HUMAN BIOLOGY
2025, VOL. 95, ISSUE 4
ORIGINAL ARTICLE

MMP-13 At the Crossroads of Inflammation and Catabolism: Unraveling Signaling Cascades in Knee Osteoarthritis

Fan Mo[1], Cheng Xian[1], Xing Huang[1], Dahong Huang[1], Xishan Lu[2], Fucai Su[2], Zhimin Hu [2], Yinghua Chen [1], Kejian Qin[1], Shiyuan Zheng[1], Yuan Yang[1, 2], Shihai Li[2], Chaoxin Liang [2*]*

ABSTRACT

Knee osteoarthritis (KOA) is a prevalent degenerative joint disease characterized by a complex pathogenesis that involves various cytokines, inflammatory responses, and the interplay of multiple signalling pathways. Matrix metalloproteinase-13 (MMP-13) is a critical extracellular matrix-degrading enzyme that plays a significant role in the onset and progression of KOA. This review aims to provide a comprehensive analysis of the role of MMP-13 in knee osteoarthritis, investigating its relationships with cytokines, inflammatory responses, and associated signalling pathways. By elucidating these interactions, we seek to identify novel therapeutic strategies and targets for the management of KOA, thereby contributing to the understanding and treatment of this debilitating condition.

INTRODUCTION

Knee osteoarthritis (KOA) is a prevalent degenerative joint disease that significantly impacts millions of individuals worldwide, characterized by the progressive degradation of articular cartilage, formation of osteophytes, and chronic inflammation within the joint space. Among the various mediators involved in the pathophysiology of KOA, matrix metalloproteinase-13 (MMP-13) has emerged as a critical player. This enzyme is primarily responsible for the degradation of extracellular matrix components, including collagen types II and IX, which are essential for maintaining the structural integrity of cartilage. Elevated levels of MMP-13 have been associated with increased cartilage degradation in KOA patients, making it a potential biomarker for disease progression and a target for therapeutic intervention Kumar P et al. (2023).

Research indicates that the activity of MMP-13 is modulated by various cytokines and inflammatory mediators present in the synovial fluid of osteoarthritic joints. For instance, pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) can upregulate the expression of MMP-13, thereby exacerbating cartilage breakdown Lai QZ et al (2021). Additionally, the signaling pathways activated by these cytokines, including the mitogen-activated protein kinase （MAPK） and nuclear factor kappa B （NF-κB pathways, play a significant role in the regulation of MMP-13 expression and activity Fan Q et al. (2025). Understanding the interplay between MMP-13, cytokines, and these signaling pathways is vital for unraveling the complex mechanisms underlying KOA and developing effective therapeutic strategies.

The role of MMP-13 in KOA extends beyond cartilage degradation; it also influences the inflammatory milieu within the joint. The chronic inflammation associated with KOA can lead to a vicious cycle where increased MMP-13 activity contributes to further inflammation and cartilage destruction Fischer AG et al. (2024). This multifaceted involvement of MMP-13 highlights its potential as a therapeutic target. Inhibitors of MMP-13 are being explored as a means to mitigate cartilage degradation and alleviate symptoms in KOA patients Petrigna L et al. (2024). Furthermore, the identification of genetic polymorphisms related to MMP-13 expression may provide insights into individual susceptibility to KOA and inform personalized treatment approaches Ikeda R et al. (2021).

In conclusion, MMP-13 is a pivotal enzyme in the pathogenesis of knee osteoarthritis, influencing both cartilage degradation and inflammatory processes. A comprehensive understanding of its role, along with the associated cytokines and signaling pathways, is essential for developing targeted therapies aimed at halting the progression of KOA and improving patient outcomes.

[1]Guangxi Medical University Kaiyuan Lingdong Hospital,Nanning,Guangxi,CHINA 530000
[2]Guangxi Hydroelectric Hospital,Nanning, Guangxi, CHINA 530219

Correspondence to: ChaoXin Liang.Guangxi Hydroelectric Hospital,Nanning, Guangxi, Email: 969398318@qq.com

Keywords: MMP-13, knee osteoarthritis, cytokines, inflammation, signaling pathways

Future research should focus on elucidating the molecular mechanisms through which MMP-13 operates and exploring novel therapeutic strategies that can effectively modulate its activity in the context of osteoarthritis.

