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Review Article

# Exploring the possible applications of catechin (gel) for oral care of the elderly and disabled individuals

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**Summary** The oral cavity contains more than hundreds of microbial species. An increase in the number of these microorganisms like high pathogenic potential species, such as cariogenic and periodontopathic bacteria, and the change of microbial biota may result in, not only oral infection, but also systemic diseases, such as infective endocarditis and aspiration pneumonia. It is very important to control the growth of these microorganisms and its biota just after oral cleaning in order to suppress disease onset. In this regard, it is useful to use the anti-microbial component which acts against pathogenic microorganisms. Here, we highlight the importance of catechin, and feature its possible oral, especially periodontal applications. By combining catechin with gel (catechin gel), antimicrobial activity of catechin was prolonged in gel and catechin anti-oxidization property was observed. Catechin gel inhibited the growth of the *Actinomyces*, periodontopathic bacteria and *Candida* strains tested, but did not inhibit that of the oral streptococci that are important in the normal oral flora. In contrast, commercially available moisture gels containing antimicrobial components showed antimicrobial activity against all of the tested strains including the oral streptococci. This show that catechin has selective antimicrobial activity, attributable to hydrogen peroxide production. This paper reviews previous works using catechin and, likewise, catechin gel may be show its possible oral application for prevent dental caries and periodontal disease.


## Contents



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## 1. Introduction

Green Tea is a product made up from the leaf and bud of the plant *Camellia sinensis*, and is classified into 'non-fermented' green tea (produced by drying and steaming the fresh leaves to inactivate the polyphenol oxidase and thus, no oxidation occurs) [1]. One of the major components of green tea is catechin. Catechin are polyphenols that are grouped into different kinds: (1) epigallocatechin (EGC); (2) epigallocatechin gallate (EGCG); (3) epicatechin (EC); (4) epicatechin gallate (ECG); (5) gallocatechin (GC); (6) catechin (C), and (7) gallocatechin gallate (GCG).

Catechin are polyphenol chemical compounds that are abundant in green tea and have been shown to exhibit physiological effects, including antibacterial [2—5], antifungal [6,7], antiviral [8—11], antioxidative [1,12], and antitumor activities [13—15]. Recent studies have suggested that catechins also promote oral health and contribute to a reduced risk for some systemic disease [16,17]. However, the advantageous effects of catechins are not evident in the oral cavity, as it serves simply as a passage for catechins and the use of catechin in oral care applications was uncommon.

## 2. Oral flora and plaque accumulation

Several microbial species reside in the human oral cavity [18]. These are composed of indigenous microbial flora that prevent the colonization and growth of foreign pathogens which would have a beneficial effect to the host [19]. However, an increase in the number of indigenous flora could cause infectious disease in the oral cavities (such as dental caries or periodontal diseases) [20,21] and mature dental plaques may be linked to systemic disease progression [22—24]. Similarly, systemic diseases, such as infective endocarditis [24,25], myocardial infarction [26], aspiration-related pneumonia [27—29], premature birth and low weight birth [30] may be linked to oral microbes.

During the dental plaque development, bacterial species (such as *Streptococcus* spp.) adhere strongly to the tooth forming an initial dental plaque [31]. These would be part of the normal oral microbial flora which is mainly composed of early colonizers forming a thin dental plaque which helps to maintain the health of the host and prevent the adhesion and proliferation of oral pathogenic microorganisms such as periodontopathic bacteria [32]. It is essential to keep this thin dental plaque for our oral health. As the existence ratio of periodontal and other pathogens is very low and the growth of these bacteria are late, the outer layer of these cells favor adhesion to *Streptococcus*, *Fusobacterium* or *Actinomyces* resulting in the accumulation and formation of mature pathogenic dental plaque which subsequently results in the accumulation of metabolic product [31,33,34]. The mature dental plaque can develop to a biofilm and obstruct the penetration of substances, such as chemotherapeutic agents and external antibodies [35,36]. The combination of cell components ingredient and metabolic product in dental plaque is considered detrimental to host tissues.

