Original Article

Advanced glycation end products (AGEs) downregulate the miR-4429/PTEN axis to promote apoptosis of fibroblasts in pelvic organ prolapse

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Background: Pelvic organ prolapse (POP) is a common degenerative disease among females. We previously reported that advanced glycation end products (AGEs), compounds derived from nonenzymatic glycoxidation reactions, accumulated in the human vaginal wall and impaired the function of fibroblasts in the pathogenesis of POP. This study investigated the apoptosis induced by AGEs in human uterosacral ligament fibroblasts and the underlying mechanism.

Methods: Human uterosacral ligament fibroblasts were cultured and identified. Quantitative real-time polymerase chain reaction (qRT-PCR) analysis was performed to identify the expression of miR-4429, phosphatase and tensin homolog (PTEN), and caspase-3. Flow cytometric analysis was applied to detect the apoptosis rate of fibroblasts. Dual-luciferase reporter assay was performed to verify the relationship between miR-4429 and PTEN. The overexpression of miR-4429 and the inhibition of PTEN were achieved by cell transfections. Western blot analysis was used to detect the protein levels of PTEN, phosphoinositide 3-kinase (PI3K), and protein kinase B (Akt).

Results: The AGEs promoted fibroblast apoptosis both in the POP and the non-POP groups. The expression of PTEN increased in fibroblasts from the POP group or fibroblasts treated with AGEs. It was confirmed that miR-4429 interacted with PTEN messenger RNA (mRNA), and the expression level of miR-4429 was reduced in fibroblasts from the POP group or fibroblasts treated with AGEs. Further, overexpression of miR-4429 alleviated increased PTEN expression and fibroblast apoptosis induced by AGEs. Similarly, inhibition of PTEN expression alleviated increased fibroblast apoptosis induced by AGEs. In addition, the protein expressions of PI3K and phosphorylated Akt were reduced in fibroblasts exposed to AGEs.

Conclusions: We proposed that AGEs induced fibroblast apoptosis by regulating the miR-4429/PTEN/PI3K/Akt pathway in POP. Our results revealed a novel mechanism by which AGEs contributed to the molecular pathological alteration in POP.

Keywords: Pelvic organ prolapse (POP); advanced glycation end products (AGEs); cell apoptosis; phosphatase and tensin homolog (PTEN); miR-4429

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Introduction

Pelvic organ prolapse (POP) is defined as protrusions of the pelvic organs into or out of the vaginal canal; it has a relatively high prevalence worldwide and markedly diminishes the quality of life of older women (1). The prevalence of POP based on diagnosis according to symptoms is 3–6%; however, the prevalence according to physical examination is up to 50% (2). The most recent report has stated that the prevalence of symptomatic POP in China is 9.6% among women over 20 years old (3). It is a multifactorial disease, and the specific pathogenesis remains to be elucidated, which has impeded the development of treatment and prevention. Research is urgently needed to define the molecular process in the pathogenesis of POP.

Advanced glycation end products (AGEs) are produced by the nonenzymatic modifications of macromolecules, including proteins, lipids, and nucleic acids. The endogenous formation of AGEs is a long-term physiological process, but the process accelerates if glucose concentration or reactive oxygen species (ROS) are elevated (4,5). A previous study showed that the level of AGEs in prolapsed tissues was higher and the collagen I level was lower than that of control tissues (6). Further, we reported that AGEs accelerated the degeneration of collagen I by upregulating the expression of matrix metallopeptidase-1 (MMP-1) and by activating the mitogen-activated protein kinase (MAPK)/nuclear factor-kappa B (NF-Kb) pathway in human vaginal fibroblasts (7). In addition to results from other previous studies (8,9), our previous findings support the notion that the increased level of AGEs in POP tissues could contribute to the pathogenesis of POP. However, the molecular mechanism of AGEs in the pathophysiology of POP remains to be further explored.

Fibroblasts regulate the processes of extracellular matrix (ECM) formation and remodeling (10,11), and cellular functional alterations of fibroblasts have been the research focus in exploring POP pathogenesis. As the primary functional cell type in pelvic supportive tissues, fibroblasts exhibit impaired behaviors and functions in prolapsed tissues, resulting in decreased collagen fibers and insufficient mechanical support to the pelvic organs (12-15). For this reason, many studies have tried to find new therapeutic avenues for POP by promoting the functions of fibroblasts (16,17). Several studies have reported increased fibroblast apoptosis in POP (18,19), but few studies have focused on the underlying mechanism. The AGEs have been investigated mainly in the pathophysiology of diabetes mellitus (20); few studies have reported the effects and the related mechanisms of AGEs on fibroblasts in POP. The increased level of AGEs in pelvic floor supportive tissues in patients with POP suggests that exploring the molecular processes underlying AGEs-induced functional alterations of fibroblasts is critical to understanding POP pathophysiology and developing novel treatments by inhibiting AGEs formation.

Phosphatase and tensin homolog (PTEN) has been investigated as a classical tumor suppressor because it antagonizes phosphoinositide 3-kinase (PI3K) (21). This inactivates downstream protein kinases, most notably protein kinase B (Akt), which influences downstream proteins and alters cellular functions (22). It has been investigated as a regulator of cell apoptosis (23), and PTEN has been found to induce apoptosis by antagonizing the PI3K-Akt pathway in physiologic and pathologic conditions (24-26). Studies have also reported that the expression of PTEN could be regulated by microRNAs (miRNAs) (27,28). In the present study, we searched for miRNAs that potentially target PTEN in databases and found that miR-4429 was the regulator of PTEN in AGEs-induced fibroblast apoptosis. We chose miR-4429 for further investigation because previous studies had reported that miR-4429 regulated cell apoptosis and prevented cancer progression (29,30).

Our investigation aimed to explore the molecular mechanisms underlying the phenomenon that AGEs promoted apoptosis of uterosacral ligament fibroblasts. We reported that fibroblasts from the POP group exhibited a higher apoptosis rate than those from the non-POP group. Considering the accumulated AGEs in POP tissues, we treated fibroblasts with AGEs *in vitro* and found increased apoptosis rates in POP and non-POP groups. Further, we detected the expression of PTEN and miR-4429 in POP and non-POP groups with or without AGEs treatment. Then, we analyzed the apoptosis rates of fibroblasts by overexpressing miR-4429 or silencing the expression of PTEN. These results demonstrated that AGEs promoted fibroblast apoptosis by influencing the miR-4429/PTEN/PI3K/Akt pathway. This study provides evidence for the molecular effects of accumulated AGEs in POP. We present the following article in accordance with the Material Design Analysis Reporting (MDAR) reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-628/rc).

Table 1 Patient characteristics

Characteristic	POP (n=10)	Non-POP (n=10)	P value
Age, mean ± SD	61.4±5.70	53.6±8.62	NS‡
BMI, mean ± SD	23.83±6.02	23.9±3.62	NS†
Parity, median [range]	1 [1–3]	1 [1–2]	NS‡
Menopause, n (%)	8 (80.0)	3 (30.0)	NS§
POP stage, median [range]	3 [3–4]	0	<0.05‡

†, *t*-test; ‡, Mann-Whitney test; §, Fisher's exact test. POP, pelvic organ prolapse; SD, standard deviation; NS, not significant; BMI, body mass index.

Methods

Patients and sample collection

Tissue samples were obtained from patients who had POP or other diseases and required a hysterectomy at the Obstetrics and Gynecology Hospital of Fudan University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University (No. 2021-234), and informed consent was provided by all participants. A total of 10 participants with stage III or IV POP (according to the pelvic organ prolapsed quantification; POP-Q) and 10 participants who underwent hysterectomy for diseases including hysteromyoma, adenomyosis, and high-grade squamous intraepithelial lesion, were respectively distributed to the POP group and the non-POP group. Donors did not have histories of pelvic operations, pelvic inflammation, serious systemic diseases, and malignant diseases. The clinical characteristics, including age, body mass index, parity, and menopausal status, were matched between the two groups (*Table 1*).

A 0.5 cm^2 piece of uterosacral ligament tissue was collected from the surgical margin of the free uterus after hysterectomy. The sample tissues were kept under aseptic conditions and prepared for cell culture.

Cell culture

Human uterosacral ligament fibroblasts were isolated and cultured as a previously indicated (7). Fresh uterosacral ligament specimens were washed 3 times with phosphate-buffered saline (PBS) (containing 100 IU/mL streptomycin-penicillin-amphotericin B) (Genom, Jiaxing, China) and cut into small pieces. The fragments of tissues were digested at 37 ℃ for 2 hours in PBS containing 2% collagenase type I (Sigma-Aldrich, St. Louis, MO, USA) until the tissue blocks disappeared. After separation by centrifuge, the cells were resuspended and cultured in Dulbecco's modified Eagle medium (DMEM) nutrient solution with 10% fetal bovine serum (FBS) and 100 IU/mL streptomycin-penicillin-amphotericin B at 37 ℃ in a 5% CO_2 atmosphere. The medium was replaced by a fresh complete culture medium every 2–3 days, and cells were passaged when they reached an 80% confluence.

Cell identification

The fibroblasts were seeded on coverslips prepared in 6-well plates. After 12 hours of culture, cells grew on the glass coverslips. Then, 4% paraformaldehyde (Servicebio, Wuhan, China) was added to the 6-well plates for cell fixation. For cell immunochemistry, drops of 3% bovine serum albumin (BSA) were added onto the coverslips and kept at room temperature for 30 minutes. The liquid was discarded. The cells were then incubated with the diluted primary antibodies at 4 ℃ for more than 10 hours and with the secondary antibody (G1213, Servicebio) for 1 hour at room temperature. The primary antibodies included anti-Cytokeratin antibody (GB11197, Servicebio) and anti-Vimentin antibody [5741, Cell Signaling Technology (CST), Danvers, MA, USA]. After being washed 3 times in PBS, slides were stained with 3,3'-diaminobenzidine (DAB) color developing solution (Servicebio) and then with hematoxylin stain solution (Servicebio) to counterstain the nucleus. Images were observed under a light microscope (Olympus, Tokyo, Japan).

Cell treatments

The AGEs used in the study were diluted with 10 mg/mL BSA-AGE, which was purchased from Abcam (Cambridge, MA, USA). The AGE-modified BSA was produced by reacting BSA with glycolaldehyde under sterile conditions, followed by extensive dialysis and purification steps. Fluorescence of AGEs was confirmed by fluorescence spectrophotometry with Ex./Em. =370/440 nm. Glycated BSA showed a 7,000% increase in fluorescence compared to control BSA. The 3–5 passage fibroblasts were cultured and serum-starved for 12 hours. Then, fibroblasts from both the POP and non-POP groups were exposed to 50 μg/mL BSA (Sigma-Aldrich) or 50 μg/mL BSA-AGE for 24 hours, according to our previous report (7).

Table 2 All primers and siRNA sequences used in this study

Name	Sequence (5' to 3')
Caspase-3 forward	CCAAAGATCATACATGGAAGCG
Caspase-3 reverse	CTGAATGTTTCCCTGAGGTTTG
PTEN forward	TTTTGAAGACCATAACCCAC
PTEN reverse	TATCATTACACCAGTTCGTC
snRNA U6	CCTGCTTCGGCAGCACA
miR-23b-3p	CACATTGCCAGGGATTACCA
miR-542	GGGCGTGACAGATTGATAACTG
miR-4429	CAAAAGCTGGGCTGAGAGG
miR-216b-5p	AAATCTCTCCAGGCAAATGTGA
miR-4429 mimics	AAAAGCUGGGCUGAGAGGCG
mimics-NC	UCACAACCUCCUAGAAAGAGUAGA
PTEN-siRNA 1	AGCUAAAGGUGAAGAUAUATT
PTEN-siRNA 2	CAGAUAAUGACAAGGAAUATT
PTEN-siRNA 3	CAAAUAAAGACAAAGCCAATT

siRNA, small interfering RNA; PTEN, phosphatase and tensin homolog; snRNA U6, small nuclear RNA U6; NC, negative control.

Quantitative polymerase chain reaction

The total RNA of cultured cells was extracted using an RNA purification kit (EZBioscience, Roseville, CA, USA). The extracted RNA was converted into complementary DNA (cDNA) through reverse transcription using a cDNA synthesis kit (TaKaRa, Tokyo, Japan). The expressions of target genes at the messenger RNA (mRNA) level were measured through a real-time polymerase chain reaction (RT-PCR) analysis using the SYBR® Green qPCR master mix (TaKaRa). The miRNA cDNAs were synthesized using a microRNA reverse transcription kit (EZBioscience), and miRNA were relatively quantified using a quantitative (q) PCR mix for microRNA (EZBioscience). The qPCR of miRNAs and mRNA were done by the QuantStudio 6 and 7 Flex Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA). The reference genes for mRNA and miRNA were respectively glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6. Moreover, results were normalized by the $2^{-\Delta\Delta CT}$ method. The primer sequences in this study are listed in *Table 2*.

Flow cytometric analysis

The apoptosis of fibroblasts was detected using a fluorescein isothiocyanate (FITC) Annexin V/propidium iodide (PI) kit [Becton, Dickinson, and Company (BD) Biosciences, San Jose, CA, USA] with flow cytometric analysis. Fibroblasts were detached and washed with PBS supplemented with 2% FBS after the indicated treatment. Fibroblasts were simultaneously stained with FITC-Annexin V and PI for 15 and 5 minutes in the dark at room temperature. After being washed twice, cells were resuspended in 300 mL buffer and passed through a 100-mm nylon sieve. A flow cytometry (BD, Franklin Lakes, NJ, USA) was used to analyze the cell samples, by which the normal cells (FITC–/PI–), early to mid-apoptotic cells (FITC+/PI–), and late apoptotic cells (FITC+/PI+) were distinguished. Data were analyzed using FlowJo version X.0.7 (FlowJo, BD, Ashland, OR, USA). Positive cells were identified according to the fluorescence values of the unstained cells, which were set as negative controls (NC).

Transfection of miR-4429 mimics and PTEN-siRNA

Fibroblasts were seeded in 6-well culture plates with the optimum density in DMEM solution with 10% FBS. Once achieving 50–60% confluence, the medium was replaced by 1.5 mL DMEM per well without FBS. Then, miR-4429 mimics or NC mimics were diluted by Opti-MEM (GIBCO BRL, Grand Island, NY, USA) and mixed with diluted Lipofectamine 2000 (Thermo Fisher Scientific, USA) (5 mL lipo2000 in 250 mL Opti-MEM). The mixture was carefully transferred to DMEM solutions without FBS to achieve a final concentration of mimics of 200 nM. The transfection method of small interfering (si)PTEN was the same as miR-4429 mimics, except that the final concentration of siPTEN was 50 nM. After 6 hours of incubation, the culture medium was changed into DMEM with 10% FBS and continued to culture for 24–48 hours. The sequences of miR-4429 mimics, mimics-NC, and PTEN-siRNAs (*Table 2*) were synthesized by the Public Protein/Plasmid Library (Nanjing, China).

miRNAs screening

To collect miRNAs that potentially interacted with PTEN, we searched the following miRNAs databases: starBase (starbase.sysu.edu.cn/starbase2/), TargetScan (www.targetscan.org/vert_71/), miRDB (mirdb.org), and miRWalk (miRWalk.umm.uni-heidelberg.de). A total of 376 miRNAs were selected from miRDB, 104 from starBase, 1,165 from TargetScan, and 1,589 from miRWalk (Table S1). Then, 24

miRNAs were screened out by taking the intersection of the 4 datasets (Table S2).

