Deciphering the function and mechanism of extracorporeal shock wave therapy in knee osteoarthritis (Review)

YIXUAN CHEN[1*], SIQI SONG[1*], YUCHEN ZHU[1*], SHIQI WANG[1], JIEYUAN HU[1], CHENXU LIU[1], YUCHEN CAI[1] and YUSHI HU[2,3]

[1]School of Sports Medicine and Health, Chengdu Sport University, Chengdu, Sichuan 641418, P.R. China; [2]Department of Traditional Chinese Medicine Orthopedics, Affiliated Sports Hospital of Chengdu Sport University, Chengdu, Sichuan 610041, P.R. China; [3]Institute of Sports Medicine and Health, Chengdu Sport University, Chengdu, Sichuan 641418, P.R. China

Received June 3, 2026; Accepted August 24, 2026

DOI: 10.3892/ijmm.2026.5980

Abstract. Knee osteoarthritis (KOA) is a chronic, disabling disease with multiple etiologies and a complex pathophysiology. Conservative treatment is the cornerstone of KOA management, and when it proves insufficient, extracorporeal shock wave therapy (ESWT) has emerged as a practical non-invasive alternative. The present narrative review systematically summarizes current preclinical and clinical evidence on ESWT for KOA through a structured literature search, aiming to integrate its therapeutic effects and identify knowledge gaps. Accumulating evidence indicates that ESWT can slow KOA progression through multiple biological pathways, encompassing anti-inflammatory, anti-apoptotic, pro-proliferative and cartilage-protective effects, while also relieving pain and improving function clinically. Summarizing the available data, this review finds that ESWT exhibits a favorable safety profile for articular tissues and disease-modifying potential in preclinical models, although treatment outcomes depend critically on energy flux density and protocol selection. In human studies, the current evidence primarily supports symptomatic relief, including pain reduction and functional improvement; high-quality trials with structural endpoints to verify cartilage regeneration or joint space preservation remain scarce. Given its non-invasive nature, safety and growing clinical support, ESWT merits consideration as an adjunctive therapy. However, heterogeneity in treatment parameters and limited long-term data preclude standardized guidelines. Despite these limitations, ESWT remains a promising adjunctive therapy for patients who are unresponsive to conventional conservative treatments. Future research should prioritize parameter optimization, extended follow-up and translational studies to bridge the gap between preclinical structural findings and clinical application. Addressing these gaps will strengthen the therapeutic role and scientific foundation of ESWT.

Contents

1. Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder worldwide and one of the leading causes of persistent pain and physical disability (1). Its high prevalence imposes heavy burdens on healthcare systems and substantially impairs patients' daily function and quality of life (2). The pathogenesis of OA is complex and varied, involving a number of factors, including age, sex, climate change and lifestyle, all of which play a role in contributing to the onset and progression of the disease (3). In addition, OA predominantly affects weight-bearing and highly mobile joints (4). As a result, the knee is most susceptible to OA (5), as it is the body's most structurally complex and weight-bearing joint. According to global statistics, ~15% of the population is affected by knee osteoarthritis (KOA), which represents a major global cause of movement impairment and disability (6). KOA is marked by the breakdown of joint cartilage, inflammation of the synovial tissue and abnormal alterations in the underlying subchondral bone. To date, there are no effective clinical methods capable of altering the course of this disease (7,8), underscoring the urgent need for safer and more effective treatment options. Clinical management generally follows a stepwise protocol,

Correspondence to: Professor Yushi Hu, Department of Traditional Chinese Medicine Orthopedics, Affiliated Sports Hospital of Chengdu Sport University, 251 Wuhouci Avenue, Wuhou, Chengdu, Sichuan 610041, P.R. China
E-mail: huyushi@cdsu.edu.cn

*Contributed equally

Key words: extracorporeal shock wave therapy, knee osteoarthritis, mechanotransduction, cartilage regeneration

prioritizing conservative approaches before considering invasive procedures (9). For early-stage KOA, non-pharmacological interventions remain the gold standard, valued for their demonstrated efficacy, cost-effectiveness and excellent safety record (10,11). When these measures prove insufficient, extracorporeal shock wave therapy (ESWT) has emerged as a widely investigated non-invasive adjuvant intervention, attracting considerable attention for its therapeutic potential in orthopedic conditions, including KOA (12,13). The different common treatments for KOA are shown in Fig. 1.

ESWT was first introduced in the 1970s for urinary tract lithotripsy (14) and later gained recognition in musculoskeletal medicine following the incidental observation of osteoblastic activity in animal models (15). Today, ESWT is widely investigated for various orthopedic conditions, including KOA (16,17). Notably, while ESWT as an adjunctive treatment for OA was still in the exploratory stage and lacked standardized protocols, veterinary medicine pioneered its application in equine KOA, providing an initial basis for clinical exploration (18). A series of preclinical animal experiments have demonstrated that ESWT intervention can delay pathological progression of KOA, relieve joint pain and improve locomotor function, alongside observable chondroprotective effects in animal OA models (12,19-21). Furthermore, when ESWT was applied to human participants, multiple clinical trials validated its analgesic and functional recovery effects (22-24). Targeting the affected area and transmitting high-energy acoustic pulses into the body of the patient is considered the therapeutic principle of ESWT. As an acoustic high-voltage wave produced through electric, electromagnetic, piezoelectric or ballistic/radial means, ESWT is believed to possess the ability to degrade fibrous tissue, break down calcifications, stimulate blood circulation, promote cell proliferation and repair tissue through its mechanical impact force (25). This biological cascade can improve the metabolism and function of chondrocytes, support cartilage integrity and promote tissue repair (25-27).

Despite encouraging progress, the precise mechanisms by which ESWT exerts its therapeutic effects in KOA remain incompletely understood, and clinical protocols are yet to be standardized. The present review summarizes current preclinical and clinical evidence on ESWT for KOA, with a focus on its biological mechanisms, therapeutic efficacy and parameter optimization. By clarifying the current state of knowledge and identifying key knowledge gaps, the review aims to provide a theoretical framework for future mechanistic investigations and evidence-based clinical decision-making.

2. Search strategy

The present narrative review retrieved literature from PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com), Web of Science (https://www.webofscience.com) and the Cochrane Library (https://www.cochranelibrary.com) from database inception to July 2026. Search terms combined MeSH headings and synonyms using Boolean operators. The specific terms and indexing syntax were adapted to each database's vocabulary (for example, MeSH for PubMed and Cochrane Library, Emtree for EMBASE and topic search for Web of Science). The following are representative examples: Block 1 (knee osteoarthritis): 'osteoarthritis, knee' [MeSH], knee osteoarthritis, gonarthrosis; Block 2 (ESWT): 'extracorporeal shockwave therapy' [MeSH], extracorporeal shock wave, shock wave, ESWT. Terms within each block were linked by OR, and two blocks were combined by AND.

The following inclusion criteria were applied: Studies related to the mechanisms and therapeutic approaches of ESWT in KOA. The following exclusion criteria were applied: Irrelevant studies as screened by title/abstract; studies missing method and/or results details; non-English articles and studies in which ESWT was not used as the primary intervention.

The screening and selection process is summarized in the PRISMA-compliant flow diagram (Fig. 2), which was designed according to the PRISMA 2020 statement (28). A total of 583 records were initially identified. After removing duplicates, 361 records were screened by title and abstract. Of these, 214 full-text articles were assessed for eligibility. Finally, 85 studies met the inclusion criteria and were included in this review.

3. Basic overview of ESWT in KOA

As a form of mechanotherapy, ESWT delivers mechanical pulsed pressure waves to target tissues. Clinically, ESWT can generally be categorized as focused and radial types, both of which have been proven to provide positive outcomes for patients with KOA. In physical terms, both focused and radial waves are forms of mechanical waves, yet they exhibit distinct waveform shapes (29). However, focused waves are more effective than radial waves in influencing deeper tissues (30). Unlike focused waves, radial waves tend to disperse energy over a broader area, affecting shallower tissues, whereas focused waves concentrate on specific deep tissue targets (31). Focused ESWT (f-ESWT) is generated by electromagnetic, electrohydraulic or piezoelectric mechanisms, producing a focused beam shape that converges energy at a defined depth. By contrast, radial ESWT (r-ESWT) is generated pneumatically and produces a diverging beam, with energy peaking at the skin surface and attenuating rapidly with tissue depth (32). As a result, f-ESWT delivers higher energy density to deeper targets, such as the bone-cartilage interface, whereas r-ESWT primarily affects more superficial tissues (30).

These physical distinctions have implications for the clinical application of ESWT across different stages of KOA. From a mechanistic standpoint, f-ESWT appears better suited for treating deep structural pathologies, such as subchondral bone remodeling or bone marrow lesions, where its superior penetration and focal energy delivery may offer a theoretical advantage (33). Conversely, r-ESWT may be preferred for superficial tissue involvement or early-stage KOA, where broad energy dispersion over a larger area may be sufficient for symptom relief (34,35). However, the distinction is not absolute; preliminary evidence also suggests that r-ESWT combined with conventional therapy may provide functional benefits even in advanced KOA (grade IV), though confirmatory studies are still needed (36). Direct comparative evidence between the two waveform types remains limited, and the optimal choice for individual patients should be guided by the predominant pathological features (for example, deep osseous lesions vs. superficial soft-tissue inflammation) and disease severity.

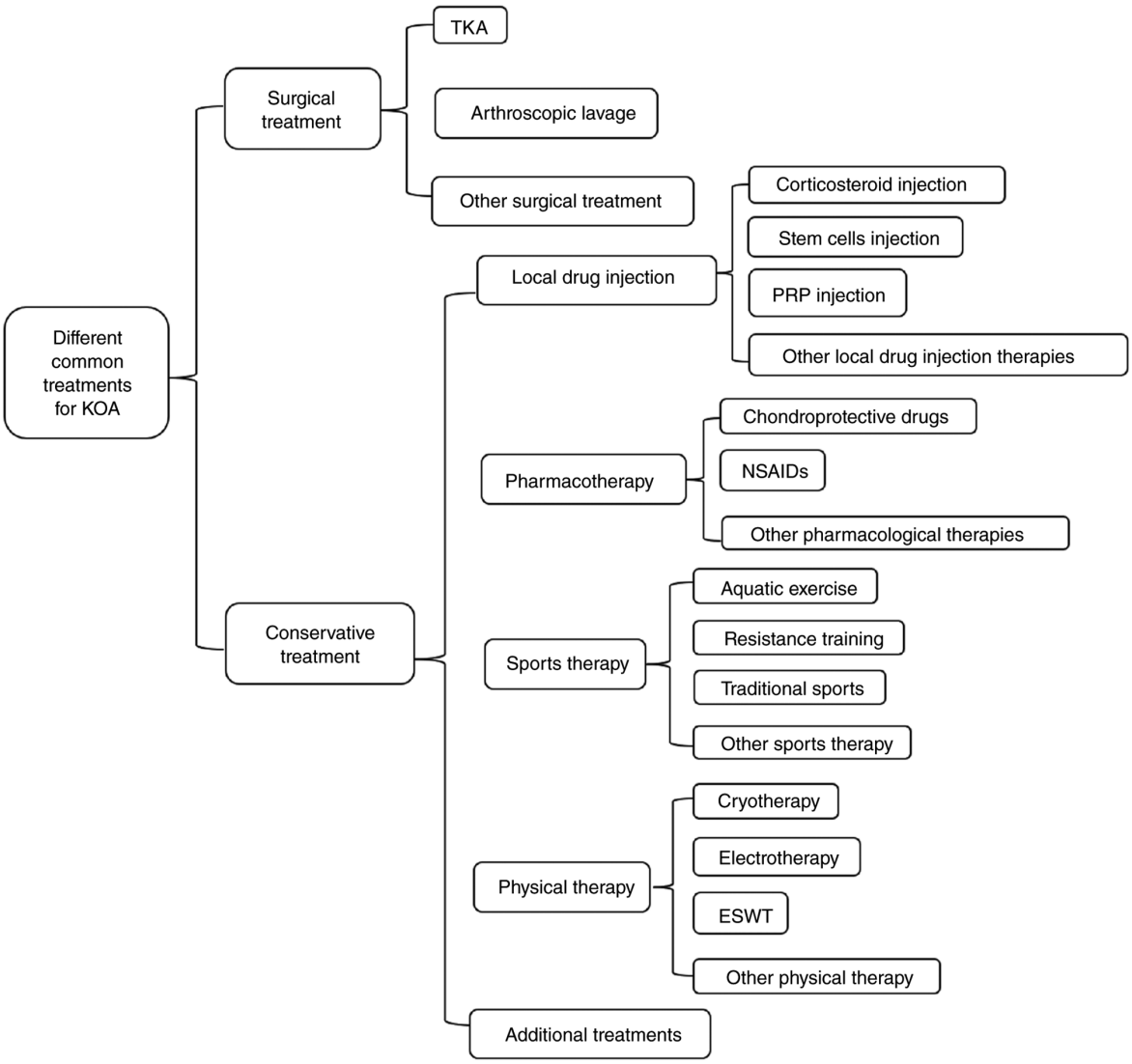

Figure 1. Different common treatments for KOA. KOA, knee osteoarthritis; TKA, total knee arthroplasty; PRP, platelet rich plasma; NSAIDs, non-steroidal anti-inflammatory drugs; ESWT, extracorporeal shock wave therapy.

