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Original Article

2-O-methylmagnolol mitigates the generation of reactive oxidative stress and inflammaging in human gingival epithelial cells and fibroblasts with advanced glycation end products stimulation

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Gingival epithelial cells;
Gingival fibroblasts

Abstract *Background/purpose:* Individuals with diabetes mellitus (DM) are more susceptible to periodontitis, largely due to the accumulation of advanced glycation end-products (AGEs), which drive oxidative stress and inflammaging. Inflammaging is a state of chronic low-grade inflammation and accelerated cellular aging that contributes to periodontal degradation, mediated by AGEs-induced cellular senescence and senescence-associated secretory phenotype (SASP). 2-O-methylmagnolol (2-MG), a bioactive compound with antioxidant and anti-inflammatory properties, remains underexplored in DM-associated periodontal degeneration. This study investigated the effects of 2-MG on AGE-induced oxidative stress and inflammaging in human gingival epithelial cells (HGEs) and human gingival fibroblasts (HGFs).
Materials and methods: The study assessed the effects of 2-MG on AGE-stimulated HGEs and HGFs by evaluating cell proliferation, wound healing capacity, reactive oxygen species (ROS)

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accumulation, cellular senescence markers, and the secretion of SASP factors, including interleukin (IL)-6 and IL-8. Additionally, Western blot analysis was performed to examine the protein expression of a senescence marker p16.
Results: Treatment with 2-MG at concentrations up to 10 μM did not significantly affect HGEs and HGFs cell proliferation ($P > 0.05$). However, 2-MG effectively improved AGEs-induced wound healing impairment and significantly attenuated ROS production in a dose-dependent manner ($P < 0.05$). Furthermore, 2-MG reduced cellular senescence and suppressed the secretion of IL-6 and IL-8 ($P < 0.05$). Western blot analysis demonstrated that 2-MG inhibited AGEs-induced p16 expression ($P < 0.05$).
Conclusion: The findings indicate that 2-MG mitigates AGEs-induced oxidative stress and inflammaging in HGEs and HGFs. These results suggest that 2-MG may have therapeutic potential in preventing or attenuating DM-associated periodontal degeneration.

Introduction

Periodontitis is a localized inflammatory disease driven by the host's immune response to microbial stimuli that accumulate within dental biofilms. It is characterized by the progressive destruction of connective tissue and alveolar bone. If periodontitis left unmanaged, it can lead to tooth loss and significantly diminish the quality of patient's life.[1–4] Among the systemic conditions that exacerbate periodontitis, diabetes mellitus (DM) plays a critical role due to its association with chronic hyperglycemia and the accumulation of advanced glycation end-products (AGEs). AGEs have been identified as a key pathogenic factor in DM-associated periodontitis, primarily through their ability to induce oxidative stress and inflammaging.[5] The excessive formation of AGEs in DM alters cellular homeostasis, triggering pathophysiological processes that accelerate periodontal tissue destruction and inflammation.[6]

One of the primary mechanisms by which AGEs contribute to periodontal degradation is through the induction of oxidative stress, a state of disrupted redox homeostasis caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms.[7,8] AGEs have been shown to enhance ROS accumulation by promoting lipid peroxidation and glycoxidation, leading to sustained oxidative damage in periodontal tissue.[9] Persistent oxidative stress activates pro-inflammatory cytokine signaling, such as interleukin (IL)-6 and IL-8, and hinders cellular repair mechanisms, further exacerbating periodontal tissue damage.[7,10]

