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Study on Catalpol inhibiting PI3K/AKT/NF-κB Signaling Pathway in the Treatment of OA through Anti-senescence of Chondrocytes

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ABSTRACT

The study aimed to explore the therapeutic effect of catalpol on articular chondrocyte senescence and osteoarthritis through cell experiments, and to explore the role of NF-κB and its upstream and downstream pathways in the therapeutic process. Rat primary chondrocytes were isolated. catalpol was added to evaluate cytotoxicity and cell viability, and the optimal catalpol concentration was determined accordingly. IL-1β was added to simulate OA inflammation, establish a cellular senescence model and detect senescence-associated β-galactosidase activity. The proportion of senescent cells, cell cycle distribution, and ROS levels in each group were measured and compared. Western blotting was used to detect the expression of Type II collagen, ADAMTS-5, MMP-13, IL-6, p16, p21, PI3K, p-PI3K, AKT, p-AKT, p65, and p-p65 proteins. After catalpol treatment, the proportion of positive chondrocytes decreased, the proportion of chondrocytes in G0-G1 phase decreased significantly, and the ROS levels of chondrocytes in the inflammatory rat model decreased significantly. IL-1β significantly elevated the expression of IL-6, p16, and p21. However, this effect of IL-1β was inhibited by catalpol. catalpol could significantly inhibit the expression of MMP-13, IL-6, ADAMTS-5, p16, and p21, significantly increased the expression of type II collagen, and significantly inhibited the activation of PI3K/AKT and NF-κB signaling pathways. Catalpol attenuated chondrocyte senescence in an IL-1β-induced in vitro OA model, suppressed PI3K/AKT/NF-κB signaling, and decreased SASP expression. These in vitro findings suggest a potential mechanistic basis for the anti-senescence effects of catalpol on chondrocytes, which requires further validation in animal models and clinical studies before any therapeutic conclusions can be drawn.

Keywords: Catalpol, OA, PI3K/AKT/NF-κB signaling pathway, Chondrocyte senescence, Inflammatory response.

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder worldwide, placing a substantial burden not only on individuals and families, but also on the global healthcare system and economy. With the aging of the global population, the prevalence of obesity and joint injuries has risen, making OA increasingly prevalent. It is estimated that about 250 million people worldwide are affected by OA. However, most patients with OA do not receive adequate treatment. OA is a complex chronic disease, affecting multiple joint tissues. Although numerous treatment options exist for OA, most are palliative and symptomatic. Among the key risk factors for OA, aging is one of the most critical. Targeting senescent joint tissues may be a promising treatment for OA[1-4]. From an orthopaedic perspective, OA is the leading indication for total knee arthroplasty (TKA), with the global volume of procedures projected to rise substantially over the coming decades. Despite advances in surgical techniques, TKA remains a salvage procedure that does not address the underlying disease biology. Identifying disease-modifying strategies that target key pathological mechanisms, such as chondrocyte senescence, is therefore of direct relevance to orthopaedic practice, as they may delay or prevent the progression to end-stage joint disease[5,6]. Published evidence in Acta Orthopaedica Belgica has further highlighted the clinical burden of knee OA managed conservatively and the psychosocial consequences affecting patients who ultimately require arthroplast[7,8], underscoring the unmet need for upstream biological interventions such as those investigated in the present study.

It has been widely accepted that cellular senescence is the main driving factor of aging and related diseases. The senescence process of chondrocytes is similar to that of most cells. Cellular senescence can be induced by stress factors, including genotoxic drugs, nutrient deprivation, mitochondrial dysfunction, and the activation of oncogenes. Senescent cells undergo irreversible growth retardation, but do not lose metabolic activity and can secrete a variety of biologically active molecules—known as the "senescence-associated secretory phenotype", or SASP for short. Studies have shown that SASP plays a beneficial role in wound healing and in stimulating the growth of adjacent cells. However, with the increase of aging, the accumulated senescent cells continue to secrete SASP, leading to a chronic inflammatory state ("inflammaging"), which can promote the occurrence of many hallmark pathological changes of aging[9,10].