Despite the physical discrepancies between the two shock wave modalities, the mechanical pulsed stimulation delivered by either type serves as the fundamental trigger for subsequent tissue and cellular biological reactions.

By delivering mechanical stimulation across molecular, cellular and tissue-level structures, it not only alleviates or repairs damage in affected tissues but also promotes the development of healthy tissue (37). The biological response induced by this mechanical stimulation is deemed to be the main pathway by which ESWT exerts treatment efficacy in its clinical applications (38). In the short term, this leads to heightened intracellular tension, enhanced cell adhesion, and increased cell movement (39). The long term outcomes appear to involve various interconnected signaling routes (40). However, the underlying mechanisms of how cells and tissues react to mechanical force signals, as well as how they translate them into intercellular bio-signals that remodel their microenvironments and govern their own behaviors, remain to be thoroughly investigated. Some researchers propose that the theory of cellular mechanotransduction may explain this (41).

The ability of cells to perceive mechanical stimuli within their specific microenvironment is defined as mechanosensation, whereas the process by which cells convert these mechanical signals into corresponding biological responses and adjust their physiological functions is termed mechanotransduction (42). During the administration of ESWT, shock waves exert pressure on the extracellular matrix (ECM), triggering morphological changes and altering interstitial fluid movement. This mechanical pressure also activates sensory units on the cell membrane, leading to cytoskeletal rearrangements that enable direct coupling with force-sensitive ion channels, thereby forming a mechanical signaling pathway (43).

Integrins, which connect the ECM to the cytoskeleton as integral transmembrane proteins, play a pivotal role as mechanical sensors in ESWT-induced signaling processes (44). Cells sense and respond to the physical properties of their surrounding environment through specialized adhesion sites mediated by integrins. At these focal adhesions, integrins function as bridges linking the ECM to the intracellular F-actin cytoskeletal network. Furthermore, they facilitate the transmission of mechanical forces into the ECM through

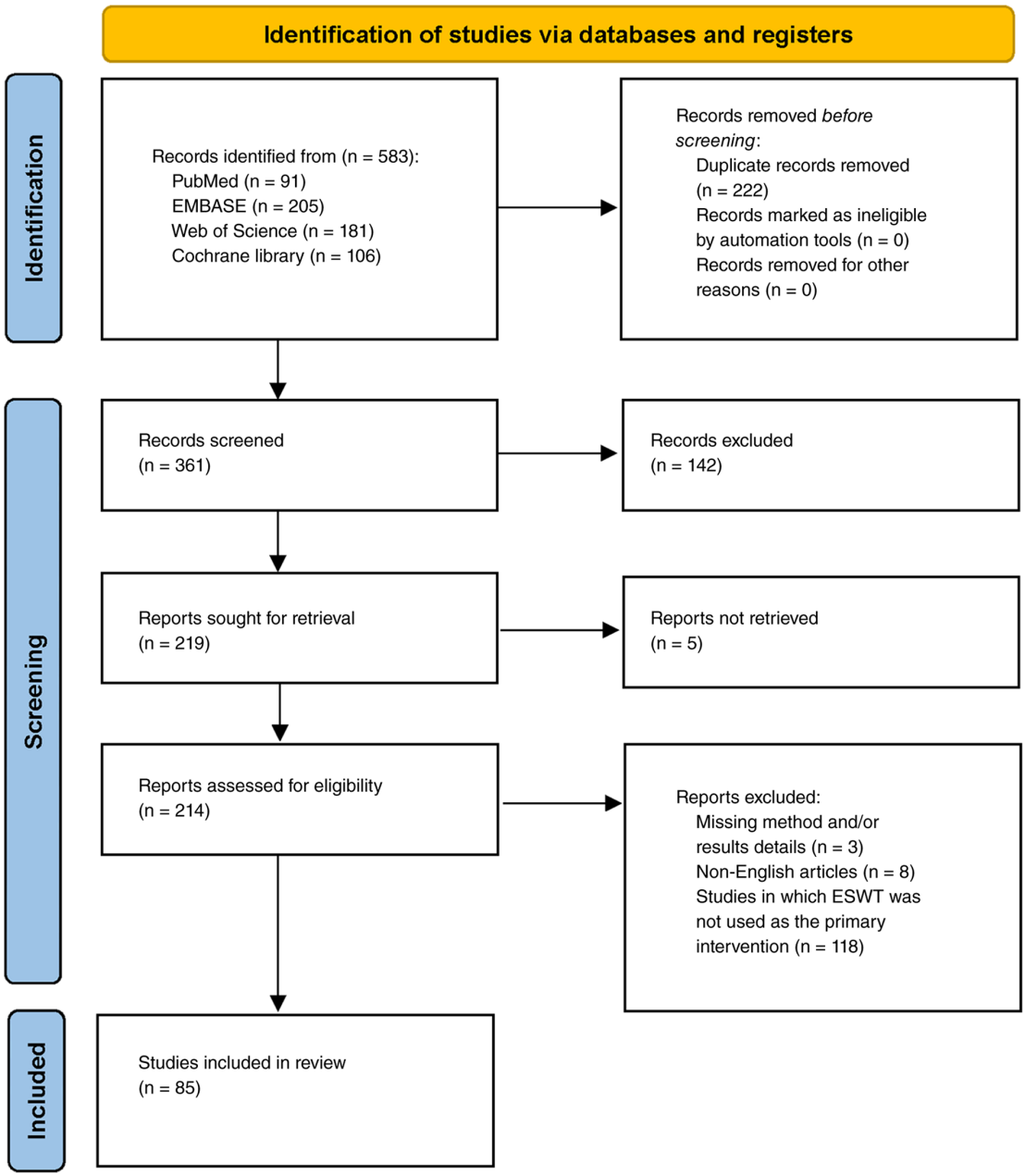

Figure 2. Article retrieval flow chart with inclusion and exclusion process. ESWT, extracorporeal shock wave therapy.

mechanosensitive adherens proteins that function collectively as force-transmitting molecular linkages. This force transmission establishes a dynamic mechanical interplay between the viscoelastic properties of the ECM and intracellular cytoskeletal tension. As mechanotransduction proceeds, these mechanical forces induce conformational changes in mechanosensitive proteins within adhesion complexes, ultimately triggering downstream biochemical signaling cascades that regulate cellular behavior (45).

In addition, ion channels are recognized as important contributors to mechanotransduction. The regulated influx and efflux of ions across the cell membrane support cellular adaptation to mechanical stress by facilitating downstream biochemical responses (46). When cells interpret external mechanical signals, a cascade of biological events is initiated, including modulation of gene expression, regulation of protein synthesis and alterations in cellular metabolism (29). Studies have further demonstrated that ESWT enhances the activity of key growth factors, such as insulin-like growth factor 1, vascular endothelial growth factor (VEGF), bone morphogenetic protein (BMP) and transforming growth factor-β1, all of which are essential for cartilage development, tissue regeneration and cellular proliferation (15,29,30,47). Collectively, these effects substantially broaden the therapeutic potential of ESWT. Fig. 3 illustrates the mediators involved in cellular mechanotransduction, highlighting the contributions of multiple molecules, cellular components and extracellular structures. The mechanotransduction process operates through distinct molecular signaling pathways. As illustrated in Fig. 4, ESWT applies mechanical stimuli to the knee joint affected by KOA. Mechanical cues are sensed by multiple cell-surface sensors that transduce physical force into

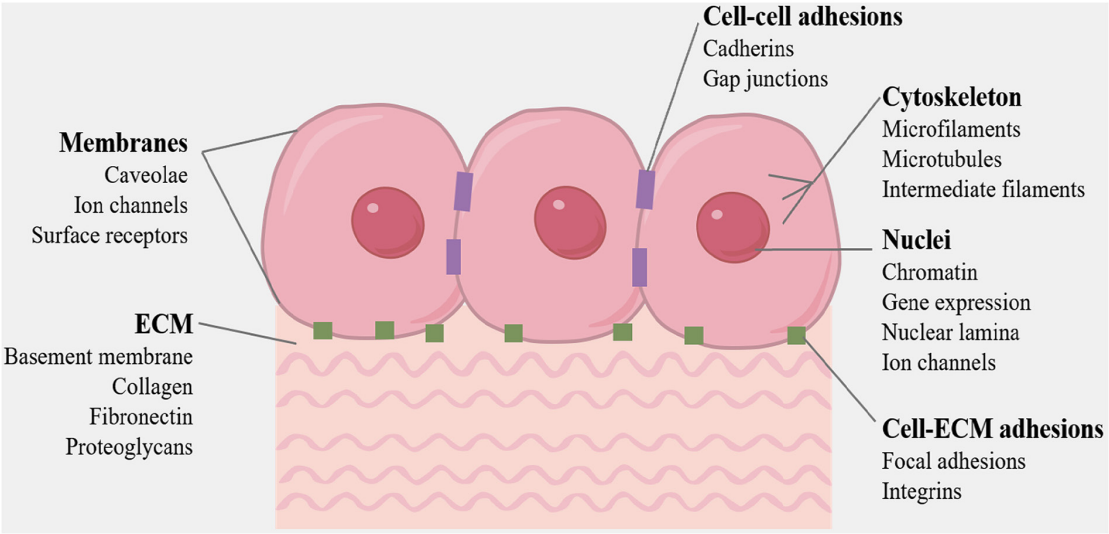

Figure 3. Mediators of cellular mechanical transduction. The mediators involved in cellular mechanical signaling are illustrated, highlighting the roles played by various molecules, cellular components and extracellular structures. The mechanotransduction process operates through distinct molecular signaling pathways. ECM, extracellular matrix.

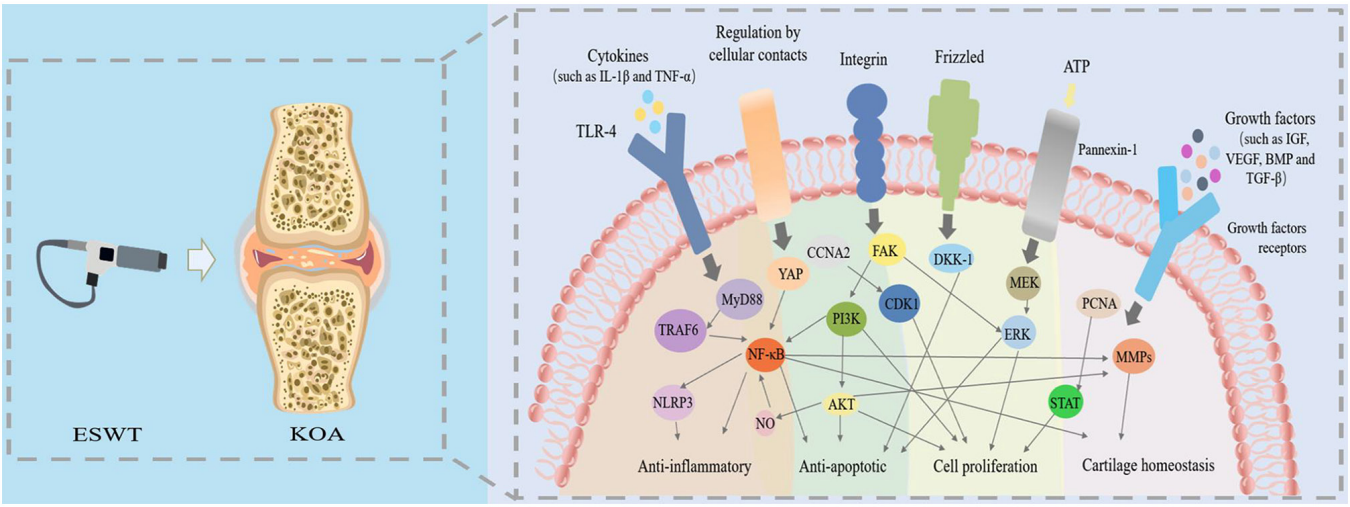

Figure 4. Important signal transduction process of ESWT in KOA. The signal transduction process of ESWT in KOA is illustrated, highlighting the key mechanisms involved in the treatment while omitting less relevant pathways. ESWT, extracorporeal shock wave therapy; KOA, knee osteoarthritis; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; ATP, adenosine triphosphate; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; BMP, bone morphogenetic protein; TGF-β, transforming growth factor-β; MyD88, myeloid differentiation factor 88; TRAF6, TNF receptor-associated factor 6; NLRP3, NOD-like receptor family pyrin domain-containing 3; NF-κB, nuclear factor-κB; NO, nitric oxide; YAP, yes-associated protein; CCNA2, cyclin A2; PI3K, phosphatidylinositol 3-kinase; AKT, serine/threonine kinase (or protein kinase B); FAK, focal adhesion kinase; CDK1, cyclin-dependent kinases 1; DKK-1, dickkopf-1; MEK, mitogen-activated protein/extracellular signal-regulated kinase kinase; ERK, extracellular regulated protein kinases; PCNA, proliferating cell nuclear antigen; STAT, signal transduction and activation of the transcription factor; MMPs, matrix metalloproteinases.

intracellular mechanotransduction signals within joint-resident chondrocytes. Membrane receptors, such as TLR-4, integrin, Frizzled, pannexin-1 channel and growth-factor receptors initiate downstream signaling cascades primarily involving PI3K-AKT, NF-κB and MEK-ERK pathways, among others. This network ultimately drives four principal chondroprotective phenotypes: Suppression of inflammation, inhibition of chondrocyte apoptosis, enhancement of cell proliferation, and preservation of cartilage homeostasis, via regulating effector molecules such as NO, CDK1, PCNA and MMPs (19,39,41,48). Several minor auxiliary signaling branches are excluded from this schematic to highlight core therapeutic mechanisms.

