ISSN: 03875547
Volume 45, Issue 01, February, 2022

Epigallocatechin-3-gallate Green Tea (*Camelia Sinensis*) Phytomedicine for Orthodontic Tooth Relapse Prevention: Narrative Review

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Keywords:
Orthodontic Tooth Movement, medicine, dentistry, Green Tea, Epigallocatechin-3-gallate

ABSTRACT

Epigallocatechin-3-gallate (EGCG) is an active compound that is abundant in green tea (*Camellia sinensis*). EGCG has potential as an antioxidant, anti-inflammatory, anti-osteoclastogenesis as well as pro-angiogenic and pro-osteoblastogenesis. Orthodontic tooth relapse (OTR) may occur due to suboptimal alveolar bone remodeling and excessive inflammation during orthodontic tooth movement (OTM) which causes inhibition of periodontal tissue regeneration. EGCG is thought to increase the regeneration of periodontal tissue after OTM so as to prevent relapse. This narrative literature review aimed to describe the potential of the active compound EGCG in green tea phytomedicine as a candidate biomaterial to prevent OTR. EGCG has strong antioxidant potential by being able to reduce High Mobility Group Box 1 (HMGB-1) and Heat Shock Protein-70 (HSP-70) during inflammation. EGCG in green tea can inhibit pro-inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α) through its antioxidant properties. Osteoclastogenesis can be suppressed by administering EGCG because of the effect of decreasing TNF-α and signaling inhibition of Receptor activator of nuclear factor κ-β (RANK) and Receptor activator of nuclear factor κ-β ligand (RANKL) so that osteoblastogenesis can increase. The increase in osteoblastogenesis after EGCG administration was due to osteoinductive effects such as Bone Morphogenic Protein-2 (BMP-2) activating runt-related transcription factor-2 (RUNX2) and osterix, resulting in osteoblast maturation. Mature osteoblasts secreted bone related proteinfor alveolar bone regeneration such as osteocalcin, osteonectin and osteopontin which can prevent relapse after OTM. EGCG, which is the active compound in green tea (*C. sinenis*) may potential to be used as phytotherapy for orthodontic tooth relapse.

1. INTRODUCTION

Orthodontics is a dentistry speciality that focuses on the examination, diagnosis, and treatment of

malocclusions by repositioning teeth through the alveolar bone sockets. The movement of teeth through the dentoalveolar complex is a synergistic series of physical and biological periodontal tissue remodeling processes. Tooth biological systems respond to changes in force magnitude, application duration, and direction via cell receptors and signaling cascades, resulting in bone remodeling and orthodontic tooth movement (OTM). OTM is a mechanism that combines physiological adaptation of the alveolar bone to mechanical stress with small reversible periodontal damage. This tooth movement is performed under normal/healthy conditions by highly coordinated and efficient bone remodeling, which necessitates the fusion of bone formation following bone resorption [1].

The most difficult aspect of an orthodontic treatment plan is generally keeping the teeth in the right position following treatment. OTR following orthodontic treatment is traditionally seen as a return to the initial malocclusion state. However, OTR does not always occur, and it may be defined as an adverse shift in tooth position following orthodontic treatment away from the treated malocclusion. These alterations might also be the consequence of typical aging processes. It is vital to have a full grasp of the etiology of recurrence and be familiar with numerous techniques to decrease relapse after OTM while doing orthodontic treatment. This involves an awareness of the benefits and drawbacks of different orthodontics retainers, as well as the ability to counsel patients on how to efficiently use orthodontic retainer [2].

Green tea is mostly made from the *Camellia sinensis var. sinensis* plant. This tea (*Camellia sinensis var. assamica*) has an excessive polyphenol concentration, which causes the green tea to taste bitter. Green tea leaves include the most fascinating group of components, polyphenols, and flavonoids. As a result, green tea may be regarded a significant food source of polyphenols, particularly flavonoids. Flavonoids are phenolic derivatives that are generated in high amounts (0.5-1.5 percent) and in numerous varieties (over 4000 recognized). Flavonoids are extensively dispersed throughout plants. Green tea contains a variety of flavonoids, the most important of which are catechins (flavan-3-ols). The four main catechins are -epigallocatechin-3-gallate (EGCG), which accounts for approximately 59 percent of total catechins; -epigallocatechin (EGC), which accounts for approximately 19 percent of total catechins; -epicatechin-3-gallate (ECG), which accounts for approximately 13.6 percent of total catechins; and -epicatechin (EC) (approximately 6.4%) [3].