Currently, medical care for the old associated to sudden increase of the senior citizen population has become a primary concern. Among the leading cause of death among senior citizens older than 60, pneumonia is the primary cause. At the moment, pneumonia is the 4th leading cause of death in Japan [37]. In the case of elderly person orally eating where there is a decline in deglutition function, aspiration-related pneumonia accounts for 70% of pneumonia cases [38].

Previous reports associate aspiration to most oral microorganisms [28]. Dental plaque is the site for bacterial progression and one of the highest pathogenic factors in aspiration-related pneumonia [29]. It has been reported that this pneumonia can be prevented by professional mouth care but mouth cleaning is difficult for the elderly, often requiring a care worker's assistance [39,40].

In addition, plaque and periodontopathic bacteria are not only a source of focal infection but may also hold inflammatory materials. Therefore, it is essential that the microbial count present in the oral cavity be strictly controlled to suppress serious diseases progression [41,42].

## 3. Medical application of catechin

Recently, catechin was suggested to contain antioxidative activity and contribute to reducing cardiovascular risk and some forms of cancer [43,44].

Antioxidant activity of catechin has previously been assessed by several methods. Cao et al. [45] found that green tea catechin has a much higher antioxidant activity against peroxyl radicals. Similarly, Saffari and Sadrzadeh [12] investigated the EGCG antioxidant capacity using membrane-bound erythrocyte. This would suggest that catechin may contribute to anti-oxidative stress damage. Similarly, catechin has antihypertensive effect and can prevent cardiovascular disease [46]. Some studies suggest that catechin can protect against neurodegenerative diseases like Parkinson's and Alzheimer's diseases and which would indicate epigenetic activity [47,48]. Furthermore, numerous studies have also demonstrated that the aqueous extracts of GTP possesses anti-inflammatory and hypocholesterolemic properties [49].

The effects of EGCG on antioxidant, dietary, obese, human malaria, cardiac muscle function, prostate cancer, innate immune receptor and cardiac muscle function has all been reported [50—56]. EGCG, exerts a growth inhibitory effect in cancer cells suggesting it possesses a promising anticancer potential due to its antioxidant, antimutagenic and chemopreventive properties [57]. Yu et al. [58] reported that EGCG inhibited the growth of prostate cancer adenoma cells and induced apoptosis. EGCG is also considered to be a topic protector agent against some types of radiation since it prevents skin disease, photoaging and potential cancer problems due to prolonged exposure [59]. Some investigations have also shown that EGCG does not only regulate the glucose level in blood, but also may rehabilitate damaged *beta*-cells, which are responsible for producing insulin [1].

The effect of EG on prostate cancer [55], and the effect of EC on prostate cancer, prevent stroke damage, fatigue resistance and oxidative capacity [56,60,61] has been previously described. Likewise, the effect of C and GC on blood circulation, fracture, chromic gastritis, rheumatoid arthritis and irregular menstruation has been shown [62].

Despite this information, few reports have described the catechin clinical application in the oral cavity.

## 4. Catechin gel as a plaque control reagent

The prevention of dental plaque formation, accumulation and maturation as a result of poor oral care is important for the control of both oral and systemic diseases. Thus, the development of novel and more effective oral hygiene methods are essential. At the moment, plaque control mainly involves mechanical means (such as toothbrushing, dental floss, and interdental brushing), however, this alone is often insufficient. Therefore, a number of chemical agents are often used to support mechanical-based plaque control, including topical antibiotics [63], chlorhexidine [64], povidone-iodine [65], xylitol [66], fluoride [67], and others [68]. However, side-effects associated with these agents have been reported, including unpleasant taste, tooth discoloration, irritation, and the induction of painful lesions in the oral mucosa [67,69]. Some reports have confirmed the emergence of drug-resistant strains of bacteria against xylitol or antibiotics [70,71] which would imply the need for a chemical plaque control reagent with a strong anti-plaque effect and causing no side-effects.