4. Molecular and cellular mechanisms of ESWT in KOA

Cumulative studies have suggested that ESWT may exert a protective effect on KOA through multiple mechanisms, including anti-inflammatory properties, anti-apoptotic effects, promotion of cell proliferation and maintenance of cartilage homeostasis (49-51). Consequently, ESWT has attracted considerable research interest as a potentially valuable complementary and alternative approach for KOA. This review summarizes the most recent studies exploring the molecular mechanisms triggered by ESWT and the signaling pathways involved in managing KOA. This section will outline

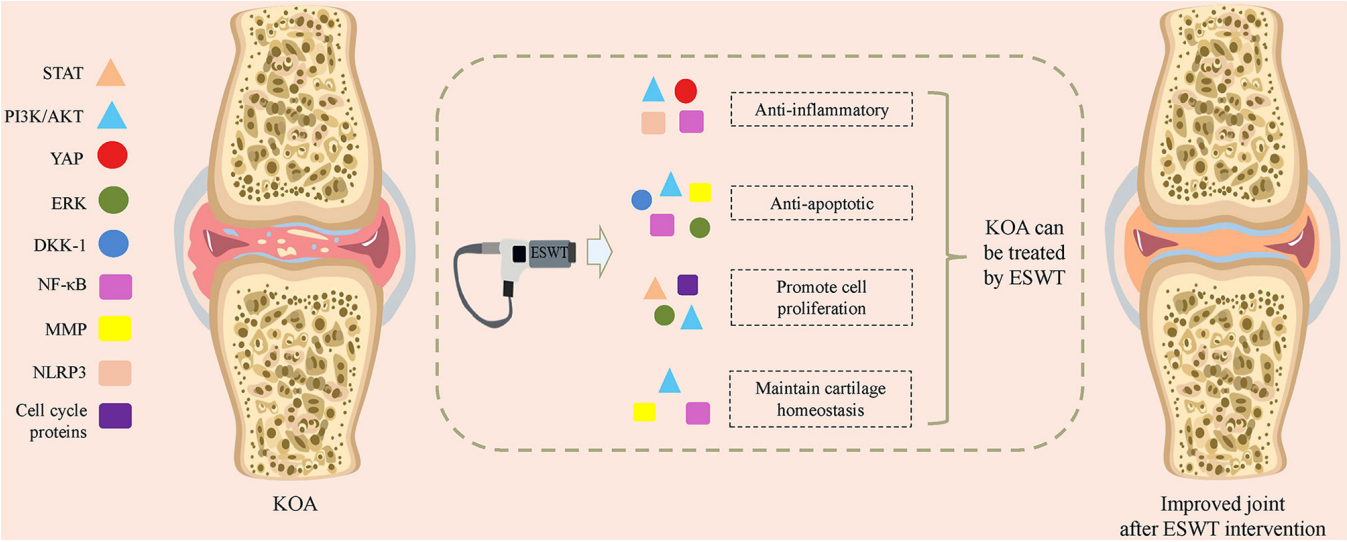

Figure 5. Mechanism of ESWT in KOA. The mechanism of action of ESWT in KOA is illustrated, focusing on the key activities involved in this process and omitting other less relevant mechanism details. ESWT, extracorporeal shock wave therapy; KOA, knee osteoarthritis; STAT, signal transduction and activation of the transcription factor; PI3K/AKT, phosphatidylinositol 3-kinase/serine/threonine kinase/protein kinase B; YAP, yes-associated protein; ERK, extracellular regulated protein kinases; DKK-1, dickkopf-1; NF-κB, nuclear factor-κB; MMP, matrix-metalloproteinase; NLRP3, NOD-like receptor family pyrin domain-containing 3.

the underlying mechanisms through which ESWT may exert its effects on joint tissues. Fig. 5 illustrates the mechanism of ESWT in KOA, focusing on the key activities involved in this process and omitting other less relevant mechanism details.

Anti-inflammatory mechanism of ESWT. In studies examining the pathophysiological progression of KOA, increasing attention has been directed toward anti-inflammatory strategies, with inflammation regulation emerging as a central therapeutic focus (49). Although nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for conservative KOA management (31), their gastrointestinal and cardiovascular adverse events limit long-term application, especially in patients with comorbidities. As a safer alternative physical intervention, ESWT has garnered substantial research attention for its anti-inflammatory efficacy in KOA treatment (52-54). ESWT has been shown to increase the expression of the anti-inflammatory factor IL-10 in chondrocytes and osteoblasts (55,56); furthermore, it reduces the expression of the pro-inflammatory factor tumor necrosis factor α (TNF-α) in chondrocytes, thereby potentially interfering with the pathological mechanisms underlying cartilage damage in OA (56). Existing evidence indicates that ESWT may exert anti-inflammatory effects through activation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway (57). PI3K has been shown to suppress activation of nuclear factor-κB (NF-κB), a key transcription factor responsible for regulating the expression of multiple pro-inflammatory genes (58). Accordingly, inhibition of NF-κB activity is widely regarded as an effective strategy for attenuating inflammatory responses. ESWT is believed to regulate the inflammatory cascade by suppressing NF-κB signaling and its downstream targets, including inducible nitric oxide synthase (iNOS), TNF-α, intercellular adhesion molecule, vascular cell adhesion molecule-1 and cyclooxygenase-2 (COX-2) (54).

NO appears to play a complex role in this regulatory process. Physiological levels of NO contribute positively to immune defense and tissue homeostasis (59), and moderate NO concentrations can exert cytotoxic effects that facilitate the elimination of damaged or invading cells (31). By contrast, excessive NO production can react with superoxide to generate peroxynitrite, a highly reactive molecule that induces severe inflammatory tissue damage (60). Notably, NO can function as a potent inhibitor of NF-κB activation when maintained within low physiological concentrations, typically below 50 nM (61). Although increased NO is observed in osteoarthritic cartilage, evidence suggests that ESWT can modulate NO levels, potentially restoring them to a beneficial physiological range, leading to suppression of NF-κB activity and resolution of inflammation.

In addition, the yes-associated protein (YAP) signaling pathway has been identified as an important negative regulator of NF-κB activity in OA (62). YAP protein has been shown to bind to the transforming growth factor-β-activated kinase 1-IκB kinase (IKK) complex, thereby inhibiting IKKα/β activation and preventing NF-κB nuclear translocation (62). Given that ESWT can activate YAP, as demonstrated in experimental settings (63), this mechanism may further contribute to NF-κB inhibition.

Beyond its regulatory roles as aforementioned, NF-κB signaling is also a key determinant of macrophage phenotype (64). Macrophages are intrinsically mechanosensitive (65) and convert physical stimuli into biochemical signals through mechanosensors such as integrins and ion channels (66). Mechanical stimuli activate cytoskeletal remodeling and downstream transcriptional programs that dictate macrophage polarization (67). Direct evidence for ESWT in this context is emerging. ESWT has been shown to potentially drive the M1-to-M2 phenotypic transition through mechanical transduction that converges on the NF-κB pathway (68-70). Collectively, these findings indicate that ESWT promotes an M1-to-M2 phenotypic shift, likely through mechanotransduction pathways that converge on NF-κB and potentially other

signaling networks. Nevertheless, the tissue-specific molecular regulatory details unique to the complex synovial microenvironment remain to be fully elucidated.

Furthermore, ESWT attenuates inflammatory responses by suppressing toll-like receptor 4 (TLR4) signaling (71). As a pattern recognition receptor, TLR4 plays a critical role in pathogen detection and serves as a key mediator of both innate and adaptive immune responses (72,73). Importantly, focusing on TLR4 as a therapeutic target shows great potential for mitigating inflammation without compromising the body's natural immune defenses (74). TLR4-mediated signaling relies heavily on myeloid differentiation factor 88 (MyD88), which initiates downstream inflammatory signaling upon receptor activation (75,76). MyD88 interacts with TNF receptor-associated factor 6 (TRAF6), leading to NF-κB activation and nuclear translocation, thereby triggering transcription of inflammatory genes (77). Blocking the TLR4/MyD88/NF-κB signaling axis has been shown to markedly reduce inflammatory responses (78).

NF-κB signaling also positively regulates activation of the NOD-like receptor family pyrin domain-containing (NLRP3) inflammasome. Dose-dependent inhibition of NLRP3 activation has been observed following pharmacological blockade of NF-κB, underscoring its essential role in inflammasome initiation (79). Overexpression of NLRP3 promotes the maturation of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18, thereby amplifying inflammation (80). Consistent with these findings, inhibition of NLRP3 activity has been shown to reduce the inflammatory response (81). Together, these studies highlight the role of ESWT in modulating NF-κB-related inflammatory pathways.

Anti-apoptotic mechanism of ESWT. Excessive chondrocyte apoptosis is a pathogenic mechanism of KOA (4), and the number of apoptotic cells correlates with disease severity (82). Therefore, targeting chondrocyte apoptosis offers an effective strategy to limit KOA progression (83). ESWT reduces chondrocyte apoptosis and exerts protective effects on cartilage and subchondral bone (84,85).

Notably, ESWT inhibits expression of dickkopf-1 (DKK-1) protein, a pro-apoptotic factor upregulated in KOA chondrocytes (86). This inhibition reduces apoptosis through at least two downstream pathways: i) Restoring AKT phosphorylation, which inactivates the pro-apoptotic factor B-cell lymphoma-2-associated agonist of cell death (87,88); and ii) enhancing the anti-apoptotic function of Bcl-2, which prevents mitochondrial permeability transition and cytochrome *c* release (89), a mechanism implicated in the pro-survival effects of DKK-1 inhibition (90). *In vitro* experimental results further support the aforementioned mechanism regulating mitochondrial apoptosis. Consistent with the aforementioned signaling cascade, ESWT markedly downregulates the protein levels of cytochrome *c* and caspase-3 in chondrocytes (84). Meanwhile, ESWT efficiently elevates chondrocyte BCL-2 protein expression, strengthening the endogenous anti-apoptotic defense system (85). Collectively, these cellular findings provide functional evidence supporting the anti-apoptotic activity of ESWT and its regulatory effect on mitochondrial apoptotic signaling. Notably, although existing studies have clarified the sequential DKK-1 downstream cascades and verified the corresponding molecular expression changes at the cellular level, two key questions remain unaddressed: i) Whether ESWT directly targets individual downstream signaling molecules and ii) what the hierarchical regulatory relationships among these pathways are. Overall, these findings suggest that ESWT may exert its chondroprotective effects by regulating multiple interconnected upstream and downstream anti-apoptotic signaling pathways through the DKK-1 axis.

Furthermore, ESWT-mediated suppression of NF-κB may contribute to chondroprotection by attenuating pro-apoptotic signaling. Research indicates that NF-κB actively mediates chondrocyte apoptosis in arthritic conditions (91). NF-κB is a central mediator of IL-1β- and TNF-α-driven chondrocyte apoptosis, promoting the expression of catabolic factors [matrix metalloproteinases (MMPs) and COX-2] and pro-apoptotic regulators [Poly(ADP-ribose) polymerase and caspase-3] (92-95). NF-κB also downregulates integrin β1 (93), thereby diminishing cell-matrix interactions and suppressing the protective extracellular regulated protein kinases (ERK)/BCL-2 survival pathway (96-99). While these NF-κB-dependent apoptotic cascades are well characterized in OA, direct evidence linking ESWT to each of these downstream nodes remains incomplete, and further mechanistic studies are needed to clarify which branches are primarily targeted by ESWT.

Pro-proliferative mechanism of ESWT. The decline in chondrocyte proliferation is strongly linked to cartilage degradation, a hallmark sign of advancing arthritis (3,100). ESWT has been shown to enhance the proliferative capacity of chondrocytes, osteoblasts and subchondral bone marrow stem cells to counteract degenerative changes in KOA. These findings suggest that ESWT's ability to stimulate cellular proliferation plays a crucial role in slowing the progression of KOA (29,41). At the molecular level, ESWT upregulates cyclin A2 and its partner cyclin-dependent kinase 1, thereby accelerating the G_1/S-to-G_2/M transition and increasing cell cycle progression (31,101,102). This effect is rapid, with mitotic activity detectable within 24 h and proliferation significantly increased by 72 h (102).