Western blot analysis

Protein expressions were semi-quantitatively analyzed by western blot. Radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China) was added to cell cultures, and proteins were collected to be prepared for gel electrophoresis. The loading buffer and the reagents for preparing gels were purchased from Beyotime. Then, proteins were isolated by gel electrophoresis and transferred to the polyvinylidene fluoride (PVDF) membranes, which were blocked by being incubated with 5% BSA (Sigma-Aldrich) or 5% nonfat-dried milk/tris-buffered saline with Tween 20 (TBST) for 1 hour at room temperature. Successively, PVDF membranes were gently shaken with the primary antibodies at 4 ℃ for more than 10 hours and with the secondary antibody for 1 hour at room temperature. The antibodies included anti-pan-Akt antibody, anti-phosphorylated Akt (S473) antibody (CST), anti-PI3K antibody, and anti-GAPDH antibody (Abcam). After washing the membranes 3 times with TBST in the interval of 2 incubations, the membranes were incubated with the chemiluminescence reagent (Merck Millipore, Billerica, MA, USA).

Luciferase reporter assay

A DNA fragment of the miR-4429 potential binding site in the 3'untranslated region (3'UTR) of PTEN was cloned into a psiCHECK-2 vector (Hanbio Biotechnology, Shanghai, China), named PTEN-wild-type (PTEN-WT). A 500 bp mutational type of all the 5 miR-4429 potential binding sites in 3'UTR of PTEN was cloned into a psiCHECK-2 vector, named PTEN-mutant (PTEN-Mut). A 500 bp DNA fragment of the miR-4429 potential binding site in 3'UTR of PTEN was cloned in a psiCHECK-2 vector, named PTEN-mutant1 (PTEN-Mut1). The 293T cell line was purchased from the Shanghai Branch of the Chinese Academy of Science. Cells were transferred into a 96-well plate and prepared for transfection once achieving 50–70% confluence. Then, 0.16 μg plasmid, 5 pmol miR-4429 mimics or NC mimics, and transfection reagent (Hanbio Biotechnology) were mixed and added to each well. After 48 hours of incubation, cells were collected, and the luciferase activities of each group were detected by a Dual-Luciferase Reporter Assay kit (Promega, Madison, WI, USA).

Statistical analysis

Data were presented as the mean ± standard deviation (SD). The student's *t*-test was used to determine the significant difference between 2 groups when the data were normally distributed with equal SDs. The Mann-Whitney test was used for the 2-group comparison when the data were not normally distributed. Data were subjected to analysis of variance (ANOVA) when determining the significant difference between 3 or more groups, and the Tukey test was used to separate the means. Differences between groups were considered statistically significant when $P<0.05$. All tests involved in the study were performed by the GraphPad Prism software (version 8.0.2; GraphPad Software Inc., San Diego, CA, USA).

Results

AGEs promoted fibroblast apoptosis in the POP and the non-POP groups

Primary cultured fibroblasts were identified by the positive expression of vimentin and the negative expression of keratin (*Figure 1*). The apoptosis rate was higher in fibroblasts from the POP group than in the non-POP group (*Figure 2A*). An increased gene expression of caspase-3 was observed in the POP group compared with the non-POP group (*Figure 2B*). The apoptosis rate was significantly increased when fibroblasts from the non-POP group were treated with AGEs compared with the untreated cells (*Figure 2C*). To further verify that the increase of fibroblast apoptosis in POP and AGEs promote apoptosis of fibroblasts, the mRNA expression of caspase-3 was relatively quantified. The relative expression of caspase-3 was upregulated in non-POP fibroblasts treated with AGEs compared to those untreated cells (*Figure 2D*). Similarly, the apoptosis rate was increased significantly when fibroblasts from the POP group were treated with AGEs compared with the untreated cells (*Figure 2E*). Further, the expression of caspase-3 was upregulated in POP fibroblasts treated with AGEs compared to those untreated cells (*Figure 2F*).

AGEs upregulated the expression of PTEN in fibroblasts from the POP and the non-POP groups

The mRNA expression level (*Figure 3A*) and the protein expression level of PTEN (*Figure 3B*) were higher in fibroblasts from the POP group than in the non-POP group. In fibroblasts from the non-POP groups, the mRNA

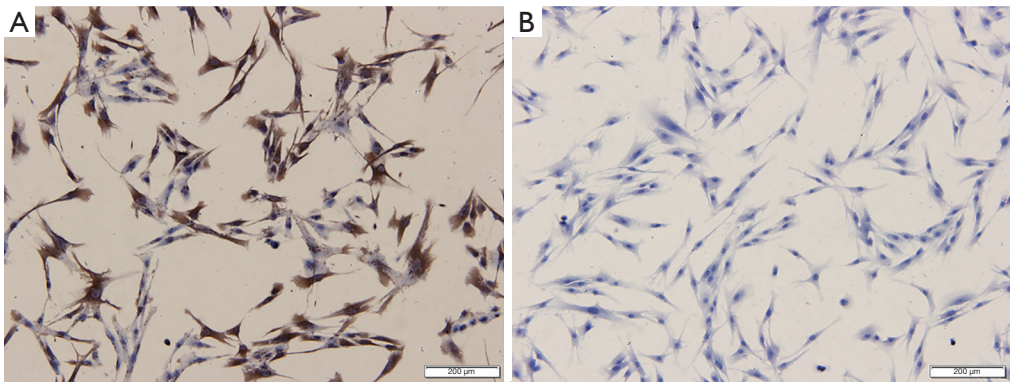

Figure 1 Identification of the primary cultured fibroblasts. (A) The immunocytochemical staining of vimentin showed a positive expression in the primary cultured fibroblasts. (B) The immunocytochemical staining of keratin showed a negative expression in the primary cultured fibroblasts. Scale bar: 200 μm.

expression level (*Figure 3C*) and the protein expression level of PTEN (*Figure 3D*) were upregulated when treated with AGEs. Likewise, in fibroblasts from the POP groups, the mRNA expression level (*Figure 3E*) and the protein expression level of PTEN (*Figure 3F*) were upregulated when treated with AGEs. Further, the western blot analysis demonstrated a reduction in the protein level of PI3K and phosphorylated Akt in fibroblasts treated by AGEs (*Figure 3G*), indicating that AGEs inhibited the PI3K/Akt pathway.

MiR-4429 directly bound to PTEN and inhibited the expression of PTEN

To further investigate the mechanism of AGE upregulating the expression of PTEN, we found 24 potential miRNAs that had binding sites on the 3'UTR of PTEN by taking the intersection of 4 recognized online databases (*Figure 4A*). The miRNAs analyzed in the study can be found in Tables S1,S2. Among the 24 potential miRNAs, the expression of miR-542, miR-4429, miR-216, and miR-23b was verified by qPCR, and the down-regulation effect of AGEs on the expression of miR-4429 was the most significant among the 4 miRNAs (*Figure 4B*).

The luciferase activity of the PTEN-WT reporter was lower in the miR-4429 mimics group than in the NC mimics group. The luciferase activity of the PTEN-Mut 1 reporter was lower in the miR-4429 mimics group than that in the NC mimics group, but it was higher in the miR-4429 mimics group than that in the PTEN-WT + miR-4429 mimics group. Further, there was no difference in luciferase activities of PTEN-Mut reporter between the miR-4429 mimics group, and the NC mimics group (*Figure 4C*). These results confirmed that miR-4429 could bind to the 3'UTR of PTEN and downregulate the expression of PTEN, but the binding site shown in *Figure 3C* was not the only binding site between miR-4429 and mRNA of PTEN.

The western blotting analysis showed that overexpression of miR-4429 in fibroblasts reduced the protein expression of PTEN (*Figure 4D*). The AGEs treatment on fibroblasts increased the protein expression of PTEN, which could be attenuated by overexpression of miR-4429 in fibroblasts (*Figure 4D*). These results suggested that miR-4429 inhibited the expression of PTEN, and AGEs upregulated the expression of PTEN by miR-4429.

AGEs reduced the expression of miR-4429 both in the non-POP and the POP groups

The expressions of miR-4429 were measured in 10 POP and 10 non-POP-derived uterosacral ligament fibroblasts, and the expression level was lower in the POP group than in the non-POP group (*Figure 5A*). Following the treatment of AGEs, fibroblasts exhibited a reduced miR-4429 expression in the POP (*Figure 5B*) and the non-POP (*Figure 5C*) groups compared with the control cells treated with BSA.

AGEs promoted fibroblast apoptosis by downregulating the miR-4429/PTEN axis

In light of the reduced expression of miR-4429 and the increased expression of PTEN in fibroblasts treated with

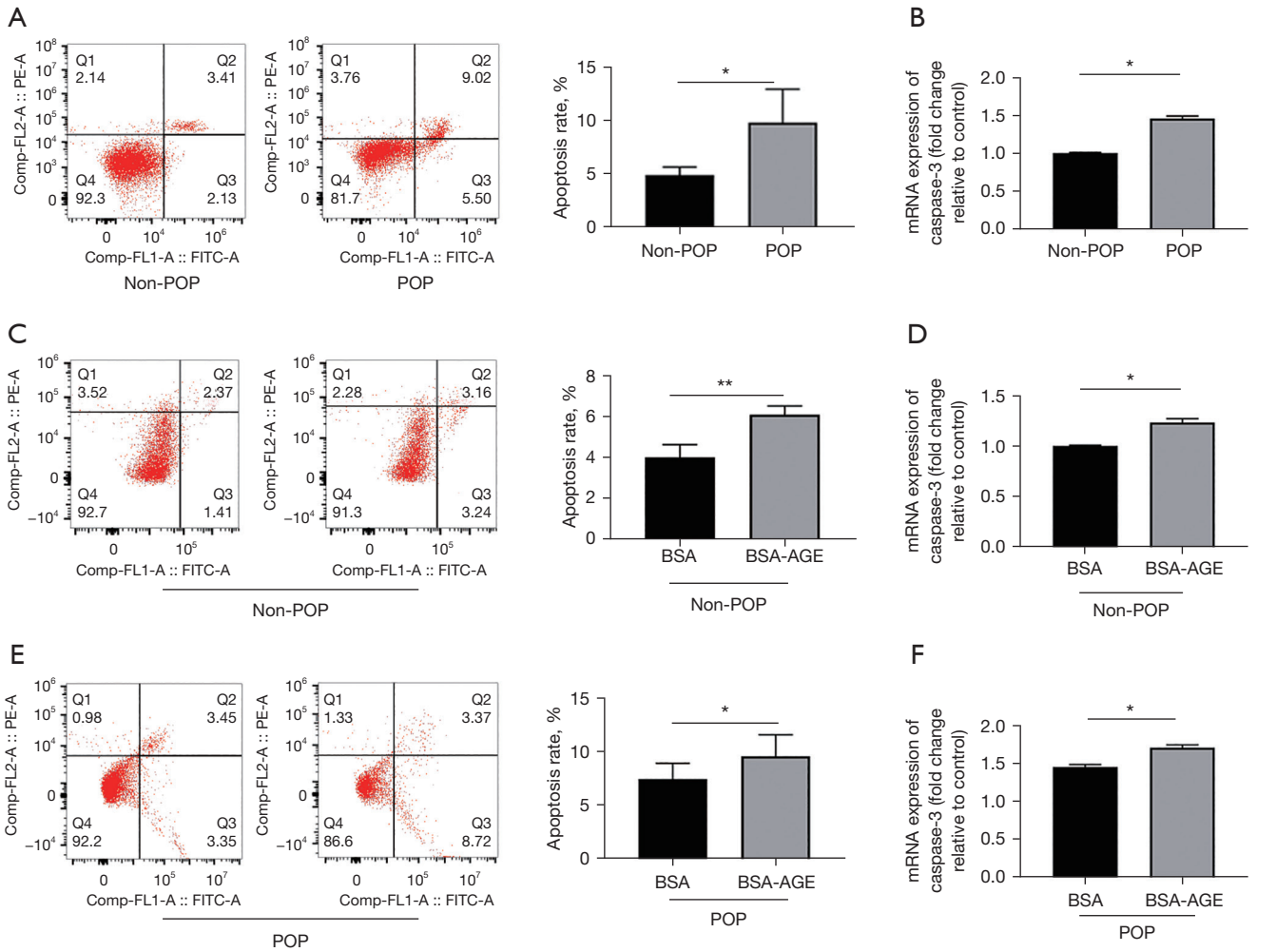

Figure 2 AGEs promoted fibroblast apoptosis in the non-POP and POP groups. (A) Cell apoptosis was analyzed by flow cytometry, and the cell apoptosis rate was higher in the POP group than in the non-POP group. (B) The mRNA expression of caspase-3 in fibroblasts from the non-POP and the POP groups. (C) Flow cytometry analysis of fibroblast apoptosis in the non-POP group and cell apoptosis rate was higher in cells treated by BSA-AGE than in cells treated by BSA. (D) The mRNA expression of caspase-3 in fibroblasts from the non-POP group, under treatment of BSA or BSA-AGE. (E) Flow cytometry analysis of fibroblast apoptosis in the POP group and cell apoptosis rate was higher in cells treated by BSA-AGE than in control cells. (F) The mRNA expression of caspase-3 in fibroblasts from the POP group, under treatment of BSA or BSA-AGE. Error bars represent mean ± SD of 3 independent experiments. *, P<0.05; **, P<0.01. FITC-A, fluorescein isothiocyanate-area; PE-A, phycoerythrin-area; POP, pelvic organ prolapse; mRNA, messenger RNA; BSA, bovine serum albumin; AGEs, advanced glycation end products; SD, standard deviation.

