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Review article

A mucoadhesive gingival patch with Epigallocatechin-3-gallate green tea (Camellia sinensis) as an alternative adjunct therapy for periodontal disease: A narrative review

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ABSTRACT

Background: *Periodontitis is a progressive destructive periodontal disease. The prevalence of periodontal disease in Indonesia reaches 74.1% and mostly occurs in the productive age group. Most of the periodontopathogenic bacteria are gram-negative bacteria and have endotoxin in the form of lipopolysaccharide (LPS), which can penetrate the periodontal tissue and induce an inflammatory response. In inflammatory conditions, osteoclastic activity is higher than osteoblastic activity, which causes bone destruction. This results in an imbalance between osteoclast-induced bone resorption and osteoblast-induced bone formation. The current preferred treatment for periodontitis is scaling root planning (SRP), but this therapy cannot repair the damaged periodontal tissue caused by periodontitis.* **Purpose:** *To describe the possibility of using a mucoadhesive gingival patch with Epigallocatechin-3-gallate (EGCG) green tea (Camellia sinensis) as alternative adjunct therapy for periodontal disease.* **Review:** *EGCG is the main component of green tea catechins, which have antitumor, antioxidant, anti-inflammatory, anti-fibrotic, and pro-osteogenic effects. However, the weaknesses so far regarding the use of EGCG as an alternative treatment is its low oral bioavailability and the concentration of EGCG absorbed by the body decreasing when accompanied by food. EGCG can be used with a mucoadhesive gingival patch to optimise bioavailability and absorption and increase local concentration and sustained release of EGCG. EGCG encourages bone development and braces mesenchymal stem cells (MSCs) differentiation for osteoblast by enhancing the expression of bone morphogenic protein 2 (BMP2). EGCG also has been proven to increase the expression of RUNX2 and ALP activity that induces osteoblast differentiation and bone mineralisation.* **Conclusion:** *A mucoadhesive gingival patch containing EGCG Green Tea (C. sinensis) may potentially induce osteoblastic activity as an adjunct therapy to repair the periodontal tissue damage due to periodontal disease.*

Keywords: *dentistry; EGCG; mucoadhesive gingival patch; osteoblast; periodontal disease*

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INTRODUCTION

Based on the Global Burden of Disease Study (2016), the incidence of severe periodontal disease ranks the eleventh highest and most common with an average prevalence percentage of 25.9%, which accounts for around 20%–50% of the world's population.[1,2] Periodontitis is a progressive periodontal disease that has the highest prevalence, at 10.5% to 12% globally, and is the most common chronic periodontitis.[3,4] Until now, the focus of treatment given to patients with periodontitis is to stop the progression of the disease and reduce the inflammation that occurs. Non-surgical therapy is still the most recommended option, namely scaling root planning (SRP), either without additional treatment or by administering a systemic antimicrobial dose of doxycycline.[5] SRP is a periodontal

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therapy in the form of a mechanical procedure to eliminate bacterial plaque and calculus on the tooth surface and is clinically able to reduce the clinical attachment loss (CAL) and pocket depth (PD).[6] The administration of SRP therapy cannot restore the damaged periodontium and does not reduce the risk of a recurrence of periodontitis, so pharmacological therapy is needed as an accompanying therapy after SRP.[7,8]

Pharmacological therapy as a support for SRP therapy can take the form of systemic or topical drug administration. The administration of supporting drugs after SRP therapy showed a better reduction in CAL and PD when compared to SRP therapy alone, but only a few drugs were able to restore the structure of the damaged periodontal tissue.[8,9] Systemic administration of drugs is considered to be less effective and shows several shortcomings, so many studies are currently being carried out to develop a drug formulation for local periodontal therapy.[10] The use of herbs in the health sector, including dentistry, has become widespread in recent years due to their medicinal and physicochemical properties that can provide additional therapeutic effects. One of the most effective and commonly used herbs for treatment is green tea.[11–13] Besides being rich in antioxidants, green tea also has many health properties, such as anti-cancer, anti-inflammatory, bone resorption, anti-diabetes, anti-hypertension, anti-tumour, anti-fibrosis, and pro-osteogenic.[14–16] The catechins in green tea also exhibit antimicrobial and anti-inflammatory properties in the periodontium.[17] Furthermore, in this narrative review, the potential of (Epigallocatechin-3-gallate) EGCG topically administered via a mucoadhesive gingival patch to repair the periodontium damaged by periodontitis was described.