In addition, ESWT can also stimulate cell proliferation through adenosine triphosphate (ATP) release. Mechanical stimulation opens Pannexin-1 channels, leading to ATP release (103). Once released, ATP activates p38 MAPK and mitogen-activated protein/extracellular signal-regulated kinase kinase 1/2-ERK1/2 signaling cascades, which converge to promote cell proliferation (39).

Moreover, ESWT has been reported to promote cell proliferation by increasing the production of proliferating cell nuclear antigen (PCNA) (31). As a non-histone nuclear polypeptide that is crucial for cell proliferation, the intracellular accumulation of PCNA can serve as an indicator of proliferative activity (104). Following ESWT treatment, PCNA expression is markedly upregulated, triggering the signal transducer and activator of transcription 3 (STAT3) signaling pathway (105). STAT3 acts as a crucial intracellular signaling mediator that stimulates the transcriptional activation of numerous genes associated with growth promotion. Ultimately, this cascade of STAT3 activation results in enhanced cell proliferation (106).

Additionally, ESWT enhances cell proliferation through the PI3K/AKT/mTOR pathway, which drives cell cycle progression and division (107-110). The PI3K catalytic subunit p110α may also contribute to cell migration and proliferation independently of AKT (111), suggesting alternative downstream routes.

Cartilage-homeostasis-regulating mechanism of ESWT. It is well established that cartilage homeostasis, the delicate equilibrium between the synthesis and degradation of the ECM in chondrocytes, plays a pivotal role in maintaining joint health (108). Under conditions of accelerated catabolism and diminished anabolism in articular cartilage, the structural integrity of the cartilage matrix will be compromised (83). Research indicates that when the degradation rate of the ECM notably exceeds its synthetic repair capacity, it inevitably drives the onset and progression of pathological processes associated with cartilage degeneration (112). ESWT is considered to stimulate ECM anabolism while reducing catabolism, which aids in maintaining cartilage homeostasis and thus exerts a chondroprotective effect in the progression of KOA (113).

Under normal physiological conditions, there is a delicate equilibrium between the activity of MMPs and the production of new matrix components. In this setting, the expression of MMPs and their natural inhibitors, tissue inhibitors of metalloproteinases (TIMPs), is carefully controlled to maintain harmony with the synthesis of fresh ECM proteins (93). Yet, in the case of arthritis, this equilibrium between synthesis and breakdown is disrupted; unchecked MMP expression and activity cause excessive breakdown of the ECM, ultimately resulting in the destruction of cartilage (114,115). Within the MMP family, MMP-1, MMP-3, MMP-9 and MMP-13 are recognized as the principal mediators driving cartilage matrix degradation and serve as key contributors to both the development and progression of KOA (116). Among these, MMP-13 is primarily expressed by chondrocytes. Compared to other MMPs, MMP-13 exhibits higher catalytic rates on type II collagen and gelatin, enabling it to be the most efficient peptidase among collagenases (117,118). Beyond that, it also facilitates the breakdown of additional cartilage proteins, including type IV collagen, type IX collagen, perlecan, osteonectin and aggrecan, contributing to accelerated cartilage breakdown (119). In addition, it appears that NF-κB is also involved in regulating the MMP-driven matrix degradation.

ESWT is considered to maintain ECM integrity by inhibiting the pathological overexpression of MMPs (120). The regulation of TIMPs is equally critical in this context, as the MMP/TIMP balance ultimately determines the net rate of ECM degradation (121). Since the direct molecular link between ESWT and TIMP-1 upregulation has yet to be fully established, further mechanistic studies are needed.

NF-κB plays a pivotal role in MMP-driven degradation. NF-κB induces catabolic genes via response elements in MMP-1 and MMP-9 promoters (122,123), and suppresses type II collagen and integrin β1 expression (93). NF-κB also activates transcription factors such as ETS domain-containing protein 1 (ELK-1), hypoxia-inducible factor 2α (HIF-2α), and E74-like factor-3 (ELF-3), which further upregulate MMP-13 and other catabolic mediators (124-126). Functioning as a direct target of NF-κB, the transcription factor ELK-1 can directly enhance basic fibroblast growth factor-induced MMP-13 expression in human articular chondrocytes (127). Studies indicate that under HIF-2α activation, this protein interacts with HIF-2β-specific binding sequences within the promoter regions of catabolic genes, thereby promoting the gene expression process of matrix degrading enzymes (124,125,128). Acting downstream of HIF-2α, CCAAT/enhancer-binding protein-β further fuels OA progression by directly upregulating MMP-13 (129). Meanwhile, ELF-3, another NF-κB-dependent factor, modulates the expression of genes such as iNOS, COX-2 and MMP-13, intensifying cartilage degradation (130).

The activation of PI3K/AKT is believed to promote the synthesis and metabolism of the ECM. AKT phosphorylation has been demonstrated to enhance the production of type II collagen and aggrecan within chondrocytes. Additionally, enhanced AKT signaling, whether through direct overexpression or upstream activation, has been shown to increase proteoglycan synthesis (131,132). Overall, the PI3K/AKT pathway serves as a central regulator in the maintenance of cartilage ECM, influencing both ECM synthesis and degradation. Dysregulation of the pathway can contribute to cartilage degradation and the progression of diseases such as osteoarthritis, highlighting the importance of this signaling pathway in the context of cartilage biology and potential therapeutic targets. These findings also suggest the potential of ESWT in treating KOA by activating the PI3K/AKT pathway.

Beyond its use as a standalone treatment, in combination therapy, ESWT increases the *COL2A*/*COL1A* ratio in primary human chondrocytes following hyaluronic acid (HA) administration by inducing CD44 overexpression (133).

5. Preclinical evidence: *In vivo* experimental studies

While the preceding section focused on basic molecular and cellular mechanistic evidence, this section presents the preclinical evidence derived from *in vivo* animal studies that assess proliferation, matrix metabolism and other functional readouts, providing functional validation for the aforementioned mechanisms. Table I summarizes the biological responses to ESWT in predominantly rat models, with one study conducted in rabbits.

Prior studies have found that ESWT exhibits chondroprotective efficacy in the early stages of KOA in rat models (48,134). Notably, further studies have also revealed that this protective effect may be present throughout all stages of KOA development (135). Some preclinical studies suggest possible disease modifying effects (20,27,134,136,137).

Mechanistically, given that ESWT suppresses DKK-1 protein expression, findings from rat KOA models treated with DKK-1-antisense oligonucleotide-mediated DKK-1 inhibition demonstrate that reduced DKK-1 signaling drives nuclear β-catenin accumulation within knee-joint tissues (90), an event that may contribute to the upregulation of pro-survival Bcl-2 and consequent chondrocyte anti-apoptosis. In terms of structural and histological outcomes, ESWT has been shown to enhance cartilage and ECM regeneration while alleviating synovitis in rat models of early KOA (137). These findings are corroborated by improvements in cartilage degradation and bone remodeling, as evidenced by reduced cartilage degradation and restored chondrocyte activity comparable with that of healthy controls (134).

Table I. Biological responses of ESWT in different animal experiments.

Authors, year	Research object type	Models establish	Dosage	Time post operation	Outcome	Conclusion	(Refs.)
Zhao *et al*, 2012	New Zealand white rabbits	ACLT KOA model	Apply three times within 1 week. 600 impulses of shock waves at 1.5x10^5 Pa to the left knee once.	4 and 8 weeks	NO↓, caspase 3↓	ESWT may reduce chondrocyte apoptosis and ultimately slow down the progression of KOA by lowering NO levels.	(19)
Wang *et al*, 2011	Sprague-Dawley rats	ACLT KOA model	EFD of 0.18 mJ/mm^2 for 800 impulses.	12 and 24 weeks	vWF↑, VEGF↑, BMP-2↑	ESWT promoted the regression of KOA in rats.	(20)
Wang *et al*, 2012	Sprague-Dawley rats	ACLT KOA model	EFD of 0.22 mJ/mm^2 for 800 impulses.	0, 2, 4, 8 and 12 weeks	VEGF↑, BMP-2↑, type II collagen↑	ESWT can effectively prevent KOA in rats, but its beneficial effects seem to be time-dependent, starting from 4 weeks after treatment.	(21)
Wang *et al*, 2017	Sprague-Dawley rats	ACLT-MM KOA model	EFD of 0.22 mJ/mm^2 for 800 impulses.	12 weeks	PCNA↑, cartilage area↑, un-calcified cartilage↑, calcified cartilage↓	ESWT promotes cartilage proliferation and improves knee joint cartilage injury.	(27)
Wang *et al*, 2011	Sprague-Dawley rats	ACLT KOA model	EFD of 0.18 mJ/mm^2 for 800 impulses.	0, 4, 8 and 12 weeks	Cell proliferation activity↑, chondrocyte apoptosis↓, cartilage degradation↓	ESWT exerts cartilage protection by promoting cell proliferation, increasing chondrocyte activity, and reducing cartilage degradation and apoptosis.	(134)
Chou *et al*, 2019	Sprague-Dawley rats	Subchondral bone of medial tibia.	EFD of 0.25 mJ/mm^2 for 800 impulses.	12 weeks	TGF-β1↑, DMP-1↓, MMP-13↓, ADAMTS-5↓	ESWT improves tissue regeneration during the progression of KOA lesions.	(137)
Wang *et al*, 2013	Sprague-Dawley rats	ACLT-MM KOA model	EFD of 0.219 mJ/mm^2 for 800 impulses.	12 and 24 weeks	MMP-13↓, type II collagen↑, VEGF↑, BMP-2↑, osteocalcin↑	ESWT can effectively prevent and regress ACLT-induced KOA in rats.	(138)
Wang *et al*, 2014	Sprague-Dawley rats	ACLT-MM KOA model	EFD of 0.22 mJ/mm^2 for 800 impulses.	12 weeks	DKK-1↓, VEGF↑, BMP-2↑, PCNA↑	Early intervention with ESWT can produce cartilage protection during the initial stage of KOA in rats.	(139)

Table I. Continued.

Authors, year	Research object type	Models establish	Dosage	Time post operation	Outcome	Conclusion	(Refs.)
Yılmaz *et al*, 2017	Sprague-Dawley rats	Induction of KOA by injection of MIA	EFD of 0.18 mJ/mm^2 for 800 impulses.	24 h	Osteoblastic activity↑, cell proliferation activity↑	ESWT can promote the proliferation and regeneration of rat cartilage tissue.	(140)
Kim *et al*, 2019	Sprague-Dawley rats	MIA treated chondrocytes	EFD of 0.068 mJ/mm^2 with 500 impulses.	Every 3 days for 2 weeks for a total of four administrations	TNF-α↓, IL-1b↓, IL-6↓, caspase 3↓, Cyt c↓, MMP-3↓, cell viability↑	ESWT exerts a protective effect on cartilage and subchondral bone structures with arthritis by reducing inflammation, cartilage degradation, and chondrocyte apoptosis.	(84)
Cheng *et al*, 2022	Sprague-Dawley rats	ACLT-MM KOA model	EFD of 0.25 mJ/mm^2 with 500 impulses.	Apply ESWT 1 week after surgery.	BV/TV↑, cartilage thickness recovery	ESWT enhances subchondral bone repair while increasing the percentage of trabecular bone volume (BV/TV) and trabecular bone number.	(136)
Chen *et al*, 2025	Sprague-Dawley rats	Induction of KOA by injection of MIA	ESWT was administered at various levels (0.096, 0.128 or 0.16 mJ/mm^2) to determine the optimal dose. The frequency was set at 4 Hz, delivering a total of 800 impulses.	Receive treatment weekly for 4 weeks	Type II collagen↑, MMP-13↓, MMP-3↓, ROS levels↓, G_1 phase cell count↓, G_2 phase cell count↑	ESWT can alleviate the increase in senescence biomarkers in osteoblasts, mitigate redox dysregulation, stabilize the cell cycle and preserve cartilage integrity. The optimal dose in experiments is 0.096 mJ/mm^2	(48)

↑, significant increase; ↓, significant decrease; ESWT, extracorporeal shock wave therapy; EFD, energy flux density; KOA, knee osteoarthritis; ACLT, anterior cruciate ligament transfer; MM, medial meniscectomy; NO, nitric oxide; caspase-3, cysteine-dependent aspartate-specific protease-3; BMP, bone morphogenetic protein; TGF-β1, transforming growth factor-β1; IL, interleukin; DMP-1, dentin matrix protein-1; MMP, matrix metalloproteinase; ADAMTS-5, aggrecanases-5; vWF, von willebrand factor; VEGF, vascular endothelial growth factor; DKK-1, dickkopf-1; PCNA, proliferating cell nuclear antigen; TNF-α, tumor necrosis factor α; CDK2, cyclin-dependent kinases2; MIA, mono-iodo-asetate; Cyt c, cytochrome *c*; BV/TV, bone volume/total volume.

Consistent with these structural observations, ESWT treatment in rat models resulted in changes in cartilage degradation biomarkers and type II collagen that were comparable to those of blank controls, while simultaneously upregulating subchondral bone remodeling markers such as VEGF, BMP-2 and osteocalcin (20,21,84,138). A further study in osteoporotic-associated KOA demonstrated that ESWT increased bone mineral density and bone strength, improved subchondral

plate thickness, reduced excessive subchondral bone porosity and downregulated DKK-1 while elevating PCNA, VEGF and BMP-2 levels (139).