AGEs, we then verified that AGEs promoted fibroblast apoptosis by downregulating the miR-4429/PTEN axis. The results showed that cells transfected with siPTEN had a reduced protein level of PTEN (*Figure 6A*), indicating that the cell transfection had succeeded. The expression of miR-4429 was not influenced by the cell transfection with siPTEN (*Figure 6B*). The apoptosis analysis revealed that overexpression of miR-4429 decreased the fibroblast apoptosis rate and inhibited the apoptosis-promoting effect of AGEs on fibroblasts (*Figure 6C*). In the same way, transfection of siPTEN decreased the fibroblast apoptosis rate and inhibited the apoptosis-promoting effect of AGEs on fibroblasts (*Figure 6D*). These results suggested that AGEs promoted fibroblast apoptosis by downregulating the expression of miR-4429 and upregulating the expression of PTEN. To further verify the results, the expression of

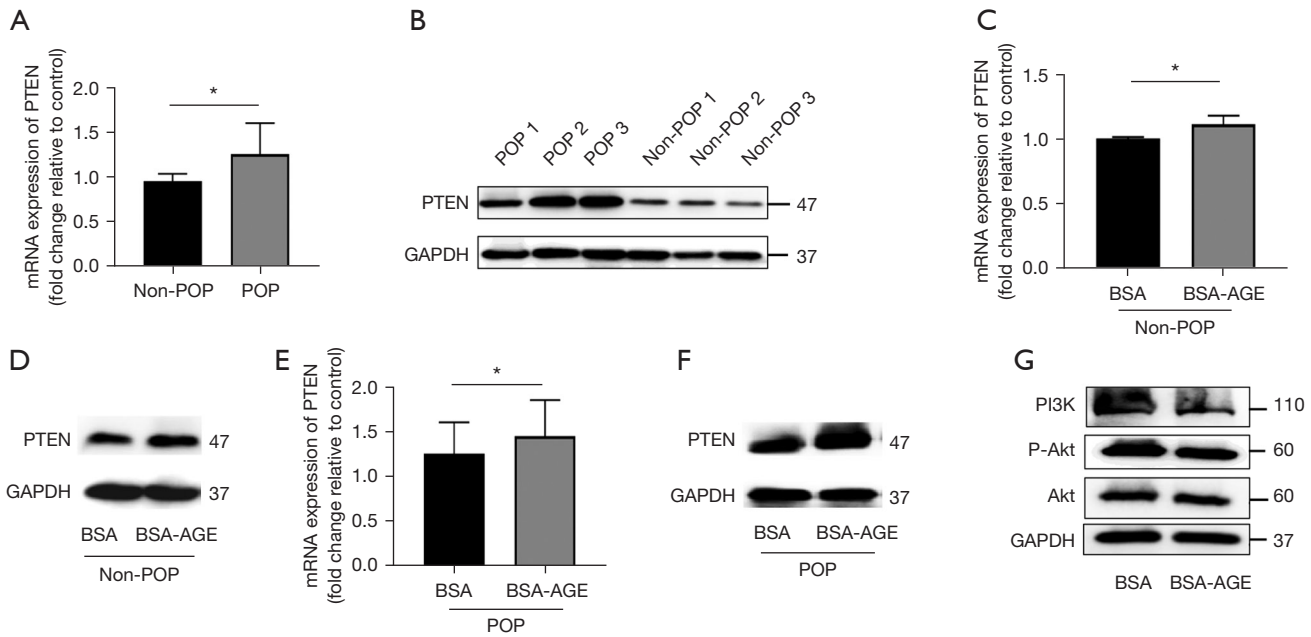

Figure 3 AGEs upregulated the expression of PTEN in fibroblasts from the non-POP and POP groups. (A,B) The mRNA and protein expressions of PTEN in POP and non-POP fibroblasts. (C,D) The mRNA and protein expression of PTEN in non-POP fibroblasts treated with BSA or BSA-AGE. (E,F) The mRNA and protein expression of PTEN in POP fibroblasts treated with BSA or BSA-AGE. (G) The protein expression of PI3K, phosphorylated Akt and Akt in POP fibroblasts treated by BSA or BSA-AGE. Error bars represent the mean ± SD of 3 independent experiments. *, P<0.05. POP, pelvic organ prolapse; mRNA, messenger RNA; PTEN, phosphatase and tensin homolog; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; BSA, bovine serum albumin; AGE, advanced glycation end products; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; P-Akt, phosphorylated Akt; SD, standard deviation.

apoptosis-related gene caspase-3 was detected by qPCR. Further, we found that the overexpression of miR-4429 could reduce the elevated expression of caspase-3 induced by AGEs on fibroblasts (*Figure 6E*). Similarly, transfection of siPTEN could reduce the elevated expression of caspase-3 induced by AGEs on fibroblasts (*Figure 6F*).

Discussion

This study demonstrated that AGEs promoted uterosacral ligament fibroblast apoptosis by downregulating miR-4429 which interacted with PTEN mRNA to inhibit the protein expression. In addition, we speculated that the increased PTEN induced by AGEs might promote cell apoptosis by suppressing the function of the PI3K/Akt pathway. The study revealed a possible mechanism through which AGEs induced fibroblast apoptosis in POP (*Figure* 7). Our findings provide evidence that the accumulation of AGEs contributes to the development of POP; AGEs could be a latent treatment point of future therapy for POP.

In this study, we verified our previous conclusion that the content of AGEs was increased in prolapse tissues compared to controls (Figure S1). The methods can be found in the Appendix 1. Although studies had shown that AGEs accumulated in prolapse tissues (8,9), the cause of this phenomenon was unknown. Apart from the hyperglycemic environment, the formation process of AGEs also accelerates under chronic inflammation or oxidative stress conditions (31,32). Previous studies have reported that ROS increase in POP (33,34), interfering with multiple cellular processes and favoring POP development. Thus, we speculate that the high level of AGEs in the prolapse tissues could result from increased ROS in POP because the formation of AGEs accelerates under the elevated ROS level in prolapse tissues (35).

Our previous results showed that AGEs increased the apoptosis rate in fibroblasts from the prolapsed vaginal wall (36), but the underlying mechanism was not studied. In the present study, we found that the cell apoptosis rate and caspase-3 (37) expression of fibroblasts from the POP

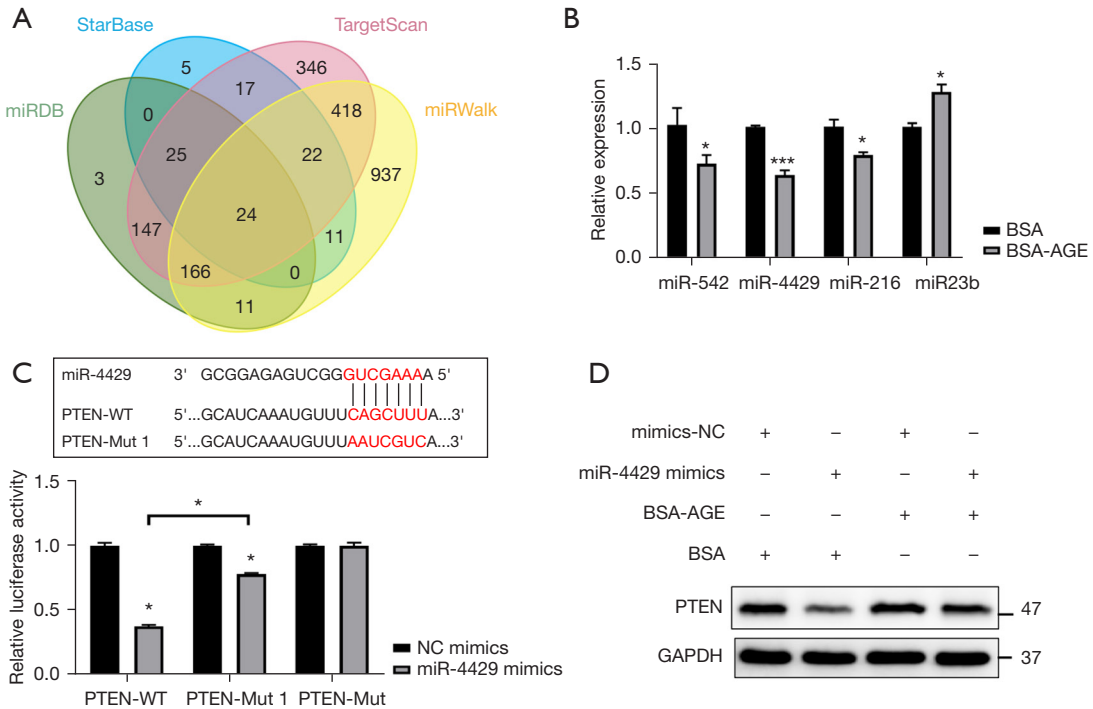

Figure 4 miR-4429 directly bound to PTEN and inhibited the expression of PTEN. (A) Twenty-four miRNAs with potential binding sites to PTEN were selected by taking the intersection of 4 bioinformatics prediction tools (miRWalk, starBase, miRDB, and TargetScan). (B) The expressions of 4 miRNAs were verified to be influenced by AGEs. (C) Luciferase reporter assay was used to show the interaction between miR-4429 and PTEN. (D) The protein expression of PTEN in fibroblasts transfected with miR-4429 mimics or mimics-NC, treated with BSA or BSA-AGE. +, the row corresponding reagent was applied in the experiment; –, the row corresponding reagent was absent in the experiment; the experimental results were shown below the corresponding column. Error bars represent mean ± SD of 3 independent experiments. *, P<0.05; ***, P<0.005. BSA, bovine serum albumin; AGE, advanced glycation end products; PTEN, phosphatase and tensin homolog; WT, wild-type; Mut, mutant; NC, negative control; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; SD, standard deviation.

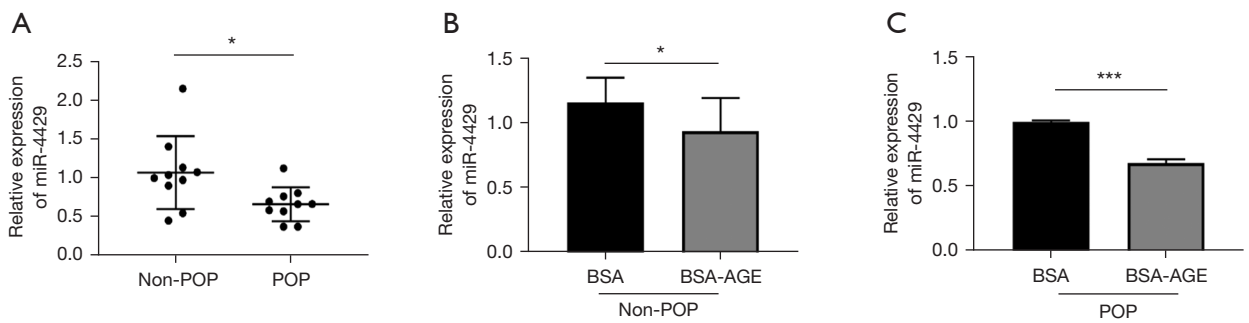

Figure 5 AGEs reduced the expression of miR-4429 both in the non-POP and POP groups. (A) The expression of miR-4429 was lower in fibroblasts from the POP group than in fibroblasts from the non-POP group (n=10). (B) The relative expression of miR-4429 in non-POP fibroblasts treated with BSA or BSA-AGE. (C) The relative expression of miR-4429 in POP fibroblasts treated with BSA or BSA-AGE. Error bars represent mean ± SD of 3 independent experiments. *, P<0.05; ***, P<0.005. POP, pelvic organ prolapse; BSA, bovine serum albumin; AGE, advanced glycation end products; SD, standard deviation.

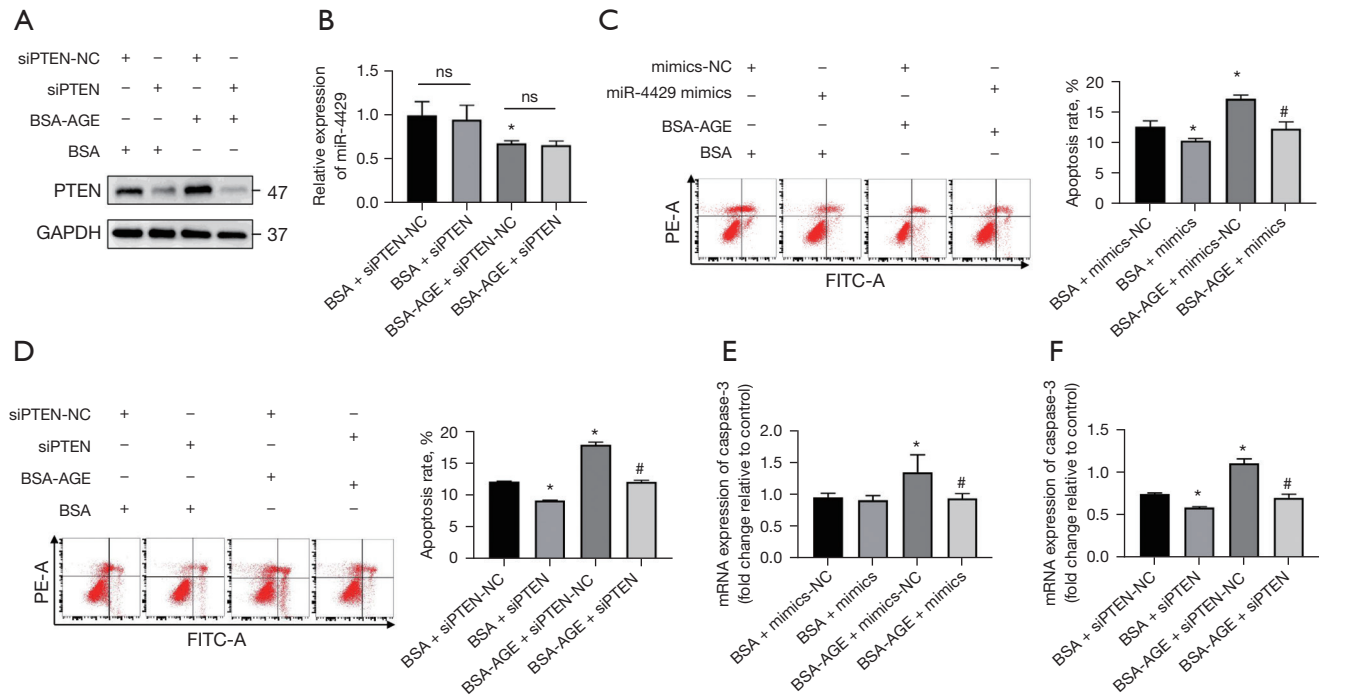

Figure 6 BSA-AGE promoted fibroblast apoptosis by downregulating the miR-4429/PTEN axis. (A) The protein expression of PTEN in fibroblasts transfected with siPTEN or siPTEN-NC, treated with BSA or BSA-AGE. (B) The expression of miR-4429 in fibroblasts transfected with siPTEN or siPTEN-NC, treated with BSA or BSA-AGE. (C) Apoptosis of fibroblasts transfected with miR-4429 mimics or mimics-NC, treated with BSA or BSA-AGE. (D) Apoptosis of fibroblasts transfected with siPTEN or siPTEN-NC, treated with BSA or BSA-AGE. (E) The mRNA expression of caspase-3 in fibroblasts transfected with miR-4429 mimics or mimics-NC, treated with BSA or BSA-AGE. (F) The mRNA expression of caspase-3 in fibroblasts transfected with siPTEN or siPTEN-NC, treated with BSA or BSA-AGE. +, the row corresponding reagent was applied in the experiment; –, the row corresponding reagent was absent in the experiment; the experimental results were shown below the corresponding column. Error bars represent mean ± SD of 3 independent experiments. *, P<0.05 compared with fibroblasts in BSA + siPTEN-NC or BSA + mimics-NC; #, P<0.05 compared with fibroblasts in BSA-AGE + siPTEN-NC or BSA-AGE + mimics-NC. PTEN, phosphatase and tensin homolog; NC, negative control; AGE, advanced glycation end products; BSA, bovine serum albumin; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; ns, not significant; FITC-A, fluorescein isothiocyanate-area; PE-A, phycoerythrin-area; SD, standard deviation.

group were higher than in the non-POP group. Caspase-3 is a recognised biochemical hallmark for apoptosis induced by different apoptotic signals (38). Previous studies have reported the elevated cell apoptosis rate of the uterosacral ligament in POP by immunohistochemical or terminal deoxynucleotidyl transferase Dutp nick end labeling (TUNEL) staining (19,33,39), consistent with the present results. However, few studies have analyzed the apoptosis of cultured fibroblasts from POP and non-POP patients. These results suggested that the aggravated fibroblast apoptosis was a pathological alteration in POP and embodied the clinical significance of investigating fibroblast apoptosis. Fibroblasts are responsible for the secretion and remodeling of ECM in ECM-rich pelvic connective tissues that primarily support the pelvic organs. The disfunction of fibroblasts resulted in a disordered metabolism of collagen and other ECM proteins (40-42). Therefore, the increased fibroblast apoptosis could result in reduced collagen expression in POP and contribute to the weakness of supportive tissues in POP (40,43). In the present study, AGEs promoted the apoptosis of fibroblasts from the non-POP group and aggregated the apoptosis of fibroblasts from the POP group, suggesting that AGEs might be a pathogenesis factor that induced the fibroblast apoptosis in POP.