METHODS

Extraction, grouping and treatment of chondrocytes

Rat primary chondrocytes were isolated according to standard protocols, with cell grouping as follows: A, the blank control group; B, the IL-1β model group; C, the IL-1β + 5 μM catalpol group; and D, the IL-1β + 20 μM catalpol group. Briefly, articular cartilage was harvested from the femoral condyles of 4-week-old Sprague-Dawley rats under sterile conditions and sequentially digested with 0.25% trypsin (Gibco, USA) for 30 min, followed by overnight incubation with 0.2% type II collagenase (Sigma-Aldrich, USA) at 37°C in DMEM/F-12. Released chondrocytes were filtered through a 70-μm cell strainer, centrifuged, and cultured in DMEM/F-12 supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin at 37°C in 5% CO2. Only passage 1 chondrocytes were used in all experiments to minimize phenotypic drift. 10 μl of IL-1β (1 ng/μl) was added to 10 ml of medium, resulting in a final concentration of 10 ng/ml IL-1β in the medium, which was added to groups B, C, and D for 24 h. This established a cell model mimicking the OA inflammatory microenvironment, which also served as a chondrocyte senescence model.

MTS cell viability and proliferation experiment

The cytotoxicity test was performed using the MTS method according to the manufacturer's instructions, and the absorbance was measured at 492 nm.

Senescence associated β-Galactosidase (SA-β-Gal) Staining

Rat chondrocytes were cultured in a 6-well plate and processed according to the manufacturer's instructions. After incubation, the staining of chondrocytes in each group was observed under a microscope and the percentage of SA-β-Gal-positive cells was calculated: In the ×400 field of view, the SA-β-Gal-positively stained chondrocytes were counted in three random fields.

Cell cycle detection

Chondrocytes in each group were obtained and processed according to the manufacturer's instructions. Then the cell cycle distribution of chondrocytes in each group was analyzed by flow cytometry, and the red fluorescence emission at an excitation wavelength of 488 nm was recorded.

Active oxygen detection

Chondrocytes from each group were prepared and observed directly using a laser confocal microscope according to the manufacturer's instructions. Cells were incubated with 10 μM DCFH-DA (2',7'-dichlorodihydrofluorescein diacetate; Beyotime Biotechnology, Shanghai, China) at 37°C for 20 min in the dark. After washing with serum-free medium, intracellular fluorescence intensity (excitation 488 nm / emission 525 nm) was measured by fluorescence spectrophotometry and quantified using a microplate reader. A fluorescence spectrophotometer and a microplate reader were used for detection.

Western blot detection

Chondrocytes were prepared from each group and processed according to the manufacturer's instructions. Primary antibodies used in this study included: anti-Type II Collagen (1:1000), anti-ADAMTS-5 (1:1000), anti-MMP-13 (1:1000), anti-IL-6 (1:1000), anti-p16^INK4a^ (1:1000), anti-p21 (1:1000), anti-PI3K p85 (1:1000), anti-phospho-PI3K p85 (1:1000), anti-AKT (1:1000), anti-phospho-AKT (Ser473) (1:1000), anti-NF-κB p65 (1:1000), anti-phospho-p65 (Ser536) (1:1000), anti-IκBα (1:1000), and anti-phospho-IκBα (Ser32) (1:1000). HRP-conjugated secondary antibodies were used at 1:5000 dilution. β-actin served as the loading control. Automatic exposure combined with manual exposure mode was used for chemiluminescence detection. Finally, ImageJ software was employed to analyze the gray values of the stored band images.

Statistical analysis

All experiments were performed in three independent biological replicates (n = 3), each using freshly isolated primary rat chondrocytes. Data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using SPSS and GraphPad Prism. The Shapiro-Wilk test was used to assess normality, and Levene's test was used to assess homogeneity of variances. For data meeting both assumptions, one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used for multiple comparisons. For data that failed to meet normality or homogeneity of variance assumptions, the Kruskal-Wallis rank-sum test was applied. A P value < 0.05 was considered statistically significant.