Beyond structural and molecular improvements, ESWT has also been associated with reduced chondrocyte apoptosis in rabbit models (19), as well as systemic proliferative and regenerative effects on cartilage in rat models (27,140). In addition, combination strategies have been explored: ESWT combined with adipose-derived mesenchymal stem cells increased the expression of TIMP-1 and type II collagen in a rat model of KOA (141), further supporting the potential of ESWT to promote ECM anabolism and restore the MMP/TIMP balance at the tissue level.

Cross-comparison of these *in vivo* studies reveals substantial heterogeneity in experimental design. Chou *et al* (137) and Wang *et al* (134) adopted rat OA models with different energy flux densities (0.18-0.25 mJ/mm^2) targeting subchondral bone, whereas Zhao *et al* (19) utilized rabbit models and prioritized chondrocyte apoptosis detection as the primary readout. Such differences in animal species, OA induction protocols, ESWT energy parameters and detection indicators may lead to a variable magnitude of therapeutic effects across different studies, although no contradictory positive protective outcomes have been reported so far.

While the results observed in these studies were generally positive, several methodological limitations should be considered when interpreting this evidence. The observation period varied across studies; some reported results for 4-12 weeks, while others extended the observation period to 24 weeks, providing partial but incomplete evidence of long-term effects. Sample sizes ranged from 6 to 12 animals per group, with the larger studies providing greater statistical power, although the overall number of animals across all studies remains modest. In addition, the energy parameters and treatment protocols varied across the included studies, which complicates direct comparisons and makes it difficult to determine an optimal dosing regimen based on the current data. Notably, despite methodological variations, no major contradictory findings were observed across these studies, suggesting a generally consistent protective effect of ESWT across different experimental conditions. These considerations highlight the need for further standardization in preclinical study design, as well as for translational studies that bridge the gap between animal models and human KOA.

It is also important to distinguish between the structural modifications observed in animal models and the symptomatic improvements reported in human clinical trials. While the preclinical findings suggest potential disease-modifying properties at the structural level, the current evidence in human patients with KOA primarily supports symptomatic relief. Notably, high-quality human trials with serial arthroscopy or quantitative magnetic resonance imaging (MRI) to verify structural changes remain scarce, and there is currently insufficient clinical proof that ESWT induces measurable cartilage regeneration or joint space preservation in patients with KOA. Therefore, the structural effects observed in animal models should not be directly extrapolated to human clinical settings. With this distinction in mind, the following section reviews the clinical evidence for ESWT in KOA.

6. Effects of ESWT on KOA based on clinical studies

The clinical manifestations of KOA typically include persistent pain and physical functional limitations, which markedly impact patients' daily functioning and overall well-being. These persistent symptoms frequently make simple activities challenging. As an emerging treatment for KOA, ESWT has been proven by several studies to be safe and effective in improving knee pain and function in clinical settings (25,142-144). These positive effects can even persist for up to 12 months (145). Moreover, ESWT has been shown to be superior to physical therapy and placebo treatment in enhancing function and relieving pain, positioning it as an effective treatment option for KOA (50,146). Notably, the International Society for Medical Shockwave Treatment guidelines recommend f-ESWT for KOA, with parameters of 2,000-4,000 pulses at 0.25-0.6 mJ/mm^2 applied to the femoral condyle and tibial plateau (147). However, the guidelines' recommendations do not necessarily imply that the other waveform type is without value; clinical responses may vary from patient to patient. For example, Imamura *et al* (148) found that r-ESWT was ineffective for patients with severe pain due to primary KOA, but the study also noted that increasing the energy settings in such cases might improve treatment outcomes. The lack of direct comparative studies precludes a definitive recommendation for one modality over the other in most clinical scenarios, and the choice should remain individualized based on the patient's specific pathological features, disease stage and treatment targets. The effects of ESWT on KOA in clinical studies are shown in Table II.

Pain. Relief of pain is regarded as a prerequisite for maintaining function and is a key factor influencing the healthcare-seeking behavior and treatment plans of patients with KOA (149,150). ESWT has been demonstrated to alleviate pain for KOA patients in clinical settings (25,49,143,145).

Systematic reviews/meta-analyses (SRs/MAs) represent highly valued clinical evidence, and high-quality SRs/MAs govern clinical practice (151). Multiple SRs/MAs have consistently demonstrated the safety and efficacy of ESWT in enhancing knee pain relief (50,142,143,152,153). Among these, the studies by Avendaño-Coy *et al* (153) underscore the superiority of ESWT over conventional or conservative treatments, as reflected by markedly lower pain scores on the visual analog scale (VAS) among patients receiving this intervention. Furthermore, the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system (154) classifies ESWT as a 'moderate' recommendation, reinforcing its role as a viable therapeutic option within evidence-based practice. Yet, most SRs/MAs on ESWT for KOA rely on subjective measures when evaluating its effectiveness. However, these criteria are not consistently defined, which may introduce bias into the findings. Consequently, achieving widespread acceptance of the efficacy of the treatment on an international level is challenging. Most reviews focus solely on immediate outcomes, neglecting to account for the likelihood of relapse, which hinders the evaluation of the lasting effectiveness of ESWT. Furthermore, only a couple of studies touched upon potential side effects, yet both were lacking in comprehensive and standardized safety criteria and were solely concerned

Table II. Effect of ESWT on KOA in clinical studies.

Authors, year	Research object type	Dosage	Time post operation	Outcome	Conclusion	(Refs.)
Zhao *et al*, 2013	70 patients with primary KOA	EFD of 0.25 mJ/mm^2 for 4,000 impulses.	4 times a week for 4 weeks.	VAS Score (pain on movement)↓, WOMAC score (pain, stiffness and limitations in physical function)↓, LI score (disability)↓, perception of clinical severity of OA↑	ESWT effectively reduces pain and improves knee function, having demonstrated superior efficacy to placebo during the 12-week treatment period.	(22)
Kim *et al*, 2015	60 patients with KOA	Low-energy group (n=30, 1,000 impulses/session, EFD/impulse 0.040 mJ/mm^2) or medium-energy group (n=30, 1,000 impulses/session, EFD/impulse 0.093 mJ/mm^2).	Once a week for 3 weeks.	VAS score↓, RM score (disability)↓, WOMAC score↓, LI score↓	Functional scores of both groups notably improved over time (P<0.001), with the medium-energy group improving more than the low-energy group.	(23)
Jhan *et al*, 2022	45 patients with KOA	EFD of 0.22 mJ/mm^2 for 3,000 impulses.	Once every 2 weeks, a total of 3 times.	BMD↑, KOOS score (pain, symptoms, daily living activity ability, leisure and sports function, quality of life)↑, VAS score↓, WOMAC score↓	The pain relief effect of the ESWT group is better than that of the NSAIDs and HA groups.	(52)
Imamura *et al*, 2017	105 women with primary KOA	2,000 impulses per session, EFD of 0.10-0.16 mJ/mm^2.	3 sessions, each 1 week apart.	VAS score↓, WOMAC score↓	Compared with placebo treatment, the ESWT group showed statistically significant improvement only in the WOMAC pain score on the treated side (P=0.038), with no significant difference in VAS score (P=0.132).	(148)
Lee *et al*, 2017	61 patients with KOA	EFD of 0.05 mJ/mm^2 for 1,000 impulses.	3 times a week.	VAS score↓, WOMAC score↓, 40-meter fast-paced walk test completion time↓, 9-step SCT completion time↓, LI score↓	ESWT can be an alternative treatment for reducing pain and improving physical function in patients with KOA (P<0.01).	(168)
Li *et al*, 2018	105 patients with KOA	EFD of 0.11 mJ/mm^2 for 3,000 impulses.	5 sessions with an interval of 3 days for a total of 12 weeks.	NRS score↓, WOMAC score (pain subscale)↓	Compared with laser therapy, ESWT showed greater relief effects on KOA symptoms in terms of NRS, WOMAC scores at 6 weeks (P<0.05) and 12 weeks (P<0.01) after treatment.	(155)

Table II. Continued.

Authors, year	Research object type	Dosage	Time post operation	Outcome	Conclusion	(Refs.)
Lizis *et al*, 2017	40 patients with KOA	EFD of 0.4 mJ/mm^2 for 800 impulses.	Once a week, a total of 5 times.	WOMAC score↓, ROM↑	ESWT is more effective than Kinesiotherapy in improving WOMAC and ROM in patients with KOA.	(175)
Zhong *et al*, 2019	63 patients with KOA	A total of 2,000 impulses of 8-Hz frequency at 2.5 bars.	Once a week for 4 consecutive weeks.	VAS score↓, WOMAC score↓, LI score↓	For patients with mild to moderate KOA, 4-week low-dose ESWT treatment is superior to placebo in relieving pain and improving function, but has some negative effects on joint cartilage.	(146)
Ko *et al*, 2022	42 patients with KOA	During each treatment session, 2,000 impulses are delivered at a frequency of 5 Hz. The intensities used during f-ESWT (0.10 mJ/mm^2) and r-ESWT (3.0 bar) are comparable.	Receive 3 treatments, once every other week.	VAS score↓, WOMAC score↓, 6-min walk test↓	Both groups showed significant improvement over time (P<0.001); however, f-ESWT was more effective than r-ESWT in improving pain (VAS P=0.01) and physical function (WOMAC P<0.001 and 6-min walk test P=0.003).	(158)
Choi *et al*, 2023	18 patients with KOA	EFD of 0.05 mJ/mm^2 total energy with 1,000 impulses.	Three times a week for 3 weeks.	VAS score↓, WOMAC score↓, LI score↓, joint effusion height↓	ESWT may be effective in reducing suprapatellar effusion and improving symptoms in mild KOA.	(144)
Zhang *et al*, 2021	89 patients with KOA	0.12 mJ/mm^2, lower density, or 0.24 mJ/mm^2, higher density.	Each group has 4 sessions every other week.	VAS score↓, WOMAC score↓	All treatment groups showed greater reductions in pain and WOMAC scores compared with the control group, and higher density may be more effective in relieving pain.	(164)
Xu *et al*, 2019	186 patients with severe KOA	2.0 bar, 0.25 mJ/mm^2, and 8 Hz/sec.	Twice a week for 4 weeks continuously.	VAS score↓, WOMAC score↓, 50-meter rapid walking time↓	ESWT has the potential to alleviate pain and improve knee joint function, and the therapeutic effect may peak 8 weeks after the end of treatment.	(176)

↑, significant increase; ↓, significant decrease; ESWT, extracorporeal shock wave therapy; EFD, energy flux density; KOA, knee osteoarthritis; VAS, visual analogue scale; RM, Roles and Maudsley; LI, Lequesne index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; BMD, bone mineral density; NSAIDs, nonsteroidal anti-inflammatory drugs; HA, hyaluronic acid; ROM, range of motion; KOOS, Knee Outcome Survey; IKDC, International Knee Documentation Committee; SCT, stair-climb test; NRS, Numeric Rating Scale; f-ESWT, focused ESWT; r-ESWT, radial ESWT.

with efficacy, thereby restricting the applicability of the findings (142,153).

Supporting the SR/MA evidence, ESWT has been proven to have superior efficacy compared with NSAIDs in patients with

KOA (52). A retrospective study conducted by Li *et al* (155) involving 105 patients with KOA provided compelling comparative data, wherein ESWT outperformed laser therapy in terms of pain reduction. Statistically significant improvements were observed at 6 weeks ($P<0.05$) and 12 weeks ($P<0.01$) post-treatment, as quantified by the Numerical Rating Scale (NRS) (156) and the pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (157). A randomized controlled trial directly comparing f-ESWT and r-ESWT further found that f-ESWT produced greater reductions in VAS pain scores and greater improvements in WOMAC scores at the 4- and 8-week follow-up, suggesting superior efficacy in pain relief and functional improvement (158). Two randomized controlled trial (RCTs) confirmed the findings from animal model studies indicating that ESWT may be an effective treatment for disability-related pain caused by primary OA (22,23). Nevertheless, the included RCTs displayed differences in shock wave energy parameters, which may partly explain the variability in reported effect sizes. Excessive energy application may exacerbate KOA progression, whereas insufficient energy delivery can compromise treatment efficacy (135,159). In clinical practice, energy flux density (EFD) values typically range from 0.001 to 0.5 mJ/mm^2 to minimize tissue damage (159-161), a range supported by experimental studies in rat models showing that EFDs >0.5 mJ/mm^2 may induce cartilage deterioration (162). Clinical evidence suggests that higher energy levels are often associated with greater improvements in pain relief and functional outcomes compared with lower energy protocols (163,164), and multiple studies support the notion that increased energy delivery may enhance treatment efficacy (23,165). However, this relationship is not absolute. For example, Schofer *et al* (166) reported no marked difference in therapeutic efficacy between higher (0.78 mJ/mm^2) and lower (0.33 mJ/mm^2) energy levels in the treatment of tendinopathy when both exceeded an EFD threshold of 0.32 mJ/mm^2. Furthermore, Liao *et al* (51) suggested that the cut-off point of EFD may influence the comparison of ESWT effects at different energy levels, which may help explain the inconsistency in previous findings. Moreover, most of these trials had notable methodological limitations, including a lack of double-blinding, a common challenge in ESWT research due to the difficulty of designing a credible sham-ESWT control that mimics the auditory and tactile sensations of active treatment without delivering therapeutic energy. Sample sizes were also relatively modest in some studies, which may limit statistical power and generalizability. In addition, adherence to the Consolidated Standards of Reporting Trials guidelines (167) was not consistently reported across the included trials, further constraining the transparency and reproducibility of the evidence.