EGCG, which has the ability to generate regeneration of alveolar bone and thereby prevent OTR. EGCG has the potential to be osteoinductive by enhancing the expression of bone regeneration markers such as bone morphogenic protein-2 (BMP-2), alkaline phosphatase (ALP), and runt related transcription factor 2 (RUNX2), all of which are significant role in bone matrix production. EGCG is one of the polyphenol catechins found in C. sinensis or green tea, and it has several advantages when consumed in significant quantities (50-80% or about 200-300mg) [4]. EGCG possesses anti-inflammatory, antioxidant, and anti-inflammatory effects. EGCG also has antimicrobial and osteoinductive ability. Previous research by found 4.41 percent EGCG in East Java green tea, Indonesia and a strong antioxidant, which is 36.71 [5]. Antioxidants contained in East Java, Indonesia green tea EGCG, can significantly reduce the expression of High Mobility Group Box 1 (HMGB- 1) and Heat Shock Protein-70 (HSP-70) during OTM after oral administration of EGCG for 7-14 days. HMGB-1 and HSP-70 are indicators of danger associated molecular pattern (DAMPs) generated by OTM in sterile inflammatory tissue cells [6].

EGCG can promote osteogenic differentiation of mesenchymal stem cells (MSCs) by boosting the expression of BMP-2, which is osteoinductive, as well as ALP, which is a phosphate regulator, and RUNX2, which is involved in osteoblast maturation during bone matrix production. EGCG can also reduce the production of Receptor activator of nuclear factor κ-β ligand (RANKL) and Prostaglandin E-2 (PGE2) in

osteoclastogenesis, hence inhibiting bone resorption and accelerating bone apposition. EGCG is a polyphenol found in green tea that helps to speed up the process of bone remodeling by decreasing osteoclastogenesis and enhancing osteoblastogenesis. EGCG can directly boost osterix expression, which subsequently increases RUNX2 expression and drives osteoblast development via the Wnt/β-catenin pathway. The antioxidant effects of EGCG are also responsible for inhibiting osteoclastogenesis by lowering the activity of RANKL [7], [8]. Furthermore, this narrative literature review aimed to describe the potential of the active compound EGCG in green tea phytomedicine as a candidate biomaterial to prevent OTR.

2. Benefits of Green Tea on Body Health

The advantages of green tea originate from the fact that it is high in catechins, polyphenols, and notably ECGC. ECGC is a potent anti-oxidant that, in addition to suppressing cancer cell development, destroys cancer cells without harming healthy tissue. Green tea is also helpful in lowering low density lipid (LDL) cholesterol levels, inhibiting aberrant blood clot formation, reducing platelet aggregation, lipid modulation, and inhibiting smooth muscle cell proliferation and migration. The prevention of aberrant blood clot formation becomes even more crucial when you know that thrombosis (abnormal blood clot formation) is a primary cause of heart attacks and strokes. Any of these factors may hold promise in terms of lowering the risk of cardiovascular disease. EGCG is the green tea benefit responsible for various biochemical or pharmacological actions [9], [10]. Green tea has been proven to be more antioxidant-active than black tea in general, owing to its increased EGCG concentration. Green tea is considered to aid with the following medical conditions: cancer, rheumatoid arthritis, excessive cholesterol levels, cardiovascular disease, infections, and reduced immunological function [11], [12].

The liver is a fundamental metabolic organ that is involved in the creation and breakdown of important biological components such as carbohydrates, proteins, and lipids. Green tea drinking has been linked to a decrease in liver disease. Green tea consumption is linked to a lower incidence of hepatocellular carcinoma, fatty liver disease, hepatitis, cirrhosis of the liver, and chronic illness. Green tea consumption has a considerable preventive impact against liver disease. Long-term tea catechin consumption may be protective against high-fat diet-induced obesity and type II diabetes, as well as lowering the risk of cardiovascular disease. Obesity is a significant risk factor for a variety of disorders, including coronary heart disease, hypertension, non-insulin-dependent diabetes, pulmonary dysfunction, osteoarthritis, and several malignancies. Tea catechins, particularly EGCG, appear to be anti-obesity and anti-diabetic. Tea's effects on obesity and diabetes have gotten a lot of attention recently. Tea catechins, particularly EGCG, appear to be anti-obesity and anti-diabetic [13].

Breast cancer is characterized by the malignant growth of epithelial cell layers, ducts, or lobules in the breast. Green tea has gained popularity due to its health advantages, particularly its anti-cancer properties. In animal tests, green tea was found to have anticarcinogenic properties against breast cancer [14].

