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Original Article

γ-Mangostin mitigates impaired wound healing and pyroptosis in human gingival fibroblasts induced by advanced glycation end products

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KEYWORDS
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Abstract *Background/purpose:* The incidence of diabetes mellitus (DM) has gradually increased in recent years. DM and its complications impose a substantial burden on healthcare systems. Chronic hyperglycemia results in the accumulation of advanced glycation end products (AGEs), which in turn elevate oxidative stress and inflammation, thereby contributing to diabetic complications, including impaired wound healing. γ-Mangostin, a mangostin isolated from the pericarp of mangosteen fruit, has been reported to possess antioxidant and anti-inflammatory properties. Our study aimed to investigate the effects of γ-mangostin on AGEs-induced impairment of wound healing and inflammaging.
Materials and methods: Human gingival fibroblasts (HGFs) were isolated from gingival tissues obtained from patients undergoing crown lengthening surgery. HGFs were treated with AGEs for 24 h, followed by treatment with 0.5–2 μg/mL γ-mangostin for another 24 h. Cell proliferation, wound healing capacity, oxidative stress, cell senescence, pyroptosis, and pro-inflammatory cytokine expression were then assessed.

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Results: Our study found that γ-mangostin at 0.5—2 μg/mL had no effect on HGFs proliferation rate. Furthermore, γ-mangostin restored AGE-induced wound healing impairment and decreased ROS generation. γ-Mangostin reduced AGEs-induced increases in senescence-related β-galactosidase (SA-β-gal) activity and senescence markers p16 and p21. Furthermore, γ-mangostin decreased the expression of pyroptosis-related markers, including as ASC, NLR family pyrin domain-containing 3 (NLRP3), pro-caspase-1, and cleaved gasdermin D (GSDMD). Finally, γ-mangostin inhibited the AGE-induced production of pro-inflammatory cytokines IL-6 and IL-8.

Conclusion: Our findings suggest that AGEs impair wound healing and promote oxidative stress, cellular senescence, pyroptosis, and inflammation. γ-Mangostin treatment mitigated these effects, potentially by attenuating inflammation and pyroptosis, thereby improving wound healing.

Introduction

Insulin resistance and insufficiency are two main characteristics of diabetes mellitus (DM).[1] Prolonged chronic hyperglycemia results in adverse effects on multiple organ systems, exhibiting symptoms including polydipsia, polyuria, blurred vision, and compromised wound healing.[2] DM complications include macrovascular and microvascular diseases, diabetic nephropathy, retinopathy, neuropathy, periodontitis, and diabetic foot ulcers.[3] Notably, diabetic periodontitis is the sixth most prevalent of these complications, as poor glycemic control exacerbates periodontal diseases and ultimately contributes to the development of periodontitis. Advanced glycation end products (AGEs) are known to have a major role in the etiology of diabetes and its complications.[4,5] Patients with diabetes endure chronic hyperglycemia, leading to elevated concentrations of AGEs in the circulation, which are attributed to the development and progression of diabetic complications.[6] Hyperglycemia also induces the production of reactive oxygen species (ROS) and amplifies oxidative stress, further exacerbating periodontal tissue damage.[7] Additionally, alveolar bone resorption and epigenetic modifications within periodontal tissues induced by diabetes may also contribute to the development of periodontitis.[8]

The destruction of soft and hard tissues in the periodontal region is a defining characteristic of periodontitis, a chronic inflammatory oral disease that ultimately leads to the loss of periodontal ligament, cementum, and alveolar bone, culminating in tooth loss.[9] Beyond these effects, periodontitis has been linked to various systemic conditions, including cancer, diabetes, liver disease, osteoporosis, and neuronal diseases.[10] Conversely, systemic inflammatory diseases exacerbate periodontitis. DM patients due to prolonged hyperglycemia, are more susceptible to infections, significantly increasing the prevalence of periodontitis.[11,12] Diabetes-related serum metabolites, hyperglycemia, and AGEs play a crucial role in delaying wound healing in periodontitis.[13] Diabetic periodontitis exacerbates alveolar bone resorption, leading to tooth loss and posing significant challenges in its management. Moreover, diabetic patients often experience poor prognosis even after receiving dental treatment.[14]