RESULTS

MTS test results

Seven concentration gradients of catalpol (0, 5, 10, 20, 40, 60, and 80 μM) were used in the experiment. The results showed that there were no significant differences in chondrocyte viability between the control group and the treatment groups. Therefore, 5 μM and 20 μM catalpol were used as the drug concentrations for subsequent experiments, as shown in Table I.

Senescence Associated-β-Galactosidase (SA-β-Gal) Staining

In the model group, IL-1β significantly induced senescence in rat chondrocytes, as evidenced by a significant increase in the percentage of SA-β-Gal-positive cells. However, catalpol could significantly reduce the percentage of SA-β-Gal-positive chondrocytes in catalpol-treated groups, as shown in Figure 1.

Cell cycle detection results

The inflammatory induction in the model group significantly increased the proportion of chondrocytes in the G0-G1 phase, and induced cell cycle arrest in chondrocytes, which was a hallmark event of senescence. The proportion of G0-G1 cells in the catalpol treatment groups decreased significantly, indicating that catalpol reduced the degree of chondrocyte cell cycle arrest, and thus alleviated cell senescence, as shown in Table II.

ROS test results

The level of ROS-positive cells in rat chondrocytes in the model group was significantly increased compared with that in the control group. catalpol could significantly reduce the number of ROS-positive chondrocytes. The effect of 20 μM catalpol on reducing the number of ROS-positive chondrocytes was significantly greater than that of the 5 μM catalpol group, as shown in Table III.

Western blot to detect the effect of Catalpol on various proteins

The inflammatory response of chondrocytes was induced in the model group; specifically, the expression of ADAMTS-5, MMP-13, and IL-6 was significantly increased, while the expression of type II collagen was decreased. IL-1β induced chondrocyte senescence, and the expression of senescence markers p16, and p21 was significantly increased. The pro-inflammatory and pro-senescent effects of IL-1β could be inhibited by catalpol, and the anti-inflammatory and anti-senescent effects of 20 μM catalpol were superior to those of 5 μM catalpol, as shown in Figure 2.

IL-1β significantly activated PI3K/AKT and NF-κB signaling pathways; the ratios of p-PI3K/PI3K,

Table I. — The effect of Catalpol on chondrocyte viability in rats.

Group	0 μM	5 μM	10μM	20μM	40μM	80μM
Cell viability (% of Control)	100.00 ± 0.00	112.03 ± 2.62	118.92 ± 3.01	123.22 ± 2.19	102.54 ± 1.18	80.83 ± 1.63

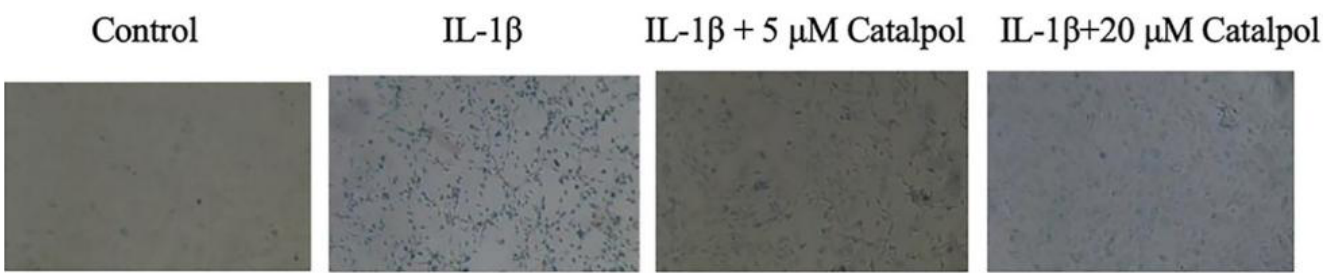

Fig. 1 — The effect of Catalpol on SA-β-Gal positive chondrocytes.

Table II. — Effect of Catalpol on cell cycle.

Group	Control	Model	5μM	20μM
Cell viability (% of Control)	38.45 ± 3.12	57.14 ± 2.41	49.96 ± 1.76	44.25 ± 2.11
** p < 0.01 vs Model ## p < 0.01 vs 5 μM !! p < 0.01 vs 20 μM.				

Table III. — Effect of Catalpol on cell ROS.