While positive collective findings position ESWT as a promising therapeutic option, with evidence supporting pain relief in the short term and suggestive preclinical data for disease modification, further large-scale randomized, double-blind and multicenter clinical trials are needed to determine the optimal treatment parameters, long-term benefits and cost-effectiveness.

Function. Certain studies have established that ESWT can improve functional outcomes in patients with KOA, including joint range of motion and the ability to engage in physical activities (24,49,168). Multiple studies using standardized functional assessment tools, including the WOMAC, Lequesne index (169), Roles and Maudsley (170), Knee Outcome Survey (171) and International Knee Documentation Committee scores (172), have consistently reported favorable functional improvements following ESWT treatment (23,52,168). These benefits have been observed across various comparators, including placebo (22,173), NSAIDs and HA (52), and physical therapy controls (174,175), with GRADE evidence rated as 'moderate' (153). By contrast, studies have shown that r-ESWT actually delivers better results in improving the WOMAC functional scores than f-ESWT (51), suggesting that the choice of ESWT modality may influence functional outcomes. Such inconsistent outcomes suggest that the therapeutic advantage of either subtype varies according to the primary outcome measured, with f-ESWT superior for pain control and r-ESWT more favorable for global soft tissue-related functional recovery.

Notably, one study by Xu *et al* (176) extended the observation period to 6 months in 186 patients with severe KOA, using a 50-meter rapid walking test and gait analysis as objective functional measures. The study confirmed that ESWT alleviates knee pain and restores knee function, with treatment effects peaking at 8 weeks post-treatment. Xu *et al* (176) also noted an intriguing trend: Obese patients tend to respond more favorably to ESWT, demonstrating more pronounced therapeutic effects. This observation suggests that KOA is not solely linked to cartilage degeneration but may also stem from surrounding soft tissue involvement.

Collectively, these studies affirm ESWT as an effective intervention for mild-to-moderate KOA, offering functional restoration with a favorable safety profile (153). However, the long-term efficacy of ESWT remains understudied, particularly regarding its durability beyond the 6-month follow-up period observed in most trials. Additionally, the mechanisms underlying the differential response in obese patients warrant further exploration, as they may involve biomechanical factors, adipose-derived inflammatory mediators or altered load distribution in weight-bearing joints. Future research should be conducted in conjunction with advanced imaging techniques, such as dynamic MRI or ultrasound elastography, to assess structural changes in periarticular soft tissues following ESWT. Moreover, standardized protocols for treatment parameters, including EFD, frequency and number of sessions, are needed to optimize clinical outcomes and enable cross-study comparisons.

7. Conclusions and perspectives

As a chronic, disabling disease characterized primarily by pain and limited joint mobility, KOA has multiple etiologies and involves complex pathophysiological mechanisms (177). Among them, the progression of synovial inflammation, degradation of articular cartilage and abnormality of subchondral bone are the primary drivers of KOA development, which may eventually result in progressive and complete joint destruction (178,179). Prioritizing conservative treatment is the treatment principle for KOA (4). When other conservative approaches prove ineffective, ESWT

frequently serves as a practical non-invasive alternative in clinical settings (180).

A noteworthy contribution to the safety research on ESWT comes from the experimental work by Renz and Rupp (181), which addresses long-standing concerns regarding potential chondrocyte toxicity. The findings suggest that previous studies using cell suspensions may not accurately reflect real-world conditions, as alginate cultures better mimic the natural viscoelastic environment of cartilage. Importantly, the investigators observed no cytotoxic effects on chondrocytes in these more physiologically relevant models following shockwave exposure. These findings substantially support the proposition that ESWT presents a favorable safety profile for articular tissues.

Mounting preclinical data suggests that ESWT may have disease-modifying potential in animal models, supporting its investigation as a non-invasive adjuvant therapy for KOA. Accumulating preclinical and clinical evidence demonstrates that ESWT relieves KOA-related symptoms and delays cartilage degeneration via diverse biological mechanisms (49,137). However, these structural effects have been consistently observed in preclinical models, whereas clinical evidence in humans primarily supports symptomatic relief, and high-quality trials confirming cartilage regeneration or joint space preservation remain limited. This non-invasive treatment appears to work through several key mechanisms, namely, reducing inflammation, inhibiting apoptosis, stimulating cell proliferation and maintaining cartilage homeostasis (19,23,85). Through these coordinated actions, ESWT may slow degenerative processes in preclinical models, while preclinical observations also suggest potential for activating reparative mechanisms, which may inform clinical investigations into pain and functional outcomes.

The EFD is crucial for effective ESWT treatment, with improper dosage potentially exacerbating KOA or reducing efficacy. The clinical range for EFD during ESWT treatment typically spans from 0.001 to 0.5 mJ/mm^2 (159-161). However, research conducted using rat models has demonstrated that cartilage deterioration can occur at EFD levels exceeding 0.5 mJ/mm^2, underscoring the need for dose regulation (162). The therapeutic potential of ESWT depends not only on energy delivery but also on the interaction between energy and the cellular environment. For instance, low-energy ESWT has been shown to induce a phenotypic shift in macrophages from the pro-inflammatory M1 polarization to the anti-inflammatory M2 polarization (68). This polarization shift is of particular interest as it may facilitate the resolution of inflammation and the promotion of tissue repair. By contrast, medium-to-high energy ESWT exerts its therapeutic effects by downregulating the expression of inflammatory mediators, thereby mitigating the inflammatory cascade and promoting cell proliferation (182). Existing clinical evidence indicates that moderate-energy ESWT may yield superior pain relief and functional recovery compared with low-energy protocols, with optimal energy settings varying according to KOA severity and disease stage (23). Considering these findings, it is important that further research be directed towards elucidating the complex molecular mechanisms underlying the therapeutic effects of ESWT. This includes a deeper understanding of the cellular and biochemical pathways that are activated or modulated by different EFD levels. Additionally, the optimization of ESWT parameter settings is crucial, as this will enable the precise tailoring of the therapeutic dose to the individual patient's needs. Furthermore, the timing of parameter application must be carefully considered, as the temporal dynamics of ESWT delivery can markedly impact the therapeutic outcome. Optimizing the precision and timing of ESWT delivery may maximize therapeutic benefits while minimizing potential risks.

Given its non-invasive property, acceptable safety performance and accumulating experimental evidence, ESWT can serve as a valuable adjunctive alternative within integrated KOA management protocols when conventional conservative treatments fail. Since clinicians rarely offer ESWT as monotherapy, future studies should evaluate more clinically tailored individualized regimens in terms of clinical efficacy. While current findings are encouraging, additional studies are needed to clarify its long-term effectiveness, ideal treatment protocols and biological mechanisms, research that will not only optimize therapeutic use but also provide a solid basis for future scientific inquiry in this area.

Acknowledgements

Not applicable.

Funding

This research was funded by the Sichuan Provincial Administration of Traditional Chinese Medicine project 'Systematic Study on the Diagnosis and Treatment Rules of Knee Osteoarthritis in Traditional Chinese Medicine' (grant no. 25ZDAZX001) and the Sports Medicine Key Laboratory of Sichuan Province Project (grant no. 2025-A011).

Availability of data and materials

Not applicable.

Authors' contributions

YC, SS and YZ designed the present manuscript. YC wrote the first draft of the manuscript. SS and YZ edited the manuscript. SW and JH performed the literature search and selected the studies to be analyzed. YC and CL were responsible for the figure preparation. YH contributed to the acquisition of funds. All authors critically revised the manuscript for important intellectual content and have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Jung JH, Bang CH, Song GG, Kim C, Kim JH and Choi SJ: Knee osteoarthritis and menopausal hormone therapy in postmenopausal women: A nationwide cross-sectional study. Menopause 26: 598-602, 2018.
2. Liu Y, Zhang M, Kong D, Wang Y, Li J, Liu W, Fu Y and Xu J: High follicle-stimulating hormone levels accelerate cartilage damage of knee osteoarthritis in postmenopausal women through the PI3K/AKT/NF-κB pathway. FEBS Open Bio 10: 2235-2245, 2020.
3. Abramoff B and Caldera FE: Osteoarthritis: Pathology, diagnosis, and treatment options. Med Clin North Am 104: 293-311, 2020.
4. Geng R, Li J, Yu C, Zhang C, Chen F, Chen J, Ni H, Wang J, Kang K, Wei Z, *et al*: Knee osteoarthritis: Current status and research progress in treatment (Review). Exp Ther Med 26: 481, 2023.
5. Nazari G: Knee osteoarthritis. J Physiother 63: 188, 2017.
6. Musumeci G, Loreto C, Imbesi R, Trovato FM, Di Giunta A, Lombardo C, Castorina S and Castrogiovanni P: Advantages of exercise in rehabilitation, treatment and prevention of altered morphological features in knee osteoarthritis. A narrative review. Histol Histopathol 29: 707-719, 2014.
7. Shu Z, Miao X, Tang T, Zhan P, Zeng L and Jiang Y: The GSK-3β/β-catenin signaling pathway is involved in HMGB1-induced chondrocyte apoptosis and cartilage matrix degradation. Int J Mol Med 45: 769-778, 2020.
8. Yang S, Sun M and Zhang X: Protective effect of resveratrol on knee osteoarthritis and its molecular mechanisms: A recent review in preclinical and clinical trials. Front Pharmacol 13: 921003, 2022.
9. Gay C, Chabaud A, Guilley E and Coudeyre E: Educating patients about the benefits of physical activity and exercise for their hip and knee osteoarthritis. Systematic literature review. Ann Phys Rehabil Med 59: 174-183, 2016.
10. Chen AT, Shrestha S, Collins JE, Sullivan JK, Losina E and Katz JN: Estimating contextual effect in nonpharmacological therapies for pain in knee osteoarthritis: A systematic analytic review. Osteoarthritis Cartilage 28: 1154-1169, 2020.
11. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, Hawker GA, Henrotin Y, Hunter DJ, Kawaguchi H, *et al*: OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 22: 363-388, 2014.
12. Ochiai N, Ohtori S, Sasho T, Nakagawa K, Takahashi K, Takahashi N, Murata R, Takahashi K, Moriya H, Wada Y and Saisu T: Extracorporeal shock wave therapy improves motor dysfunction and pain originating from knee osteoarthritis in rats. Osteoarthritis Cartilage 15: 1093-1096, 2007.
13. Frisbie DD, Kawcak CE and McIlwraith CW: Evaluation of the effect of extracorporeal shock wave treatment on experimentally induced osteoarthritis in middle carpal joints of horses. Am J Vet Res 70: 449-454, 2009.
14. Chung B and Wiley JP: Extracorporeal shockwave therapy: A review. Sports Med 32: 851-865, 2002.
15. Wang CJ: Extracorporeal shockwave therapy in musculoskeletal disorders. J Orthop Surg Res 7: 11, 2012.
16. Speed C: A systematic review of shockwave therapies in soft tissue conditions: Focusing on the evidence. Br J Sports Med 48: 1538-1542, 2014.
17. Reilly JM, Bluman E and Tenforde AS: Effect of shockwave treatment for management of upper and lower extremity musculoskeletal conditions: A narrative review. PM R 10: 1385-1403, 2018.
18. Revenaugh MS: Extracorporeal shock wave therapy for treatment of osteoarthritis in the horse: Clinical applications. Vet Clin North Am Equine Pract 21: 609-625, vi, 2005.
19. Zhao Z, Ji H, Jing R, Liu C, Wang M, Zhai L, Bai X and Xing G: Extracorporeal shock-wave therapy reduces progression of knee osteoarthritis in rabbits by reducing nitric oxide level and chondrocyte apoptosis. Arch Orthop Trauma Surg 132: 1547-1553, 2012.
20. Wang CJ, Weng LH, Ko JY, Wang JW, Chen JM, Sun YC and Yang YJ: Extracorporeal shockwave shows regression of osteoarthritis of the knee in rats. J Surg Res 171: 601-608, 2011.
21. Wang CJ, Sun YC, Wong T, Hsu SL, Chou WY and Chang HW: Extracorporeal shockwave therapy shows time-dependent chondroprotective effects in osteoarthritis of the knee in rats. J Surg Res 178: 196-205, 2012.
22. Zhao Z, Jing R, Shi Z, Zhao B, Ai Q and Xing G: Efficacy of extracorporeal shockwave therapy for knee osteoarthritis: A randomized controlled trial. J Surg Res 185: 661-666, 2013.
23. Kim JH, Kim JY, Choi CM, Lee JK, Kee HS, Jung KI and Yoon SR: The dose-related effects of extracorporeal shock wave therapy for knee osteoarthritis. Ann Rehabil Med 39: 616-623, 2015.
24. Cho SJ, Yang JR, Yang HS and Yang HE: Effects of extracorporeal shockwave therapy in chronic stroke patients with knee osteoarthritis: A pilot study. Ann Rehabil Med 40: 862-870, 2016.
25. Hsieh CK, Chang CJ, Liu ZW and Tai TW: Extracorporeal shockwave therapy for the treatment of knee osteoarthritis: A meta-analysis. Int Orthop 44: 877-884, 2020.
26. Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS and Yang LC: Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 21: 984-989, 2003.
27. Wang CJ, Cheng JH, Chou WY, Hsu SL, Chen JH and Huang CY: Changes of articular cartilage and subchondral bone after extracorporeal shockwave therapy in osteoarthritis of the knee. Int J Med Sci 14: 213-223, 2017.
28. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
29. d'Agostino MC, Craig K, Tibalt E and Respizzi S: Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction. Int J Surg 24 (Pt B): 147-153, 2015.
30. Moya D, Ramón S, Schaden W, Wang CJ, Guiloff L and Cheng JH: The role of extracorporeal shockwave treatment in musculoskeletal disorders. J Bone Joint Surg Am 100: 251-263, 2018.
31. Chen Y, Lyu K, Lu J, Jiang L, Zhu B, Liu X, Li Y, Liu X, Long L, Wang X, *et al*: Biological response of extracorporeal shock wave therapy to tendinopathy in vivo (review). Front Vet Sci 9: 851894, 2022.
32. Cleveland RO, Chitnis PV and McClure SR: Acoustic field of a ballistic shock wave therapy device. Ultrasound Med Biol 33: 1327-1335, 2007.
33. Al-Abbad H, Reznik JE, Biros E, Paulik B, Will R, Gane S, Moss P and Wright A: Evaluation of treatment parameters for focused-extracorporeal shock wave therapy in knee osteoarthritis patients with bone marrow lesions: A pilot study. J Rehabil Med 56: jrm13207, 2024.
34. Yang T, Ma T, Liu X, Wang Y, Wang Y, Chen X, Wei H and Chen D: Radial extracorporeal shock wave therapy improves pain and plantar pressure in patients with early-to-mid-stage unilateral knee osteoarthritis: A retrospective before-after controlled study. Front Med (Lausanne) 12: 1707739, 2025.
35. Pasin T and Dogruoz Karatekin B: Comparison of short-term effects of extracorporeal shock wave therapy, low-level laser therapy and pulsed electromagnetic field therapy in knee osteoarthritis: A randomized controlled study. J Clin Med 14: 594, 2025.
36. Cp A, Jayaraman K, Babkair RA, Nuhmani S, Nawed A, Khan M and Alghadir AH: Effectiveness of extracorporeal shock wave therapy on functional ability in grade IV knee osteoarthritis - a randomized controlled trial. Sci Rep 14: 16530, 2024.
37. Modena DAO, Soares CD, Candido EC, Chaim FDM, Cazzo E and Chaim EA: Effect of extracorporeal shock waves on inflammation and angiogenesis of integumentary tissue in obese individuals: Stimulating repair and regeneration. Lasers Med Sci 37: 1289-1297, 2022.
38. Wang CJ, Wang FS, Yang KD, Weng LH, Sun YC and Yang YJ: The effect of shock wave treatment at the tendon-bone interface-an histomorphological and biomechanical study in rabbits. J Orthop Res 23: 274-280, 2005.
39. Liu T, Shindel AW, Lin G and Lue TF: Cellular signaling pathways modulated by low-intensity extracorporeal shock wave therapy. Int J Impot Res 31: 170-176, 2019.
40. Jaalouk DE and Lammerding J: Mechanotransduction gone awry. Nat Rev Mol Cell Biol 10: 63-73, 2009.
41. Ji Q, Wang P and He C: Extracorporeal shockwave therapy as a novel and potential treatment for degenerative cartilage and bone disease: Osteoarthritis. A qualitative analysis of the literature. Prog Biophys Mol Biol 121: 255-265, 2016.
42. Pirri C, Caroccia B, Angelini A, Piazza M, Petrelli L, Caputo I, Montemurro C, Ruggieri P, De Caro R and Stecco C: A new player in the mechanobiology of deep fascia: Yes-associated protein (YAP). Int J Mol Sci 24: 15389, 2023.