In this study, we began with a finding that AGEs

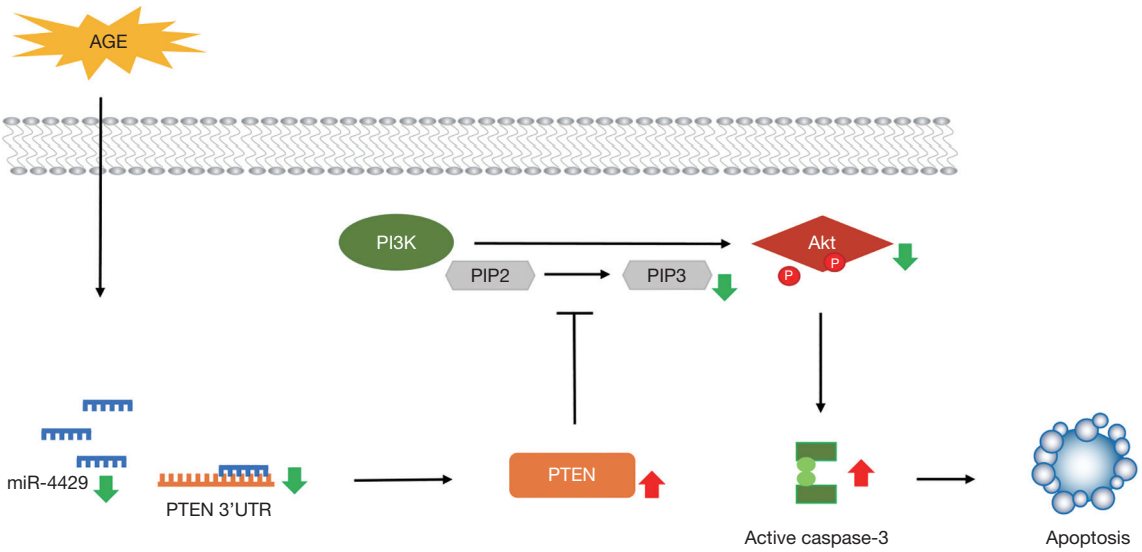

Figure 7 Schematic diagram of the AGEs-induced apoptosis mechanism in fibroblasts. We speculated that AGEs upregulated PTEN, which antagonized the PI3K/Akt pathway and hindered the anti-apoptosis effect of Akt downstream processes, thereby increasing the apoptosis of fibroblasts. AGE, advanced glycation end products; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-triphosphate; Akt, protein kinase B; p, phosphorylation; PTEN, phosphatase and tensin homolog; UTR, untranslated region.

promoted fibroblast apoptosis. Then, we focused on PTEN, which is recognized as a regulator of cell apoptosis (23) and was previously unreported in the molecular alterations in POP. Our results suggested that the expression of PTEN increased in POP as opposed to non-POP fibroblasts, which was consistent with cell apoptosis results. Further, the increased apoptosis rate was alleviated after silencing the expression of PTEN. These results suggested that PTEN played an essential role in fibroblast apoptosis in POP. In addition, the effect of PTEN on apoptosis in this study was consistent with the previous reports. They all showed that the changing trend of PTEN expression was in line with the apoptosis rate (44,45).

miRNAs are small non-coding RNAs that regulate gene expression at the post-transcriptional stage by interacting with target mRNAs at 3'UTR (46). Many researchers have previously reported that miRNAs might be implicated in developing AGEs-related diseases and interfere with the AGE/receptor for IAGE signaling. For instance, the expression levels among a series of miRNAs were reported to be regulated by AGEs (47-49). Moreover, Piperi *et al.* (50) reviewed miRNAs interacting with the AGE/RAGE signaling and the diabetic complications. To determine whether AGEs upregulated the expression of PTEN by miRNAs, we screened out 24 miRNAs with potential binding sites to PTEN using bioinformatics prediction tools and verified 4 of the 24 miRNAs. The results showed that the expression level of miR-4429 was lower in the POP group than in the non-POP group, and AGEs downregulated the expression of miR-4429 both in POP and non-POP fibroblasts.

Moreover, miR-4429 was shown to combine with the 3'UTR of PTEN directly and downregulate the expression of PTEN. The function of miR-4429 was previously mainly explored in cancer cells and was reported to prevent the progression of several cancers (30,51). However, no study has reported that AGEs could regulate miR-4429, and no study has shown miR-4429 could bind with mRNA of PTEN and downregulate the expression of PTEN. The AGEs induced apoptosis of fibroblasts, but this could be alleviated by overexpression of miR-4429, which could also almost be neutralized by silencing PTEN expression. Further, the expression of miR-4429 was only influenced by AGEs exposure but not by the transfection of siPTEN. Taken together, we showed that AGEs induced fibroblast apoptosis through the miR-4429/PTEN axis.

Further, the protein expression of total Akt was not changed, while the phosphorylated Akt was downregulated when fibroblasts were treated with AGEs. This result demonstrated that AGEs-induced upregulation of PTEN

indeed antagonized the PI3K/Akt pathway, in line with the well-known function of PTEN (52). As a lipid phosphatase, PTEN negatively regulated phosphatidylinositol-3,4,5-triphosphate-dependent Akt signaling to inhibit growth, protein synthesis, cell cycle progression, metabolism, and apoptosis (53). The only difference was that the expression of PI3K was reduced under the treatment of AGEs, which implied that the inhibition of AGEs on the PI3K/Akt pathway was not only regulated by the miR-4429/PTEN axis. The PI3K/Akt pathway regulated cell viability and proliferation (54,55), and the inhibition of this pathway logically promoted cell apoptosis (56,57). Further, several studies have reported that upregulated miRNAs targeted PTEN and activated the PI3K/Akt pathway to promote cell proliferation and inhibit apoptosis (58,59).

In conclusion, we demonstrated that AGEs induced fibroblast apoptosis by regulating the miR-4429/PTEN/PI3K/Akt pathway in POP. The AGEs reduced the expression of miR-4429, thereby increasing the expression of PTEN and promoting fibroblast apoptosis. In addition, PI3K/Akt was inhibited by AGEs, which caused increased cell apoptosis.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-628/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-628/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-628/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University (No. 2021-234) and informed consent was taken from all the patients.

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Appendix 1

Methods

Tissue samples were fixed with 4% paraformaldehyde (Servicebio, Wuhan, China) and then made into paraffin sections in 4 microns. After deparaffinization, rehydration, and antigen retrieval and serum sealing, the paraffin sections were incubated with the 1:100 diluted anti-advanced glycation end products (AGEs) antibody (ab23722, Abcam, Cambridge, MA, USA). Subsequently, the 3,3'-diaminobenzidine (DAB) color developing solution (Servicebio) was used to stain sections, and the hematoxylin stain solution (Servicebio) was used to counterstain nucleus. Images were obtained using a light microscope (Olympus, Tokyo, Japan).

https://dx.doi.org/10.21037/atm-22-628

Table S1 Names of miRNAs selected from four databases

miRDB	StarBase	TargetScan	miRWalk
hsa-miR-1297	hsa-miR-200b-3p	hsa-miR-1297	hsa-let-7a-5p
hsa-miR-5011-5p	hsa-miR-200a-3p	hsa-miR-4465	hsa-let-7a-3p
hsa-miR-23a-3p	hsa-miR-429	hsa-miR-26b-5p	hsa-let-7a-2-3p
hsa-miR-5692c	hsa-miR-30e-5p	hsa-miR-26a-5p	hsa-let-7b-5p
hsa-miR-26a-5p	hsa-miR-30c-5p	hsa-miR-202-5p	hsa-let-7c-5p
hsa-miR-26b-5p	hsa-miR-186-5p	hsa-miR-219a-2-3p	hsa-let-7c-3p
hsa-miR-23c	hsa-miR-320b	hsa-miR-10a-5p	hsa-let-7d-5p
hsa-miR-23b-3p	hsa-miR-190b	hsa-miR-10b-5p	hsa-let-7d-3p
hsa-miR-4465	hsa-miR-92b-3p	hsa-miR-519d-3p	hsa-let-7e-5p
hsa-miR-5692b	hsa-miR-214-3p	hsa-miR-526b-3p	hsa-let-7f-5p
hsa-miR-4775	hsa-miR-181b-5p	hsa-miR-20b-5p	hsa-miR-15a-5p
hsa-miR-1277-5p	hsa-miR-181a-5p	hsa-miR-106b-5p	hsa-miR-17-5p
hsa-miR-513a-3p	hsa-miR-29c-3p	hsa-miR-93-5p	hsa-miR-17-3p
hsa-miR-29c-3p	hsa-miR-29b-3p	hsa-miR-20a-5p	hsa-miR-18a-5p
hsa-miR-29a-3p	hsa-miR-107	hsa-miR-17-5p	hsa-miR-19a-5p
hsa-miR-486-5p	hsa-miR-146b-5p	hsa-miR-106a-5p	hsa-miR-19b-1-5p
hsa-miR-29b-3p	hsa-miR-4295	hsa-miR-340-5p	hsa-miR-19b-2-5p
hsa-miR-494-3p	hsa-miR-210-3p	hsa-miR-542-3p	hsa-miR-20a-5p
hsa-miR-190a-3p	hsa-miR-130a-3p	hsa-miR-19b-3p	hsa-miR-20a-3p
hsa-miR-513c-3p	hsa-miR-200c-3p	hsa-miR-19a-3p	hsa-miR-22-3p
hsa-miR-32-5p	hsa-miR-141-3p	hsa-miR-3666	hsa-miR-23a-5p
hsa-miR-30d-3p	hsa-miR-148b-3p	hsa-miR-454-3p	hsa-miR-24-3p
hsa-miR-92b-3p	hsa-miR-26a-5p	hsa-miR-130b-3p	hsa-miR-24-2-5p
hsa-miR-3944-5p	hsa-miR-320d	hsa-miR-130a-3p	hsa-miR-25-5p
hsa-miR-8485	hsa-miR-1297	hsa-miR-301a-3p	hsa-miR-25-3p
hsa-miR-30a-3p	hsa-miR-17-5p	hsa-miR-301b-3p	hsa-miR-26a-5p
hsa-miR-3606-3p	hsa-miR-19a-3p	hsa-miR-4295	hsa-miR-26a-1-3p
hsa-miR-373-5p	hsa-miR-20a-5p	hsa-miR-338-3p	hsa-miR-26b-3p
hsa-miR-616-5p	hsa-miR-19b-3p	hsa-miR-186-5p	hsa-miR-27a-5p
hsa-miR-30e-3p	hsa-miR-92a-3p	hsa-miR-29c-3p	hsa-miR-27a-3p
hsa-miR-92a-3p	hsa-miR-299-3p	hsa-miR-29a-3p	hsa-miR-28-5p
hsa-miR-371b-5p	hsa-miR-494-3p	hsa-miR-29b-3p	hsa-miR-29a-5p
hsa-miR-367-3p	hsa-miR-543	hsa-miR-22-3p	hsa-miR-30a-3p
hsa-miR-363-3p	hsa-miR-495-3p	hsa-miR-486-5p	hsa-miR-31-5p
hsa-miR-188-5p	hsa-miR-539-5p	hsa-miR-205-5p	hsa-miR-31-3p
hsa-miR-25-3p	hsa-miR-382-5p	hsa-miR-188-5p	hsa-miR-33a-5p
hsa-miR-6866-3p	hsa-miR-134-5p	hsa-miR-6866-3p	hsa-miR-33a-3p
hsa-miR-590-3p	hsa-miR-485-5p	hsa-miR-224-5p	hsa-miR-92a-1-5p
hsa-miR-3064-3p	hsa-miR-154-5p	hsa-miR-193a-3p	hsa-miR-92a-3p
hsa-miR-4482-3p	hsa-miR-496	hsa-miR-193b-3p	hsa-miR-92a-2-5p
hsa-miR-3148	hsa-miR-410-3p	hsa-miR-382-5p	hsa-miR-93-5p
hsa-miR-3065-3p	hsa-miR-190a-5p	hsa-miR-103a-3p	hsa-miR-95-3p
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hsa-miR-130b-3p	hsa-miR-7855-5p	hsa-miR-379-5p
hsa-miR-454-3p	hsa-miR-449b-3p	hsa-miR-380-3p
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hsa-miR-4662b	hsa-miR-519c-3p	hsa-miR-151a-3p
hsa-miR-208b-5p	hsa-miR-519b-3p	hsa-miR-148b-3p
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hsa-miR-6867-5p	hsa-miR-4762-3p	hsa-miR-412-5p
hsa-miR-4307	hsa-miR-944	hsa-miR-376b-5p
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hsa-miR-1183	hsa-miR-4530	hsa-miR-485-5p
hsa-miR-548n	hsa-miR-525-5p	hsa-miR-485-3p
hsa-miR-664b-3p	hsa-miR-520a-5p	hsa-miR-486-5p
hsa-miR-3143	hsa-miR-198	hsa-miR-486-3p
hsa-miR-3159	hsa-miR-8076	hsa-miR-488-5p

Table S1 (*continued*)