In addition to oxidative stress, AGEs are also a key inducer of inflammaging, a state of chronic low-grade inflammation associated with cellular senescence.[11] The interaction between AGEs and their receptor, RAGE (receptor for advanced glycation end-products), triggers prolonged endoplasmic reticulum stress, leading to cellular senescence in periodontal tissues.[12] Senescent cells, in turn, develop a senescence-associated secretory phenotype (SASP), characterized by the secretion of pro-inflammatory cytokines, chemokines, and matrix-degrading enzymes.[13] Studies in DM mouse models have demonstrated that periodontal cells exhibit increased senescence markers and SASP cytokine expression, further linking cellular aging to DM-associated periodontitis.[14] Among SASP-associated cytokines, IL-6 and IL-8 are the most abundantly expressed, with significantly elevated levels detected in periodontal tissues and systemic circulation of individuals with DM and periodontitis.[15,16] Collectively, oxidative stress and inflammaging induced by AGEs play a central role in DM-associated periodontitis, accelerating tissue destruction, inflammation, and disease progression.[17–19] Given these findings, therapeutic strategies targeting AGEs-mediated oxidative stress and inflammaging may offer new approaches for mitigating periodontal complications in individuals with DM.

Magnolol (MG), a primary bioactive compound derived from Magnolia officinalis, has garnered significant attention for its potent anti-inflammatory and antioxidant properties.[20,21] Structurally, MG is characterized by a symmetrical hydroxylated biphenyl framework with an allyl group at the C5 and C5′ positions. Functionally, MG has been shown to lower hyperglycemia, mitigate DM-related complications, and reduce oxidative stress.[22–24] In periodontal disease, it alleviates inflammation in ligature-induced periodontitis in rats[25] and suppresses *Porphyromonas gingivalis* lipopolysaccharide (LPS)-induced inflammation in macrophages,[26] and human gingival fibroblasts (HGFs).[27] These findings highlight MG's potential as a therapeutic agent for oxidative stress and inflammaging in DM-associated periodontitis.

One recent research has explored the methylation of natural compounds to enhance their delivery, bioavailability, and anti-inflammatory potency.[28] Methoxylated magnolol, known as 2-O-methylmagnolol (2-MG), has demonstrated improved skin absorption, leading to greater anti-inflammatory activity.[29] Given its potential, magnolol derivatives may also improve transgingival penetration and therapeutic efficacy against periodontitis. However, despite its promising pharmacological properties, studies on 2-MG in DM-associated periodontitis remain limited. Given that human gingival epithelial cells (HGEs) serve as the first line of defense against microbial invasion,[30] while HGFs regulate extracellular matrix remodeling, wound healing, and immune responses.[31] The aims of this study were to investigate the effects of 2-MG on these cells to evaluate its potential in ameliorating DM-associated periodontitis.

Materials and methods

Cell culture

All experimental procedures were conducted in accordance with the guidelines approved by the Institutional Review Board at Chung Shan Medical University Hospital. Human gingival fibroblasts (HGFs) were isolated from two healthy individuals following crown lengthening procedures using an explant technique. In this study, HGFs between the third and eighth passages were used. An immortalized human gingival epithelial Smulow-Glickman (SG) cells was selected as HGEs. AGEs-bovine serum albumin (BSA) was obtained from BioVision (Milpitas, CA, USA), while 2-MG were prepared as described as previously.[29]

Cell viability assay

Both HGEs and HGFs were seeded at 10,000 cells/well in 96-well plates (Corning Inc., Rochester, NY, USA) and cultured for 48 h until they adhered. Cells were then treated with 2-MG at concentrations of 0, 2.5, 5, 10, and 20 μM for an additional 24 h. Cell viability was assessed using the MTT assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (Thermo Fisher Scientific, Waltham, MA, USA) according to manufacturer's protocol. The absorbance at 570 nm of untreated control cells (0 μM 2-MG) was set to 100 %, and results were expressed as a percentage of control group.

Wound healing assay

Once HGEs and HGFs reached 80 % confluence, a sterile 200-μL pipette tip was used to create a linear wound in the cell monolayer in a 12-well culture plate. Cells were incubated for 48 h, and migration into the wound area was documented using phase-contrast microscopy at 0 and 48 h. The wound closure percentage was quantified to assess the effect of 2-MG on AGEs-induced impairment of cell migration.