MAIN BODY

Biological characteristics of MMP-13

MMP-13 is a crucial enzyme involved in the degradation of extracellular matrix (ECM) components, particularly type II collagen, which is a primary constituent of articular cartilage. This enzyme plays a significant role in various physiological and pathological processes, including tissue remodeling, wound healing, and the progression of osteoarthritis (OA). MMP-13 is secreted as an inactive proenzyme and requires proteolytic activation to exert its enzymatic functions. The regulation of MMP-13 activity is complex and involves various signaling pathways, including those activated by pro-inflammatory cytokines such as IL-1β and TNF-α Kumar P et al. (2023). In the context of OA, MMP-13 expression is significantly upregulated, contributing to the degradation of cartilage and the subsequent joint dysfunction associated with this disease Wang XJ et al. (2021).

Structure and Function of MMP-13

MMP-13 is characterized by a conserved structure that includes a pro-domain, a catalytic domain, and a hemopexin-like domain. The catalytic domain contains a zinc-binding site essential for its proteolytic activity, allowing MMP-13 to cleave various ECM components [8]. This enzyme is particularly known for its ability to degrade type II collagen, making it a key player in cartilage breakdown during OA progression. The activity of MMP-13 is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs), which bind to the active form of matrix metalloproteinases （MMPs） and inhibit their enzymatic function [9]. Dysregulation of this balance between MMPs and TIMPs is critical in OA, as excessive MMP-13 activity can lead to significant cartilage degradation and joint dysfunction Hu Q et al. (2021).

The regulatory mechanism of MMP-13 expression

The expression of MMP-13 is regulated at multiple levels, including transcriptional, post-transcriptional, and post-translational mechanisms. Various signaling pathways, such as the NF-ϰB and MAPK pathways, are activated by pro-inflammatory cytokines like IL-1β and TNF-α, leading to increased MMP-13 expression in chondrocytes Hrabia A et al. (2021). Additionally, microRNAs (miRNAs) have been identified as key regulators of MMP-13 expression, with specific miRNAs such as miR-204-5p shown to inhibit MMP-13 levels in osteoarthritic synovial fibroblasts Wang Q et al. (2022). Furthermore, the mechanosensitive adaptor protein Hic-5 has been implicated in the regulation of MMP-13 through its interaction with various signaling pathways in response to mechanical stress Miyauchi A et al. (2023). Overall, the regulation of MMP-13 is a complex interplay of signaling pathways, transcription factors, and non-coding RNAs, reflecting its critical role in the pathogenesis of OA and other degenerative diseases.

Interaction of MMP-13 with Cytokines

Role of Cytokines in OA

In OA, inflammatory cytokines play a pivotal role in the disease's pathogenesis, contributing to cartilage degradation and joint inflammation. Key pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), TNF-α, and interleukin-6 (IL-6) have been shown to be elevated in the synovial fluid of OA patients, correlating with the severity of the disease Kumar P et al. (2023) These cytokines not only promote inflammation but also stimulate MMPs, particularly MMP-13, which is crucial for the breakdown of extracellular matrix components like type II collagen and aggrecan, leading to cartilage loss Lai QZ et al. (2021). The imbalance between pro-inflammatory and anti-inflammatory cytokines is significant, as it can exacerbate the degenerative processes in OA. For instance, while IL-10 and transforming growth factor-beta (TGF-β) serve protective roles, their levels are often insufficient to counteract the effects of pro-inflammatory cytokines in OA Garcia JP et al. (2021).

Furthermore, the inflammatory environment in OA is characterized by the recruitment and activation of immune cells, which release additional cytokines that perpetuate the cycle of inflammation and cartilage degradation. Studies have indicated that macrophages, particularly M1 macrophages, are significant sources of these pro-inflammatory cytokines, further contributing to the inflammatory milieu of OA Hu Q et al. (2024). The chronic inflammation associated with OA not only leads to pain and functional impairment but also influences the progression of the disease, making cytokines potential therapeutic targets for managing OA Liu S et al. (2022). Overall, the role of cytokines in OA is multifaceted, impacting both the inflammatory response and the structural integrity of the joint.