Inflammaging is a chronic and low-grade systemic inflammation that accompanies aging, exacerbates age-related diseases including cellular senescence, immune dysfunction, and organ damage.[15,16] Inflammaging is characterized by elevated plasma levels of proinflammatory cytokines such as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-α, c reactive protein (CRP), and serum amyloid A.[16,17] Inflammaging causes age-related pathological changes and increases the risk of mortality by increasing cellular senescence and promoting the senescence-associated secretory phenotype (SASP).[4] In recent years, studies have found that NLRP3 inflammasome is associated with periodontal disease. *In vivo* study revealed that NLRP3 knockout periodontal disease mice had reduced alveolar bone loss induced by *Porphyromonas gingivalis*.[18] Previous studies have shown that damage and metabolic imbalance caused by hyperglycemia lead to the accumulation of pro-inflammatory SASP in serum and promote inflammaging.[10,19]

Mangosteen (*Garcinia mangostana* L.) is a fruit prevalent in subtropical areas. The mangosteen pericarp constitutes more than 50 % of the entire fruit; however it is rarely ingested owing to its tough texture and harsh flavor. Recently, scientists have identified that mangosteen pericarp encompasses various bioactive constituents, such as mangostin (α, β, γ-mangostin), isoflavones, flavonoids, tannins, and anthocyanins,[20] which possesses antioxidant, anti-inflammatory, antibacterial, and anticancer properties.[21,22] Among the constituents of mangosteen pericarp, α and γ-mangostin are the most extensively examined. α-mangostin exhibits antibacterial, anti-aging, anti-inflammatory, anti-diabetic, antioxidant, and anticancer properties.[23] Recent research suggests that γ-mangostin has bioactivities including anti-inflammatory, anti-fibrotic, and hypoglycemic properties.[24] Chen et al. demonstrated that γ-mangostin administered to diet-induced obesity (DIO) mice for 7 weeks can reduce fasting blood glucose and improve oral glucose tolerance test (OGTT) by regulating AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor (PPAR)-γ, suggesting its potential as an insulin sensitizer.[25] However, the effects of γ-mangostin on diabetic periodontitis and wound healing remain to be elucidated. Therefore, we sought to investigate whether γ-mangostin has the capacity to suppress

inflammaging and the underlying mechanism of human gingival fibroblast induced by AGEs.

Materials and methods

Cell culture

Human gingival fibroblasts (HGFs) were collected from three healthy patients who had crown lengthening surgery. All experimental techniques followed the Institutional Review Board (IRB) guidelines of the National Chung Shan Medical University Hospital (IRB Number: CSMUH-CS2-23059). To prevent the alteration of fibroblast properties, cells from the third to the eighth generation were cultivated for the study. HGFs were procured from the gingiva at the upper one third of the root, and the gingival tissues were soaked in sterile saline for 1–4 h prior to the experiment. Following multiple washes with phosphate-buffered saline (PBS), the gingival tissues were chopped with a scalpel and incubated with 3 mg/mL collagenase type I at 37 °C. HGFs were then cultured for 30 min and subsequently filtered through a 70 mm strainer to achieve a single-cell solution for culture. The culture medium for human fibroblast cultivation is DMEM supplemented with 10 % FBS, and HGFs were subcultured upon reaching 90 % confluence. γ-Mangostin (Sigma Chemical Co., St. Louis, MO, USA) was dissolved in methanol and prepared in various concentrations for research use. In this study, human fibroblasts were cultivated with 200 μg/mL AGE-BSA (BioVision, Milpitas, CA, USA) for 24 h, after which they were treated with 0.5 and 1 μg/mL γ-mangostin for an additional 24 h. Each experiment was conducted three times using fibroblasts from two distinct donors.

Cell viability assay

HGFs (10000 cells/well) were inoculated into 96-well plates (Corning Inc., Rochester, NY, USA) for 24 h. After the cells had attached, 200 μg/mL AGE-BSA was added for 24 h 0.5–2 μg/mL γ-mangostin was added and cultured for another 24 h. Prestoblue was diluted 10-fold and 100 μL was added to each well and the absorbance at 570 nm was measured to evaluate cell viability and proliferation ability. The absorbance at 570 nm of the group without γ-mangostin was set as 100 % cell viability, and the cell viability of the remaining groups were calculated relative to control.