Senescence activity detection

Cellular senescence-associated β-galactosidase (SA-β-Gal) activity was detected using the Cellular Senescence Assay Kit (Merck Millipore, Burlington, MA, USA). The cells were cultured in 6-well plates for 24 h, followed by PBS washing, fixation, and incubation with SA-β-Gal Detection Solution. Stained cells were examined under light microscopy, and SA-β-Gal-positive cells were quantified to assess cellular senescence levels.

Western blot analysis

Western blotting was performed as previously described.[32] Primary antibodies targeting cellular senescence marker (p16, Invitrogen Inc., Waltham, MA, USA) was utilized. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as a loading control.

ROS analysis

Intracellular ROS levels were quantified using flow cytometry with the DCFHDA probe (10 μM, Merck Sigma–Aldrich, Burlington, MA, USA). Both cells were incubated with DCFH-DA at 37 °C for 30 min, followed by PBS washing and trypsinization. Fluorescence intensity was analyzed in 10,000 cells using BD FACSCalibur (Becton Dickinson, CA, USA) at an excitation/emission wavelength of 404/524 nm.

Enzyme-linked immunosorbent assay (ELISA) analysis

HGFs were co-treated with AGEs-BSA and 2-MG at the indicated concentrations for 48 h, and conditioned media were collected and supplemented with a protease inhibitor cocktail. The secretion levels of IL-6 and IL-8 were measured using ELISA kits (R&D Systems, Minneapolis, MN, USA). Absorbance was recorded at 450 nm using a microplate reader (MRX, Dynatech Laboratories, Chantilly, VA, USA). All samples were analyzed in triplicate.

Statistical analysis

All experiments were performed in triplicate. One-way analysis of variance (ANOVA) was used for statistical comparisons, followed by Duncan's post hoc test. A *P*-value of <0.05 was considered statistically significant.

Results

Initially, it was observed that 2-MG at concentrations up to 10 μM did not exert any significant effects on the proliferation rate of HGEs as well as HGFs *($P > 0.05$)*. These results indicated that the compound does not exhibit cytotoxicity at the tested concentrations (Fig. 1). To mimic the pathological conditions of DM-associated periodontitis, AGEs were introduced to HGEs and HGFs in subsequent experiments. Notably, co-administration of 2-MG significantly ameliorated AGEs-induced impairment of wound healing ($P < 0.05$), suggesting its potential role in enhancing tissue regeneration (Fig. 2).

To further investigate the molecular mechanisms of 2-MG, we examined its effects on ROS accumulation, cellular senescence, and the senescence-associated secretory phenotype (SASP). AGEs exposure resulted in a significant increase in ROS levels, which was effectively mitigated by 2-MG in a dose-dependent manner ($P < 0.05$), indicating its antioxidant capacity (Fig. 3). Additionally, AGEs markedly promoted cellular senescence, as evidenced by increased SA-β-Gal staining and elevated p16 protein expression ($P < 0.05$), both of which were attenuated upon 2-MG