Among the several beneficial properties of catechin, catechins antimicrobial activity would have beneficial effects against oral diseases. However, few reports have described the clinical applications of catechins in the oral cavity since EGCG is readily absorbed by the digestive tract and distributed to many animal and human organs. Generally, catechin solutions are held for only a very short time in the oral cavity which is not sufficiently enough time for an effective antimicrobial action [72]. Moreover, catechin antimicrobial activity against the many species of oral microorganisms is not fully elucidated. Understanding the range of catechin antimicrobial activity and developing methods to prolong catechin duration in the oral cavity would be essential to achieve oral health benefits.

Catechin gel (gel-entrapped catechins) is a mixture of catechin and a gel that can be applied to the oral cavity of elderly patients [41]. The gel would enable catechins to be retained in the oral cavity prolonging catechin action. Moisture gel without catechin showed no effect against all employed strains in this study.

Minimal inhibitory concentration (MIC) by microdilution assay and agar diffusion methods (ADM) was used to show absence turbidity and the occurrence of growth inhibitory zones using catechin gel and catechin components [41]. From the 28 microbial strains used, the MIC-ADM difference was found in each strain used (Table 1). Antimicrobial activity of catechin gel was observed in all strains of *Streptococcus mutans*, *Actinomyces naeslundii*, *Staphylococcus aureus* including MRSA, *Candida albicans*, *Fusobacterium nucleatum*, and periodontopathic bacteria. MIC-ADM values were less than 0.10 mg/ml against *Prevotella intermedia*, *F. nucleatum*, *A. naeslundii*, and *Porphyromonas gingivalis*. In contrast, no growth inhibition zone was observed for early colonizing streptococci, including *Streptococcus mitis*, *S. sanguinis*, *S. oralis*, and *S. gordonii*, or for *Lactobacillus* or *Escherichia*. These bacterial strains appeared to be resistant to the antibacterial activity of catechins. The highest concentration (2.50 mg/ml) was found in *Prevotella nigrescens*, one of the periodontal pathogens. These results established the ideal concentration (2.75 mg/ml) for use in future studies in clinical applications. It is worth mentioning, that the catechin concentration in a tea beverage is 2–3 mg/ml [73], which would imply that the catechin concentration (2.75 mg/ml) is enough for clinical use.

Diameters of the growth inhibition zones produced by catechin gel and EGCG gel (as a positive control) using the gel diffusion method are shown (Fig. 1) [41]. Catechin gel displayed antibacterial effects against oral pathogenic microorganisms, with inhibition zones evident for all tested strains of *A. naeslundii*, *S. mutans*, *C. albicans*, *S. aureus* and periodontopathic bacteria. Notably, the diameters of the growth inhibition zones for *Actinomyces* and *S. aureus* were greater than 20 mm. The antibacterial effects of catechin gel were similar to, or in some cases greater than, to those of

**Table 1** Antimicrobial activity of catechin gel.

| | | | | | |
|---|---|---|---|---|---|
| **(a) Gram positives** | | | **(b) Fungi** | | |
| *S. mutans* | ATCC25175 | 0.75 | *C. albicans* | NUD-201 | 0.38 |
| *S. mtis* | ATCC903 | >3.00 | | | |
| *S. sanguinis* | ATCC10556 | >3.00 | | | |
| *S. oralis* | ATCC10557 | >3.00 | **(c) Gram negatives** | | |
| *S. gordonii* | ATCC10558 | >3.00 | *P. gingivalis* | ATCC33277 | 0.09 |
| *A. naeslundii* | ATCC12104 | 0.09 | *P. intermedia* | ATCC25611 | 0.05 |
| *L. casei* | IFO3353 | >3.00 | *P. nigrescens* | ATCC33563 | 2.50 |
| *L. salivarius* | TI2711 | >3.00 | *A. a.* | Y4 | 0.75 |
| *S. aureus* | 209P | 0.38 | *F. nucleatum* | JCM6328 | 0.05 |
| MRSA | NUD-101 | 0.38 | *E. coli* | 12D-5203 | >3.00 |

Minimal inhibitory concentration of agar diffusion assay (MIC-ADM: mg/ml).