Periodontitis

Periodontitis is a destructive, multifactorial inflammatory disease of periodontal tissue, characterised by attachment and progressive loss of bone. The etiology of periodontal disease is influenced by the interaction of the microbial environment with the host's immune response.[4] The causative microbial biofilms are similar in aggressive and chronic periodontitis, so they cannot be distinguished based on certain periodontal pathogens.[18] The global prevalence of periodontal disease ranks eleventh for severe periodontal diseases.[1,2]

Destruction of the host's immune and inflammatory responses by the dysbiotic microbiome is believed to be one of the leading causes of the initiation, formation, and progression of periodontitis and tissue destruction. Cytokines and inflammatory mediators play important roles in the pathogenesis of periodontal disease. Several inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-8, and IL-17, enhance the inflammatory process of periodontal tissue. Currently, there are several anti-inflammatory cytokines that reduce the regulation of periodontal inflammation, such as IL-4 and IL-10, and transform growth factor β (TGF-β).[19,20] Expressed pro-inflammatory mediators are able to stimulate osteoclastic activity and can cause damage to the periodontal tissue.[4] Treatment of periodontal disease requires a combination of mechanical treatments, such as debridement, scaling, and SRP, to reduce stagnant bacteria. SRP can effectively reduce the concentration of microbes present in the periodontal pocket and improve clinical parameters, such as bleeding and clinical adhesion levels, at probing and probing depth.[4,21]

Porphyromonas gingivalis (P. gingivalis)

Porphyromonas gingivalis is a type of gram-negative anaerobic bacteria in the oral cavity that belongs to the group of black-pigment Bacteroides. This group of bacteria form dark brown colonies on the blood agar plate. *P. gingivalis* is an important cause of periodontal disease. These bacteria produce many extracellular virulence factors and proteases that lead to the destruction of gingival tissue, including lipopolysaccharides (LPS), pili, collagenase, hemolysin, endotoxins, fatty acids, ammonia, hydrogen sulphide, and indol. The various components on the surface of *P. gingivalis* enable the bacteria to interact easily with external media and support their growth, colonisation, nutrient absorption, and formation of a biofilm that protects it from the immune system.[22,23]

The pathogenesis of *P. gingivalis* has been observed in various animal models, such as mice, rabbits, Drosophila, and cellular models, suggesting a complex mechanism of host interaction with *P. gingivalis* at the level of periodontal disease. The pathogenic mechanism is also influenced by genetic and environmental factors. The molecules involved in the pathogenesis of periodontitis can be divided into two major groups: those derived from the subgingival microbial flora (microbial virulence factor) of *P. gingivalis* and the host's inflammatory immunity.[4,22]

Green tea (*Camellia sinensis*)

Green tea is a type of plant that has been used as a drink for 5,000 years. Green tea is consumed because it can remove toxins, improve blood circulation, and increase resistance to illness. Green tea beverages contain polyphenolic compounds, such as phenolic acids, flavanols, flavonoids, and flavandiols. Most of the polyphenols in green tea are flavanols called catechins. Catechins are also found in other plants, but these plants contain a lower quantity of catechins. The content of the tea rinse depends on the soil, climate, and general growing conditions.[24,25]

Tea is an important product with economic and health benefits. As a result, the per capita consumption of tea in Indonesia is about 0.35kg/person/year. In the field of health, green tea is known to have many benefits, including its effectiveness as an antifungal and immunomodulatory agent and for promoting of bone formation and bone resorption. Green tea is a member of the genus *Camellia*, which consists of shrubs and trees. The genus *Camellia* is composed of more than 200 species, including *Camellia*