The relationship between MMP-13 and major cytokines

MMP-13, a key enzyme in the degradation of cartilage

has a complex relationship with various cytokines in the context of OA. It is primarily regulated by pro-inflammatory cytokines such as IL-1β and TNF-α, which stimulate its expression in chondrocytes and synovial cells Milaras C et al. (2024). Elevated levels of MMP-13 have been observed in the synovial fluid of OA patients, correlating with the severity of cartilage damage and joint dysfunction [1]. The upregulation of MMP-13 is a response to the inflammatory signals that characterize OA, highlighting its role as a mediator of cartilage degradation.

Moreover, the interaction between MMP-13 and cytokines is bidirectional. While cytokines promote the expression of MMP-13, the activity of MMP-13 can also influence cytokine production. For instance, MMP-13 has been implicated in the release of pro-inflammatory cytokines, thus perpetuating the inflammatory cycle within the joint Lai QZ et al. (2021). This feedback loop underscores the importance of MMP-13 in the pathophysiology of OA, as its activity not only contributes to cartilage breakdown but also enhances the inflammatory response through cytokine signaling.

Additionally, genetic polymorphisms in the MMP-13 gene have been associated with an increased risk of developing OA, suggesting that individual variations in MMP-13 expression can influence susceptibility to the disease Milaras C et al. (2021). Understanding the intricate relationships between MMP-13 and cytokines is crucial for developing targeted therapies aimed at modulating these interactions to slow down the progression of OA and alleviate symptoms. Overall, MMP-13 serves as a critical link between inflammation and cartilage degradation in OA, making it a focal point for therapeutic intervention.

The Role of MMP-13 in Inflammatory Responses

MMP-13 plays a crucial role in the inflammatory processes associated with OA. OA is characterized by the progressive degradation of articular cartilage, which is exacerbated by inflammatory mediators that promote the expression of MMPs, including MMP-13. The inflammatory mechanisms in OA involve various cytokines, such as IL-1β and TNF-α, which can induce the expression of MMP-13 in chondrocytes and synovial cells, leading to increased cartilage degradation and joint dysfunction Kumar P et al. (2021). The activation of MMP-13 contributes to the breakdown of collagen and other extracellular matrix components, which is a hallmark of OA progression. Furthermore, the expression of MMP-13 has been shown to correlate with the severity of knee OA, as higher levels of MMP-13 are found in patients with advanced stages of the disease Lai QZ et al. (2021) This suggests that MMP-13 could serve as a potential biomarker for disease progression and a target for therapeutic interventions aimed at mitigating inflammation and cartilage degradation in OA.

Inflammatory Mechanisms in OA

The inflammatory mechanisms underlying OA are complex and involve a myriad of biochemical pathways and cellular interactions. Key inflammatory mediators, such as IL-1β and TNF-α, are known to activate signaling pathways that promote the expression of MMPs, including MMP-13, in chondrocytes Shi GX et al. (2020). These cytokines trigger a cascade of inflammatory responses that lead to synovial inflammation, cartilage degradation, and pain. In particular, IL-1β has been shown to upregulate MMP-13 expression through the activation of the NF-ϰB signaling pathway, which is crucial for the transcription of various inflammatory genes Cheng X et al. (2021). Additionally, the presence of inflammatory cytokines can create a feedback loop that further exacerbates joint inflammation and cartilage damage, as elevated MMP-13 levels contribute to the breakdown of the extracellular matrix, leading to a vicious cycle of inflammation and degeneration Milaras C et al. (2024). Understanding these inflammatory mechanisms is essential for developing targeted therapies that can effectively manage OA symptoms and slow disease progression.