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Table S1 (continued)

miRDB	StarBase	TargetScan	miRWalk
hsa-miR-3020-5p		hsa-miR-1273f	hsa-miR-489-5p
hsa-miR-744-3p		hsa-miR-620	hsa-miR-489-3p
hsa-miR-15b-3p		hsa-miR-1270	hsa-miR-490-5p
hsa-miR-579-3p		hsa-miR-4683	hsa-miR-490-3p
hsa-miR-4526		hsa-miR-3135b	hsa-miR-491-3p
hsa-miR-548m		hsa-miR-3121-3p	hsa-miR-511-5p
hsa-let-7a-3p		hsa-miR-6867-5p	hsa-miR-1468-5p
hsa-miR-4282		hsa-miR-3650	hsa-miR-1468-3p
hsa-miR-98-3p		hsa-miR-6730-5p	hsa-miR-202-3p
hsa-miR-559		hsa-miR-3133	hsa-miR-492
hsa-miR-1910-3p		hsa-miR-4744	hsa-miR-493-5p
hsa-miR-5587-5p		hsa-miR-3137	hsa-miR-432-5p
hsa-miR-4667-5p		hsa-miR-1183	hsa-miR-432-3p
hsa-miR-140-3p		hsa-miR-488-5p	hsa-miR-494-3p
hsa-miR-3163		hsa-miR-1238-3p	hsa-miR-495-5p
hsa-miR-582-3p		hsa-miR-2277-3p	hsa-miR-1930-5p
hsa-miR-4694-3p		hsa-miR-5190	hsa-miR-1930-3p
hsa-miR-567		hsa-miR-4519	hsa-miR-497-5p
hsa-miR-6511a-5p		hsa-let-7i-3p	hsa-miR-497-3p
hsa-let-7b-3p		hsa-miR-5682	hsa-miR-1814-5p
hsa-miR-8089		hsa-miR-6871-3p	hsa-miR-1814-3p
hsa-miR-6728-5p		hsa-miR-1397-3p	hsa-miR-498-5p
hsa-miR-4436b-5p		hsa-miR-627-3p	hsa-miR-502a-5p
hsa-miR-369-3p		hsa-miR-6882-3p	hsa-miR-502a-3p
hsa-miR-5088-3p		hsa-miR-10b-3p	hsa-miR-515-3p
hsa-let-7f-1-3p		hsa-miR-5683	hsa-miR-519a-5p
hsa-miR-1226-5p		hsa-miR-3230-3p	hsa-miR-519a-3p
hsa-miR-183-3p		hsa-miR-7152-5p	hsa-miR-520f-3p
hsa-miR-7152-5p		hsa-miR-1298-5p	hsa-miR-519c-5p
hsa-miR-4310		hsa-miR-6853-3p	hsa-miR-526b-5p
hsa-miR-4709-3p		hsa-miR-298	hsa-miR-519b-5p
hsa-miR-4529-3p		hsa-miR-1273h-3p	hsa-miR-525-5p
hsa-miR-518b-3p		hsa-miR-3678-3p	hsa-miR-523-5p
hsa-miR-4765		hsa-miR-4684-3p	hsa-miR-523-3p
hsa-miR-519a-3p		hsa-miR-4662b	hsa-miR-526a-5p
hsa-miR-6083		hsa-miR-4647	hsa-miR-520c-5p
hsa-miR-6740-3p		hsa-miR-4426	hsa-miR-520c-3p
hsa-miR-3133		hsa-miR-6833-5p	hsa-miR-518c-5p
hsa-miR-4516		hsa-miR-6640-3p	hsa-miR-519d-5p
hsa-miR-6876-5p		hsa-miR-5713-3p	hsa-miR-519d-3p
hsa-miR-3925-3p		hsa-miR-5696	hsa-miR-521
hsa-miR-548ae-5p		hsa-miR-5088-3p	hsa-miR-520d-5p
hsa-miR-548t-5p		hsa-miR-6083	hsa-miR-520d-3p
hsa-miR-548t-5p		hsa-miR-4289	hsa-miR-520g-5p
hsa-miR-511-3p		hsa-miR-616-3p	hsa-miR-520g-3p
hsa-miR-4476		hsa-miR-564-5p	hsa-miR-518b-5p
hsa-miR-224-5p		hsa-miR-219-2-3p	hsa-miR-518e-5p
hsa-miR-3936		hsa-miR-758-5p	hsa-miR-518a-5p
hsa-miR-5192		hsa-miR-4729	hsa-miR-518d-5p
hsa-miR-519c-3p		hsa-miR-6877-3p	hsa-miR-520h
hsa-miR-7155-3p		hsa-miR-6819-3p	hsa-miR-522-5p
hsa-miR-3201		hsa-miR-6844	hsa-miR-519a-5p
hsa-miR-6615-5p		hsa-miR-498	hsa-miR-527
hsa-miR-141-5p		hsa-miR-518a-3p	hsa-miR-516a-5p
hsa-miR-561-3p		hsa-miR-409-3p	hsa-miR-499a-3p
hsa-miR-8058		hsa-miR-551b-5p	hsa-miR-500a-3p
hsa-miR-4716-5p		hsa-miR-570-3p	hsa-miR-501-5p
hsa-miR-7154-5p		hsa-miR-539-5p	hsa-miR-501-3p
hsa-miR-3136-3p		hsa-miR-580-3p	hsa-miR-502-5p
hsa-miR-143-5p		hsa-miR-4461	hsa-miR-502-3p
hsa-miR-6965-5p		hsa-miR-7849-3p	hsa-miR-503a-2-3p
hsa-miR-3923		hsa-miR-4434	hsa-miR-503-5p
hsa-miR-4291		hsa-miR-5703	hsa-miR-504-5p
hsa-miR-6128		hsa-miR-4316	hsa-miR-504-3p
hsa-miR-4666a-5p		hsa-miR-4531	hsa-miR-505-5p
hsa-miR-708-3p		hsa-miR-4534	hsa-miR-513a-3p
hsa-miR-1269a		hsa-miR-8082	hsa-miR-506-5p
hsa-miR-7160-5p		hsa-miR-6868-5p	hsa-miR-508-3p
hsa-miR-1269b		hsa-miR-4768-3p	hsa-miR-509-5p
hsa-miR-4680-3p		hsa-miR-6768-5p	hsa-miR-510-5p
hsa-miR-4735-5p		hsa-miR-4672	hsa-miR-514a-5p
hsa-miR-8076		hsa-miR-3941	hsa-miR-532-5p
hsa-miR-4534		hsa-miR-3176	hsa-miR-455-5p
hsa-miR-7157-5p		hsa-miR-3922-3p	hsa-miR-455-3p
hsa-miR-4326		hsa-miR-585-5p	hsa-miR-4675-5p
hsa-miR-6847-5p		hsa-miR-3746-3p	hsa-miR-4676-3p
hsa-miR-6758-3p		hsa-miR-4680-3p	hsa-miR-552-3p
hsa-miR-3160-5p		hsa-miR-4427	hsa-miR-554
hsa-miR-18b-3p		hsa-miR-5187-3p	hsa-miR-555
hsa-miR-7159-3p		hsa-miR-4637	hsa-miR-556-5p
hsa-miR-548j-5p		hsa-miR-3136-5p	hsa-miR-557
hsa-miR-488-5p		hsa-miR-4439	hsa-miR-558
hsa-miR-5590-3p		hsa-miR-6855-3p	hsa-miR-564
hsa-miR-548c-5p		hsa-miR-4513	hsa-miR-567
hsa-miR-708-5p		hsa-miR-6857-3p	hsa-miR-5010-5p
hsa-miR-1267		hsa-miR-943	hsa-miR-571
hsa-miR-548b-5p		hsa-miR-495-5p	hsa-miR-573
hsa-miR-142-5p		hsa-miR-595	hsa-miR-574-3p
hsa-miR-548ad-5p		hsa-miR-628-3p	hsa-miR-575
hsa-miR-548d-5p		hsa-miR-3923	hsa-miR-578
hsa-miR-548h-5p		hsa-miR-7844-5p	hsa-miR-579-5p
hsa-miR-548a-5p		hsa-miR-4678	hsa-miR-580-5p
hsa-miR-28-5p		hsa-miR-3619-5p	hsa-miR-584-5p
hsa-miR-4672		hsa-miR-761	hsa-miR-585-5p
hsa-miR-6689-3p		hsa-miR-214-3p	hsa-miR-585-3p
hsa-miR-548		hsa-miR-140-3p.1	hsa-miR-548ai-3p
hsa-miR-548as-5p		hsa-miR-8060	hsa-miR-586
hsa-miR-548w		hsa-miR-5589-3p	hsa-miR-550a-5p
hsa-miR-6842-3p		hsa-miR-4514	hsa-miR-593-5p
hsa-miR-548ab		hsa-miR-4692	hsa-miR-593-3p
hsa-miR-875-3p		hsa-miR-6511b-5p	hsa-miR-596
hsa-miR-548ay-5p		hsa-miR-6811-3p	hsa-miR-597-5p
hsa-miR-548o-5p		hsa-miR-4327	hsa-miR-598-5p
hsa-miR-548ap-5p		hsa-miR-100-3p	hsa-miR-598-3p
hsa-miR-548ar-5p		hsa-miR-3204-5p	hsa-miR-599
hsa-miR-4764-5p		hsa-miR-224-5p	hsa-miR-600
hsa-miR-3139		hsa-miR-7157-5p	hsa-miR-601
hsa-miR-548au-5p		hsa-miR-4310	hsa-miR-602
hsa-miR-548y		hsa-miR-3944-5p	hsa-miR-604
hsa-miR-548am-5p		hsa-miR-1443-5p	hsa-miR-605-5p
hsa-miR-548an-5p		hsa-miR-5008-3p	hsa-miR-605-3p
hsa-miR-548ao-5p		hsa-miR-6737-3p	hsa-miR-608
hsa-miR-548ak		hsa-miR-7157-3p	hsa-miR-613
hsa-miR-548bb-5p		hsa-miR-6889-3p	hsa-miR-614
hsa-miR-5692a		hsa-miR-4743-3p	hsa-miR-615-3p
hsa-miR-150-5p		hsa-miR-4652-3p	hsa-miR-616-5p
hsa-miR-5009-5p		hsa-miR-513c-3p	hsa-miR-616-3p
hsa-miR-16-5p		hsa-miR-3606-3p	hsa-miR-617
hsa-miR-146a-5p		hsa-miR-513a-3p	hsa-miR-619-5p
hsa-miR-146b-3p		hsa-miR-3127-5p	hsa-miR-619-3p
hsa-miR-628-3p		hsa-miR-373-5p	hsa-miR-621
hsa-miR-6738-3p		hsa-miR-371b-5p	hsa-miR-625-5p
hsa-miR-6529-3p		hsa-miR-4693-5p	hsa-miR-628-5p
hsa-miR-15a-5p		hsa-miR-675-5p	hsa-miR-631
hsa-miR-195-5p		hsa-miR-4711-5p	hsa-miR-330-5p
hsa-miR-450a-1-3p		hsa-miR-7112-3p	hsa-miR-330-3p
hsa-miR-5010-5p		hsa-miR-372-3p	hsa-miR-632
hsa-miR-876-3p		hsa-miR-302e	hsa-miR-634
hsa-miR-6754-3p		hsa-miR-520e	hsa-miR-635
		hsa-miR-520d-3p	hsa-miR-637
		hsa-miR-302c-3p.1	hsa-miR-638
		hsa-miR-520c-3p	hsa-miR-639
		hsa-miR-520b	hsa-miR-641
		hsa-miR-520a-3p	hsa-miR-642a-3p
		hsa-miR-373-3p	hsa-miR-643
		hsa-miR-302b-3p	hsa-miR-644a
		hsa-miR-302d-3p	hsa-miR-646
		hsa-miR-302a-3p	hsa-miR-647
		hsa-miR-5585-3p	hsa-miR-648
		hsa-miR-337-5p	hsa-miR-650
		hsa-miR-6745	hsa-miR-652-3p
		hsa-miR-363-5p	hsa-miR-661
		hsa-miR-3974	hsa-miR-662
		hsa-miR-511-3p	hsa-miR-663a
		hsa-miR-2054	hsa-miR-4458c-5p
		hsa-miR-6664-3p	hsa-miR-4459c-3p
		hsa-miR-4760-3p	hsa-miR-653-3p
		hsa-miR-1468-3p	hsa-miR-654-5p
		hsa-miR-548aj-5p	hsa-miR-654-3p
		hsa-miR-548g-5p	hsa-miR-655-5p
		hsa-miR-548x-5p	hsa-miR-657
		hsa-miR-548f-5p	hsa-miR-658
		hsa-miR-548ae	hsa-miR-659-5p
		hsa-miR-548ao-3p	hsa-miR-660-3p
		hsa-miR-589	hsa-miR-542-5p
		hsa-miR-6883-3p	hsa-miR-542-3p
		hsa-miR-5697	hsa-miR-758-5p
		hsa-miR-16-1-3p	hsa-miR-758-3p
		hsa-miR-222-3p	hsa-miR-1264
		hsa-miR-506-5p	hsa-miR-671-5p
		hsa-miR-892c-3p	hsa-miR-668-5p
		hsa-miR-630	hsa-miR-550a-5-5p
		hsa-miR-3924	hsa-miR-767-5p
		hsa-miR-4528	hsa-miR-767-3p
		hsa-miR-1277-5p	hsa-miR-1224-5p
		hsa-miR-889-3p	hsa-miR-1224-3p
		hsa-miR-302c-5p	hsa-miR-151b
		hsa-miR-552-5p	hsa-miR-3208c
		hsa-miR-4735-5p	hsa-miR-3208c
		hsa-miR-618	hsa-miR-1296-5p
		hsa-miR-891b	hsa-miR-1323
		hsa-miR-4772-3p	hsa-miR-1271-3p
		hsa-miR-4418	hsa-miR-1301-5p
		hsa-miR-509-3-5p	hsa-miR-1185-2-3p
		hsa-miR-509-5p	hsa-miR-449c-5p
		hsa-miR-507-3p	hsa-miR-449c-3p
		hsa-miR-488-3p	hsa-miR-378d
		hsa-miR-6818-5p	hsa-miR-1185-1-3p
		hsa-miR-147a	hsa-miR-670-3p
		hsa-miR-5010-3p	hsa-miR-1298-5p
		hsa-miR-2113	hsa-miR-1298-3p
		hsa-miR-129-5p	hsa-miR-2113
		hsa-miR-511-5p	hsa-miR-761
		hsa-miR-6830-3p	hsa-miR-759
		hsa-miR-106-5p	hsa-miR-765
		hsa-miR-7853-5p	hsa-miR-770-5p
		hsa-miR-548c-3p	hsa-miR-873-3p
		hsa-miR-4724-5p	hsa-miR-891a-3p
		hsa-miR-1197	hsa-miR-892a
		hsa-miR-8065	hsa-miR-4508-3p
		hsa-miR-6835-3p	hsa-miR-874-5p
		hsa-miR-4422	hsa-miR-888-3p
		hsa-miR-95-5p	hsa-miR-541-5p
		hsa-miR-6826-5p	hsa-miR-541-3p
		hsa-miR-29a-2-3p	hsa-miR-875-5p
		hsa-miR-26a-1-3p	hsa-miR-708-5p
		hsa-miR-652-5p	hsa-miR-708-3p
		hsa-miR-548d-3p	hsa-miR-1473-3p
		hsa-miR-548ac	hsa-miR-744-5p
		hsa-miR-548z	hsa-miR-744-3p
		hsa-miR-548bk-3p	hsa-miR-885-3p
		hsa-miR-548h-3p	hsa-miR-877-5p
		hsa-miR-7159-5p	hsa-miR-877-3p
		hsa-miR-421	hsa-miR-887-5p
		hsa-miR-580-5p	hsa-miR-887-3p
		hsa-miR-5680	hsa-miR-665
		hsa-miR-3185	hsa-miR-760
		hsa-miR-1343-5p	hsa-miR-3016-5p
		hsa-miR-939-5p	hsa-miR-216b-5p
		hsa-miR-4723-5p	hsa-miR-920
		hsa-miR-5698	hsa-miR-921
		hsa-miR-7111-5p	hsa-miR-922
		hsa-miR-6870-5p	hsa-miR-509-3-5p
		hsa-miR-4787-5p	hsa-miR-933
		hsa-miR-5588-3p	hsa-miR-936
		hsa-miR-2114-5p	hsa-miR-937-5p
		hsa-miR-554	hsa-miR-939-5p
		hsa-miR-1843-3p	hsa-miR-939-3p
		hsa-miR-4786-3p	hsa-miR-941
		hsa-miR-127-5p	hsa-miR-943
		hsa-miR-3653-3p	hsa-miR-297
		hsa-miR-3658	hsa-miR-1178-3p
		hsa-miR-7856-5p	hsa-miR-1180-5p
		hsa-miR-3682-3p	hsa-miR-1180-3p
		hsa-miR-1272	hsa-miR-1182
		hsa-miR-1322	hsa-miR-1183
		hsa-miR-3671	hsa-miR-1184
		hsa-miR-3945	hsa-miR-1226-3p
		hsa-miR-4253	hsa-miR-1227-5p
		hsa-miR-6862-5p	hsa-miR-1231
		hsa-miR-5189-5p	hsa-miR-1233-5p
		hsa-miR-1260-3p	hsa-miR-1233-3p
		hsa-miR-6860	hsa-miR-1234-3p
		hsa-miR-3187-5p	hsa-miR-1236-5p
		hsa-miR-612	hsa-miR-1236-3p
		hsa-miR-378g	hsa-miR-1237-3p
		hsa-miR-4486	hsa-miR-1238-5p
		hsa-miR-4668-3p	hsa-miR-1238-3p
		hsa-miR-3613-3p	hsa-miR-1200
		hsa-miR-4703-3p	hsa-miR-1202
		hsa-miR-1244	hsa-miR-1204
		hsa-miR-208-5p	hsa-miR-1205
		hsa-miR-208a-5p	hsa-miR-1207-5p
		hsa-miR-208b-5p	hsa-miR-1208
		hsa-miR-5579-3p	hsa-miR-548j-5p
		hsa-miR-6837-3p	hsa-miR-1285-5p