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sinensis (L.) Kuntze.[24] The following is the taxonomy of *Camellia sinensis (L.) Kuntze*: kingdom, *Plantae*; super division, *Embryophyta*; division, *Tracheophyta*; subdivision, *Spermatophytina*; class, *Magnoliopsida*; order, *Ericales*; family, *Theaceae*; genus, *Camellia L*; and species, *Camellia sinensis (L.) Kuntze*.[25,26]

EGCG

EGCG is the most abundant catechin compound in green tea, accounting for about 59% of the total content of green tea. Green tea contains 19% (-) Epigallocatechin (EGC), 13% (-) Epicatechin gallate (ECG), and about 6% (-) Epicatechin (EC). Epigallocatechin-3-gallate (EGCG) is poorly absorbed by the body, so EGCG levels that enter the bloodstream are present only at low micromolar concentrations and disappear from plasma within hours. The bioavailability of EGCG in humans ranges from 0.1–0.3%.[27,28]

The EGCG has a higher content of superoxide and free lipid radicals and higher neutralisation activity of free radicals than EGC and EC. EGCG may alter biological activity and reduce the antioxidant capacity of the compartment.[29] The main action of EGCG is to suppress the expression of reactive oxygen species (ROS) and to inhibit signal transduction during the inflammatory process. Systemic dysfunction has decreased. EGCG can inhibit osteoclast differentiation by inhibiting the transcriptional activity of the nuclear factor of activated T cell-cytoplasmic 1 (NFATc1) and nuclear factor kappa beta (NF-kB).[30]

Catechins exhibit antioxidant activity through a variety of mechanisms: electron transfer, hydrogen atom transfer, and catalytic metal chelation. In EGCG, the free radical inhibitory effect is due to the presence of defective groups at the 3-position of the trihydroxy bring structure and its chemical structure. EGCG, which has eight hydroxyl groups mainly at positions 31, 41, and 51 and has a defect group at C3, is a better electron donor than other catechins and is therefore the best suppressor of free radical expression.[31,32]

EGCG is widely used in the treatment of oral diseases, primarily due to its anti-inflammatory and antioxidant properties and its ability to inhibit bone resorption.[33] EGCG suppresses LPS-induced alveolar bone resorption *in vitro* and suppresses LPS-induced alveolar bone loss *in vivo*. The effective amount of EGCG *in vitro* and *in vivo* is similar to the effective amount of polymethoxyflavonoids, such as nobiletin.[16]

Catechins in green tea continue to be studied and developed as anti-virus and cancer therapy. According to Kharisma et al.,[34] tea catechin compounds may act as antiviral agents against HIV1 through apoptotic agonists and triple inhibitor mechanisms. Apoptosis can occur during the interaction between the EGCG and intracellular apoptosis-promoting proteins. As an anti-cancer, EGCG inhibits angiogenesis, protects DNA from carcinogens, and promotes apoptosis of cancer cells.[26,34]

Mucoadhesive gingival patch

Mucoadhesives, either organic or synthetic, may be prescribed because of their ability to stick to organic tissue. Generally, mucoadhesives are used without difficulty on available surfaces in the gingival, buccal, ocular, and nasal areas. Mucoadhesive patches are long lasting, even on the floor of a membrane or mucosa, and might improve the absorption of the drug as it is not affected by metabolism, travelling first to the liver.[35]

Mucosal adhesives provide direct contact between the surface and the adhesive. The American Society for Testing and Materials defines mucosal adhesion as a condition in which two subjects are held together by interlocking interfacial forces. The word 'muco' refers to the mucous membrane. The mucous membrane is the moist surface that covers most of the body's cavities, especially the inside of the oral cavity, and is responsible for lubrication and protection.[36]

The mucosal adhesion mechanism consists of two main stages: the contact stage and the consolidation stage. At the contact stage, there is strong contact between the adhesive and the surface of the periodontal tissue, which initiates the distribution of the target active ingredient. At the consolidation stage, the adhesive is activated by moisture, the system becomes plastic, the molecules break and open, and they bond to each other via weak van der Waals forces and hydrogen bonds.[37]