Regulatory Role of MMP-13 in Inflammatory Responses

MMP-13 not only contributes to cartilage degradation but also plays a regulatory role in the inflammatory responses associated with OA. Studies have shown that MMP-13 can modulate the activity of various pro-inflammatory cytokines, thereby influencing the overall inflammatory environment within the joint Kumar P et al. (2021). For instance, MMP-13 can cleave and inactivate certain cytokines, potentially dampening the inflammatory response. Conversely, its overexpression can lead to enhanced inflammation and further degradation of the cartilage matrix. The regulation of MMP-13 expression is tightly controlled by several factors, including mechanical stress, cytokine signaling, and epigenetic modifications Hu Q et al. (2021). Furthermore, therapeutic interventions aimed at inhibiting MMP-13 activity have shown promise in reducing inflammation and protecting cartilage integrity in preclinical models of OA Cheng X et al. (2021). Therefore, MMP-13 represents a double-edged sword in the context of OA, acting as both a mediator of cartilage degradation and a modulator of inflammatory responses, highlighting its potential as a therapeutic target in

managing OA.

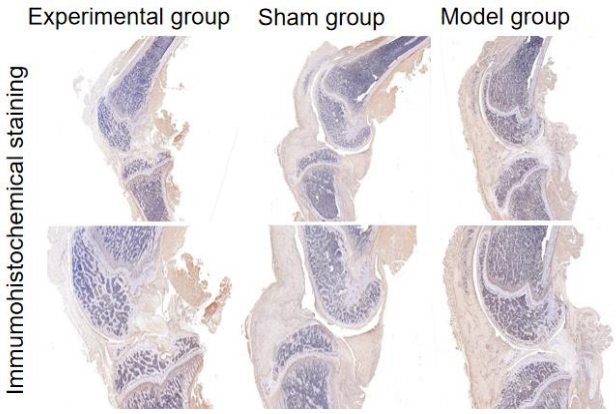
To determine the immunohistochemical expression of MMP-13 in osteoarthritis

To determine the immunohistochemical expression of MMP-13 in osteoarthritis, 30 male SD rats aged 8.5 weeks were selected from the Animal Experiment Center of Guangxi Medical University (License No: SYXK Gui 2020-0004, Ethical Approval No: 202105004). The experimental group (10 rats) underwent no surgical intervention. Twenty SD male rats were anesthetized with 10% chloral hydrate (3 ml/kg) via intraperitoneal injection, and once satisfactory anesthesia was achieved, the rats were placed in a supine position and fixed to the surgical table, followed by routine disinfection and draping. The skin of the left and right hind limbs was shaved with a surgical razor, and the hind limbs were cleaned with gauze soaked in new chlorhexidine, followed by disinfection with iodine. In the model group (10 rats), a 2 cm incision was made parallel to the medial collateral ligament at the left and right knees, with the skin, muscle, and fascia separated in sequence, the joint capsule incised, and the patella displaced at a 90° flexion to open the joint cavity. The anterior cruciate ligament was located and cut with scissors, and a drawer test was performed to ensure complete transection of the anterior cruciate ligament. The joint cavity was flushed with 0.9% sodium chloride solution, and the joint capsule and skin were sutured. In the sham surgery group (10 rats), only the joint capsule was incised without any further treatment, and then sutured. After all rats recovered, they were returned to their cages. One month later, the articular cartilage tissues from each group of rats were dewaxed and activated for enzyme assays, followed by routine paraffin embedding and sectioning.

Knee joint immunohistochemical staining: The paraffin sections were dewaxed to water, followed by antigen retrieval, and placed in a 3% hydrogen peroxide solution for 25 minutes at room temperature in the dark. The slides were washed 3-5 times in PBS (pH 7.4) on a decolorizing shaker, with each wash lasting 5 minutes, and then blocked with serum for 30 minutes. After removing the blocking solution, the prepared primary antibody was added to the sections, which were then incubated in a humid box at 4°C for 12 hours. The corresponding secondary antibody was applied at room temperature for 50 minutes. The slides were washed 3 times in PBS, with each wash lasting 5 minutes. DAB chromogenic solution was added, and the chromogenic time was controlled under a microscope; a brown-yellow color indicated a positive result, after which the slides were rinsed with running water to stop the reaction. The cell nuclei were stained with hematoxylin, dehydrated, and mounted. The expression of MMP-13 related antibodies was detected.

