the enzymatic level [2, 12], but also down-regulated the expression of *ldh* gene at the transcriptional level, thereby inhibiting the synthesis of lactate[2]. Inhibition of LDH at the transcriptional and enzymatic levels may also increase NADH level and reduce the REDOX potential of cells, leading to NAD/NADH imbalance and/or accumulation of glycolytic intermediates in cells, which may have a certain toxic effect on *S. mutans*[2]. This suggests that EGCG can reduce the production of lactate and inhibit the glucose metabolism activity of *S. mutans*. Its inhibition of glycometabolism activity may also further reduce the production of lactate, thereby reducing the cariogenic virulence of *S. mutans*.

3.3.1.2 Inhibiting the activity of enzymes involved in sugar transport

The phosphoenolpyruvate-dependent phosphotransferase system (PEP-PTS) is a series of membrane-associated enzymes involved in sugar uptake and phosphorylation. Sugar-specific membrane-bound enzyme II complex (EIIC) is an important component of the PEP-PTS system, which is involved in the transport and phosphorylation of related carbohydrates [1].

By inhibiting the activity of PEP-PTS, EGCG was found to inhibit sugar uptake, glycolysis and acid production in *S. mutans* [1, 2]. Through molecular docking simulation, Han et al. found that EGCG could bind to the glucose transport domain of EIIC and form hydrogen bonds with conserved amino acid residues in EIIC[1], indicatingthat EGCG may bind to EIIC and inhibit the glucose transport-related functions of EIIC, thereby inhibiting the activity of PEP-PTS.

3.3.1.3 Inhibiting the synthesis of enolase

Even at a high concentration, EGCG had little inhibition on enolase activity of *S. mutans*, but EGCG at a sub-minimum inhibitory concentration (MIC) significantly inhibited *eno* gene expression. The *eno* gene encodes enolase, indicating that EGCG inhibits the production of enolase at the transcriptional level, which may not only directly inhibit glycolysis, but also reduce the downstream phosphoenolpyruvate (PEP) produced by enolase. This may inhibit the function of PEP-PTS and ultimately reduce the amount of sugar internalization and glycolytic activity of *S. mutans*, thereby reducing the acid production of *S. mutans*[2].

3.3.2 Inhibiting acid resistance of *Streptococcus mutans*

The inhibitory effect of EGCG on acid resistance of *S. mutans* was mainly reflected in the inhibition of the activities of F_1F_0-atpase and AgDS.

atpD gene encodes the β subunit of F_1 protein in F_1F_0-atpase. The *aguD* gene encodes the agmatine-putrescine Antiporter protein, through which agmatine enters the cell and is hydrolyzed to N-carbamoylputrescine and ammonia by agmatine deiminase. EGCG with sub-MIC significantly inhibited the expression of *atpD* and *aguD* genes at the transcriptional level and the activity of F_1F_0-atpase at the enzymatic level. The inhibition of *atpD* expression and F_1F_0-atpase activity may lead to cytoplasmic acidification of *S. mutans*, which may interfere with the normal function of a series of enzymes involved in glycolysis and EPS production, thereby inhibiting the glucose metabolism and adhesion ability of *S. mutans* in an acidic environment. In addition, because AgDS is also related to ATP production, the inhibition of AgDS activity caused by the down-regulation of *aguD* expression not only acidizes the cytoplasm of *S. mutans*, but also reduces ATP production and aggravates its starvation stress.

Combined with the inhibition of *eno* gene expression, it can be speculated that the inhibition of F_1F_0-atpase and AgDS activity by EGCG and the inhibition of enolase expression by EGCG may act together to inhibit ATP production and the normal process of glycolysis. The inhibition of glycolysis, in turn, reduces ATP production, further inhibits the activity of F_1F_0-atpase, and aggravates the acidification of cytoplasm, thereby inhibiting the metabolic activity of *S. mutans* in an acidic environment, and ultimately inhibiting the acid resistance and biofilm formation of *S. mutans*[2].

