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Original Article

# Corylin ameliorates inflammaging and pyroptosis in diabetic periodontitis: A preliminary *in vitro* study

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**Abstract** *Background/purpose:* Diabetic periodontitis (DP) is a severe oral disease characterized by hyperinflammation and impaired wound healing, with inflammaging and pyroptosis playing key roles in its pathogenesis. Corylin, an isoflavone compound, has shown promising anti-inflammatory and anti-pyroptotic properties, but its specific effects on DP remain largely unexplored. This study aimed to evaluate the effects of Corylin on inflammaging and pyroptosis in an in vitro model of DP, potentially offering novel insights into therapeutic strategies for this challenging condition.

*Materials and methods:* This in vitro study evaluated the effects of Corylin on inflammaging and pyroptosis in human gingival fibroblasts (HGFs) exposed to advanced glycation end products (AGEs) to mimic the diabetic environment. We then examined the reactive oxygen species (ROS) generation and wound healing ability in the cells. To assess the inflammaging, we probed into cell senescence activity and senescence marker p16 as well as its senescence associated secretory phenotype (SASP) such as interleukins (IL)-6 and IL-8. Next, we measured the levels of pyroptosis markers including nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3), apoptosis-associated speck-like protein containing a CARD (ASC), caspase-1 in cells with and without Corylin.

*Results:* Corylin reduced ROS production and enhanced wound healing in AGEs-treated HGFs in a dose-dependent manner. Furthermore, Corylin attenuated the heightened inflammaging

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markers, which included cellular senescence and the secretion of SASP, IL-6 and IL-8. Additionally, Corylin downregulated the expression of pyroptosis-related components, including NLRP3, ASC, and caspase-1, in AGEs-treated HGFs.
*Conclusion:* These findings suggest that Corylin may have therapeutic potential in DP by mitigating AGE-induced inflammaging and pyroptosis. Corylin's ability to promote wound healing and inhibit both cellular senescence and pyroptosis highlights its potential as a novel therapeutic agent for DP.


## Introduction

Diabetes mellitus (DM) represents a significant global health challenge, characterized by chronic metabolic dysfunction and persistent hyperglycemia. Recent epidemiological data indicate that DM affects approximately 10.5 % of the global population aged 20—79 years, with projections suggesting an increase to 12.2 % by 2045.[1] The hyperglycemic state inherent to DM induces a cascade of pathophysiological changes, notably elevated systemic inflammation and oxidative stress, which subsequently manifest in various tissue and organ complications.[2] Among these complications, diabetic periodontitis (DP) has emerged as a particularly significant concern, presenting as a chronic inflammatory condition that progressively destroys tooth-supporting tissues through connective tissue degradation and alveolar bone resorption.[3]

The pathogenic mechanisms underlying DP have been increasingly elucidated, with advanced glycation end-products (AGEs) emerging as central mediators in disease progression.[4,5] These accumulated AGEs subsequently contribute to the development of inflammaging, a state of chronic low-grade inflammation that substantially increases periodontal tissue susceptibility to pathogenic assault.[6] The major contributors to inflammaging have been found to be the promotion of cellular senescence and its senescence-associated secretory phenotype (SASP). Cell senescence is termed as an irreversible arrest of the cell cycle which can significantly impacts tissue homeostasis. These senescent cells can release a variety of pro-inflammatory cytokines, such as IL-6 and IL-8. This process, known as the senescence-associated secretory phenotype (SASP), further contributes to the perpetuation of the inflammatory environment.[7,8] In the context of DP, periodontal cells exhibit enhanced cellular senescence and SASP secretion, establishing a self-sustaining cycle of inflammation that accelerates disease progression.[9,10]