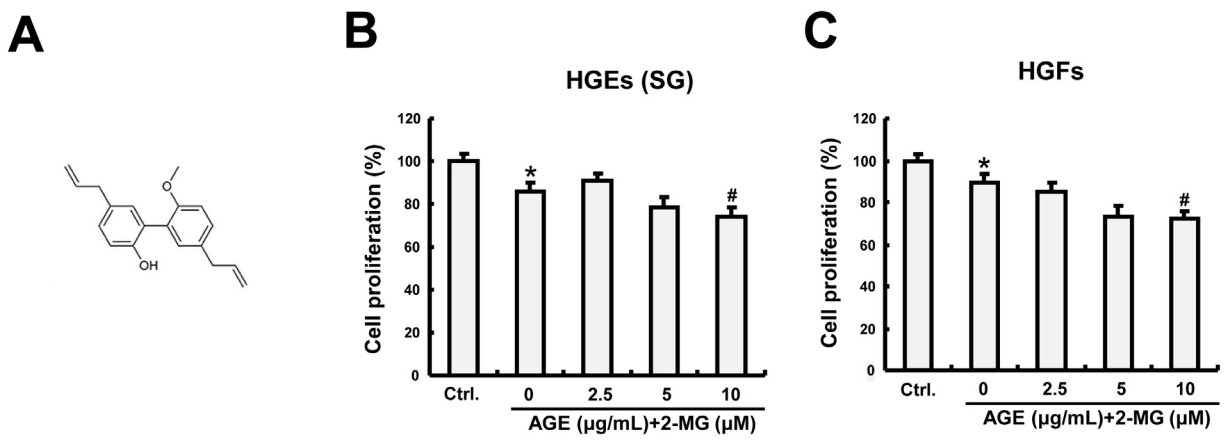

Figure 1 Effects of 2-O-methylmagnolol (2-MG) on cell proliferation in advanced glycation end-products (AGEs)-stimulated human Smulow-Glickman (SG) gingival epithelial cells (HGEs) and human gingival fibroblasts (HGFs). (A) Chemical structure of 2-MG. (B) Cell viability was assessed in HGEs following treatment with AGEs (100 μg/mL) alone or in combination with increasing concentrations of 2-MG (2.5, 5, and 10 μM) for 24 h. Ctrl. represents as control. (C) A similar experiment was performed in HGFs. 2-MG at 20 μM and below did not have any significant impact on HGFs proliferation. Data represent the mean ± standard deviation. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to the AGEs only group.

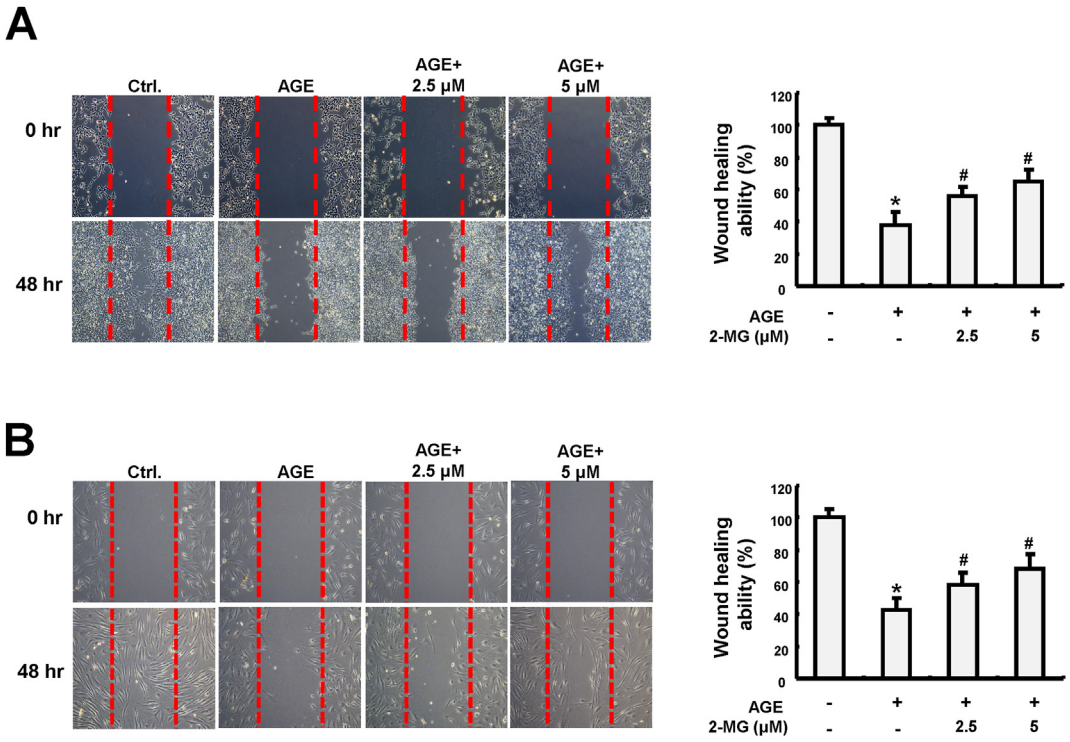

Figure 2 2-O-methylmagnolol (2-MG) enhances wound healing ability in advanced glycation end-products (AGEs)-treated human gingival epithelial cells (HGEs) and human gingival fibroblasts (HGFs). Representative images of wound healing assay and wound closure percentage in (A) HGEs and (B) HGFs at 0 and 48 h after scratch induction, showing the differences in cell migration among control (Ctrl.), AGEs-treated, and 2-MG co-treated groups. Data from three independent experiments, each in triplicate. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to the AGEs only group.