43. Vogel V: Mechanotransduction involving multimodular proteins: Converting force into biochemical signals. Annu Rev Biophys Biomol Struct 35: 459-488, 2006.
44. Puklin-Faucher E and Sheetz MP: The mechanical integrin cycle. J Cell Sci 122 (Pt 2): 179-186, 2009.
45. Sun Z, Guo SS and Fässler R: Integrin-mediated mechanotransduction. J Cell Biol 215: 445-456, 2016.
46. Ingber DE: Cellular mechanotransduction: Putting all the pieces together again. FASEB J 20: 811-827, 2006.
47. Frairia R and Berta L: Biological effects of extracorporeal shock waves on fibroblasts. A review. Muscles Ligaments Tendons J 1: 138-147, 2011.
48. Chen L, Zhang Z, Ma X, Zhang D, Xu Q, Wang Q, Pan S, He Y and Liu X: Radial extracorporeal shockwave therapy reduces subchondral osteoblast senescence in knee osteoarthritis. AJSM 53: 2352-2362, 2025.
49. Tang P, Wen T, Lu W, Jin H, Pan L, Li H, Zeng B, Zhou Y, Xiao W and Li Y: The efficacy of extracorporeal shock wave therapy for knee osteoarthritis: An umbrella review. Int J Surg 110: 2389-2395, 2024.
50. Li T, Ma J, Zhao T, Gao F and Sun W: Application and efficacy of extracorporeal shockwave treatment for knee osteoarthritis: A systematic review and meta-analysis. Exp Ther Med 18: 2843-2850, 2019.
51. Liao CD, Tsauo JY, Liou TH, Chen HC and Huang SW: Clinical efficacy of extracorporeal shockwave therapy for knee osteoarthritis: A systematic review and meta-regression of randomized controlled trials. Clin Rehabil 33: 1419-1430, 2019.
52. Jhan SW, Wang CJ, Wu KT, Siu KK, Ko JY, Huang WC, Chou WY and Cheng JH: Comparison of extracorporeal shockwave therapy with non-steroid anti-inflammatory drugs and intra-articular hyaluronic acid injection for early osteoarthritis of the knees. Biomedicines 10: 202, 2022.
53. Zissler A, Steinbacher P, Zimmermann R, Pittner S, Stoiber W, Bathke AC and Sänger AM: Extracorporeal shock wave therapy accelerates regeneration after acute skeletal muscle injury. Am J Sports Med 45: 676-684, 2017.
54. Mariotto S, de Prati AC, Cavalieri E, Amelio E, Marlinghaus E and Suzuki H: Extracorporeal shock wave therapy in inflammatory diseases: Molecular mechanism that triggers anti-inflammatory action. Curr Med Chem 16: 2366-2372, 2009.
55. Iannone F, Moretti B, Notarnicola A, Moretti L, Patella S, Patella V and Lapadula G: Extracorporeal shock waves increase interleukin-10 expression by human osteoarthritic and healthy osteoblasts in vitro. Clin Exp Rheumatol 27: 794-799, 2009.
56. Moretti B, Iannone F, Notarnicola A, Lapadula G, Moretti L, Patella V and Garofalo R: Extracorporeal shock waves down-regulate the expression of interleukin-10 and tumor necrosis factor-alpha in osteoarthritic chondrocytes. BMC Musculoskelet Disord 9: 16, 2008.
57. Feng B, Dong Z, Wang Y, Yan G, Yang E, Cheng H, Liang C, Hao Z, Zhang X, Song Z, *et al*: Li-ESWT treatment reduces inflammation, oxidative stress, and pain via the PI3K/AKT/FOXO1 pathway in autoimmune prostatitis rat models. Andrology 9: 1593-1602, 2021.
58. Khasnavis S, Jana A, Roy A, Mazumder M, Bhushan B, Wood T, Ghosh S, Watson R and Pahan K: Suppression of nuclear factor-κB activation and inflammation in microglia by physically modified saline. J Biol Chem 287: 29529-29542, 2012.
59. Rastaldo R, Pagliaro P, Cappello S, Penna C, Mancardi D, Westerhof N and Losano G: Nitric oxide and cardiac function. Life Sci 81: 779-793, 2007.
60. Schroeder RA and Kuo PC: Nitric oxide: Physiology and pharmacology. Anesth Analg 81: 1052-1059, 1995.
61. Colasanti M and Persichini T: Nitric oxide: An inhibitor of NF-kappaB/Rel system in glial cells. Brain Res Bull 52: 155-161, 2000.
62. Deng Y, Lu J, Li W, Wu A, Zhang X, Tong W, Ho KK, Qin L, Song H and Mak KK: Reciprocal inhibition of YAP/TAZ and NF-κB regulates osteoarthritic cartilage degradation. Nat Commun 9: 4564, 2018.
63. Zhao Z, Wang Y, Wang Q, Liang J, Hu W, Zhao S, Li P, Zhu H and Li Z: Radial extracorporeal shockwave promotes subchondral bone stem/progenitor cell self-renewal by activating YAP/TAZ and facilitates cartilage repair in vivo. Stem Cell Res Ther 12: 19, 2021.
64. Zou X, Xu H and Qian W: Macrophage polarization in the osteoarthritis pathogenesis and treatment. Orthop Surg 17: 22-35, 2025.
65. Yu D, Xu C, Jiang J, Shen W and Zhu H: How do mechanical forces impact macrophages in the processes of mechanosensing and mechanotransduction? J Zhejiang Univ Sci B 27: 129-148, 2025.
66. Khanmohammadi M, Mirzaalikhan Y and Baratchi S: Immunity in motion: The role of mechanics in macrophage biology. Cell Chem Biol 32: 1442-1457, 2025.
67. Zhang X, Kim TH, Thauland TJ, Li H, Majedi FS, Ly C, Gu Z, Butte MJ, Rowat AC and Li S: Unraveling the mechanobiology of immune cells. Curr Opin Biotechnol 66: 236-245, 2020.
68. Abe Y, Ito K, Hao K, Shindo T, Ogata T, Kagaya Y, Kurosawa R, Nishimiya K, Satoh K, Miyata S, *et al*: Extracorporeal low-energy shock-wave therapy exerts anti-inflammatory effects in a rat model of acute myocardial infarction. Circ J 78: 2915-2925, 2014.
69. Sukubo NG, Tibalt E, Respizzi S, Locati M and d'Agostino MC: Effect of shock waves on macrophages: A possible role in tissue regeneration and remodeling. Int J Surg 24 (Pt B): 124-130, 2015.
70. Holsapple JS, Cooper B, Berry SH, Staniszewska A, Dickson BM, Taylor JA, Bachoo P and Wilson HM: Low intensity shockwave treatment modulates macrophage functions beneficial to healing chronic wounds. Int J Mol Sci 22: 7844, 2021.
71. Bae WJ, Shin D, Piao JJ, Kim S, Choi YS, Park BH, Jung HJ, Sorkhi S, Chawla S, Cheon CW, *et al*: Extracorporeal shockwave therapy alleviates inflammatory pain by down-regulating NLRP3 inflammasome in experimental chronic prostatitis and chronic pelvic pain syndrome. World J Mens Health 42: 157-167, 2024.
72. Steinman RM and Hemmi H: Dendritic cells: Translating innate to adaptive immunity. Curr Top Microbiol Immunol 311: 17-58, 2006.
73. Cooper DM, Radom-Aizik S, Schwindt C and Zaldivar F Jr: Dangerous exercise: lessons learned from dysregulated inflammatory responses to physical activity. J Appl Physiol (1985) 103: 700-709, 2007.
74. Chilton PM, Embry CA and Mitchell TC: Effects of differences in lipid a structure on TLR4 pro-inflammatory signaling and inflammasome activation. Front Immunol 3: 154, 2012.
75. Ruan A, Wang Q, Ma Y, Zhang D, Yang L, Wang Z, Xie Q and Yin Y: Efficacy and mechanism of electroacupuncture treatment of rabbits with different degrees of knee osteoarthritis: A study based on synovial innate immune response. Front Physiol 12: 642178, 2021.
76. Jun T, Ruipeng G and Bin X: TLR4 knockdown by miRNA-140-5p improves tendinopathy: An in vitro study. Arch Med Sci 20: 582-601, 2024.
77. Madera-Salcedo IK, Cruz SL and Gonzalez-Espinosa C: Morphine prevents lipopolysaccharide-induced TNF secretion in mast cells blocking IκB kinase activation and SNAP-23 phosphorylation: Correlation with the formation of a β-arrestin/TRAF6 complex. J Immunol 191: 3400-3409, 2013.
78. Jin X, Yu Y, Lin Y, Yang J and Chen Z: Tendon-regulating and bone-setting manipulation promotes the recovery of synovial inflammation in rabbits with knee osteoarthritis via the TLR4-MyD88-NF-κB signaling pathway. Ann Transl Med 11: 245, 2023.
79. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, Fernandes-Alnemri T, Wu J, Monks BG, *et al*: Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol 183: 787-791, 2009.
80. Kelley N, Jeltema D, Duan Y and He Y: The NLRP3 inflammasome: An overview of mechanisms of activation and regulation. Int J Mol Sci 20: 3328, 2019.
81. Yin H, Guo Q, Li X, Tang T, Li C, Wang H, Sun Y, Feng Q, Ma C, Gao C, *et al*: Curcumin suppresses IL-1β secretion and prevents inflammation through inhibition of the NLRP3 inflammasome. J Immunol 200: 2835-2846, 2018.
82. Hashimoto S, Ochs RL, Rosen F, Quach J, McCabe G, Solan J, Seegmiller JE, Terkeltaub R and Lotz M: Chondrocyte-derived apoptotic bodies and calcification of articular cartilage. Proc Natl Acad Sci USA 95: 3094-3099, 1998.
83. Hwang HS and Kim HA: Chondrocyte apoptosis in the pathogenesis of osteoarthritis. Int J Mol Sci 16: 26035-26054, 2015.
84. Kim YH, Bang JI, Son HJ, Kim Y, Kim JH, Bae H, Han SJ, Yoon HJ and Kim BS: Protective effects of extracorporeal shockwave on rat chondrocytes and temporomandibular joint osteoarthritis; preclinical evaluation with in vivo(99m)Tc-HDP SPECT and ex vivo micro-CT. Osteoarthritis Cartilage 27: 1692-1701, 2019.
85. Ramesh S, Zaman F, Madhuri V and Sävendahl L: Radial extracorporeal shock wave treatment promotes bone growth and chondrogenesis in cultured fetal rat metatarsal bones. Clin Orthop Relat Res 478: 668-678, 2020.