Apart from inflammaging, recent research has also linked DP to pyroptosis, a highly inflammatory form of cell death.[11,12] This process is characterized by cell swelling, membrane pore formation, and the release of pro-inflammatory cytokines, playing a significant role in the hyperinflammatory response observed in DP.[13—16] Pyroptosis is triggered by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), involving the formation of the NLRP3 inflammasome complex. This complex, comprising NLRP3, pro-caspase-1, and apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), activates caspase-1. Activated caspase-1 then cleaves GSDMD and pro-IL-1β/18.[15] The N-terminal domain of cleaved GSDMD then forms pores in the cell membrane, facilitating the release of mature IL-1β and IL-18 and inducing an inflammatory response.[15,17] This process, observed in various oral cells including gingival fibroblasts and periodontal ligament fibroblasts.[18—24] In addition. elevated levels of NLRP3 inflammasome components have been found in periodontal cells exposed to high glucose or AGEs, conditions characteristic of diabetes.[25—27] Clinically, DP patients exhibit increased NLRP3 and ASC protein expression in their periodontal tissues, correlating with more severe inflammation.[28] The current body of evidence strongly suggests that inflammaging and pyroptosis play a regulatory role in diabetes-associated periodontitis.

In the search for therapeutic interventions targeting these pathological processes, Corylin, an isoflavone compound isolated from *Psoralea corylifolia L.*, has emerged as a promising candidate. This naturally occurring compound exhibits a remarkable array of biological activities, as antioxidant,[29,30] anti-inflammatory,[31—33] antidiabetic,[34] anti-obesity[35] and antimicrobial.[36] Of particular relevance to DP, recent studies have demonstrated Corylin's capacity to ameliorate cellular senescence[37] as well as NLRP3 inflammasome activation and reduce pyroptosis-associated markers.[31,38] Additionally, Corylin has shown promising effects in promoting wound healing and modulating osteoclast differentiation,[39,40] though its specific effects on DP and its underlying mechanism remain to be elucidated.

Given the intricate interplay between inflammaging and pyroptosis in DP pathogenesis, coupled with Corylin's demonstrated therapeutic properties, investigation of this compound's potential in treating DP represents a compelling research direction. This study aimed to evaluate the effects of Corylin on inflammaging and pyroptosis in an in vitro model of DP, potentially offering novel insights into therapeutic strategies for this challenging condition. Understanding these mechanisms may provide a foundation for the development of more effective treatments for patients suffering from this debilitating complication of diabetes.

## Materials and methods

### Cell culture

The study was approved by the Institutional Review Board at Chung Shan Medical University Hospital (CSMUH No: CS1-

22047). Primary human gingival fibroblasts (HGFs) were isolated from two healthy individuals undergoing crown lengthening procedures, utilizing a previously reported approach.[41] HGFs between the third and eighth passages were used in this study. Advanced glycation end-products (AGEs)-BSA were obtained from (BioVision, Milpitas, CA, USA), and Corylin was purchased from (Sigma Chemical Co, St. Louis, MO, USA). To investigate the impact of Corylin, HGFs were exposed to AGEs-BSA in the presence of Corylin at various concentrations for 24 h.

### Cell viability assay

To mimic the diabetic milieu in vitro, HGFs were cultured with AGEs. 10,000 cells/well were seeded onto 96-well plates and incubated for 24 h. Following pre-treatment with AGEs (500 μg/ml) for 24 h, Corylin was added at serial doses (10 and 20 μM) for a further 24 h. Cell viability was assessed using the MTT assay, and absorbance was measured at 570 nm. The proliferation rate of HGFs was calculated relative to the untreated control (0 μM Corylin).

### Flow cytometry

Flow cytometry was employed to analyze ROS production by measuring the fluorescence intensity of 2′,7′-dichlorofluorescein (DCF) in treated and non-treated HGFs stimulated with AGEs. The fluorescence of DCF and ethidium (ETH) was generated from the oxidation of 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA; Sigma–Aldrich) and dihydroethidium (DHE; Molecular Probes, Eugene, OR, USA), which are sensitive to $H_2O_2$/NO-based radicals and superoxide ($O_2^{\cdot-}$), respectively. Cells were incubated for 60 min at 37 °C with 10 μM DCFH-DA or DHE, then washed twice with PBS. Flow cytometry (Becton–Dickinson, San Jose, CA, USA) was used to detect ETH and DCF fluorescence in 10,000 cells, with excitation and emission wavelengths of 488 nm and 525 nm, respectively.

### Wound healing assay

Cells were seeded into 12-well plates and grown to approximately 80 % confluence. A sterile 200 μL pipette tip was used to create a scratch wound in the cell monolayer. Cell migration into the wound area was monitored and photographed at 0 and 24 h under a microscope.