Wound healing assay

After the HGFs have reached 80 % confluence, the monolayer was scraped across the center of the well in a 12-well plate using a sterile 200 μL tip. A further 48 h were allowed for the growth of HGF cells. Images of cell migration toward the denuded region were captured using a microscope at both 0 and 48 h.

ROS analysis

HGF cells were rinsed with PBS, and subsequently, fresh culture medium was introduced. Subsequently, 10 μM 2′,7′-dichlorodihydrofluorescein diacetate indicator was introduced, and the cells were placed back in the 37 °C incubator with 5 % CO_2 for 1 h. After 24 h, the cell culture medium was discarded, and the cells were rinsed with PBS. Trypsin–EDTA was subsequently added and incubated at 37 °C for 5 min to facilitate the detachment of adherent cells from the growth plate. Next, trypsin–EDTA was incorporated into the cell culture medium to stop the reaction. The culture media with suspended cells was transferred to a 15 mL centrifuge tube and spun at 1200 rpm for 5 min using a high-speed centrifuge. The supernatant was discarded, and the cells were rinsed with PBS. Finally, flow cytometry was employed to assess the fluorescence efficacy of DCF and examine the levels of intracellular ROS.

Cellular senescence assay

The Senescence Detection Kit (BioVision) was used to measure the proportion of cells positive for senescence-associated β-galactosidase (SA-β-gal). HGFs were inoculated onto 6-well culture plates and then rinsed with PBS. Subsequently, the cells were subjected to SA-β-gal staining fixative at ambient temperature for 20 min, followed by three washes with PBS. 470 μl of staining solution, 5 μl of staining additive, and 25 μl of 20 mg/mL X-gal were included. The specimens were stained using a DMF solution. Subsequent to the application of the stain, the cells were incubated overnight at 37 °C in a 5 % CO_2 environment. The cells were rinsed twice with PBS every other day, and the staining outcomes were assessed using an optical microscope. Three distinct microscopic fields were chosen for quantitative investigation.

Western blot

Western blot was conducted as previously mentioned.[26] The primary antibodies against senescence markers p16 (Invitrogen, Waltham, MA, USA), p21 (Abcam, Cambridge, UK) and pyroptosis markers ASC (Cell signaling technology, Danvers, MA, USA), NLRP3 (Invitrogen), pro-caspase-1 (Abcam), cleaved GSDMD (Cell signaling technology), GAPDH (Invitrogen) were used. Secondary antibodies against anti Mouse (Millipore, Burlington, MA, USA) and Polyclonal Rabbit Anti Human (DakoCytomation, DK, EU).

ELISA analysis

The supernatants were collected and analyzed for IL-6 and IL-8 concentrations using ELISA kits (R&D Systems, Minneapolis, MN, USA) after HGFs were treated with AGEs and γ-mangostin. The procedures were carried out according to the manufacturer's recommendations, and the absorbance at a wavelength of 450 nm was measured for analysis (MRX; Dynatech Laboratories, Chantilly, VA, USA). Each sample was measured three times.

Statistical analysis

Results were presented as the mean ± standard deviation (SD), and the experiments were performed three times. One-way analysis of variance (ANOVA) and Duncan's test

were employed to conduct statistical analysis. Significant differences were defined as $P < 0.05$.

Results

Human gingival fibroblasts (HGFs), the major cell type in the oral cavity are essential for the repair of gingival tissue wounds,[27] were utilized to investigate the effects of γ-mangostin on advanced glycation end product (AGE)-induced impairment of wound healing. HGFs were pre-treated with 200 μg/mL of advanced glycation end products-bovine serum albumin (AGEs-BSA) for 24 h. Subsequently, HGFs cells were treated with γ-mangostin at various concentrations (0.5—2 μg/mL) for another 24 h. Treatment with γ-mangostin at indicated concentrations did not significantly affect cell proliferation of AGE-treated HGFs (Fig. 1). Therefore, concentrations of 0.5—1 μg/mL γ-mangostin were selected for subsequent experiments.