Table S1 (continued)

Table S1 (continued)

miRDB	StarBase	TargetScan	miRWalk
		hsa-miR-4412-3p	hsa-miR-1285-3p
		hsa-miR-6754-3p	hsa-miR-1286
		hsa-miR-141-5p	hsa-miR-1287-5p
		hsa-miR-5692c	hsa-miR-1287-3p
		hsa-miR-5692b	hsa-miR-1289
		hsa-miR-875-3p	hsa-miR-1290
		hsa-miR-1299	hsa-miR-1293
		hsa-miR-6706	hsa-miR-1294
		hsa-miR-4782-5p	hsa-miR-1295a
		hsa-miR-5195-5p	hsa-miR-1299
		hsa-miR-4709-3p	hsa-miR-5488
		hsa-miR-483-3p	hsa-miR-1304-5p
		hsa-miR-4761-5p	hsa-miR-1244
		hsa-miR-5130-3p	hsa-miR-1245a
		hsa-miR-607	hsa-miR-1246
		hsa-miR-6074	hsa-miR-1248
		hsa-miR-3201	hsa-miR-1249-5p
		hsa-miR-4791	hsa-miR-1250-5p
		hsa-miR-1287-5p	hsa-miR-1250-3p
		hsa-miR-3652	hsa-miR-1257
		hsa-miR-4430	hsa-miR-1258
		hsa-miR-6842-3p	hsa-miR-1263
		hsa-miR-5787	hsa-miR-1265
		hsa-miR-4505	hsa-miR-548c-3p
		hsa-miR-889-5p	hsa-miR-1268a
		hsa-miR-4698	hsa-miR-1268a
		hsa-miR-6512-5p	hsa-miR-1272
		hsa-miR-3144-3p	hsa-miR-1275
		hsa-miR-4694-3p	hsa-miR-1278
		hsa-miR-3065-3p	hsa-miR-1278
		hsa-miR-383-3p	hsa-miR-1282
		hsa-miR-4291	hsa-miR-1284
		hsa-miR-205-3p	hsa-miR-1288-5p
		hsa-miR-3606-5p	hsa-miR-1288-3p
		hsa-miR-370-5p	hsa-miR-1292-5p
		hsa-miR-1193	hsa-miR-1250b-2-3p
		hsa-miR-708-3p	hsa-miR-664a-5p
		hsa-miR-4742-3p	hsa-miR-1306-5p
		hsa-miR-325	hsa-miR-1306-3p
		hsa-miR-1301-5p	hsa-miR-513b-3p
		hsa-miR-6502-5p	hsa-miR-513c-3p
		hsa-miR-138-2-3p	hsa-miR-1322
		hsa-miR-5001-3p	hsa-miR-1197
		hsa-miR-6738-3p	hsa-miR-1324
		hsa-miR-4727-5p	hsa-miR-1469
		hsa-miR-6674-3p	hsa-miR-1538
		hsa-miR-148b-5p	hsa-miR-3204
		hsa-miR-148a-5p	hsa-miR-1825
		hsa-miR-4670-3p	hsa-miR-1827
		hsa-miR-8061	hsa-miR-1909-5p
		hsa-miR-4760-5p	hsa-miR-1910-5p
		hsa-miR-6507-5p	hsa-miR-1910-3p
		hsa-miR-4699-3p	hsa-miR-1911-3p
		hsa-miR-3688-3p	hsa-miR-1912-5p
		hsa-miR-624-3p	hsa-miR-1912-3p
		hsa-miR-888-3p	hsa-miR-1914-5p
		hsa-miR-4738-3p	hsa-miR-1915-5p
		hsa-miR-2053	hsa-miR-1972
		hsa-miR-605-5p	hsa-miR-1973
		hsa-miR-190a-3p	hsa-miR-2110
		hsa-miR-5011-5p	hsa-miR-2114-5p
		hsa-miR-5684	hsa-miR-2114-3p
		hsa-miR-4705	hsa-miR-2115-5p
		hsa-miR-556-5p	hsa-miR-2116-5p
		hsa-miR-5209-5p	hsa-miR-548q
		hsa-miR-6818-3p	hsa-miR-2276-5p
		hsa-miR-593-3p	hsa-miR-2276-3p
		hsa-miR-6865-3p	hsa-miR-2277-5p
		hsa-miR-3152-3p	hsa-miR-2681-5p
		hsa-miR-7854-3p	hsa-miR-2682-5p
		hsa-miR-6134	hsa-miR-711
		hsa-miR-1294	hsa-miR-2861
		hsa-miR-4710	hsa-miR-3116
		hsa-miR-4792	hsa-miR-3117-3p
		hsa-miR-6815-5p	hsa-miR-3118
		hsa-miR-6865-5p	hsa-miR-3119
		hsa-miR-6509-5p	hsa-miR-3120-5p
		hsa-miR-201-5p	hsa-miR-3120-3p
		hsa-miR-153-5p	hsa-miR-3121-5p
		hsa-miR-16-2-3p	hsa-miR-3121-3p
		hsa-miR-195-3p	hsa-miR-3122
		hsa-miR-7-2-3p	hsa-miR-3124-5p
		hsa-miR-7-1-3p	hsa-miR-548s
		hsa-miR-194-5p	hsa-miR-3125
		hsa-miR-4746-3p	hsa-miR-3126-5p
		hsa-miR-5583-3p	hsa-miR-3126-3p
		hsa-miR-4517	hsa-miR-3129-3p
		hsa-miR-548at-5p	hsa-miR-3130-5p
		hsa-miR-1279	hsa-miR-3132-3p
		hsa-miR-5580-3p	hsa-miR-3131
		hsa-miR-4716-5p	hsa-miR-3132
		hsa-miR-4290	hsa-miR-378b
		hsa-miR-6851-3p	hsa-miR-3134
		hsa-miR-6775-3p	hsa-miR-3135a
		hsa-miR-1291	hsa-miR-486
		hsa-miR-621	hsa-miR-3136-5p
		hsa-miR-3661	hsa-miR-3136-3p
		hsa-miR-5692a	hsa-miR-644b
		hsa-miR-6758-3p	hsa-miR-3138
		hsa-miR-8063	hsa-miR-3139
		hsa-miR-510-3p	hsa-miR-3140-3p
		hsa-miR-3613-3p	hsa-miR-3141
		hsa-miR-513c-5p	hsa-miR-3142
		hsa-miR-5140-5p	hsa-miR-3144-5p
		hsa-miR-6815-3p	hsa-miR-3144-3p
		hsa-miR-4708-3p	hsa-miR-1273c
		hsa-miR-3662	hsa-miR-3147
		hsa-miR-587	hsa-miR-548v
		hsa-miR-568	hsa-miR-3150a-3p
		hsa-miR-5192	hsa-miR-3152-3p
		hsa-miR-4428	hsa-miR-3153
		hsa-miR-3173-3p	hsa-miR-3074-5p
		hsa-miR-4691-5p	hsa-miR-3154
		hsa-miR-548a-5p	hsa-miR-3155a
		hsa-miR-548ar-5p	hsa-miR-3156-5p
		hsa-miR-548h-3p	hsa-miR-3157-5p
		hsa-miR-548c-5p	hsa-miR-3157-3p
		hsa-miR-548am-5p	hsa-miR-3158-5p
		hsa-miR-548j-5p	hsa-miR-3158-3p
		hsa-miR-548au-5p	hsa-miR-3159
		hsa-miR-548o-5p	hsa-miR-3160-5p
		hsa-miR-548ap-5p	hsa-miR-3160-3p
		hsa-miR-548w	hsa-miR-3161
		hsa-miR-548ak	hsa-miR-3162-5p
		hsa-miR-548as-5p	hsa-miR-3162-3p
		hsa-miR-548ae-5p	hsa-miR-3163
		hsa-miR-548i	hsa-miR-3165
		hsa-miR-548y	hsa-miR-3166
		hsa-miR-548b-5p	hsa-miR-3167
		hsa-miR-548ab-5p	hsa-miR-3169
		hsa-miR-548d-5p	hsa-miR-3171
		hsa-miR-548bb-5p	hsa-miR-3173-3p
		hsa-miR-548ay-5p	hsa-miR-1193
		hsa-miR-548ab	hsa-miR-3236-3p
		hsa-miR-548aq-5p	hsa-miR-3174
		hsa-miR-559	hsa-miR-3175
		hsa-miR-8054	hsa-miR-3176
		hsa-miR-548ae-5p	hsa-miR-3177-5p
		hsa-miR-548k	hsa-miR-3177-3p
		hsa-miR-548l	hsa-miR-3178
		hsa-miR-6857-5p	hsa-miR-548w
		hsa-miR-4450	hsa-miR-3181
		hsa-miR-6890-5p	hsa-miR-3183
		hsa-miR-3675-5p	hsa-miR-3184-5p
		hsa-miR-7159-3p	hsa-miR-3185
		hsa-miR-3655	hsa-miR-3065-3p
		hsa-miR-578	hsa-miR-3186-3p
		hsa-miR-4703-5p	hsa-miR-3187-5p
		hsa-miR-3942-5p	hsa-miR-3187-3p
		hsa-miR-4766-3p	hsa-miR-3188
		hsa-miR-3908	hsa-miR-3189-3p
		hsa-miR-1826	hsa-miR-3190-5p
		hsa-miR-4704-3p	hsa-miR-3190-3p
		hsa-miR-3117-3p	hsa-miR-3191-3p
		hsa-miR-8083	hsa-miR-3192-5p
		hsa-miR-4759	hsa-miR-3192-3p
		hsa-miR-3169	hsa-miR-3193
		hsa-miR-6817-5p	hsa-miR-3194-3p
		hsa-miR-4769-3p	hsa-miR-3196
		hsa-miR-3155b	hsa-miR-3198
		hsa-miR-3155a	hsa-miR-3199
		hsa-miR-484	hsa-miR-3200-3p
		hsa-miR-5700	hsa-miR-514b-5p
		hsa-miR-4756-3p	hsa-miR-3202
		hsa-miR-3919	hsa-miR-4297
		hsa-miR-3190-5p	hsa-miR-378c
		hsa-miR-320e	hsa-miR-4294
		hsa-miR-1324	hsa-miR-4299
		hsa-miR-5581-5p	hsa-miR-4298
		hsa-miR-4297	hsa-miR-4300
		hsa-miR-3609	hsa-miR-4304
		hsa-miR-548ah-5p	hsa-miR-4302
		hsa-miR-548t-5p	hsa-miR-4303
		hsa-miR-548ac-5p	hsa-miR-4306
		hsa-miR-548n	hsa-miR-4309
		hsa-miR-302a-5p	hsa-miR-4308
		hsa-miR-3160-5p	hsa-miR-4312
		hsa-miR-7155-3p	hsa-miR-4313
		hsa-miR-3136-3p	hsa-miR-4315
		hsa-miR-7160-3p	hsa-miR-4316
		hsa-miR-3918	hsa-miR-4314
		hsa-miR-150-3p	hsa-miR-4319
		hsa-miR-6579-5p	hsa-miR-4320
		hsa-miR-6728-5p	hsa-miR-4322
		hsa-miR-5187-5p	hsa-miR-4324
		hsa-miR-769-3p	hsa-miR-4258
		hsa-miR-6513-5p	hsa-miR-4259
		hsa-miR-4506-3p	hsa-miR-4251
		hsa-miR-5089-5p	hsa-miR-4255
		hsa-miR-1283	hsa-miR-4252
		hsa-miR-187-5p	hsa-miR-4326
		hsa-miR-4633-3p	hsa-miR-4265
		hsa-miR-6500-5p	hsa-miR-4266
		hsa-miR-3139	hsa-miR-4267
		hsa-miR-708-5p	hsa-miR-2355-3p
		hsa-miR-28-5p	hsa-miR-4269
		hsa-miR-205-5p	hsa-miR-4264
		hsa-miR-4470	hsa-miR-4270
		hsa-miR-183-5p.1	hsa-miR-4271
		hsa-miR-6832-3p	hsa-miR-4274
		hsa-miR-4790-3p	hsa-miR-4277
		hsa-miR-545-3p	hsa-miR-4278
		hsa-miR-3120-3p	hsa-miR-4283
		hsa-miR-1227-3p	hsa-miR-4289
		hsa-miR-1914-5p	hsa-miR-4290
		hsa-miR-649	hsa-miR-4291
		hsa-miR-490-3p	hsa-miR-4329
		hsa-miR-9-3p	hsa-miR-4330
		hsa-miR-5003-3p	hsa-miR-5000-3p
		hsa-miR-8067	hsa-miR-3605-5p
		hsa-miR-6508-5p	hsa-miR-3609
		hsa-miR-518d-5p	hsa-miR-3612
		hsa-miR-518f-5p	hsa-miR-3613-3p
		hsa-miR-520c-5p	hsa-miR-3614-3p
		hsa-miR-526a	hsa-miR-3616-3p
		hsa-miR-4777-5p	hsa-miR-3617-3p
		hsa-miR-5190-5p	hsa-miR-3619-5p
		hsa-miR-523-5p	hsa-miR-3619-3p
		hsa-miR-519c-5p	hsa-miR-3620-3p
		hsa-miR-519a-5p	hsa-miR-3621
		hsa-miR-522-5p	hsa-miR-3622b-5p
		hsa-miR-519e-5p	hsa-miR-3622b-3p
		hsa-miR-196a-3p	hsa-miR-3648
		hsa-miR-3688-5p	hsa-miR-3649
		hsa-miR-891a-3p	hsa-miR-3650
		hsa-miR-7108-5p	hsa-miR-3651
		hsa-miR-4474-3p	hsa-miR-3652
		hsa-miR-548aj	hsa-miR-3654
		hsa-miR-548at	hsa-miR-3655
		hsa-miR-570-5p	hsa-miR-3657
		hsa-miR-548ba	hsa-miR-3659
		hsa-miR-6576	hsa-miR-3661
		hsa-miR-6797-3p	hsa-miR-3662
		hsa-miR-20a-3p	hsa-miR-3663-5p
		hsa-miR-6756-3p	hsa-miR-3663-3p
		hsa-miR-3127-3p	hsa-miR-3664-5p
		hsa-miR-584-3p	hsa-miR-3667-5p
		hsa-miR-4671-3p	hsa-miR-3667-3p
		hsa-miR-4473	hsa-miR-3670
		hsa-miR-3991-5p	hsa-miR-3675-5p
		hsa-miR-4286	hsa-miR-3677-5p
		hsa-miR-3943	hsa-miR-3678-3p
		hsa-miR-582-5p	hsa-miR-3679-5p
		hsa-miR-1139-5p	hsa-miR-3679-3p
		hsa-miR-8084	hsa-miR-3680-3p
		hsa-miR-605-3p	hsa-miR-3681-5p