3.4 The effect of EGCG on oral microecology

The cariogenic process of *Streptococcus mutans* is inseparable from its interaction with other bacteria. The previous article described the effect of EGCG on *Streptococcus mutans.* What is the role of EGCG in the co-existence of other bacteria?

Lactobacillus can synergize with *S. mutans* to produce acid and promote the cariogenic transition of oral microecology. However, under physiological conditions, as an oral probiotic, Lactobacillus can inhibit the adhesion and biofilm formation of *S. mutans* by binding to *S. mutans*, occupying specific adhesion sites, and releasing hydrogen peroxide and biosurfactant to maintain a healthy oral microecology.

Previous studies have confirmed that the MIC of EGCG against *S. mutans* is significantly lower than that of EGCG against Lactobacillus. Although EGCG solution at a certain concentration can reduce the number of *S. mutans* and Lactobacillus in saliva, its effect on Lactobacillus is relatively small[13]. Even some studies have found that EGCG at a low concentration can improve the cell viability of Lactobacillus, and the combination of EGCG and Lactobacillus shows a good biological effect against pathogenic microorganisms.

In addition, *Streptococcus sobrinus* (*S. sobrinus*) and *Actinomyces naeslundii* (*A. naeslundii*) are closely related to the occurrence of caries. *S. sobrinus* has a strong cariogenic ability and synergism with *S. mutans*, while *A. naeslundii* is related to the occurrence of root surface caries. Low concentration of EGCG could not only inhibit the biofilm formation of *S. sobrinus* [14], but also inhibit the adhesion of *A. naeslundii* to hard surfaces such as glass by reducing the surface hydrophobicity of them [5].

What's more, some researchers have also found that using EGCG as a mouthwash can significantly inhibit the acid production of dental plaque[12], and reduce the number of *Streptococcus mutans* and Lactobacillus in saliva, and its effect on *Streptococcus mutans* is more significant[13]. This suggests that EGCG plays a positive role in inhibiting the cariogenic transformation of oral microecology.

With the rapid development of sequencing technology, more and more attention has been paid to

the field of microecology. As a microecology-related disease, the pathogenesis of dental caries is usually considered to be related to the imbalance of microecology. The prevention and treatment of dental caries requires attention to the balance of microecology. If blindly killing or eliminating cariogenic bacteria leads to the imbalance of specific microecosystem, the gains will outweigh the losses.

In conclusion, EGCG at an appropriate concentration can inhibit the growth of *S. mutans* without affecting the normal oral microecology too much, and inhibit the synergistic interaction between other cariogenic microorganisms and *S. mutans* by inhibiting their adhesion, thereby inhibiting the cariogenic transition of oral microecology. EGCG may be effective in regulating the balance of oral microecosystem under certain conditions of imbalance.

4. Summary and Prospect

EGCG could significantly inhibit the cariogenic virulence of *S. mutans* through its bactericidal ability, inhibition of biofilm formation, and acid production and acid resistance. EGCG has good biocompatibility and has the advantages of multi-level and multi-target inhibition on the cariogenicity of *S. mutans*. However, EGCG at a certain concentration may also inhibit the colonization of oral commensal bacteria such as *Streptococcus salivarius* and *Streptococcus gordornii* on the dental surface[5].

In order to ensure that EGCG can exert its anti-caries effect without affecting the normal oral microecology as much as possible, the appropriate administration concentration of EGCG may be one of the future research directions. In addition, the Cariogenic factors of *S. mutans* are complex, so the specific mechanisms of EGCG inhibiting *S. mutans* caries should be further explored, such as the effects of EGCG on other surface proteins and two-component signal transduction system as well as membrane vesicle secretion, so as to further analyze the material basis of EGCG caries prevention to provide a more solid theoretical basis for the clinical application of EGCG.

In conclusion, EGCG has promising potential as a natural phytochemical component. If the bitter taste of EGCG can be improved while ensuring its anti-caries effect, it is expected to become a safe, effective and popular anti-caries drug.

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