Group	Control	Model	5μM	20μM
% ROS Positive cells	4.67 ± 0.17	60.11 ± 0.32	38.91 ± 1.11	21.93 ± 0.94
** p < 0.01 vs Model ## p < 0.01 vs 5 μM !! p < 0.01 vs 20 μM.				

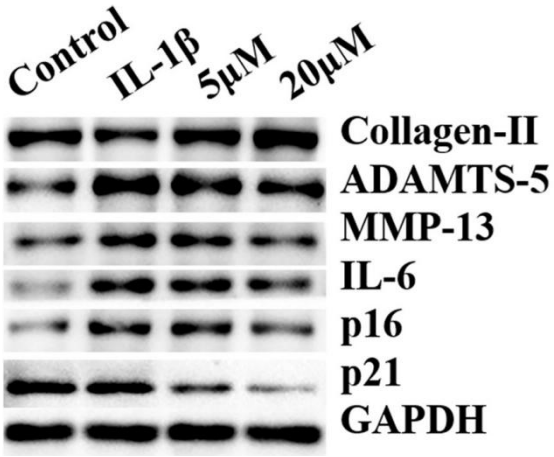

Fig. 2 — The effect of Catalpol on the expression levels of Collagen-II, ADAMTS-5, MMP-13, IL-6, p16 and p21 proteins.

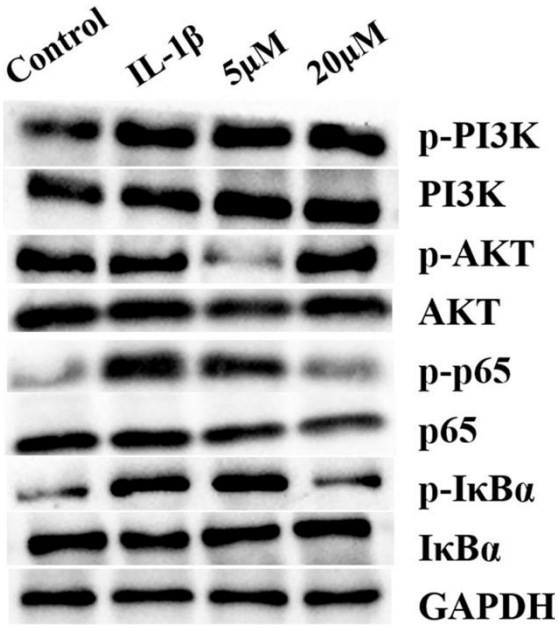

Fig. 3 — The effect of Catalpol on the expressions of PI3K/AKT/NF-κB signaling pathways related proteins.

p-AKT/AKT, p-p65/p65, and the expression of p-IκBα increased significantly, while 5 μM and 20 μM catalpol could significantly inhibit the activation of PI3K/AKT and NF-κB signaling pathways, as shown in Figure 3.

DISCUSSION

This study was designed to evaluate whether catalpol, an iridoid glycoside derived from Rehmannia glutinosa, could attenuate chondrocyte senescence in an IL-1β-induced in vitro osteoarthritis model, and to elucidate the mechanistic role of the PI3K/AKT/NF-κB signaling axis in mediating its effects. Our findings demonstrate that catalpol dose-dependently reduced multiple hallmarks of cellular senescence, suppressed catabolic matrix remodeling, and inhibited the PI3K/AKT/NF-κB pathway, collectively suggesting a senomorphic mechanism of action relevant to OA pathobiology.

The reduction in the proportion of SA-β-Gal-positive cells following catalpol treatment represents one of the most direct indicators of attenuated chondrocyte senescence in our model. SA-β-Gal activity, reflecting enhanced lysosomal biogenesis in senescent cells, is widely regarded as a canonical hallmark of cellular senescence and correlates with OA severity in human cartilage[6,11]. Our observations align closely with studies employing comparable IL-1β-driven models. Chen et al. recently reported that orientin, a natural flavone glycoside, similarly reduced SA-β-Gal positivity in IL-1β-treated chondrocytes through the PI3K/AKT/NF-κB axis[12], Corroborating the feasibility of targeting this pathway with plant-derived compounds. Notably, our data extend these findings by demonstrating that catalpol achieves comparable anti-senescent efficacy while offering a distinct chemical scaffold, which may confer complementary pharmacological advantages.