treatment (Fig. 4). Similar decreased pattern was revealed in HGEs and HGFs.

Furthermore, 2-MG suppressed the AGEs-induced secretion of pro-inflammatory cytokines IL-6 and IL-8 ($P < 0.05$), demonstrating its ability to attenuate SASP-mediated inflammatory responses (Fig. 5). Collectively, these findings suggest that 2-MG exhibits anti-oxidative and inflammaging properties in HGEs and HGFs.

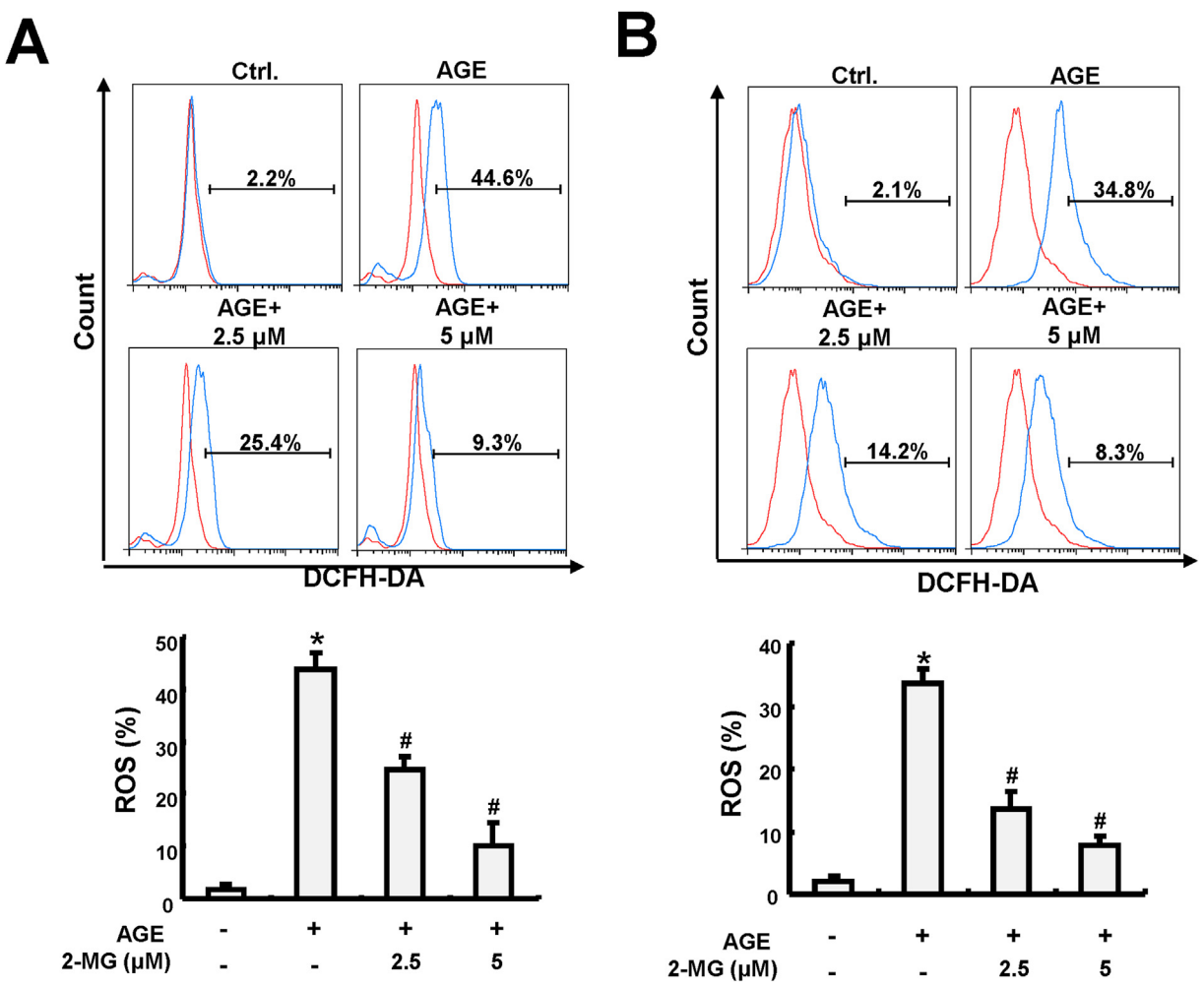

Figure 3 2-O-methylmagnolol (2-MG) reduces reactive oxygen species (ROS) accumulation in advanced glycation end-products (AGEs)-treated human gingival epithelial cells (HGEs) and human gingival fibroblasts (HGFs). Representative flow cytometry histograms showing DCFH-DA fluorescence intensity and its quantification in (A) HGEs and (B) HGFs under different treatment conditions. The presence of AGEs significantly increased ROS production, which was mitigated by 2-MG in a dose-dependent manner. Data from three independent experiments, each in triplicate. Ctrl. represents as control. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to the AGEs only group.

Discussion

DM is a major risk factor for periodontitis, largely due to the accumulation of AGEs, which drive oxidative stress and inflammaging.