Letter to Editor

Resveratrol as a supplemental treatment for periodontitis

Dear Editor,

Periodontitis is a multifactorial disease caused by many factors such as oral micro-organisms, genetics disorders, tobacco and alcohol use, nutrition, diabetes, stress and impaired host response.[1] The immune-inflammatory response, which is present in the gingival and periodontal tissues, causes destruction of structural components of the periodontium in response to chronic accumulation of plaque bacteria.[2] Although components of periodonto pathogenic micro-organisms and products from the subgingival biofilm trigger the production of anti-inflammatory molecules, such as IL1-β, IL-6, IL-8, and cyclooxygenase (COX)-2, but infiltrating immunoinflammatory and resident cells of the periodontium initiate and perpetuate soft tissue degradation and bone resorption.[3] On the other hand, persistent microbial challenge in the presence of mentioned risk factors also results in the destruction of both soft and hard tissues by cytokine and prostanoid cascades. So active periodontitis can cause bone loss without sufficient treatment.[1]

Resveratrol, trans-3,5,4′-trihydroxy-trans-stilbene ($C_{14}H_{12}O_3$) is a phytoalexin found in plants, and specially in skin of red grapes.[4] It has been reported to exhibit a wide range of biological and pharmacological properties that regulates several metabolic pathways.[5] The resveratrol properties includes aging control,[6] anti-cancer effect, which affects all stages of carcinogenesis; tumor initiation, promotion and progression,[7] cardiovascular protection[8] and neuroprotective effect.[9] Resveratrol inhibits inflammation and oxidative stress and platelet aggregation[10] and it has a direct stimulatory effect on bone formation.[11-13]

HYPOTHESIS

Resveratrol promotes osteogenesis via direct effect on bone formation,[11-13] and on the other hand, it shows anti-inflammatory and analgesic effect.[14,15] Thus, it can be hypothesized that resveratrol plays an important role in supplemental treatment of periodontitis. Successful treatment of periodontal diseases can be achieved by using resveratrol as a non-surgical treatment of periodontitis.

Background and Evidence

Inflammation that extends deep into the tissues and causes loss of supporting connective tissue and alveolar bone is known as periodontitis.[1] Treatment of periodontitis should prevent recurrence of disease, which can be achieved by various non-surgical and surgical therapies depending on the specific treatment goal. Resveratrol can be considered as a supplemental method for non-surgical treatment of periodontitis due to its anti-inflammatory effects and stimulatory effects on osteoblastic cells.

Resveratrol stimulated osteoblastic proliferation and differentiation by increasing expression of Runx2, Ocn, Osterix genes, alkaline phosphatase (ALP) and prolyl hydroxylase in a dose-dependent manner.[11,16,17] It also enhances the differentiation of osteoblasts from mesenchymal stem cells[12] and inhibits adipogenesis.[16]

Resveratrol induced ER signaling and ERK1/2 activity and increased osteogenic genes Runx2/cbfa1 expression, which is a critical transcription factor in the osteoblast differentiation.[18] Biological effects of resveratrol are associated with MAPK signaling pathways, which are involved in human bone metabolism, including the commitment of Human bone marrow mesenchymal stem cells (HBMSCs) to the osteogenic lineages.[19] Resveratrol also inhibited bone loss in ovariectomized rats.[20] It also inhibits RANKL-induced osteoclast differentiation and bone resorption.[16,17] It is known that the presence of PGE2 or parathyroid hormone caused a significant decrease in bone ALP activity and a corresponding increase in bone acid phosphatase activity.[11]

Resveratrol is a potent inhibitor of inflammatory molecules. Its anti-inflammatory properties is associated with inhibition of NF-kappa B in LPS, TNF-α, or PMA-mediated macrophages, dendritic, myeloid (U-937), Jurkat, and epithelial (HeLa) cells.[21,22]

Resveratrol significantly suppresses the secretion of TNF-α and nitric oxide in LPS-stimulated rat cortical microglia and N9 microglial cells[23] and also inhibits the production of TNF-α, IL-1, IL-6, IL-12 and

IFN by splenic lymphocytes and macrophages.[21,24] Resveratrol also exhibits strong anti-inflammatory activity of C5 anaphylatoxin (C5a)-mediated inflammation *in-vivo* condition.

Additionally, resveratrol inhibits C5a-stimulated neutrophil migration/recruitment, and production of inflammatory cytokines in a mouse model of C5a-induced acute peritonitis.[25]

Several effects of resveratrol including platelet aggregation attenuation,[26] cardiovascular protection,[8] and anti-cancer activity[7] have been reported in the recent years.

Resveratrol shows inhibitory effects on the expression of cell adhesion molecules. Resveratrol attenuated the IL-6 induced expression of ICAM-1 in endothelial cells[27] and also inhibited *Porphyromonas gingivalis* LPS-induced endothelial dysfunction in human microvascular endothelial cells. Furthermore, it blocked the expression of adhesion molecules, ICAM-1, and VCAM-1 on HMECs by inhibiting NF-kappa B activation.[28]

The pathogenesis of inflammatory induced bone resorption has been attributed to local signals stimulating activity and recruitment of osteoclasts. These local factors include bacterial products such as lipopolysaccharides, lipoteichoic acid, and several peptides produced by invading leukocytes as well as factors from blood proteins. Bacterial products can all directly stimulate *in-vitro* bone resorption. Leukocytes present in inflammatory reactions produce several cytokines with bone resorption stimulatory activity. The monokines interleukin-1 and tumor necrosis factor α (TNF- α) enhance bone resorption *in-vitro*.[29]

Periodontitis is an inflammatory disease of periodontal tissues, which is determined by inflammation extending deeply to the tooth supporting structures. It seems that resveratrol is influencing many factors and mediators involved in the pathogenesis of periodontitis. The degree of destruction caused by this disease depends on the interaction of microorganisms with host defense. Micro-organisms cause direct tissues destruction or immune response stimulation indirectly. The immune system's rule is to prevent the local infection from becoming a fetal systemic infection. According to all the matters mentioned above, it seems that induction of resveratrol whether systemic or by local delivery affects different aspects of periodontitis pathogenesis and can be useful by inhibiting the progression of periodontitis.

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