### Western blot

The Western blot analysis was utilized following the previously described protocol.[42] Primary antibodies against senescence marker p16 were used. Bound antibodies were detected using enhanced chemiluminescence (ECL), and images were captured using an ImageQuant LAS 4000 Mini.

### Enzyme-linked immunosorbent assay (ELISA) analysis

IL-6 and IL-8 concentrations in cell culture supernatants were determined using ELISA kits, following the manufacturer's instructions. Absorbance was measured at 450 nm using a microplate reader. Each HGF sample was analyzed in triplicate.

### Senescence-associated beta-galactosidase (SA-β-gal) activity

Cellular senescence was measured by assessing SA-β-Gal activity using a Cellular Senescence Assay kit (BioVision), as described previously.[43] SA-β-Gal positive cells were visualized and counted under a microscope.

#### Quantitative RT-PCR (qRT-PCR)

Total RNA was extracted using Trizol reagent, and reverse transcription was performed using Superscript III first-strand synthesis technology. qRT-PCR was conducted using ABI StepOneTM Real-Time PCR Systems (Applies Biosystems, Waltham, MA, USA), with GAPDH serving as an internal control. Primer sequences (5′-3′) for pyroptosis markers were as follows using the gene database from National Center for Biotechnology Information (NCBI): Forward-CTGGGTCAGTTGTGGTGGAT and Reverse- ATGATCGCATGAGGGCTTGT for NLRP3; Forward- TCCGGTAGAGCAGCTTTGTT and Reverse- AGCTGGTCAGCTTCTACCTG for ASC; and Forward- CCAGCCCCTTCCAAAACTCT and Reverse- GTACAGGCCCTGCCAAAAAG for CASP1.[44]

### Statistical analysis

Each experiment was replicated three times. One-way analysis of variance (ANOVA) was used for statistical analysis, and Duncan's test was used to examine differences between treatment groups. A *P*-value less than 0.05 was considered statistically significant.

## Results

First, we assessed the potential cytotoxicity of Corylin on human gingival fibroblasts (HGFs). Our results revealed that Corylin, up to a concentration of 40 μM, had no significant effect on the cell proliferation rate (Fig. 1). To investigate Corylin's therapeutic potential, we exposed HGFs to advanced glycation end products (AGEs) to mimic the diabetic periodontal environment. As expected, AGE stimulation increased ROS production in HGFs. However, Corylin treatment effectively repressed ROS generation in a dose-dependent manner (Fig. 2). Given the critical role of fibroblasts in wound healing, we conducted a wound healing scratch assay to assess their migratory capacity. We found that the presence of AGEs impaired the wound healing ability of HGFs. Conversely, Corylin treatment reversed this impairment in a dose-dependent manner (Fig. 3).

To explore the mechanisms underlying Corylin's beneficial effects on wound healing, we investigated its impact on inflammaging and pyroptosis. AGEs markedly enhanced senescence activity in HGFs, as evidenced by increased SA-β-Gal staining and p16 expression. However, Corylin treatment effectively counteracted this AGE-induced senescence (Fig. 4). Furthermore, Corylin suppressed the AGE-elicited secretion of pro-inflammatory cytokines IL-6 (Fig. 5A) and IL-8 (Fig. 5B) in a dose-dependent manner,