Green tea's effects on blood pressure, including antioxidants and vasodilators, have been studied in a wide number of experimental and observational research over several decades. Obesity is one of the most major risk factors for the development of hypertension and increases cardiovascular morbidity and mortality linked with hypertension, according to evidence. Tea is one of the most widely consumed beverages, with differing quantities ingested in different nations. Green tea contains antioxidant polyphenols including catechins and flavonols, and tea extracts have been proven to have vasodilator properties, both of which lead to heart health advantages. Green tea's physiological effects on risk factors for cardiovascular disease, such as blood pressure [15], [16].

Green tea polyphenols are photoprotective and, following additional human clinical studies, may be employed as pharmacological agents for the prevention of skin problems induced by ultraviolet B (UVB) radiation from the sun, such as aging characteristics, melanoma and non-melanoma skin cancer. As an antioxidant, green tea is a popular neutraceutical [17], [18]. Antioxidants are chemicals that protect cells from the oxidative stress caused by reactive oxygen species (ROS) such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals, and peroxynitrite. Oxidative stress is caused by an imbalance between antioxidants and reactive oxygen species, which causes cellular damage. Catechins are effective antioxidants both in vitro and in vivo. Furthermore, various minerals and vitamins boost green tea's antioxidant capacity. Green tea catechins boost overall antioxidant activity in the blood [19], [20].

3. Benefits of Green Tea on Dental and Oral Health

Tooth enamel is made up of hydroxyapatite crystals, and the solubility of hydroxyapatite rises when pH decreases, which is bad for tooth enamel. By blocking the enzyme lactate dehydrogenase, which is responsible for creating lactic acid from pyruvate, EGCG from green tea reduces acid generation and preserves pH. Another mechanism that explains anti-cariogenicity is the prevention of bacterial attachment to the glycoprotein layer. Gargling with green tea mouthwash for one week dramatically lowered the salivary level of Streptococcus mutans. Green tea lessens the susceptibility of humans to dental caries [21]. Even in the presence of sugar in the diet, regular use of green tea can greatly prevent caries development. Green tea extract also decreases amylase activity in saliva, making it an anticariogenic agent. Volatile sulfur compounds are the major cause of halitosis, which is produced by tooth cavities and poor oral hygiene. In gingivitis patients, green tea mouthwash dramatically lowered levels of volatile sulfur components. Green tea extract is capable of removing sulfur odor from the oral cavity [22]. Green tea has also been proven to have antiviral properties against the human immunodeficiency virus type 1, herpes simplex virus, Epstein-Barr virus, and adenovirus [23]. *Candida albicans* growth is inhibited when EGCG and modest dosages of azoles are used together and the effect was fungicidal [24].

In periodontitis, the gingival sulcus, which contains numerous bacteria, particularly anaerobes, deepens to develop periodontal pockets. Periodontitis is characterized by polymorphic local infiltration and serum exudate. Periodontal disease is frequently linked with black pigmented anaerobic bacteria such as Prevotella sp. and Porphyromonas gingivalis. Green tea EGCG has been shown in vitro to decrease the growth of P. gingivalis. Green tea EGCG also promotes osteoblastogenesis while suppressing osteoclastogenesis, minimizing bone deterioration and maintaining the periodontium. Green tea catechins are believed to suppress bacterial development when supplied via a local delivery method employing hydroxypropyl cellulose strips. The use of green tea catechins on a regular basis has been shown to be a successful approach of treating periodontitis [25].

4. Effects of EGCG on Bone Remodeling during Orthodontic Tooth Movement

In osteoporosis, EGCG has an influence on bone density. By altering bone remodeling pathways, EGCG can accelerate bone resorption [26]. Signal transmissions and the transcription of multiple genes regulate the development of osteoblasts and osteoclasts. The related transcription factors Runt 2 (RUNX2) and Osterix are two important transcription factors for osteoblasts. Several osteoblasts signaling pathways were discovered, with higher transcriptional expression of RUNX2 and Osterix directly leading to greater osteoblast production. In the osteogenic development of bone marrow stem cells (BMSCs), EGCG enhances the expression of BMP2 mRNA and other osteogenic-related genes, including RUNX2, ALP, osteonectin, and osteocalcin [27].

The expression of RUNX2 and Osterix, as well as growth factors such as VEGF and FGF-2, on osteoblasts

in the alveolar bone during OTM and after oral administration of EGCG for 7-14 days, was considerably elevated compared to the OTM group that did not receive EGCG orally in the tension side [28], [29]. Meanwhile, following oral administration of EGCG for 7-14 days, the expression of Sclerostin and Nuclear Factor Associated T-cell 1 (NFATc1), a hallmark of osteoclast development, dropped dramatically during OTM in the compression side [30]. This demonstrates that EGCG has an effect on alveolar bone remodeling during OTM.