One of the hallmark features of cellular senescence is irreversible cell cycle arrest, predominantly at the G0/G1 phase. Our cell cycle analysis revealed that IL-1β treatment significantly increased the proportion of chondrocytes in G0/G1, and that catalpol dose-dependently reversed this arrest. These findings are consistent with a recent large-scale review in Bone

Research that mechanistically attributed chondrocyte senescence in OA to p16- and p21-dependent CDK inhibition leading to G1-phase arrest[13]. Importantly, p21-positive senescent cells have been increasingly identified as the predominant senescent subpopulation in degenerated cartilage, and their selective targeting via JAK inhibition has recently been demonstrated to alleviate OA progression in human tissue samples[14]. Our data suggest that catalpol may achieve a functionally similar outcome through upstream pathway inhibition, rather than direct senolytic elimination.

Intracellular ROS accumulation is a well-established driver of stress-induced premature senescence (SIPS) in chondrocytes. In our experiments, catalpol significantly reduced ROS levels in IL-1β-stimulated chondrocytes in a concentration-dependent manner. This result is mechanistically congruent with the established ROS/PI3K/AKT signaling loop, wherein excessive ROS activates PI3K/AKT to propagate catabolic and pro-senescent signals[15]. Several independent studies have confirmed that sustained Akt activation in articular chondrocytes drives ROS accumulation and accelerates OA-like senescent phenotypes[16], And that antioxidant interventions can suppress this cascade, thereby mitigating cartilage degeneration[17]. The present findings specifically establish Catalpol as capable of intercepting the ROS-driven senescence amplification cycle, though the upstream antioxidant mechanism of Catalpol itself warrants further characterization.The upregulation of p16^INK4a^ and p21^CIP1^ in IL-1β-stimulated chondrocytes, and their suppression by Catalpol, provide molecular evidence for the drug's anti-senescence activity at the level of CDK inhibitor expression. Whereas p16 serves primarily as a biomarker of chondrocyte dysfunction and is more abundant in histologically intact cartilage, p21 is increasingly recognized as the functional driver of senescence in actively degenerating cartilage, coordinating both cell cycle arrest and SASP production[18]. The simultaneous suppression of both p16 and p21 by Catalpol, in conjunction with the reduction in the SASP factor IL 6, suggests a broad spectrum anti senescent effect rather than a selective modulation of either pathway. This breadth of activity may be mechanistically advantageous, as targeting either arm alone has shown incomplete efficacy in preclinical models[18].

The catabolic ECM alterations observed in our model, including elevated MMP-13 and ADAMTS-5 expression and reduced type II collagen expression, are well-characterized SASP outputs of senescent chondrocytes. MMP-13 and ADAMTS-5 are the principal collagenase and aggrecanase implicated in irreversible cartilage matrix degradation in osteoarthritis (OA)[19]. Catalpol treatment significantly reversed all three parameters in a dose-dependent manner. Comparable reversal of the MMP-13/ADAMTS-5/type II collagen triad by natural compounds that suppress NF-κB signaling has been reported for orientin as well[12], pterostilbene[20], and the royal jelly-derived compound 10-hydroxydecanoic acid (10-HDA)[21]. While the magnitude of ECM restoration in our model is consistent with these reports, a distinctive feature of the present study is the concurrent documentation of all three markers alongside upstream senescence pathway data in a single experimental platform, providing an integrated mechanistic picture.