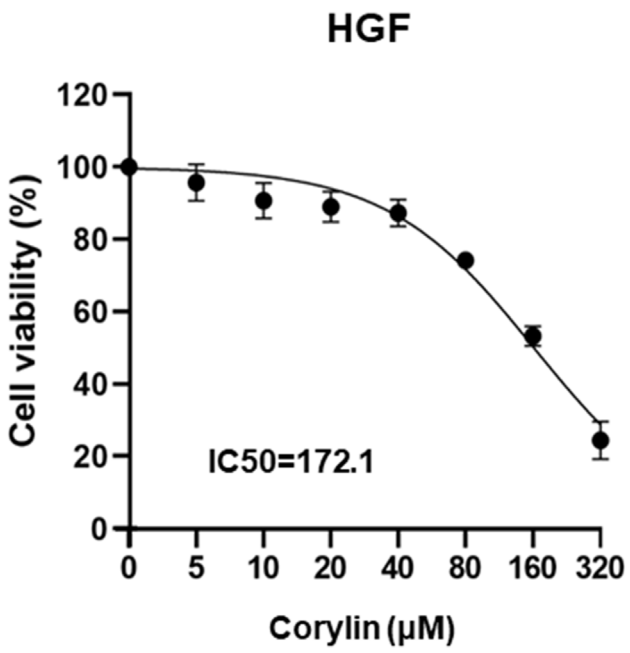


**Figure 1 Effects of Corylin on the cell proliferation rate in AGEs-treated HGFs** Corylin concentrations up till 40 μM did not significantly affect the cell proliferation rate in HGFs induced with AGEs. Data represent the mean ± SD.

indicating its anti-inflammaging potential. Finally, we examined the effect of Corylin on pyroptosis-related mRNA, including NLRP3, ASC, and caspase-1, in AGE-treated HGFs. Corylin effectively restored the expression of these pyroptosis markers, which were upregulated in AGE-stimulated cells (Fig. 6).

## Discussion

The accumulation of advanced glycation end products (AGEs) in hyperglycemia has been linked to an increased risk of diabetic periodontitis (DP). Recent research has implicated inflammaging and pyroptosis in the pathogenesis of DP. However, conventional DP treatments, such as mechanical debridement and antibiotics, primarily target the bacterial source and do not address the hyperinflammatory host immune response. Therefore, understanding the underlying mechanisms of DP and exploring alternative adjunct therapies that target the host immune response represents a promising avenue for improving treatment outcomes.

Our study found that AGEs increased oxidative stress in human gingival fibroblasts (HGFs), accelerated cell senescence, and promoted the secretion of cytokines IL-6 and IL-8, consistent with previous findings.[45,46] AGEs are well-known for their role in stimulating cellular senescence, which can lead to tissue malfunction and impaired regenerative capacity.[7] The mechanism underlying AGEs-induced senescence involves the induction of p21, a potent cyclin-dependent kinase inhibitor. Upon binding to their receptor (RAGE), AGEs sustain endoplasmic reticulum stress, leading to p21 activation and subsequent cell cycle inhibition, ultimately promoting premature aging or senescence.[47,48] This cellular senescence, coupled with a hyper-inflammatory state, contributes significantly to the perpetuation of inflammaging and the progression of DP.[10] Studies have shown increased expression of periodontal IL-6[49] and systemic IL-8[50] in patients with DP compared to those with periodontitis alone, further highlighting the role of AGEs in promoting inflammaging in the context of DP. However, administration of Corylin successfully suppressed the inflammaging induced by AGEs in HGFs in a dose-dependent manner. In agreement with an in vitro study on human umbilical vein endothelial cells, RNA sequencing data showed that Corylin ameliorates cellular senescence.[37]

In our study, AGEs significantly increased the expression of pyroptosis markers mRNA, including NLRP3, ASC, and pro-caspase 1. This aligns with previous findings where elevated levels of key pyroptosis cytokines were detected in the gingival crevicular fluid and tissues of DP patients.[28,51] These pyroptotic cytokines, particularly IL-1β and IL-18, stimulate matrix metalloproteinases (MMPs), leading to the degradation of connective tissue in the periodontium and contributing to tissue destruction in DP.[52] The severity of periodontal tissue destruction has been correlated with increased levels of NLRP3, caspase-1, and IL-18 in the gingival crevicular fluid of DP patients.[53]

Importantly, the addition of Corylin dramatically reversed the upregulation of these pyroptosis markers,