[33] Inflammaging, a state of chronic low-grade inflammation and accelerated cellular senescence, exacerbates periodontal tissue destruction in individuals with DM.[7–10] The present study demonstrated that when HGEs and HGFs were exposed to AGEs, they exhibited hallmark signs of increased oxidative stress and inflammaging, characterized by cellular senescence, and heightened secretion of SASP factors IL-6 and IL-8. These findings align with previous studies, reinforcing the role of AGEs in promoting periodontal degradation through oxidative stress and inflammaging pathways.[11,14,34,35]

Our study found that 2-MG significantly reduced ROS accumulation in AGEs-stimulated HGEs and HGFs, indicating its strong antioxidant capacity. These results are in line with previous studies that demonstrated the ability of magnolol and its derivatives to scavenge ROS and modulate oxidative stress-related pathways in a rat model of intracerebral hemorrhage and skin disorders.[23,24] The antioxidant effects of 2-MG may be mediated through the activation of the Nrf2 pathway, a critical regulator of cellular redox homeostasis. Nrf2 enhances the expression of antioxidant enzymes such as HO-1 and SOD, which mitigate ROS-induced damage. Given that magnolol derivatives have been shown to upregulate Nrf2 expression, 2-MG may exert similar protective effects by modulating this pathway.[26]