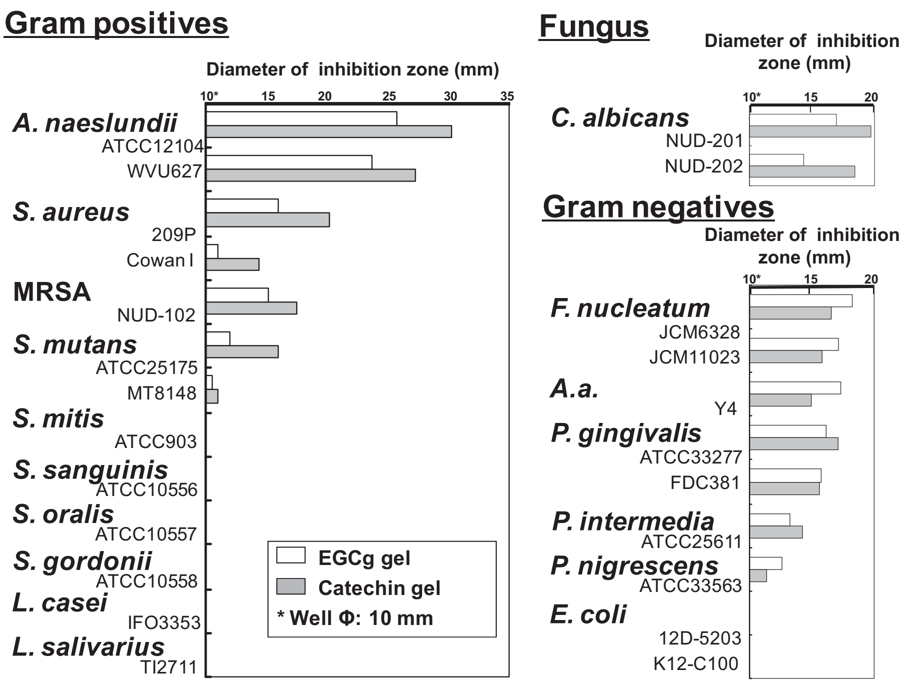


**Figure 1** Optimum antimicrobial activity of catechin gel. Bars indicate the diameters of the growth inhibition zones produced by catechin gel (white bars) and EGCG gel (black bars) for the listed strains. The diameter of the well was 10 mm. (a) Gram-positive bacteria and fungi. (b) Gram-negative bacteria. Catechin concentration used was 2.75 mg/ml.

EGCG gel. In contrast, no growth inhibition zone was observed for early colonizing streptococci (*S. mitis*, *S. sanguinis*, *S. oralis*, and *S. gordonii*), *Lactobacillus* or *Escherichia*. These bacterial strains appeared to be resistant to the antibacterial activity of catechins, this would imply that catechins may be useful for the control of dental plaque accumulation, since it was formed efficient against *Actinimyces* and *Fusobacterium* (plaque-causing bacteria) [31,33,34]. Antimicrobial effects of catechins were also observed against *Staphylococcus* strains (including MRSA, which cause suppuration-related inflammation and bedsores [74]) and *Candida* (which causes oral candidiasis [75]) suggesting that catechins may aid in the prevention of oral candidiasis and suppuration as well. Moreover, it has been suggested that the ability of catechins to inhibit the growth of *Staphylococcus*, *C. albicans*, and periodontopathic bacteria may help to suppress aspiration pneumonia [29,76].

Unlike the commercial gels, catechin gel did not show antimicrobial activity against early colonizing oral streptococci such as *S. sanguinis*, *S. oralis*, *S. gordonii* and *S. mitis* streptococci which are part of the normal oral microbial flora and help maintain healthy oral cavity by preventing the adhesion and proliferation of some pathogenic microorganism [32]. Early colonizing streptococci have been associated with low numbers of periodontopathic bacteria and the absence of periodontal disease [77]. It is very important to keep the thin layer of bacterial accumulation formed during the early stage of dental plaque since it possess low pathogenicity. Therefore, it is necessary to not only suppress the oral pathogenic microorganisms that cause disease but also to protect the oral flora that play an important role in innate immunity and catechin gel can efficiently do so.