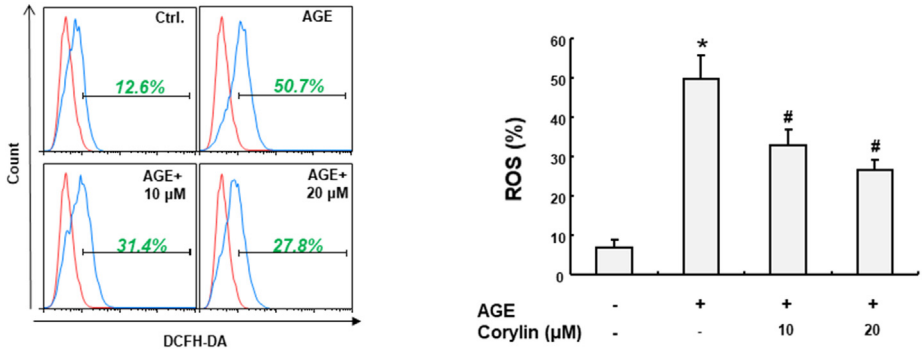


**Figure 2 Effects of Corylin on the production of ROS in the AGEs-treated HGFs** The effect of Corylin on ROS production was evaluated using DCFH-DA. AGEs-treated HGFs exhibited significantly elevated ROS level, which was mitigated by Corylin in a dose-dependent fashion. Data represent the mean ± SD. *$P < 0.05$ indicates a significant difference compared to the control group, and #$P < 0.05$ indicates a significant difference compared to the AGEs-treated group.

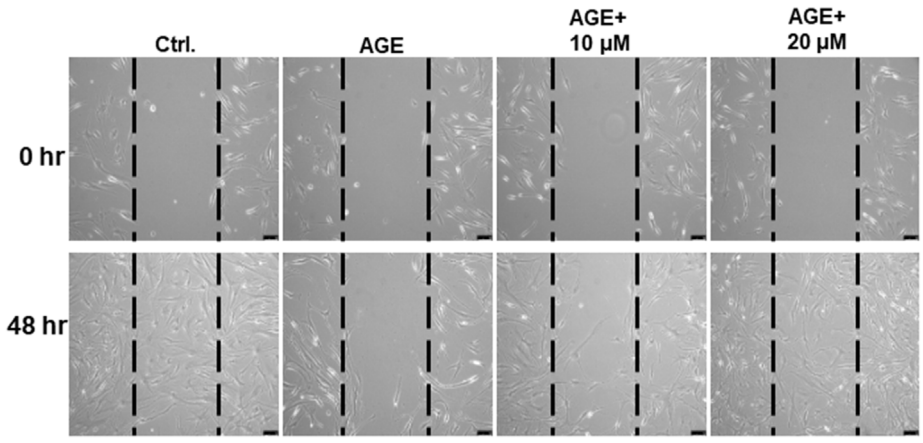


**Figure 3 Effects of Corylin on wound healing in the AGEs-stimulated HGFs** Wound healing, which was markedly impaired in AGEs-stimulated HGFs, was restored by Corylin treatment in a dose-dependent manner.

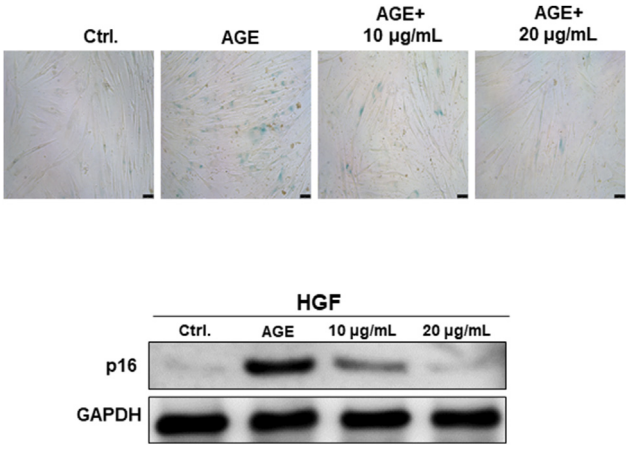


**Figure 4 Effects of Corylin on the cell senescence activity in the AGEs-treated HGFs** Indicators of cellular senescence, including SA-β-Gal staining (upper panel) and p16 expression (lower panel), were elevated in AGEs-treated HGFs. Corylin treatment reversed these senescence markers.

indicating its anti-pyroptotic activity. Corylin has demonstrated potent anti-pyroptotic effects in several studies. Huang et al. showed that Corylin inhibits NLRP3 inflammasome activation and reduces IL-1β production in microglia, indicating its ability to suppress pyroptosis and inflammation.[31] Similarly, Corylin effectively reduced pyroptosis-associated caspase-3 and IL-1β levels in a mouse model of liver fibrosis, further highlighting its anti-pyroptotic properties.[38] Given its ability to modulate both inflammaging and pyroptosis, further investigation into whether Corylin influences cellular migration, extracellular matrix production, or angiogenesis could provide deeper insights into its potential role in promoting wound healing in DP.