Our study revealed that 200 μg/mL AGE-BSA impeded wound healing. Meanwhile, treatment with 0.5 and 1 μg/mL γ-mangostin markedly enhanced wound healing, indicating a protective effect against AGE-induced injury (Fig. 2). To determine whether γ-mangostin can prevent reactive oxygen species (ROS) production in HGFs induced by AGE stimuli, the DCFH-DA assay demonstrated a significant elevation in ROS production after treatment with AGE-BSA. Significantly, treatment of γ-mangostin decreased ROS generation in a dose-dependent manner (Fig. 3).

Additionally, we investigated the effects of γ-mangostin on cellular senescence. AGE-BSA markedly elevated senescence-associated β-galactosidase (SA-β-gal) activity, an indicator of cellular senescence. SA-β-gal activity and senescence markers p16 and p21 induced by AGE-BSA was considerably inhibited by γ-mangostin (Fig. 4). The results suggest that γ-mangostin can alleviate cellular aging induced by AGEs. Chronic inflammation triggered by the NLRP3 inflammasome has been found to accelerate the progression of type 2 diabetes mellitus (T2DM) and its consequences, including diabetic nephropathy, diabetic retinopathy, diabetic cardiomyopathy, and diabetes-associated atherosclerosis.[28] Inflammasome is an intracellular signaling complex consisting of NLR family pyrin domain (NLRP), ASC, and caspase-1.[29] Considering the significance of inflammation in diabetes-associated complications, we evaluated the impact of γ-mangostin on the NLRP3 inflammasome, a crucial modulator of inflammation. AGEs treatment resulted in a significant upregulation of NLRP3 inflammasome components, such as ASC, NLRP3, pro-caspase-1, and cleaved gasdermin D (GSDMD), and treatment with γ-mangostin markedly diminished the proteins expression of these pyroptosis markers (Fig. 5). IL-6 and IL-8 are pro-inflammatory cytokines, and their expression levels have a positive correlation with the extent of inflammation.[30] Ultimately, we assessed the production of the pro-inflammatory cytokines IL-6 and IL-8. AGE-BSA induced the secretion of IL-6 and IL-8. Nonetheless, γ-mangostin administration markedly reduced this pro-inflammatory response (Fig. 6).

Discussion

Our investigation revealed that AGEs significantly contribute to inflammaging through multiple interconnected pathways, ultimately leading to impaired wound healing (Figs. 2 and 3). The findings demonstrate that AGEs stimulate inflammaging in human gingival fibroblasts (HGFs) through increased oxidative stress, cellular senescence, and the secretion of pro-inflammatory cytokines.[31—33] This aligns with previous studies establishing the link between persistent hyperglycemia and inflammaging,[19] particularly in the context of periodontal conditions.[33,34]

A key finding of our study is the role of AGE-induced oxidative stress in promoting cell senescence and SASP expression. The resulting inflammation and paracrine signaling create a detrimental cycle that disrupts tissue function, potentially exacerbating both diabetes and its complications.[35] Moreover, the circulation of SASP factors contributes to a chronic inflammatory state that deteriorates insulin resistance.[36] Our results showing increased β-gal staining and elevated expression of cell