## 5. Advantages of catechin gel over catechin

A comparison between catechin gel and catechin solution mixed solution is show in Fig. 2 [78]. The quantity of residual catechin was measured by spectrophotometer [73]. Most of the catechins in solution were removed after first washing, whereas more than 90% of the catechins in catechin gel remained after five rounds of washing (Fig. 2a). The difference in residual catechins between the catechin gel and the solution was significant ($p < 0.01$). The inhibition zones for *S. mutans* were similar between washed and non-washed catechin gel (Fig. 2b). In contrast, the catechin solution produced no growth inhibition after the first wash. Same results were observed against *A. naeslundii* and *S. aureus*. Furthermore, incubation of *S. mutans* either with catechin gel or solution showed that the antimicrobial activity of the catechin gel was higher than that of catechin solution and was nearly equivalent to that of freshly prepared one (Fig. 2c). This further supports the possible clinical applications of catechin gel. Same results were also observed against *A. naeslundii* and *S. aureus*. It is worth mentioning that when comparing catechin gel with other commercially available moisture gels containing antimicrobial agents such as gel A (containing lactoperoxidase, glucose oxidase, lysozyme, and lactoferrin) and gel B (containing cetylpyridinium chloride), the results showed that the antimicrobial activity of catechin gel was higher than that of commercially available gels, each of which contained antimicrobial agents directed against the pathogenic microorganisms examined (Fig. 3) [41]. Surprisingly, both commercial gels inhibited the growth of oral streptococci suggesting that these gels appear to lack selective antimicrobial action. The catechin gel showed both