Taken together, this study demonstrates that Corylin may have therapeutic potential in diabetic periodontitis models by acting against AGE-induced inflammaging and pyroptosis. We have shown that Corylin promotes wound healing in human gingival fibroblasts by inhibiting cellular senescence and its associated secretory phenotype (SASP), including IL-6 and IL-8, as well as pyroptosis. Given its anti-inflammaging and anti-pyroptosis properties, Corylin could

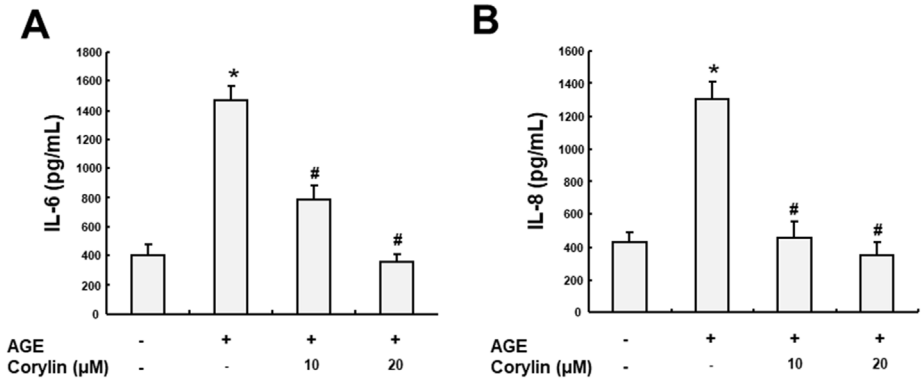


**Figure 5 Effects of Corylin on the production of pro-inflammatory cytokines in HGFs treated with AGEs** The secretion of IL-6 (A) and IL-8 (B) was evaluated in AGEs-treated HGFs after treatment with 10 and 20 μM Corylin. Results are expressed as mean ± SD. *$P < 0.05$ indicates a significant difference compared to the control group, and #$P < 0.05$ indicates a significant difference compared to the AGEs-treated group.

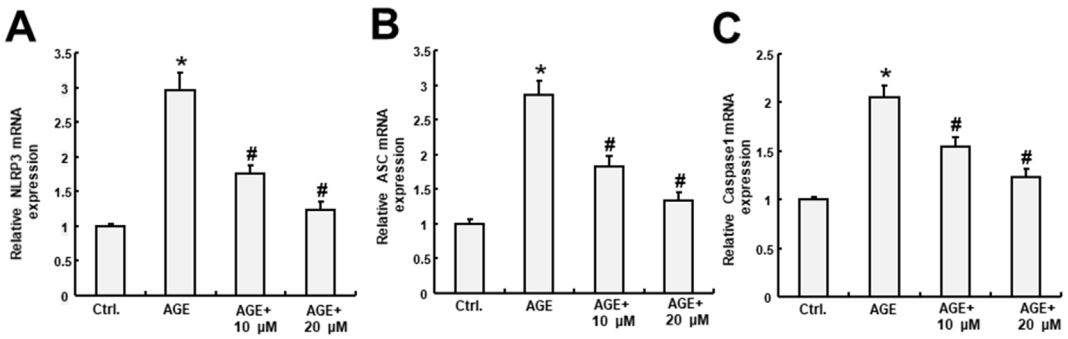


**Figure 6** **Impact of Corylin on pyroptosis-related marker genes in HGF treated with AGEs** qRT-PCR analysis was used to determine the effect of Corylin on the expression of pyroptosis-related marker genes, including NLRP3 (A), ASC (B), and caspase-1 (C), in AGEs-treated HGFs. Data are shown as mean ± SD, with $*P < 0.05$ representing a significant difference compared to the control group and $\#P < 0.05$ representing a significant difference compared to the AGEs-treated group.

complement existing therapies like scaling and root planing or systemic antibiotics, offering a more comprehensive approach to managing periodontitis in diabetic patients.

## Declaration of competing interest

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

## Acknowledgments

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