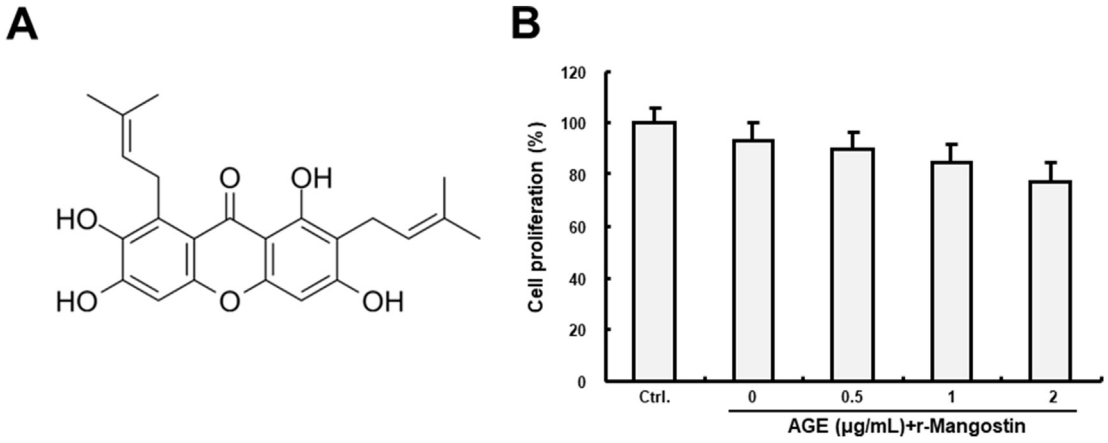

Figure 1 The effect of γ-mangostin on cell proliferation of human gingival fibroblasts (HGFs) induced by advanced glycation end products (AGEs). (A) Chemical structure of γ-mangostin. (B) 1×10^4 cells/well of HGFs were inoculated and treated with 200 μg/mL AGEs for 24 h and then treated with 0, 0.5, 1, or 2 μg/mL of mangostin for another 24 h 2 μg/mL mangostin and the concentration below showed no cytotoxicity on HGFs. Data are presented as mean ± SD.