Table S1 (continued)

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Table S1 (continued)

miRDB	StarBase	TargetScan	miRWalk
		hsa-miR-3154	hsa-miR-3682-3p
		hsa-miR-4650-3p	hsa-miR-3683
		hsa-miR-6831-5p	hsa-miR-3684
		hsa-miR-3927-3p	hsa-miR-3685
		hsa-miR-4736	hsa-miR-3688-5p
		hsa-miR-7150	hsa-miR-3689a-3p
		hsa-miR-4763-3p	hsa-miR-3690
		hsa-miR-1207-5p	hsa-miR-3691-5p
		hsa-miR-6868-5p	hsa-miR-3691-3p
		hsa-miR-2000-3p	hsa-miR-3692-5p
		hsa-miR-7158-3p	hsa-miR-3692-3p
		hsa-miR-4499	hsa-miR-3180
		hsa-miR-4494	hsa-miR-3689b-3p
		hsa-miR-4687-3p	hsa-miR-3908
		hsa-miR-759	hsa-miR-3909
		hsa-miR-150-3p	hsa-miR-3911
		hsa-miR-3929	hsa-miR-3912-3p
		hsa-miR-4419b	hsa-miR-3913-3p
		hsa-miR-4478	hsa-miR-3914
		hsa-miR-3200-5p	hsa-miR-3916
		hsa-miR-1273g-3p	hsa-miR-3917
		hsa-miR-4252	hsa-miR-3918
		hsa-miR-8485	hsa-miR-3150b-5p
		hsa-miR-603	hsa-miR-3150b-3p
		hsa-miR-3713	hsa-miR-3921
		hsa-miR-7223-5p	hsa-miR-3922-5p
		hsa-miR-5681b	hsa-miR-3922-3p
		hsa-miR-1827	hsa-miR-3924
		hsa-miR-1255a	hsa-miR-3925-5p
		hsa-miR-12556-5p	hsa-miR-3925-3p
		hsa-miR-3920	hsa-miR-3927-3p
		hsa-miR-29a-5p	hsa-miR-3928-5p
		hsa-miR-577	hsa-miR-3928-3p
		hsa-miR-4653-3p	hsa-miR-3929
		hsa-miR-34a-3p	hsa-miR-3934-5p
		hsa-miR-3672	hsa-miR-3934-3p
		hsa-miR-6864-3p	hsa-miR-3936
		hsa-miR-873-3p	hsa-miR-3937
		hsa-miR-4503	hsa-miR-3938
		hsa-miR-6792-5p	hsa-miR-3939
		hsa-miR-5009-5p	hsa-miR-3940-5p
		hsa-miR-8058	hsa-miR-3940-3p
		hsa-miR-4641	hsa-miR-3941
		hsa-miR-647	hsa-miR-3943
		hsa-miR-604	hsa-miR-3944-5p
		hsa-miR-6782-3p	hsa-miR-3945
		hsa-miR-3149	hsa-miR-374c-5p
		hsa-miR-548x-3p	hsa-miR-642b-3p
		hsa-miR-548aq-3p	hsa-miR-500b-3p
		hsa-miR-548ah-3p	hsa-miR-1268b
		hsa-miR-548am-3p	hsa-miR-378e
		hsa-miR-548j-3p	hsa-miR-548ab
		hsa-miR-548ae-3p	hsa-miR-4418
		hsa-miR-548aj-3p	hsa-miR-378f
		hsa-miR-873-5p.2	hsa-miR-4420
		hsa-miR-6165	hsa-miR-4421
		hsa-miR-8080	hsa-miR-4422
		hsa-miR-1252-5p	hsa-miR-4423-5p
		hsa-miR-6126	hsa-miR-378g
		hsa-miR-6864-5p	hsa-miR-4425
		hsa-miR-4307	hsa-miR-4429
		hsa-miR-15a-3p	hsa-miR-4432
		hsa-miR-1972	hsa-miR-4433a-5p
		hsa-miR-4650-5p	hsa-miR-4433a-3p
		hsa-miR-3664-3p	hsa-miR-4436a
		hsa-miR-4518	hsa-miR-4437
		hsa-miR-1266-5p	hsa-miR-4438
		hsa-miR-4524b-3p	hsa-miR-4440
		hsa-miR-411-5p.1	hsa-miR-4441
		hsa-miR-6869-5p	hsa-miR-4443
		hsa-miR-18b-3p	hsa-miR-4444
		hsa-miR-6831-3p	hsa-miR-4445-5p
		hsa-miR-573	hsa-miR-4446-5p
		hsa-miR-3616-5p	hsa-miR-4446-3p
		hsa-miR-4795-5p	hsa-miR-4447
		hsa-miR-4666a-3p	hsa-miR-4448
		hsa-let-7b-3p	hsa-miR-548aq
		hsa-let-7a-5p	hsa-miR-4450
		hsa-let-7f-1-3p	hsa-miR-548ah-3p
		hsa-miR-98-3p	hsa-miR-4451
		hsa-miR-300	hsa-miR-4453
		hsa-miR-381-3p	hsa-miR-4457
		hsa-miR-1185-1-3p	hsa-miR-378h
		hsa-miR-1185-2-3p	hsa-miR-3130b
		hsa-let-7f-2-3p	hsa-miR-4463
		hsa-miR-218-5p	hsa-miR-4466
		hsa-miR-636	hsa-miR-4467
		hsa-miR-8066	hsa-miR-4468
		hsa-miR-5687	hsa-miR-4472
		hsa-miR-6503-3p	hsa-miR-4475
		hsa-miR-4436a	hsa-miR-4476
		hsa-miR-5000-3p	hsa-miR-4477b
		hsa-miR-4529-3p	hsa-miR-4478
		hsa-miR-1269a	hsa-miR-3689c
		hsa-miR-1269b	hsa-miR-3150a
		hsa-miR-422-5p	hsa-miR-548ak
		hsa-miR-4263	hsa-miR-4480
		hsa-miR-576-5p	hsa-miR-4481
		hsa-miR-502-3p	hsa-miR-4482-5p
		hsa-miR-501-3p	hsa-miR-4483
		hsa-miR-215-3p	hsa-miR-4484
		hsa-miR-6773-3p	hsa-miR-4487
		hsa-miR-6719-3p	hsa-miR-4489
		hsa-miR-2110	hsa-miR-4490
		hsa-miR-4725-3p	hsa-miR-4491
		hsa-miR-6780b-5p	hsa-miR-4492
		hsa-miR-4271	hsa-miR-4494
		hsa-miR-8089	hsa-miR-4496
		hsa-miR-4667-5p	hsa-miR-4497
		hsa-miR-4700-5p	hsa-miR-4498
		hsa-miR-7155-5p	hsa-miR-4499
		hsa-miR-637	hsa-miR-4500
		hsa-miR-4314	hsa-miR-4502
		hsa-miR-4762-5p	hsa-miR-4503
		hsa-miR-4509	hsa-miR-4506
		hsa-miR-8075	hsa-miR-2392
		hsa-miR-4728-3p	hsa-miR-4507
		hsa-miR-6806-3p	hsa-miR-4508
		hsa-miR-3928-5p	hsa-miR-4510
		hsa-miR-3646	hsa-miR-4512
		hsa-miR-1252-3p	hsa-miR-4513
		hsa-miR-433-3p	hsa-miR-4514
		hsa-miR-6882-5p	hsa-miR-4515
		hsa-miR-6731-3p	hsa-miR-4519
		hsa-miR-7702	hsa-miR-4520-5p
		hsa-miR-151a-3p	hsa-miR-4521
		hsa-miR-6507-3p	hsa-miR-1268b
		hsa-miR-19a-3p	hsa-miR-4524a-5p
		hsa-miR-4474-5p	hsa-miR-4524a-3p
		hsa-miR-5681a	hsa-miR-4525
		hsa-miR-1251-3p	hsa-miR-4526
		hsa-miR-4724-3p	hsa-miR-4528
		hsa-miR-556-3p	hsa-miR-4529-5p
		hsa-let-7c-3p	hsa-miR-4529-3p
		hsa-let-7g-3p	hsa-miR-4530
		hsa-let-7a-2-3p	hsa-miR-4531
		hsa-miR-493-5p	hsa-miR-4533
		hsa-miR-6500-3p	hsa-miR-4534
		hsa-miR-138-1-3p	hsa-miR-378i
		hsa-miR-934	hsa-miR-4535
		hsa-miR-3618	hsa-miR-548am-3p
		hsa-miR-3143	hsa-miR-1587
		hsa-miR-4301	hsa-miR-4536-5p
		hsa-miR-3156-3p	hsa-miR-4536-3p
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		hsa-miR-30e-5p	hsa-miR-4539
		hsa-miR-30a-5p	hsa-miR-3960
		hsa-miR-30d-5p	hsa-miR-3973
		hsa-miR-30c-5p	hsa-miR-3978
		hsa-miR-30b-5p	hsa-miR-4652-3p
		hsa-miR-4495	hsa-miR-4653-5p
		hsa-miR-4802-3p	hsa-miR-4653-3p
		hsa-miR-942-3p	hsa-miR-4635
		hsa-miR-4666a-5p	hsa-miR-4637
		hsa-miR-137	hsa-miR-4638-5p
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		hsa-miR-3177-5p	hsa-miR-4640-5p
		hsa-miR-1755-5p	hsa-miR-4640-3p
		hsa-miR-4712-5p	hsa-miR-4642
		hsa-miR-3925-3p	hsa-miR-4644
		hsa-miR-508-5p	hsa-miR-4646-5p
		hsa-miR-4778-3p	hsa-miR-4646-3p
		hsa-miR-6740-3p	hsa-miR-4647
		hsa-miR-499b-3p	hsa-miR-4648
		hsa-miR-489a-3p	hsa-miR-4649-5p
		hsa-miR-4482-3p	hsa-miR-4649-3p
		hsa-miR-6504-3p	hsa-miR-4650-5p
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		hsa-miR-6858-3p	hsa-miR-4652-5p
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		hsa-miR-5093	hsa-miR-4655-3p
		hsa-miR-5571-5p	hsa-miR-4656
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		hsa-miR-6757-3p	hsa-miR-4658
		hsa-miR-448	hsa-miR-4659a-5p
		hsa-miR-596	hsa-miR-4660
		hsa-miR-671-5p	hsa-miR-4661-5p
		hsa-miR-6079	hsa-miR-4662a-5p
		hsa-miR-6828-5p	hsa-miR-4662a-3p
		hsa-miR-7109-3p	hsa-miR-4659b-3p
		hsa-miR-193a-5p	hsa-miR-4663
		hsa-miR-1182	hsa-miR-4664-3p
		hsa-miR-6882-5p	hsa-miR-4665-3p
		hsa-miR-4477b	hsa-miR-4667-5p
		hsa-miR-26-3p	hsa-miR-4667-3p
		hsa-miR-6838-5p	hsa-miR-4668-3p
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		hsa-miR-16-5p	hsa-miR-4670-3p
		hsa-miR-15a-5p	hsa-miR-4671-3p
		hsa-miR-195-5p	hsa-miR-4672
		hsa-miR-150-5p	hsa-miR-4673
		hsa-miR-4524a-5p	hsa-miR-4674
		hsa-miR-4524b-5p	hsa-miR-4675
		hsa-miR-503-5p	hsa-miR-4676-5p
		hsa-miR-646	hsa-miR-4677-5p
		hsa-miR-6516-3p	hsa-miR-4678
		hsa-miR-548b-3p	hsa-miR-4681
		hsa-miR-3128	hsa-miR-4682
		hsa-miR-5588-5p	hsa-miR-4684-5p
		hsa-miR-4720-5p	hsa-miR-4684-3p
		hsa-miR-4799-3p	hsa-miR-4685-3p
		hsa-miR-3126-3p	hsa-miR-4686
		hsa-miR-1298-3p	hsa-miR-4687-5p
		hsa-miR-4711-3p	hsa-miR-4687-3p
		hsa-miR-576-3p	hsa-miR-4688
		hsa-miR-4432	hsa-miR-4689
		hsa-miR-8087	hsa-miR-4691-5p
		hsa-miR-208a-3p	hsa-miR-4691-3p
		hsa-miR-208b-3p	hsa-miR-4692
		hsa-miR-4539	hsa-miR-4693-5p
		hsa-miR-513b-5p	hsa-miR-4693-3p
		hsa-miR-4740-5p	hsa-miR-4694-5p
		hsa-miR-1288-3p	hsa-miR-4695-5p
		hsa-miR-6115	hsa-miR-4695-3p
		hsa-miR-7850-5p	hsa-miR-4696
		hsa-miR-4520-2-3p	hsa-miR-4700-5p
		hsa-miR-4709-5p	hsa-miR-4700-3p
		hsa-miR-29b-1-5p	hsa-miR-4701-5p
		hsa-miR-1343-3p	hsa-miR-4701-3p
		hsa-miR-6783-3p	hsa-miR-4704-5p
		hsa-miR-3074-5p	hsa-miR-4708
		hsa-miR-1266-3p	hsa-miR-4707-3p
		hsa-miR-886-5p	hsa-miR-4708-5p
		hsa-miR-548z	hsa-miR-4708-3p
		hsa-miR-7161-5p	hsa-miR-4709-5p
		hsa-miR-3620-5p	hsa-miR-4709-3p
		hsa-miR-3920-3p	hsa-miR-2030-3p
		hsa-miR-892-3p	hsa-miR-4711-5p
		hsa-miR-8057	hsa-miR-4712-5p
		hsa-miR-4715-5p	hsa-miR-4713-3p
		hsa-miR-3651	hsa-miR-4713-2p
		hsa-miR-4576	hsa-miR-4714-3p
		hsa-miR-6027	hsa-miR-4715-5p
		hsa-miR-7-5p	hsa-miR-4715-3p
		hsa-miR-7151-3p	hsa-miR-4716-5p
		hsa-miR-3156-5p	hsa-miR-4716-3p
		hsa-miR-3192-3p	hsa-miR-3529-5p
		hsa-miR-4784	hsa-miR-4717-5p
		hsa-miR-6844-5p	hsa-miR-4717-3p
		hsa-miR-892b	hsa-miR-4718
		hsa-miR-345-5p	hsa-miR-4720-5p
		hsa-miR-1231	hsa-miR-4721