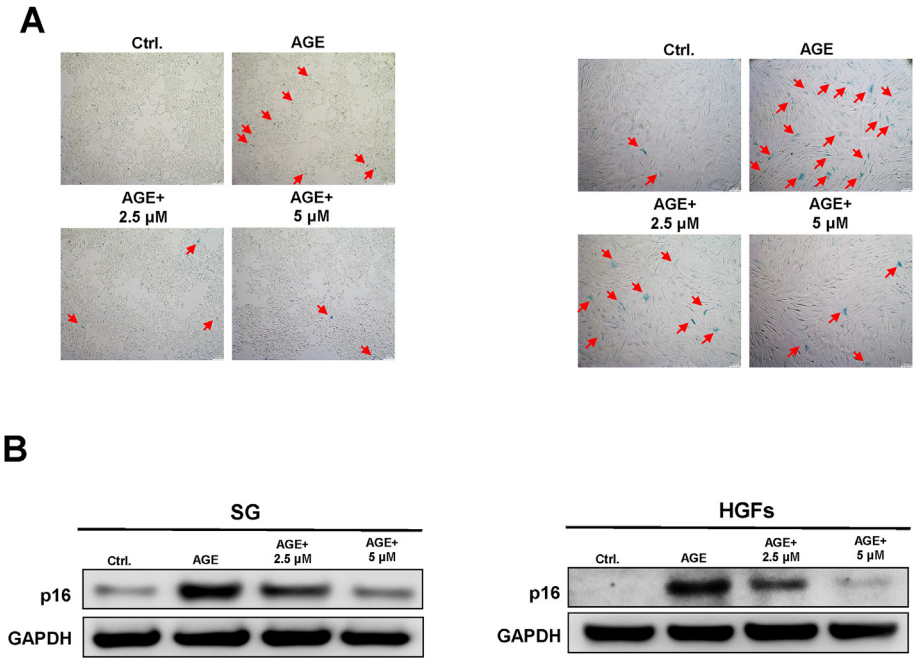

Figure 4 2-O-methylmagnolol (2-MG) reduces cell senescence and p16 expression in advanced glycation end-products (AGEs)-treated Smulow-Glickman (SG) cells and human gingival fibroblasts (HGFs). (A) SA-β-Gal staining of the cells treated with AGEs alone or in combination with 2-MG (2.5 and 5 μM), arrows indicate the differences in cellular senescence in SG and HGFs, respectively. Ctrl. represents as control. (B) p16 expression levels in SG and HGFs under the same conditions. 2-MG treatment suppressed AGEs-induced cell senescence and p16 upregulation. The quantitative results of p16 protein levels were adjusted by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) levels.

Cellular senescence is a key feature of inflammaging, characterized by irreversible cell cycle arrest and the secretion of SASP factors, which sustain chronic inflammation and tissue degradation.[13] The present study demonstrated that AGEs significantly upregulated SA-β-Gal staining and expression p16, both of which are well-established markers of senescence, in HGEs and HGFs. However, treatment with 2-MG effectively suppressed them, suggesting its potential anti-inflammaging activity in periodontal cells. Magnolol derivatives have been shown to exert superior anti-senescence activity in a *Caenorhabditis elegans* model, where it ameliorates aging, age-related neurodegeneration, and extend their lifespan.[36,37]

The SASP plays a central role in propagating chronic inflammation in DM-associated periodontitis, as senescent cells secrete high levels of IL-6, IL-8, and matrix metalloproteinases, which contribute to extracellular matrix degradation and periodontal tissue destruction.[16,18] Our study showed that 2-MG significantly reduced the secretion of IL-6 and IL-8 in AGEs-stimulated HGEs and HGFs, indicating its ability to modulate the inflammatory microenvironment. It is possible that 2-MG exerts its anti-inflammatory effects by blocking the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) nuclear translocation and inhibiting the phosphorylation of its upstream kinases, such as IκB kinase.[20] The NF-κB signaling pathway serves as a master regulator of inflammatory cytokine expression. Its activation by AGEs has been associated with increased SASP factor transcription, thereby sustaining the inflammatory cycle in periodontal disease.[38]

2-MG demonstrated the ability to enhance wound healing in AGEs-stimulated HGEs and HGFs. Given that chronic hyperglycemia impairs periodontal wound healing by promoting oxidative stress and inflammation, the wound-healing effects of 2-MG suggest its potential as a regenerative agent in DM-associated periodontitis. One possible explanation for the pro-repair effects of 2-MG is its ability to enhance fibroblast proliferation and migration. Previous studies have shown that magnolol promotes fibroblast-mediated tissue remodeling by stimulating transforming growth factor-β signaling, a key regulator of wound healing.[21]

In summary, this study demonstrated that 2-MG enhances wound healing by mitigating AGEs-induced oxidative stress, cellular senescence, and SASP-mediated inflammation in HGEs and HGFs. With its multi-targeted therapeutic effects, the methylation of magnolol may enhance transgingival penetration, making 2-MG a promising non-invasive treatment for DM-associated periodontitis. However, further in vivo studies and clinical trials are essential to determine its optimal dosage, bioavailability, and long-term safety, paving the way for its integration into future periodontal treatment protocols.