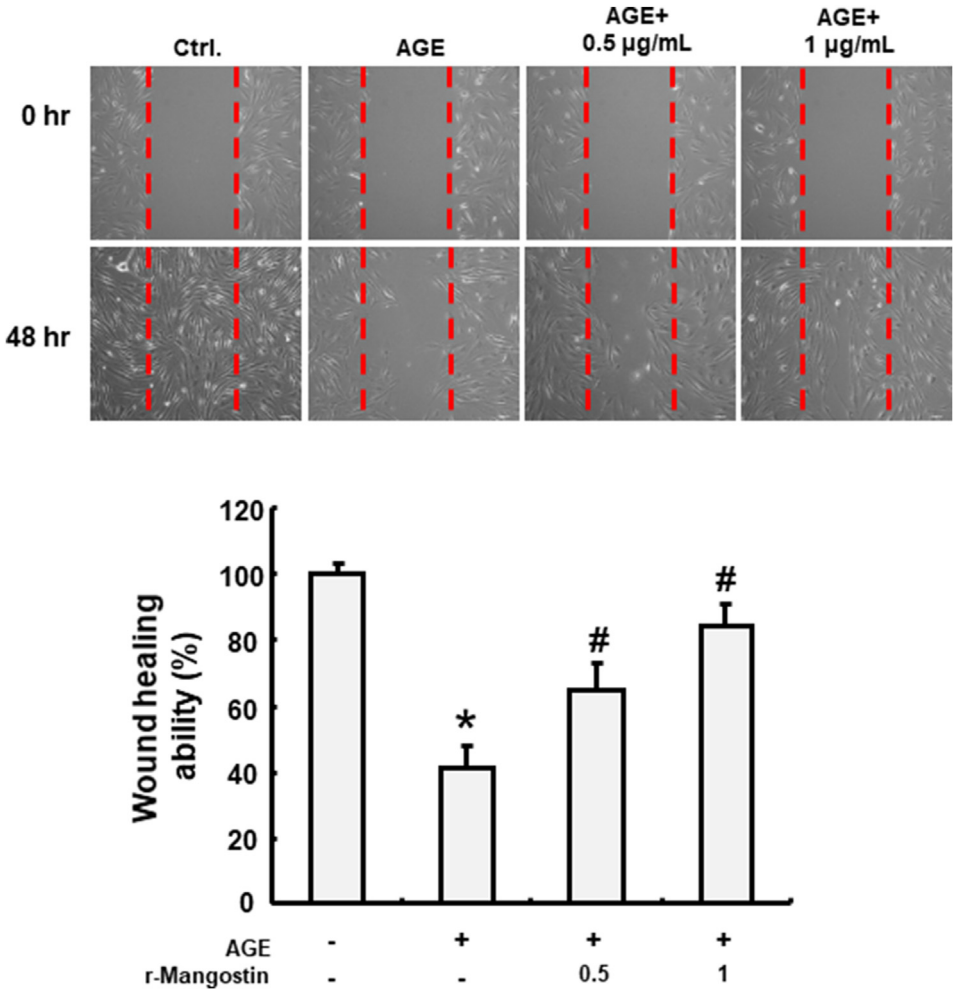

Figure 2 γ-Mangostin reverse impaired wound healing in human gingival fibroblasts (HGFs) treated with advanced glycation end products (AGEs). Human gingival fibroblasts were treated with AGE-BSA (200 μg/mL) for 24 h, followed by 0.5 and 1 μg/mL γ-mangostin for 24 h to assess wound healing. The results are based on at least three independent experiments. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to the AGE group.

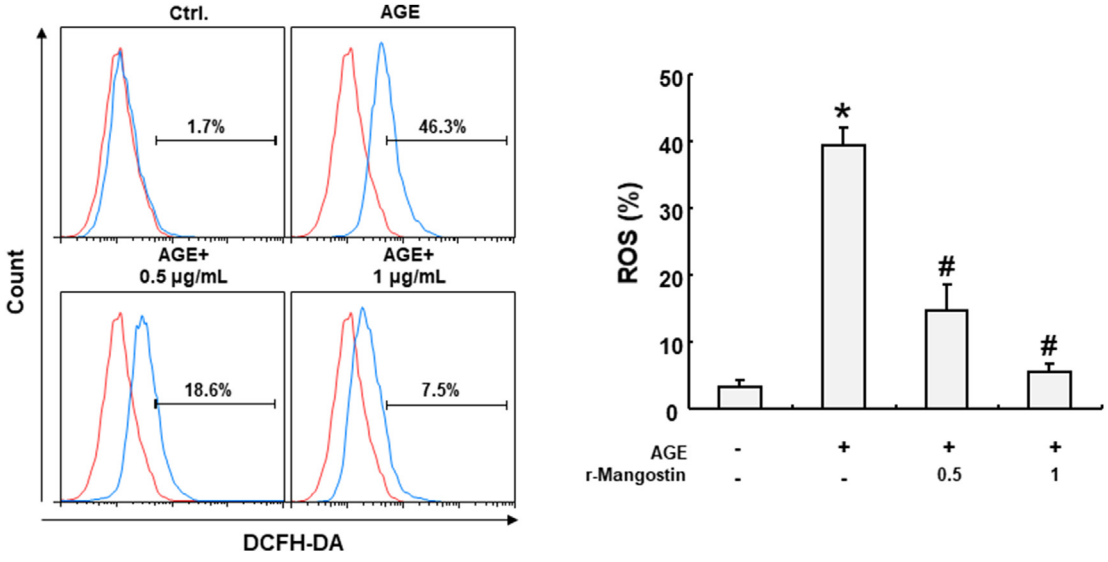

Figure 3 γ-Mangostin diminished the production of ROS in human gingival fibroblasts (HGFs) induced by advanced glycation end products (AGEs). The AGEs-induced ROS in HGFs was diminished in a dose-dependent manner following 0.5–1 μg/mL mangostin administration. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to the AGE group.