Table S1 (continued)

Table S1 (*continued*)

miRDB	StarBase	TargetScan	miRWalk
		hsa-miR-632	hsa-miR-4722-5p
		hsa-miR-4288	hsa-miR-4722-3p
		hsa-miR-4421	hsa-miR-4520-2-3p
		hsa-miR-5699-3p	hsa-miR-4723-5p
		hsa-miR-6748-3p	hsa-miR-4723-3p
		hsa-miR-3124-3p	hsa-miR-4724-5p
		hsa-miR-2355-3p	hsa-miR-4725-3p
		hsa-miR-4646-3p	hsa-miR-4726-5p
		hsa-miR-330-3p	hsa-miR-4726-3p
		hsa-miR-4804-3p	hsa-miR-4727-5p
		hsa-miR-590-5p	hsa-miR-4727-3p
		hsa-miR-21-5p	hsa-miR-4728-5p
		hsa-miR-8070	hsa-miR-4730
		hsa-miR-5701	hsa-miR-4731-5p
		hsa-miR-8062	hsa-miR-4731-3p
		hsa-miR-4765	hsa-miR-4732-5p
		hsa-miR-1236-5p	hsa-miR-4732-3p
		hsa-miR-3159	hsa-miR-4733-3p
		hsa-miR-125a-3p	hsa-miR-4736
		hsa-miR-766-3p	hsa-miR-4737
		hsa-miR-654-3p	hsa-miR-3064-5p
		hsa-miR-4803	hsa-miR-3064-3p
		hsa-miR-508-3p	hsa-miR-4738-5p
		hsa-miR-6766-3p	hsa-miR-4738-3p
		hsa-miR-219a-5p	hsa-miR-4739
		hsa-miR-4782-3p	hsa-miR-4740-5p
		hsa-miR-4445-5p	hsa-miR-4740-3p
		hsa-miR-490-5p	hsa-miR-4741
		hsa-miR-101-3p.2	hsa-miR-4742-5p
		hsa-miR-101-3p.1	hsa-miR-4742-3p
		hsa-miR-4772-5p	hsa-miR-4743-5p
		hsa-miR-383-5p.2	hsa-miR-4743-3p
		hsa-miR-7154-5p	hsa-miR-4744
		hsa-miR-106a-3p	hsa-miR-122b-5p
		hsa-miR-4502	hsa-miR-4745-3p
		hsa-miR-1468-5p	hsa-miR-4746-5p
		hsa-miR-6760-3p	hsa-miR-4746-3p
		hsa-miR-1208	hsa-miR-4747-5p
		hsa-miR-34b-3p	hsa-miR-4747-3p
		hsa-miR-134-3p	hsa-miR-4748
		hsa-miR-380-3p	hsa-miR-4750-5p
		hsa-miR-606	hsa-miR-4750-3p
		hsa-miR-4320	hsa-miR-4752
		hsa-miR-541-5p	hsa-miR-4753-5p

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hsa-miR-6089
hsa-miR-6124

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		hsa-miR-6129
		hsa-miR-6130
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		hsa-miR-6500-3p
		hsa-miR-548az-5p
		hsa-miR-6501-5p
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		hsa-miR-6722-3p
		hsa-miR-6724-5p
		hsa-miR-892c-3p
		hsa-miR-6726-5p
		hsa-miR-6727-5p
		hsa-miR-6727-3p
		hsa-miR-6728-5p

Table S1 (*continued*)

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Table S1 (continued)

miRDB	StarBase	TargetScan	miRWalk
			hsa-miR-6729-3p
			hsa-miR-6730-5p
			hsa-miR-6730-3p
			hsa-miR-6731-5p
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			hsa-miR-6732-5p
			hsa-miR-6734-5p
			hsa-miR-6735-5p
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			hsa-miR-6736-3p
			hsa-miR-6737-5p
			hsa-miR-6738-5p
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			hsa-miR-6843-3p
			hsa-miR-6845-5p
			hsa-miR-6845-3p
			hsa-miR-6846-5p
			hsa-miR-6846-3p
			hsa-miR-6847-5p
			hsa-miR-6847-3p
			hsa-miR-6848-5p
			hsa-miR-6848-3p
			hsa-miR-6849-5p
			hsa-miR-6850-5p
			hsa-miR-6851-5p
			hsa-miR-6851-3p
			hsa-miR-6852-5p
			hsa-miR-6852-3p
			hsa-miR-6853-5p
			hsa-miR-6853-3p
			hsa-miR-6854-5p
			hsa-miR-6854-3p
			hsa-miR-6855-5p
			hsa-miR-6856-5p
			hsa-miR-6857-5p
			hsa-miR-6858-5p
			hsa-miR-6858-3p
			hsa-miR-6859-5p
			hsa-miR-6760b-5p
			hsa-miR-6760b-3p
			hsa-miR-6861-5p
			hsa-miR-6861-3p
			hsa-miR-6862-5p
			hsa-miR-6862-3p
			hsa-miR-6863
			hsa-miR-6864-3p
			hsa-miR-6865-5p
			hsa-miR-6865-3p
			hsa-miR-6866-5p
			hsa-miR-6866-3p
			hsa-miR-6867-5p
			hsa-miR-6867-3p
			hsa-miR-6868-5p
			hsa-miR-6868-3p
			hsa-miR-6869-5p
			hsa-miR-6870-5p
			hsa-miR-6871-5p
			hsa-miR-6871-3p
			hsa-miR-6872-3p
			hsa-miR-6873-5p
			hsa-miR-6873-3p
			hsa-miR-6874-5p
			hsa-miR-6874-3p
			hsa-miR-6875-5p
			hsa-miR-6876-5p
			hsa-miR-6877-3p
			hsa-miR-6878-5p
			hsa-miR-6878-3p
			hsa-miR-6879-5p
			hsa-miR-6880-5p
			hsa-miR-6881-5p
			hsa-miR-6881-3p
			hsa-miR-6882-5p
			hsa-miR-6883-5p
			hsa-miR-6884-5p
			hsa-miR-6884-3p
			hsa-miR-6885-5p
			hsa-miR-6886-5p
			hsa-miR-6886-3p
			hsa-miR-6887-5p
			hsa-miR-6887-3p
			hsa-miR-6888-5p
			hsa-miR-6888-3p
			hsa-miR-6889-3p
			hsa-miR-6890-5p
			hsa-miR-6891-5p
			hsa-miR-6891-3p
			hsa-miR-6892-5p
			hsa-miR-6893-5p
			hsa-miR-6894-5p
			hsa-miR-6894-3p
			hsa-miR-6895-5p
			hsa-miR-7106-5p
			hsa-miR-7107-5p
			hsa-miR-7107-3p
			hsa-miR-7108-3p

Table S1 (continued)

Table S1 (*continued*)

miRDB	StarBase	TargetScan	miRWalk
			hsa-miR-7109-5p
			hsa-miR-7110-5p
			hsa-miR-7110-3p
			hsa-miR-7111-5p
			hsa-miR-7111-3p
			hsa-miR-7112-3p
			hsa-miR-7113-5p
			hsa-miR-7114-3p
			hsa-miR-7150
			hsa-miR-7152-5p
			hsa-miR-7152-3p
			hsa-miR-7154-5p
			hsa-miR-7154-3p
			hsa-miR-7155-5p
			hsa-miR-7156-5p
			hsa-miR-7156-3p
			hsa-miR-7157-3p
			hsa-miR-7158-5p
			hsa-miR-7161-3p
			hsa-miR-7159-5p
			hsa-miR-7160-3p
			hsa-miR-7162-5p
			hsa-miR-7162-3p
			hsa-miR-7515
			hsa-miR-7703
			hsa-miR-7706
			hsa-miR-7843-5p
			hsa-miR-7843-3p
			hsa-miR-4433b-5p
			hsa-miR-4433b-3p
			hsa-miR-1273h-5p
			hsa-miR-1273h-3p
			hsa-miR-6516-5p
			hsa-miR-6516-3p
			hsa-miR-7844-5p
			hsa-miR-7846-3p
			hsa-miR-7847-3p
			hsa-miR-7849-3p
			hsa-miR-7850-5p
			hsa-miR-7851-3p
			hsa-miR-7852-3p
			hsa-miR-7854-3p
			hsa-miR-7856-5p
			hsa-miR-7977
			hsa-miR-7978
			hsa-miR-8052
			hsa-miR-8055
			hsa-miR-8056
			hsa-miR-8057
			hsa-miR-8059
			hsa-miR-8060
			hsa-miR-8064
			hsa-miR-8065
			hsa-miR-8069
			hsa-miR-8070
			hsa-miR-8073
			hsa-miR-8074
			hsa-miR-8075
			hsa-miR-8077
			hsa-miR-8079
			hsa-miR-8080
			hsa-miR-8082
			hsa-miR-8083
			hsa-miR-8085
			hsa-miR-8086
			hsa-miR-8087
			hsa-miR-8088
			hsa-miR-8485
			hsa-miR-9500
			hsa-miR-9718
			hsa-miR-9898
			hsa-miR-9900
			hsa-miR-9901
			hsa-miR-9902
			hsa-miR-9903
			hsa-miR-9985
			hsa-miR-1843
			hsa-miR-9986
			hsa-miR-10226
			hsa-miR-10396a-3p
			hsa-miR-10397-5p
			hsa-miR-10397-3p
			hsa-miR-10399-3p
			hsa-miR-10400-5p
			hsa-miR-10400-3p
			hsa-miR-10396b-3p
			hsa-miR-10523-5p
			hsa-miR-9983-3p
			hsa-miR-10524-5p
			hsa-miR-10526-3p
			hsa-miR-11181-5p
			hsa-miR-11181-3p
			hsa-miR-11399
			hsa-miR-11401
			hsa-miR-3059-3p
			hsa-miR-3085-5p
			hsa-miR-6529-5p
			hsa-miR-6529-3p
			hsa-miR-9851-5p
			hsa-miR-12114
			hsa-miR-12115
			hsa-miR-12116
			hsa-miR-12117
			hsa-miR-12118
			hsa-miR-12119
			hsa-miR-12120
			hsa-miR-12122
			hsa-miR-12127
			hsa-miR-12128
			hsa-miR-12129
			hsa-miR-12130
			hsa-miR-12131

miRNA, micro RNA.

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Table S2 Names of miRNAs screened from the four databases

miRNAs
hsa-miR-200a-3p
hsa-miR-320b
hsa-miR-214-3p
hsa-miR-181b-5p
hsa-miR-181a-5p
hsa-miR-130a-3p
hsa-miR-141-3p
hsa-miR-148b-3p
hsa-miR-26a-5p
hsa-miR-320d
hsa-miR-92a-3p
hsa-miR-494-3p
hsa-miR-22-3p
hsa-miR-152-3p
hsa-miR-301a-3p
hsa-miR-320c
hsa-miR-181d-5p
hsa-miR-371a-5p
hsa-miR-4429
hsa-miR-216b-5p
hsa-miR-25-3p
hsa-miR-23b-3p
hsa-miR-363-3p
hsa-miR-542-3p

miRNA, micro RNA.

https://dx.doi.org/10.21037/atm-22-628

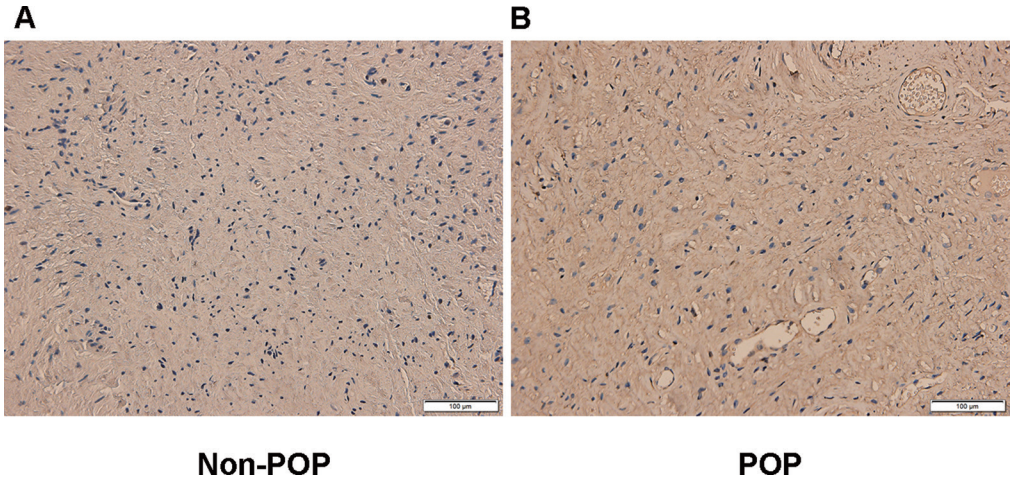

Figure S1 The immunohistochemical staining of AGEs. (A,B) The immunohistochemical staining of AGEs suggested that the extracellular AGEs were increased in the POP tissue compared with the non-POP tissue. Scale bar: 100 μm. POP, pelvic organ prolapse; AGEs, advanced glycation end products.

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