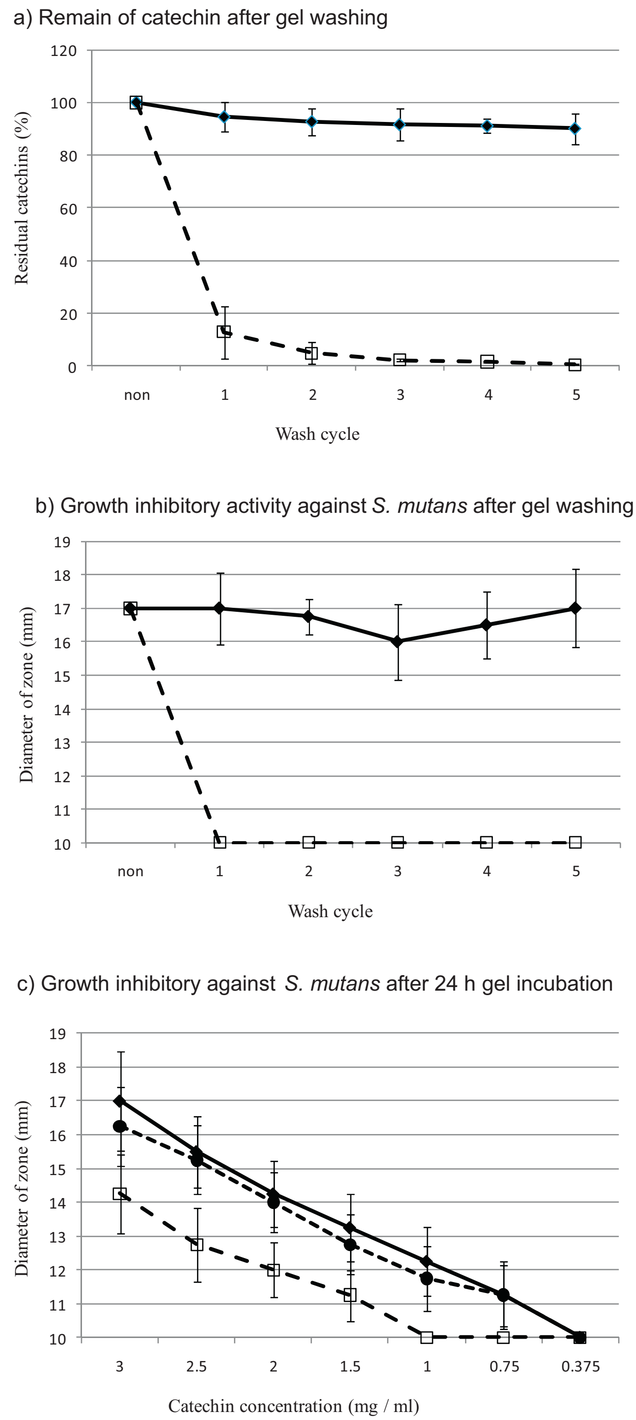


**Figure 2** Height catechin retention was detected in catechin gel. (a) The percentage of catechins remaining after a series of washes with artificial saliva. There was a significant difference between catechin gel (◆) and catechin solution (□) ($p < 0.01$). (b) Antimicrobial activities of catechin gel and solution after a series of washes with artificial saliva. Values are the diameters of the growth inhibition zones of *S. mutans* ATCC25175 produced by catechin gel (◆) and catechin solution (□) after each wash cycle. There was a significant difference between the catechin gel and solution ($p < 0.01$). (c) Antimicrobial activities of the catechin gel and solution after incubation at 37 °C for 24 h. Values are the diameters of the growth inhibition zones of *S. mutans* ATCC25175 produced by catechin gel (●), catechin solution (□) and freshly prepared catechin gel (◆). After a 24-h incubation, the catechin gel and solution showed significantly different antimicrobial activity ($p < 0.01$).

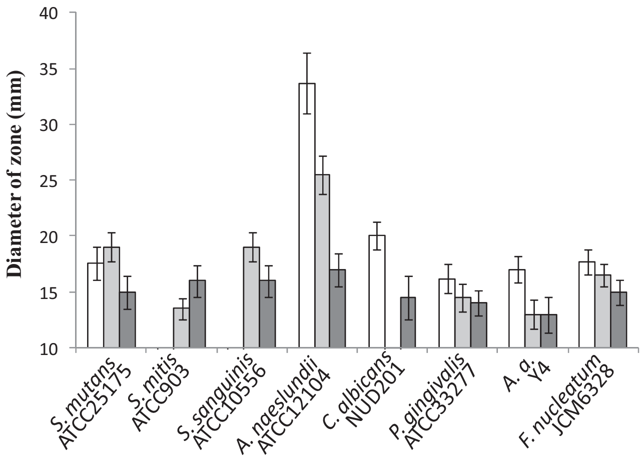


**Figure 3** Comparison between catechin gel and commercial gels. Diameters of the microbial growth inhibition zones produced by catechin gel and the commercially available gels A and B. White bars, catechin gel. Gray bars, gel A. Black bars, gel B. The well diameter was 10 mm.

higher antimicrobial activity than commercially available gels and selective antimicrobial activity.

## 6. Mechanisms of antimicrobial activity

Catechin antimicrobial activities are mainly dependent on the charges and tertiary structure of the target molecule. EGCG caused strong aggregation and NPN-fluorescence quenching of PC-liposomes and these actions were markedly lowered in the presence of negatively charged lipids [79]. These results show that bactericidal catechins primarily act on and damage bacterial membranes [80]. In addition, some reports have indicated that catechins promote the production of hydrogen peroxide [81,82]. Authors reported that catalase prevented catechin gel-induced growth inhibition of *S. mutans*, *A. naeslundii* [38] and, likewise, the antimicrobial activity was dependent mainly on hydrogen peroxide and significant quantities of hydrogen peroxide were produced by *S. mitis*, *S. sanguinis*, *S. oralis*, and *S. gordonii* (Fig. 4) [41]. By comparison, less hydrogen peroxide was produced by *S. mutans* and *A. naeslundii*. Previous studies have reported that *Streptococcus* spp. and most *A. naeslundii* strains lack catalase activity [83] and that the alpha-hemolytic activity of *S. gordonii* is related to the production of hydrogen peroxide [84].