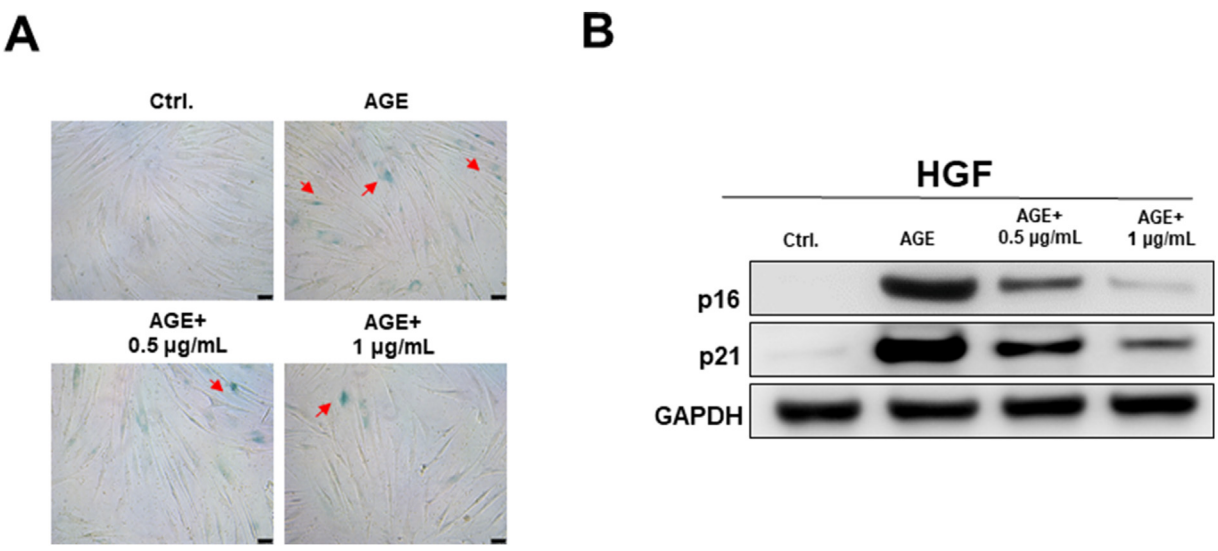

Figure 4 **γ-Mangostin attenuated cell senescence and the protein level of senescence markers p16 and p21 in human gingival fibroblasts (HGFs) produced by advanced glycation end products (AGEs).** (A) γ-Mangostin treatment suppressed SA-β-gal staining cells. (B) γ-Mangostin reduced the protein levels of cell senescence markers (p16 and p21) in HGF cells with AGE stmulation by western blotting. * $P < 0.05$ compared to control group; # $P < 0.05$ compared to the AGE group.

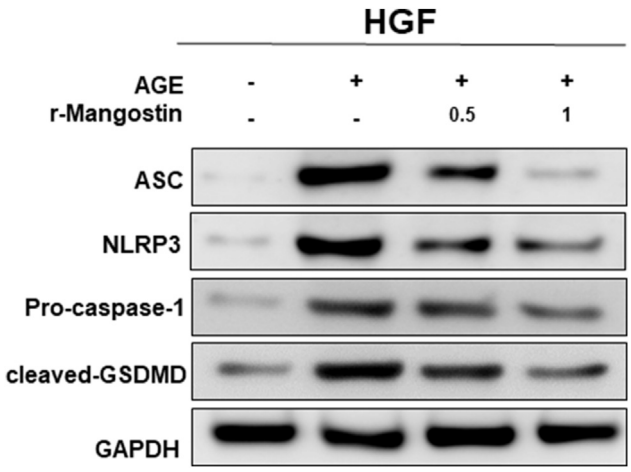

Figure 5 **γ-Mangostin decreased the protein level of pyroptosis markers in human gingival fibroblasts (HGFs) induced by advanced glycation end-products (AGEs).** Western blot analysis revealed that AGEs significantly increased the protein levels of pyroptosis markers, including ASC, NLRP3, pro-caspase-1, and cleaved GSDMD. However, γ-mangostin treatment effectively attenuated this AGEs-induced increase in pyroptosis markers.

senescence-related proteins p16 and p21 in AGE-treated HGFs provide strong evidence for AGE-induced cellular senescence (Fig. 4).

The impairment of wound healing in diabetic conditions emerges as a critical consequence of these molecular changes. At wound sites, significant ROS production triggers enhanced SASP release from senescent cells, leading to decreased angiogenesis and vascular permeability.[37] This process is further complicated by the aging effect on epithelial cells and reduced immunological activity of age-related macrophages, resulting in persistent inflammation at wound sites. The situation worsens with bacterial infiltration of chronic wounds, where keratinocyte overgrowth and migratory inhibition are observed. Furthermore, the senescence of fibroblasts and macrophages, accompanied by SASP acquisition and ROS generation, creates a self-perpetuating cycle of inflammation.[38]