The composition of mucosal adhesive plasters consists of active ingredients, polymers, plasticisers, and fortifiers. The polymer supplies the active ingredient and stays in contact with the mucosal surface longer. The active ingredient content of the patch is in the range of 5–25% by weight of the polymer. There are several polymers that can be used as gypsum materials, such as polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC), and hydroxypropyl methyl cellulose (HPMC). Stucco plasticisers are used to prevent plaster damage if the plaster breaks or tears. Glycerine, propylene glycol, and polyethylene glycol 400 (PEG 400) can be used as plasticisers.[38] Enhancers work to increase the ability of the membrane to absorb drugs and active ingredients. Enhancers that can be used include dimethyl sulfoxide (DMSO), linoleic acid (LA), isopropyl myristate (IPM), and oleic acid (OA).[39]

Osteoblasts

Osteoblasts are bone cells with a single nucleus, located more peripherally. The cytoplasm is basophilic, cuboidal in shape, and are abundant on the surface of the bone matrix that makes up 4–6% of all bone cells. Osteoblasts can be derived from differentiated mesenchymal stem cells and can secrete organic bone matrix proteins (osteoids) that are important for calcification and bone formation. Morphologically, osteoblasts have the same organelles as other cells that can secrete proteins, such as rough endoplasmic reticulum, Gorgi complexes, large mitochondria, and numerous secretory vesicles. Osteoblasts can secrete molecules that can affect surrounding cells,

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such as an osteoblast-derived vascular endothelial growth factor, which play a role in accelerating the healing process and bone formation. Osteoblasts are also known to be able to secrete pro-collagenase enzymes that play a role in breaking down collagen fibres. The ability of osteoblasts to produce cytokines, such as receptor activator nuclear kappa beta ligand, osteoprotegrin, and macrophage colony-stimulating factor, means these cells have an important role in regulating bone homeostasis.[40,41]

In periodontitis, bone destruction occurs progressively due to higher osteoclastic activity than osteoblastic activity. Based on a study conducted on a rat calvaria model injected with *P. gingivalis, Troponema denticola,* and *Tannerella forsythia* bacteria, it showed that bone resorption occurred on days 3 to 5 after bacterial infection and on days 7 to 14. Bone formation occurs as part of the bone healing process.[42]

DISCUSSION

P. gingivalis is a normal flora in the oral cavity that has many virulence factors that cause periodontal tissue damage, such as LPS. LPSs are found in bacterial cell membranes and can interact with host cell components, toll-like receptor 2, and toll-like receptor 4.[43] *P. gingivalis* was chosen by many researchers to trigger the periodontal process.[44]

Periodontal disease is a chronic inflammation characterised by many reactions, including B. Vasodilation and the recruitment of immune cells and plasma proteins to the site of infection or tissue damage. There are four main components to the inflammatory response: (1) intrinsic or extrinsic factors, such as pathogen-associated molecular patterns bacteria, viruses, fungi, parasites, and damage-associated molecular patterns derived from cell damage; (2) cellular receptors in the form of pattern recognition receptors, such as toll-like receptors; (3) inflammatory mediators, such as cytokines and chemokines; and (4) target cell or tissue.[45]

One of the drug delivery systems through the membrane of oral cavity is the buccal bioadhesive patch. One example is the mucoadhesive gingival patch, which creates a mucosal adhesion mechanism by forming an interaction between polymer and mucus. The mechanism of mucosal adhesion can be divided into two steps. The first is the contact step, and the second is the consolidation/integration step. In the first step, the mucous membrane comes into contact with the mucoadhesive, causing the formulation to swell and then spread over the mucous membranes. In the second, which is consolidation step, the moisture activates the mucosal adhesive material, which plasticises the system. This causes the separation of mucosal adherent molecules and allows them to connect to weak van der Waals forces via hydrogen bonds.[46]

The theory of diffusion and dehydration explains the integration steps. The diffusion theory explains the interaction of mucosal adherent molecules with mucous glycoproteins and the formation of secondary bonds by the interpenetration of their chains. According to dehydration theory, the material turns into a gel when it comes into contact with mucus in an aqueous environment. This process increases the mucosal contact time between the formulation and the mixture of mucus. Therefore, the movement of water, not the interpenetration of polymer chains, leads to the strengthening of the adhesive junction.[46,47]