The most mechanistically novel contribution of this study lies in the demonstration that Catalpol suppresses the PI3K/AKT/NF-κB signaling cascade, evidenced by reduced p-PI3K/PI3K, p-AKT/AKT, and p-p65/p65 ratios, as well as decreased p-IκBα expression. The PI3K/AKT pathway is positioned upstream of NF-κB and functions as a central hub that integrates pro-inflammatory cytokine signals into transcriptional activation of catabolic and senogenic genes[22]. Sustained AKT activation has been causally linked to chondrocyte senescence in transgenic mouse model[16], while pharmacological inhibition of the pathway has been shown to attenuate both SASP expression and cartilage degradation[12,20]. Our findings specifically demonstrate that Catalpol simultaneously attenuates PI3K/AKT activation and downstream NF-κB p65 phosphorylation, indicating that the compound acts at or upstream of the PI3K node. One plausible mechanistic basis for this upstream activity involves ROS-mediated regulation of phosphatase and tensin homolog (PTEN), the principal lipid phosphatase that opposes PI3K signaling. Excessive intracellular ROS can oxidize and inactivate PTEN, thereby enabling unopposed PI3K/AKT activation in stressed chondrocytes[23]. By reducing ROS levels, catalpol may indirectly restore PTEN function and attenuate PI3K phosphorylation. This inference is supported by our concurrent observation that ROS suppression and PI3K/AKT inhibition occurred in parallel across catalpol-treated groups, suggesting a ROS–PTEN–PI3K mechanistic cascade rather than a direct kinase-level interaction. Whether catalpol acts through a direct antioxidant mechanism, modulation of antioxidant enzyme expression (e.g., SOD, catalase), or upstream regulatory signals to achieve PTEN

restoration warrants further investigation, for example through PTEN activity assays or selective PI3K isoform inhibition studies. This is mechanistically distinct from compounds that target only the NF-κB subunit directly, and thus may offer broader regulatory coverage of the senescence-inflammation axis[24].

This study provides the first in vitro evidence that Catalpol functions as a senomorphic agent in chondrocytes, suppressing the SASP through PI3K/AKT/NF-κB inhibition without inducing apoptosis at the tested concentrations. In the current therapeutic landscape, no disease-modifying OA drug (DMOAD) has achieved clinical approval, and senomorphic strategies have emerged as a promising pharmacological frontier. Compared with established senomorphics such as pterostilbene and rapamycin, Catalpol offers favorable safety data from its longstanding use (removing redundant "traditional") and emerging neuroprotective and anti-inflammatory profiles. However, several limitations must be acknowledged. This study was conducted exclusively in primary rat chondrocytes using an IL-1β-induced model, which may not fully recapitulate the complexity of in vivo OA, particularly the biomechanical and multicellular contributions of subchondral bone, synovium, and immune cells. Future studies employing animal OA models, human chondrocytes, and intra-articular delivery systems will be required to establish translational relevance and therapeutic feasibility.

CONCLUSIONS

It was found in our study that Catalpol could reduce the degree of senescence of chondrocytes in the IL-1β-induced inflammatory OA model, inhibit the PI3K/AKT/NF-κB signaling pathway, and reduce the expression of SASP, suggesting a potential mechanistic pathway through which Catalpol may exert anti-senescence effects on chondrocytes. It is important to note that these conclusions are based solely on in vitro experiments using primary rat chondrocytes. The translational relevance of these findings remains to be established through animal models and prospective clinical studies.

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Ethics declarations: The animal study was approved by The Second Affiliated Hospital of Zhejiang University School of Medicine. The study was conducted in accordance with the local legislation and institutional requirements. No human studies are presented in the manuscript. No potentially identifiable images or data are presented in this study.