The biochemical mechanisms underlying diabetes-related wound healing impairment, particularly in periodontal tissues, remain an area of active investigation. Current evidence suggests that oxidative stress plays a central role in the pathogenesis of both diabetes and periodontal disease, with these conditions mutually exacerbating oxidative stress in periodontal tissues.[39] Recent research has identified that chronic hyperglycemia impairs periodontal disease progression through the promotion of macrophage pyroptosis and IL-1β secretion, primarily via the mTOR-ULK1 pathway.[7] The activation of this pathway suppresses autophagy and promotes excessive mitochondrial ROS accumulation, ultimately triggering pyroptosis and inflammasome activation in LPS-stimulated macrophages.[8] Nevertheless, further investigation is essential to elucidate the specific role of the mTOR/ULK1 signaling pathway in the AGE-induced reduction of HGF wound healing.

In a nutshell, our findings indicate that AGE treatment in HGFs leads to increased oxidative stress and cell senescence, along with elevated levels of pyroptosis-related proteins and a reduced wound healing capacity. These results highlight the intricate relationship between these pathways. The therapeutic potential of γ-mangostin, which can mitigate these harmful processes and promote wound healing, offers a promising avenue for intervention. Targeting the AGE-induced inflammaging pathway, particularly by modulating oxidative stress and cellular senescence, could be a valuable strategy for enhancing wound healing in diabetic patients. However, due to the complexity of the

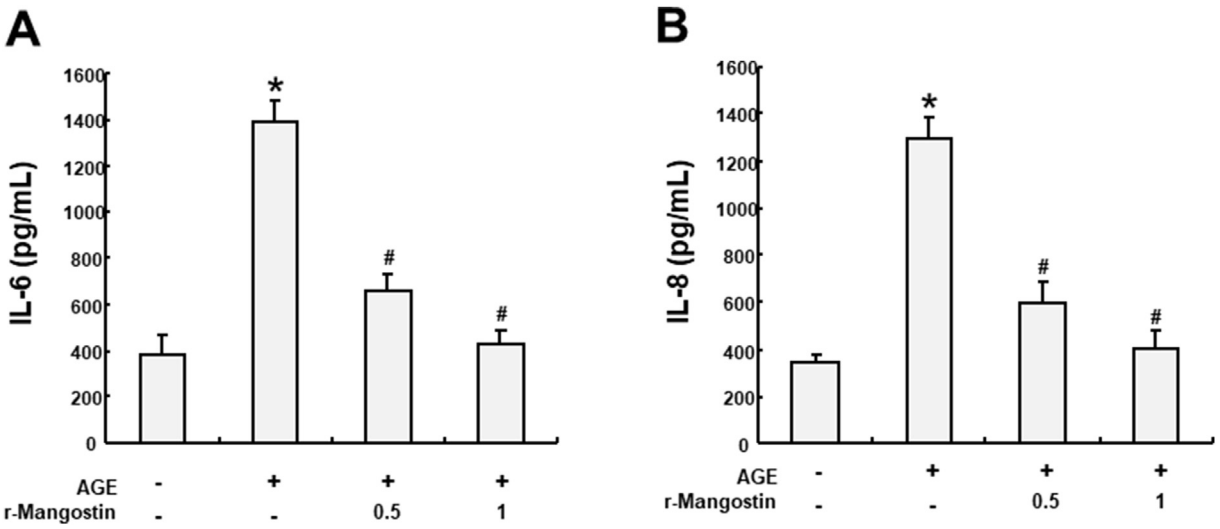

Figure 6 γ-Mangostin inhibited the production of pro-inflammatory cytokines in human gingival fibroblasts (HGFs) induced by advanced glycation end products (AGEs). The concentrations of IL-6 and IL-8 in the cell culture medium were measured using ELISA kit. AGEs significantly induced the production of both IL-6 (A) and IL-8 (B) by HGFs. γ-Mangostin treatment effectively attenuated AGEs-induced cytokine production in a dose-dependent manner. Data represent the mean ± SD. *$P < 0.05$ compared to control group; #$P < 0.05$ compared to AGE group.

wound healing process, further research is necessary to fully explore the effects of such treatments on macrophages, angiogenesis, and different stages of healing.

Declaration of competing interest

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

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