The EGCG content present in mucosal adherent gingival tissue will inhibit the induction of pro-inflammatory cytokine production from LPS released by *P. gingivalis*. EGCG is able to inhibit the expression of chemokines, such as IL-8, monocyte chemoattractant protein-1 (MCP-1) and Macrophage Inflammatory Protein-1 Alpha (MIP-1α), by infected epithelial cells. The inhibited expression of IL-8, MCP-1, and MIP-1α resulted in the disruption of the chemotaxis process of inflammatory cells to areas of infection, such as macrophages, neutrophils, and lymphocytes. Inflammatory cells have an important role in the severity of inflammation by expressing several inflammatory mediators, such as tumour necrosis factor alpha (TNF-α), IL-1, IL-6, IL-17, prostaglandin E2, and ROS metabolites. EGCG was also able to inhibit the NF-κB inflammatory pathway activation by bacterial LPS. Inflammatory cell migration and inhibited NF-κB activation resulted in decreased expression of cytokines and inflammatory products. IL-1, IL-6, TNF-α, and ROS are responsible for the apoptosis of osteoblast cells. The decreased expression of IL-1, IL-6, TNF-α, and ROS will inhibit osteoblast cell death so that there is an obstacle in the decline of osteoblast cells.[48–51]

Previous studies of EGCG have demonstrated that EGCG promotes differentiation of bone formation in bone marrow mesenchymal stem cells (BMSCs) of mice. At certain doses, EGCG can also promote differentiation of BMSCs bone formation. The effect of EGCG was found in a similar mouse BMSC: increased expression of bone-forming genes, such as bone morphogenetic protein-2 (BMP2), runt-related transcription factor 2 (RUNX2), alkaline phosphatase (ALP), osteonectin, and osteocalcin; increased ALP activity; and, finally, improved mineralisation.[52] In another study, topical use of EGCG in the femoral defect improved bone formation by increasing bone mass, which includes the bone's maximum load, fracture point, stiffness, maximum load sub-curve area, area under the breakpoint curve, and ultimate stress. Local EGCG can be used to treat bone defects.[53]

Bone formation will be induced by decreasing the osteoclast differentiation and increasing the differentiation of bone formation. Green tea and its catechin compounds have been shown to suppress osteoclast differentiation. As shown in the result of research by Nishioku et al.,[30] EGCG could inhibit osteoclastogenesis by suppressing the expression of NFATc1 in primary osteoclast cultures, a key regulator of osteoclast differentiation.

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The differentiation of osteoblast is important for bone formation, and osteoblast-specific gene products are involved in the differentiation process. RUNX2 is an important transcription factor and a central regulator of osteoblast-specific target genes such as osteocalcin during bone formation, transient activation, inhibition of cell proliferation, and osteoblast differentiation. RUNX2 regulates osteoblast progenitor cell proliferation and osteoblast differentiation through the mutual regulation of FGF, Hedgehog, Wnt, and Pthlh signalling molecules with transcription factors, including Sp7 and Dlx5.[54,55] This theory is supported by the results of a study conducted by Byun et al.,[56] which stated that the catechins in green tea can stimulate osteoblast differentiation with the help of a mediator in the form of RUNX2, the main regulator of transcription of osteoblast marker genes. Furthermore, the EGCG increases the transcriptional and post-transcriptional expression of the transcriptional coactivator with PDZ-binding motif, a transcriptional coregulator involved in osteogenesis.[57] Although this mucoadhesive gingival patch containing EGCG has the potential to be an alternative therapy for periodontitis, unfortunately, it is not known what the most effective dose and duration of application are to provide optimal results. In conclusion, a mucoadhesive gingival patch containing EGCG green tea (*Camellia sinensis*) can potentially repair damaged periodontal tissue by inducing osteoblastogenesis activity directly or through its anti-inflammation characteristic. For that, further research to find the right dose and duration of application of this mucoadhesive gingival patch with EGCG is needed.

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