In this study, in the control group, MMP-13 antibody showed positive expression in immunohistochemical staining.See Figure 1.

Figure 1: Immunohistochemical manifestations of osteoarthritis pathology in SD rats.



The signaling pathway of MMP-13

Overview of the main signaling pathways

MMP-13 is a crucial enzyme involved in the degradation of the extracellular matrix (ECM), particularly in the context of OA and other degenerative joint diseases. MMP-13 is primarily regulated by various signaling pathways, including the NF-κB, MAPK, and TGF-β pathways. These pathways are activated by pro-inflammatory cytokines such as IL-1β and TNF-α, which are known to increase MMP-13 expression in chondrocytes, leading to cartilage degradation Hu Q et al. (2021). The activation of these signaling cascades results in the transcriptional upregulation of MMP-13, contributing to the pathological processes associated with OA. Additionally, the Wnt/β-catenin signaling pathway has also been implicated in MMP-13 regulation, where its activation can enhance MMP-13 expression, further promoting cartilage destruction Minghua S et al. (2024). Understanding these signaling pathways is essential for developing therapeutic strategies aimed at inhibiting MMP-13 activity, thereby potentially slowing down the progression of OA and other related diseases.

The role of MMP-13 in signal transduction

MMP-13 plays a significant role in signal transduction processes that modulate inflammatory responses and tissue remodeling in osteoarthritis. Its expression is notably induced by pro-inflammatory cytokines such as IL-1β and TNF-α, which activate various signaling

pathways, including the NF-κB and MAPK pathways Milaras C et al. (2024). Upon activation, these pathways lead to the increased transcription of MMP-13, which in turn contributes to the breakdown of cartilage matrix components, exacerbating joint degeneration. Furthermore, MMP-13 is not only a marker of cartilage degradation but also acts as a mediator in the inflammatory response, influencing the production of other inflammatory cytokines and matrix metalloproteinases Hwang HS et al. (2023). This reciprocal relationship highlights MMP-13's dual role in both promoting cartilage degradation and perpetuating the inflammatory cycle in OA. Inhibition of MMP-13, therefore, presents a promising therapeutic target to mitigate cartilage loss and improve joint function in patients suffering from osteoarthritis [10]. Additionally, recent studies have suggested that targeting the upstream signaling pathways that regulate MMP-13 expression may provide a novel approach to controlling its activity and the subsequent pathological effects in joint diseases Milaras C et al. (2024).

The Potential of MMP-13 as a Therapeutic Target

Current Treatment Strategies

Current treatment strategies for OA primarily focus on symptom management and slowing disease progression, as no definitive cure exists. The conventional approaches include pharmacological interventions such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and analgesics, which aim to alleviate pain and inflammation. Disease-modifying osteoarthritis drugs (DMOADs) are also being explored, although their efficacy remains controversial. In addition to pharmacotherapy, physical therapy and lifestyle modifications, including weight management and exercise, are recommended to improve joint function and overall quality of life. Recent studies have indicated the importance of targeting specific biomarkers associated with OA pathogenesis, such as MMP-13, which is implicated in cartilage degradation. Thus, there is a growing interest in developing targeted therapies that inhibit MMP-13 activity to potentially slow down the progression of OA and preserve joint integrity Kumar P et al. (2021), Lai QZ et al. (2021), Singh A et al. (2021).

Interventional Research Targeting MMP-13

Research targeting MMP-13 has gained traction due to its pivotal role in the degradation of extracellular matrix components, particularly collagen type II in articular cartilage. Various intervention studies have demonstrated the potential of MMP-13 inhibitors in reducing cartilage degradation and inflammation associated with OA. For instance, a study utilizing salvia miltiorrhiza-asarum ointment showed significant reductions in MMP-13 levels alongside improved cartilage integrity in a rat model of knee OA Lai QZ et al. (2021). Additionally, the use of natural compounds such as genistein has been shown to modulate MMP-13 expression, thereby preserving articular cartilage in experimental models Cheng X et al. (2021). Moreover, the development of novel pharmacological agents specifically designed to inhibit MMP-13 is underway, with promising results observed in preclinical trials. These agents aim to selectively target MMP-13 without affecting other MMPs, minimizing potential side effects associated with broad-spectrum MMP inhibition Kumar P et al. (2023), Hu Q et al. (2024). The integration of these targeted therapies into clinical practice could revolutionize the management of OA by addressing the underlying mechanisms of cartilage degradation rather than merely alleviating symptoms.