## 7. Proposed antimicrobial activity in the oral cavity

Some commensal bacterium is protected against the deleterious effect of hypothiocyanite ($OSCN^-$) which is produced by oral peroxidases (salivary peroxidase, myeloperoxidase) or lactoperoxidase in the presence of thiocyanate ($SCN^-$) and hydrogen peroxide [85]. This resistance was previously attributed to the activity of a bacterial NADH:hypothiocyanate oxidoreductase (NHOR) which can reduce hypothiocyanite into thiocyanate with no effect on the bacterium (Fig. 5) [86]. Thus, we previously examined the detoxification ability of $OSCN^-$ with hydrogen peroxide generated from catechin [87]. As NHOR activity could not be measured directly, activity was measured based on $NADH_2$ consumption which was indispensable to enzymatic reaction [88]. *S. mitis, S. sanguinis, S. oralis* and *S. gordonii* used NHOR for enzymatic activity. On the other hand, most of the $NADH_2$ consumption was not recognized as is the case of *S. mutans* and *A. naeslundii* (Fig. 6) [86]. From this result, it seems that catechin in an environment with oral peroxidase has an antibacterial effect against *S. mutans* and *A. naeslundii*, but not towards streptococci.

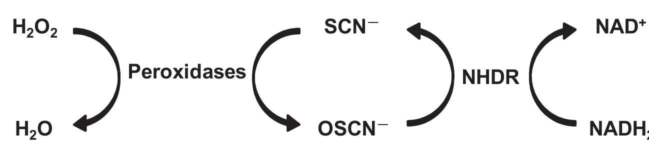


**Figure 5** Schematic illustration of relationship between hydrogen peroxide and NADH:hypothiocyanate oxidoreductase (NHOR) in oral cavity [80].

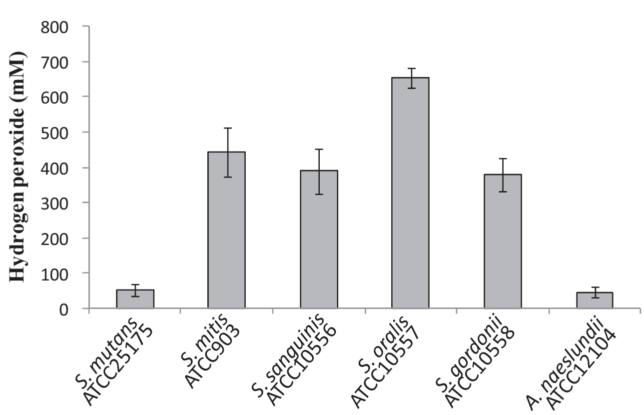


**Figure 4** Hydrogen peroxide production. The bars indicate the concentrations of hydrogen peroxide produced by the listed microbial strains.

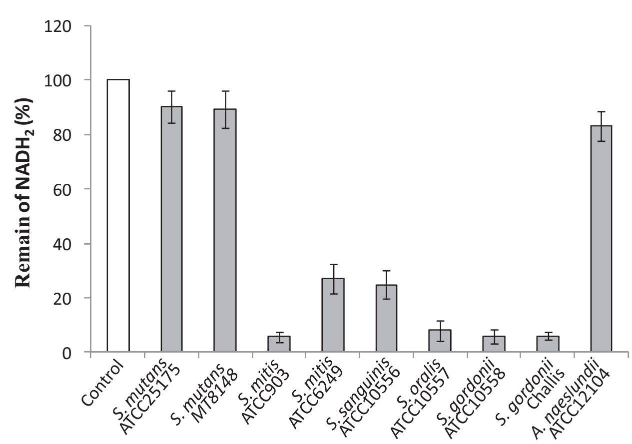


**Figure 6** Consumption of $NADH_2$ [81]. The consumption of $NADH_2$ was accompanied by NHOR activity.

## 8. Conclusion

This review presents a detailed overview of the advantage and benefits of catechin. In addition, we highlight the possible use of catechin gel against oral diseases, such as dental caries, periodontal diseases and candidiasis.

## Conflict of interest statement

The authors declare no conflict of interest.

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