5. Biomolecular of Orthodontic Tooth Relapse

As a therapy for malocclusion, orthodontic treatment can be performed to shift the teeth to establish normal occlusion. In an unstable state, post-orthodontic therapy affects the alveolar bone and periodontal ligament fibers [31]. This is due to the fact that the periodontal tissue remodeling process takes more than 4 months [2]. Neglecting this issue will result in a relapse condition. However, after utilizing fixed orthodontic equipment for ten years, 33 percent of patients under orthodontic treatment develop recurrence. Relapse is a condition in which the teeth revert to their pre-orthodontic position due to a lack of alveolar bone in the tension region to keep the teeth in place. Because of the relapse situation, the orthodontic treatment that has been completed is not optimum, and malocclusion might emerge again [32], [33].

Periodontal tissue is also involved in the development of OTR. OTR, according to one idea, is produced by the relaxation of strained fibers in the periodontal ligament (PDL) and/or supra-alveolar area.2 Recent research, however, has revealed that the rate of collagen fiber turnover in normal PDL and supra-alveolar areas is quite high. Furthermore, the PDL structure on the leading side is totally regenerated within a few days after the commencement of orthodontic treatment, but on the final side, part of the original fibers are entrenched in the alveolar bone, and freshly manufactured collagen fibers bridge the gap with the moving teeth [34- 36].

The strain mark shifts from positive to negative on the front side of the relapsed tooth, and the opposite happens on the rear side. As a result, cellular signaling and responses are reversed in the PDL, cementum, and alveolar bone. This clearly implies that the identical mechanisms observed during active tooth displacement will now take place on the opposite side of the tooth [37]. Histological investigations have revealed that during early recurrence, the PDL on the leading edge is hyalinization in certain instances. The normal structure of PDL is totally destroyed once the hyalinization tissue is removed, or soon after the commencement of relapse in situations where no hyalinization develops, due to the activation of matrix metalloproteinases (MMPs) by their inducers. Type I collagen is replaced by loose connective tissue, and type III collagen fibers parallel to the root surface do not link the tooth to the alveolar bone. In this region, osteoclasts differentiate and commence alveolar bone resorption. This osteoclastogenesis and alveolar bone resorption might be linked to NFATc1 expression and its interactions with RANKL and VEGF. The PDL on the relapsed tooth's posterior side includes freshly generated type I and III collagen, osteoclasts are no longer present, and osteoblasts develop and regenerate the bone tissue [39].

6. Orthodontic Tooth Relapse Prevention

Until now, post-orthodontic retainers were used as preventive therapy for post-relapsed orthodontic treatment, but their use is considered less effective because patients are less cooperative in complying with the dentist's instructions to use retainers after each orthodontic treatment, or it can occur due to other factors. According to a prior study, there were still 19% of cases of recurrence following the usage of retainers [2]. As a result, there is a need for innovation to limit the occurrence of recurrence following orthodontic treatment.

7. EGCG as phytomedicine to Prevents Orthodontic Tooth Relapse

EGCG is a catechin found mostly in *C. sinensis* (green tea) that has osteoinductive potential by raising the expression of bone markers such as BMP-2, ALP, and RUNX2 in the production of bone matrix [28], [41]. EGCG is a polyphenol found in green tea that helps to speed up the bone remodeling process by lowering osteoclastogenesis and enhancing osteoblastogenesis [42].

In bone mineral production, EGCG stimulates ALP, RUNX2, and BMP2. Signal transduction and gene transcription complexes on essential components for osteoblast development, such as RUNX2 and osterix, impact MSCs differentiation into osteoblasts. EGCG can directly boost osterix expression as a cofactor of RUNX2, which subsequently stimulates RUNX2 expression and drives osteoblast development via the Wnt pathway. The antioxidant effects of EGCG are also responsible for inhibiting osteoclastogenesis by lowering the activity of RANKL [28], [43].

8. Conclusion

Green tea's active ingredient, EGCG, may be employed as a prospective biomaterial to prevent relapse following orthodontic tooth movement. In vitro and in vivo investigations on EGCG as a possible biomaterial for reducing orthodontic tooth relapse are needed.

9. Conflict of Interest

The authors declare that there is no conflict of interest in this study

10. Acknowledgement

The authors would like to thanks Publication Center, Faculty of Dental Medicine, Universitas Airlangga, Surabaya for the support.

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