CONCLUSION

The role of MMP-13 in the pathogenesis of KOA is increasingly recognized as a pivotal area of research. This matrix metalloproteinase is intricately involved in the degradation of cartilage, which is a hallmark of KOA progression. Through its interactions with various cytokines, inflammatory mediators, and signaling pathways, MMP-13 emerges as a potential therapeutic target that could reshape the landscape of OA treatment.

The exploration of MMP-13's functionality has revealed not only its detrimental role in cartilage degradation but also its involvement in the broader inflammatory milieu that characterizes KOA. By dissecting the molecular mechanisms through which MMP-13 operates, researchers can identify new avenues for intervention that may mitigate the disease's progression. This understanding is crucial for developing targeted therapies that are more effective than current treatment modalities, which often focus on symptomatic relief rather than addressing the underlying pathophysiology.

From an expert perspective, balancing the diverse research findings on MMP-13 necessitates a multi-faceted approach. As studies continue to elucidate the complex interactions between MMP-13 and other biological factors, it is essential to integrate these insights into a cohesive framework that informs both basic and clinical research. This involves not only recognizing the potential of MMP-13 as a therapeutic target but also understanding the broader context of its interactions within the joint environment, which includes other matrix metalloproteinases, proteolytic enzymes, and

inflammatory cytokines.

Furthermore, the translation of this research into clinical practice will require rigorous validation of potential therapeutic strategies targeting MMP-13. Clinical trials must be designed to assess the safety and efficacy of these interventions, ensuring that they not only reduce MMP-13 levels but also lead to meaningful improvements in patient outcomes, such as pain relief and enhanced joint function.

In conclusion, the ongoing investigation into MMP-13's role in knee osteoarthritis holds great promise for advancing our understanding of the disease and improving therapeutic approaches. By fostering collaboration among researchers across disciplines and emphasizing the importance of integrating various research perspectives, we can pave the way for innovative strategies that address the complexities of KOA. As we move forward, the commitment to elucidating MMP-13's multifaceted role will be instrumental in enhancing the prognosis for KOA patients and ultimately improving their quality of life.

REFERENCES

1. Kumar P, Kumar S, Abhilasha A, Singh A, et al. 2023. The Role of Matrix Metalloproteinase 13 and Vitamin D in Osteoarthritis: A Hospital-Based Observational Study. Cureus.15(9): e45437.

2. Lai QZ, Zhang XJ, Chen ML, et al. 2021. Salvia miltiorrhiza-asarum ointment combined with Chinese medical massage alleviates symptoms of osteoarthritis in a rat model through the Notch1/ matrix metalloproteinase-13 signaling pathway. J Tradit Chin Med. 41(4):600-07.

3. Fan Q, Zhao M, Zhang XD, et al. 2025. Research progress and prospect of MAPK signaling pathway in knee osteoarthritis. Eur J Orthop Surg Traumatol. 35(1):134.

4. Fischer AG, Titchenal MR, Migliore E, et al. 2024. Elevated proinflammatory cytokines in response to mechanical stimulus are associated with reduced knee loading 2 years after anterior cruciate ligament reconstruction. Clin Biomech (Bristol). 116:106286.

5. Petrigna L, Amato A, Roggio F, et al. 2024.Thermal threshold for knee osteoarthritis people evaluated with infrared thermography: A scoping review. J Therm Biol. 123:103932.

6. Ikeda R, Arimura D, Saito M. 2021. Expression of Piezo mRNA is unaffected in a rat model of knee osteoarthritis. Mol Pain. 17:17448069211014059.