REFERENCES

1. Hunter DJ, March L, Chew M. Osteoarthritis in 2020 and beyond: a Lancet Commission. Lancet (London, England). 2020;396(10264):1711-2.
2. Zhang B, Tian L, Xie J, Chen G, Wang F. Targeting miRNAs by natural products: A new way for cancer therapy. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2020;130:110546.
3. Lin Z, Miao J, Zhang T, He M, Wang Z, Feng X, et al. JUNB-FBXO21-ERK axis promotes cartilage degeneration in osteoarthritis by inhibiting autophagy. Aging cell. 2021;20(2):e13306.
4. Blaker CL, Ashton DM, Doran N, Little CB, Clarke EC. Sex- and injury-based differences in knee biomechanics in mouse models of post-traumatic osteoarthritis. Journal of biomechanics. 2021;114:110152.
5. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023;5(9):e508-e22.
6. Diekman BO, Loeser RF. Aging and the emerging role of cellular senescence in osteoarthritis. Osteoarthritis and cartilage. 2024;32(4):365-71.
7. Allaeys C, Arnout N, Van Onsem S, Govaers K, Victor JJAOB. Conservative treatment of knee osteoarthritis. 2020;86(3):412-21.
8. Dong Y, Cai C, Liu M, Liu L, Zhou F. Improvement and prognosis of anxiety and depression after total knee arthroplasty. Acta orthopaedica Belgica. 2024;90(2):211-6.
9. Nagira K, Ikuta Y, Shinohara M, Sanada Y, Omoto T, Kanaya H, et al. Histological scoring system for subchondral bone changes in murine models of joint aging and osteoarthritis. Scientific reports. 2020;10(1):10077.
10. Yu D, Hu J, Sheng Z, Fu G, Wang Y, Chen Y, et al. Dual roles of misshapen/NIK-related kinase (MINK1) in osteoarthritis

subtypes through the activation of TGFβ signaling. Osteoarthritis and cartilage. 2020;28(1):112-21.
11. Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. Nature reviews Rheumatology. 2016;12(7):412-20.
12. Chen H, Liu S, Xing J, Wen Y, Chen L. Orientin alleviates chondrocyte senescence and osteoarthritis by inhibiting PI3K/AKT pathway. Bone & joint research. 2025;14(3):245-58.
13. Han Z, Wang K, Ding S, Zhang M. Cross-talk of inflammation and cellular senescence: a new insight into the occurrence and progression of osteoarthritis. Bone research. 2024;12(1):69.
14. Zhao X, Lin J, Liu F, Zhang Y, Shi B, Ma C, et al. Targeting p21-Positive Senescent Chondrocytes via IL-6R/JAK2 Inhibition to Alleviate Osteoarthritis. Advanced science (Weinheim, Baden-Wurttemberg, Germany). 2025;12(11):e2410795.
15. Bolduc JA, Collins JA, Loeser RF. Reactive oxygen species, aging and articular cartilage homeostasis. Free radical biology & medicine. 2019;132:73-82.
16. Xie J, Lin J, Wei M, Teng Y, He Q, Yang G, et al. Sustained Akt signaling in articular chondrocytes causes osteoarthritis via oxidative stress-induced senescence in mice. Bone research. 2019;7:23.
17. Zhang H, Cai D, Bai X. Macrophages regulate the progression of osteoarthritis. Osteoarthritis and cartilage. 2020;28(5):555-61.
18. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nature reviews Molecular cell biology. 2021;22(2):75-95.
19. Aigner T, Sachse A, Gebhard P, Roach HJAddr. Osteoarthritis: pathobiology—targets and ways for therapeutic intervention. 2006;58(2):128-49.
20. Wang Y, Zhao H, Jia S, Wang Q, Yao W, Yang Y, et al. Senomorphic agent pterostilbene ameliorates osteoarthritis through the PI3K/AKT/NF-κB axis: an in vitro and in vivo study. American journal of translational research. 2022;14(8):5243-62.
21. Geng N, Fan M, Kuang B, Zhang F, Xian M, Deng L, et al. 10-hydroxy-2-decenoic acid prevents osteoarthritis by targeting aspartyl β hydroxylase and inhibiting chondrocyte senescence in male mice preclinically. Nature communications. 2024;15(1):7712.
22. Sun K, Luo J, Guo J, Yao X, Jing X, Guo F. The PI3K/AKT/mTOR signaling pathway in osteoarthritis: a narrative review. Osteoarthritis and cartilage. 2020;28(4):400-9.
23. Xie J, Lin J, Wei M, Teng Y, He Q, Yang G, et al. Sustained Akt signaling in articular chondrocytes causes osteoarthritis via oxidative stress-induced senescence in mice. 2019;7(1):23.
24. Lu H, Fu C, Kong S, Wang X, Sun L, Lin Z, et al. Maltol prevents the progression of osteoarthritis by targeting PI3K/Akt/NF-κB pathway: In vitro and in vivo studies. Journal of cellular and molecular medicine. 2021;25(1):499-509.