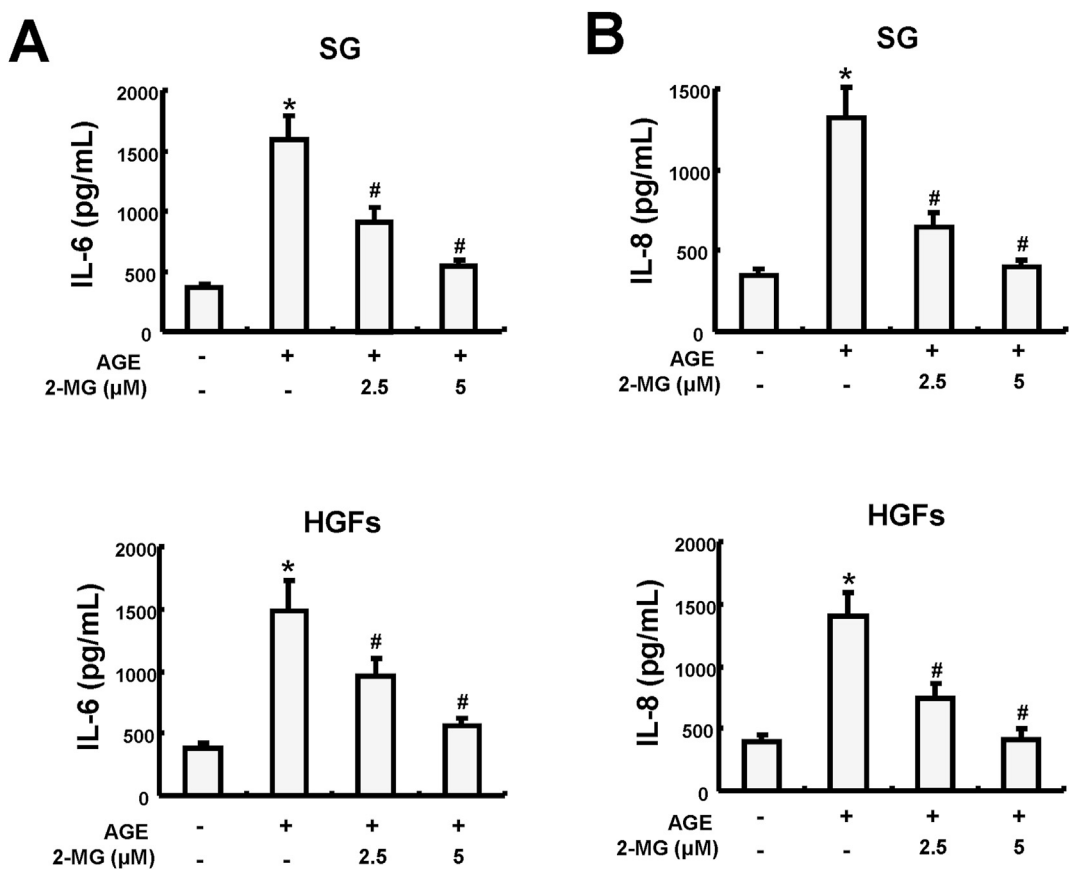

Figure 5 2-O-methylmagnolol (2-MG) suppresses advanced glycation end-products (AGEs)-induced senescence-associated senescence phenotype (SASP) production in Smulow-Glickman (SG) cells and human gingival fibroblasts (HGFs). (A) IL-6 and (B) IL-8 secretion levels were measured by enzyme-linked immunosorbent assay in the supernatants of AGE-treated SG and HGFs with or without 2-MG co-treatment. AGEs stimulation significantly increased cytokine release, while 2-MG co-treatment effectively attenuated this response. Data are expressed as mean ± SD. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to the AGEs only group.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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