7. Wang XJ, Wei L, Xue Y, et al. 2021. Experimental observation of the sequence of tibial plateau chondrocyte and matrix degeneration in spontaneous osteoarthritis in Guinea pigs. BMC Musculoskelet Disord. 22(1):395.

8. Vassallo V, Di Meo C, Toro G, et al. 2023. Hyaluronic Acid-Based Injective Medical Devices: In Vitro Characterization of Novel Formulations Containing Biofermentative Unsulfated Chondroitin or Extractive Sulfated One with Cyclodextrins. Pharmaceuticals (Basel).16(10).

9. Zheng T, Zhou Q, Huang J, et al. 2021. Xanthohumol Inhibited Mechanical Stimulation-Induced Articular ECM Degradation by Mediating lncRNA GAS5/miR-27a Axis. Front Pharmacol. 12:737552.

10. Hu Q, Ecker M. 2021. Overview of MMP-13 as a Promising Target for the Treatment of Osteoarthritis. Int J Mol Sci. 22(4):1742.

11. Hrabia A, Wolak D, Sechman A. 2021. Response of the matrix metalloproteinase system of the chicken ovary to prolactin treatment. Theriogenology. 169:21-8.

12. Wang Q, Peng J, Liu Y, et al. 2022. Therapeutic effects of alkaloids in Tibetan medicine Bangna (Aconiti Penduli et Aconiti Flavi Radix) on osteoarthritis rats and mechanisms. Zhongguo Zhong Yao Za Zhi. 47(17):4715-22.

13. Miyauchi A, Noguchi M, Lei XF, et al. 2023. Knockdown of mechanosensitive adaptor Hic-5 ameliorates post-traumatic osteoarthritis in rats through repression of MMP-13. Sci Rep. 13(1):7446.

14. Garcia JP, Utomo L, Rudnik-Jansen I, et al. 2021. Association between Oncostatin M Expression and Inflammatory Phenotype in Experimental Arthritis Models and Osteoarthritis Patients. Cells. 10(3):508.

15. Hu Q, Williams SL, Palladino A, et al. 2024. Screening of MMP-13 Inhibitors Using a GelMA-Alginate Interpenetrating Network Hydrogel-Based Model Mimicking Cytokine-Induced Key Features of Osteoarthritis In Vitro. Polymers (Basel). 16(11):1572.

16. Liu S, Deng Z, Chen K, et al. 2022. Cartilage tissue engineering: From proinflammatory and anti-inflammatory cytokines to osteoarthritis treatments (Review). Mol Med Rep. 25(3):99.

17. Milaras C, Lepetsos P, Pampanos A, et al. 2024. The Association of MMP-2, MMP-9, and MMP-13 Gene Polymorphisms with Knee Osteoarthritis in the Greek Population. Cureus.16(7): e65379.

18. Milaras C, Lepetsos P, Dafou D, et al. 2021.

Association of Matrix Metalloproteinase (MMP) Gene Polymorphisms with Knee Osteoarthritis: A Review of the Literature. Cureus.13(10): e18607.

19. Shi GX, Tu JF, Wang TQ, et al. 2020. Effect of Electro-Acupuncture (EA) and Manual Acupuncture (MA) on Markers of Inflammation in Knee Osteoarthritis. J Pain Res. 13:2171-79.

20. Cheng X, Xu P. 2021.The articular cartilage preservative effects of genistein in an experimental model of knees osteoarthritis. Appl Physiol Nutr Metab. 46(11):1331-36.

21. Singh A, Venn A, Blizzard L, et al. 2025. Association between osteoarthritis-related serum biochemical markers over 10-13 years and knee symptoms in middle-aged adults. Mod Rheumatol. 35(3):585-93.

22. Minghua S, Jiwei T, Lei Z, et al. 2024. Wnt5a manipulate the progression of osteoarthritis via MMP-13 dependent signaling pathway. Medicine (Baltimore). 103(50): e40676.

23. Hwang HS, Lee MH, Kim HA. et al. 2021. The TLR-2/TonEBP signaling pathway regulates 29-kDa fibronectin fragment-dependent expression of matrix metalloproteinases. Sci Rep.11(1):8891.