86. Weng LH, Wang CJ, Ko JY, Sun YC, Su YS and Wang FS: Inflammation induction of Dickkopf-1 mediates chondrocyte apoptosis in osteoarthritic joint. Osteoarthritis Cartilage 17: 933-943, 2009.
87. Nagahara Y, Shinomiya T, Kuroda S, Kaneko N, Nishio R and Ikekita M: Phytosphingosine induced mitochondria-involved apoptosis. Cancer Sci 96: 83-92, 2005.
88. Zha J, Harada H, Osipov K, Jockel J, Waksman G and Korsmeyer SJ: BH3 domain of BAD is required for heterodimerization with BCL-XL and pro-apoptotic activity. J Biol Chem 272: 24101-24104, 1997.
89. Zamzami N, Marzo I, Susin SA, Brenner C, Larochette N, Marchetti P, Reed J, Kofler R and Kroemer G: The thiol crosslinking agent diamide overcomes the apoptosis-inhibitory effect of Bcl-2 by enforcing mitochondrial permeability transition. Oncogene 16: 1055-1063, 1998.
90. Weng LH, Wang CJ, Ko JY, Sun YC and Wang FS: Control of Dkk-1 ameliorates chondrocyte apoptosis, cartilage destruction, and subchondral bone deterioration in osteoarthritic knees. Arthritis Rheum 62: 1393-1402, 2010.
91. Largo R, Alvarez-Soria MA, Díez-Ortego I, Calvo E, Sánchez-Pernaute O, Egido J and Herrero-Beaumont G: Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. Osteoarthritis Cartilage 11: 290-298, 2003.
92. Barnes PJ and Karin M: Nuclear factor-kappaB: A pivotal transcription factor in chronic inflammatory diseases. N Engl J Med 336: 1066-1071, 1997.
93. Shakibaei M, John T, Schulze-Tanzil G, Lehmann I and Mobasheri A: Suppression of NF-kappaB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. Biochem Pharmacol 73: 1434-1445, 2007.
94. Aggarwal BB: Nuclear factor-kappaB: The enemy within. Cancer Cell 6: 203-208, 2004.
95. Aggarwal BB and Takada Y: Pro-apototic and anti-apoptotic effects of tumor necrosis factor in tumor cells. Role of nuclear transcription factor NF-kappaB. Cancer Treat Res 126: 103-127, 2005.
96. Shakibaei M, Schulze-Tanzil G, de Souza P, John T, Rahmanzadeh M, Rahmanzadeh R and Merker HJ: Inhibition of mitogen-activated protein kinase kinase induces apoptosis of human chondrocytes. J Biol Chem 276: 13289-13294, 2001.
97. Kim SJ, Ju JW, Oh CD, Yoon YM, Song WK, Kim JH, Yoo YJ, Bang OS, Kang SS and Chun JS: ERK-1/2 and p38 kinase oppositely regulate nitric oxide-induced apoptosis of chondrocytes in association with p53, caspase-3, and differentiation status. J Biol Chem 277: 1332-1339, 2002.
98. Tamura Y, Simizu S, and Osada H: The phosphorylation status and anti-apoptotic activity of Bcl-2 are regulated by ERK and protein phosphatase 2A on the mitochondria. FEBS Lett 569: 249-255, 2004.
99. Mobasheri A, Carter SD, Martín-Vasallo P and Shakibaei M: Integrins and stretch activated ion channels; putative components of functional cell surface mechanoreceptors in articular chondrocytes. Cell Biol Int 26: 1-18, 2022.
100. Varela-Eirin M, Loureiro J, Fonseca E, Corrochano S, Caeiro JR, Collado M and Mayan MD: Cartilage regeneration and ageing: Targeting cellular plasticity in osteoarthritis. Ageing Res Rev 42: 56-71, 2018.
101. Lindqvist A, Rodríguez-Bravo V and Medema RH: The decision to enter mitosis: Feedback and redundancy in the mitotic entry network. J Cell Biol 185: 193-202, 2009.
102. Aschermann I, Noor S, Venturelli S, Sinnberg T, Mnich CD and Busch C: Extracorporal shock waves activate migration, proliferation and inflammatory pathways in fibroblasts and keratinocytes, and improve wound healing in an open-label, single-arm study in patients with therapy-refractory chronic leg ulcers. Cell Physiol Biochem 41: 890-906, 2017.
103. Weihs AM, Fuchs C, Teuschl AH, Hartinger J, Slezak P, Mittermayr R, Redl H, Junger WG, Sitte HH and Rünzler D: Shock wave treatment enhances cell proliferation and improves wound healing by ATP release-coupled extracellular signal-regulated kinase (ERK) activation. J Biol Chem 289: 27090-27104, 2014.
104. Shiina H, Igawa M, Shigeno K, Wada Y, Yoneda T, Yagi H, Shirakawa R and Nagasaki M: Relationship of serum testosterone level with proliferating cell nuclear antigen and nm23 protein in human prostatic carcinoma tissue. Oncology 54: 482-489, 1997.
105. Chen YJ, Wang CJ, Yang KD, Kuo YR, Huang HC, Huang YT, Sun YC and Wang FS: Extracorporeal shock waves promote healing of collagenase-induced Achilles tendinitis and increase TGF-beta1 and IGF-I expression. J Orthop Res 22: 854-861, 2004.
106. Wang L, Kong W, Liu B and Zhang X: Proliferating cell nuclear antigen promotes cell proliferation and tumorigenesis by up-regulating STAT3 in non-small cell lung cancer. Biomed Pharmacother 104: 595-602, 2018.
107. Zhang J, Kang N, Yu X, Ma Y and Pang X: Radial extracorporeal shock wave therapy enhances the proliferation and differentiation of neural stem cells by notch, PI3K/AKT, and Wnt/β-catenin signaling. Sci Rep 7: 15321, 2017.
108. Sun K, Luo J, Guo J, Yao X, Jing X and Guo F: The PI3K/AKT/mTOR signaling pathway in osteoarthritis: A narrative review. Osteoarthritis Cartilage 28: 400-409, 2020.
109. Schiaffino S and Mammucari C: Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: Insights from genetic models. Skelet Muscle 1: 4, 2011.
110. Li H, Dan C, Gong X, Zeng W, Yao Q, Yang Y, Gong X, Wang L, Chen C and Huang L: Sorghumol triterpene inhibits the growth of circulating renal cancer cells by promoting cell apoptosis, G2/M cell cycle arrest and downregulating m-TOR/PI3K/AKT signalling pathway. J BUON 24: 310-314, 2019.
111. Basta MD, Menko AS and Walker JL: PI3K isoform-specific regulation of leader and follower cell function for collective migration and proliferation in response to injury. Cells 11: 3515, 2022.
112. Roman-Blas JA and Jimenez SA: NF-kappaB as a potential therapeutic target in osteoarthritis and rheumatoid arthritis. Osteoarthritis Cartilage 14: 839-848, 2006.
113. Ai X, Zhu C, Xie Y, Luo X and Zhang C: ITGB1-mediated focal adhesion signaling underlies the chondroprotective effects of extracorporeal shockwave therapy in knee osteoarthritis. Am J Phys Med Rehabil 105: 704-713, 2026.
114. Gowen M, Wood DD, Ihrie EJ, Meats JE and Russell RG: Stimulation by human interleukin 1 of cartilage breakdown and production of collagenase and proteoglycanase by human chondrocytes but not by human osteoblasts in vitro. Biochim Biophys Acta 797: 186-193, 1984.
115. Schmitz JP, Dean DD, Schwartz Z, Cochran DL, Grant GM, Klebe RJ, Nakaya H and Boyan BD: Chondrocyte cultures express matrix metalloproteinase mRNA and immunoreactive protein; stromelysin-1 and 72 kDa gelatinase are localized in extracellular matrix vesicles. J Cell Biochem 61: 375-391, 1996.
116. Plsikova Matejova J, Spakova T, Harvanova D, Lacko M, Filip V, Sepitka R, Mitro I and Rosocha J: A preliminary study of combined detection of COMP, TIMP-1, and MMP-3 in synovial fluid: Potential indicators of osteoarthritis progression. Cartilage 13 (2_suppl): 1421S-1430S, 2021.
117. Knäuper V, López-Otin C, Smith B, Knight G and Murphy G: Biochemical characterization of human collagenase-3. J Biol Chem 271: 1544-1550, 1996.
118. Walling HW, Raggatt LJ, Irvine DW, Barmina OY, Toledano JE, Goldring MB, Hruska KA, Adkisson HD, Burdge RE, Gatt CJ Jr, *et al*: Impairment of the collagenase-3 endocytotic receptor system in cells from patients with osteoarthritis. Osteoarthritis Cartilage 11: 854-863, 2003.
119. Shiomi T, Lemaître V, D'Armiento J and Okada Y: Matrix metalloproteinases, a disintegrin and metalloproteinases, and a disintegrin and metalloproteinases with thrombospondin motifs in non-neoplastic diseases. Pathol Int 60: 477-496, 2010.
120. An S, Li J, Xie W, Yin N, Li Y and Hu Y: Extracorporeal shockwave treatment in knee osteoarthritis: Therapeutic effects and possible mechanism. Biosci Rep 40: BSR20200926, 2020.
121. Cawston T: Matrix metalloproteinases and TIMPs: Properties and implications for the rheumatic diseases. Mol Med Today 4: 130-137, 1998.
122. Bond M, Fabunmi RP, Baker AH and Newby AC: Synergistic upregulation of metalloproteinase-9 by growth factors and inflammatory cytokines: An absolute requirement for transcription factor NF-kappa B. FEBS Lett 435: 29-34, 1998.
123. O'Kane CM, Elkington PT, Jones MD, Caviedes L, Tovar M, Gilman RH, Stamp G and Friedland JS: STAT3, p38 MAPK, and NF-kappaB drive unopposed monocyte-dependent fibroblast MMP-1 secretion in tuberculosis. Am J Respir Cell Mol Biol 43: 465-474, 2010.
124. Saito T, Fukai A, Mabuchi A, Ikeda T, Yano F, Ohba S, Nishida N, Akune T, Yoshimura N, Nakagawa T, *et al*: Transcriptional regulation of endochondral ossification by HIF-2alpha during skeletal growth and osteoarthritis development. Nat Med 16: 678-686, 2010.

125. Yang S, Kim J, Ryu JH, Oh H, Chun CH, Kim BJ, Min BH and Chun JS: Hypoxia-inducible factor-2alpha is a catabolic regulator of osteoarthritic cartilage destruction. Nat Med 16: 687-693, 2010.
126. Grall F, Gu X, Tan L, Cho JY, Inan MS, Pettit AR, Thamrongsak U, Choy BK, Manning C, Akbarali Y, *et al*: Responses to the proinflammatory cytokines interleukin-1 and tumor necrosis factor alpha in cells derived from rheumatoid synovium and other joint tissues involve nuclear factor kappaB-mediated induction of the Ets transcription factor ESE-1. Arthritis Rheum 48: 1249-1260, 2003.
127. Muddasani P, Norman JC, Ellman M, van Wijnen AJ and Im HJ: Basic fibroblast growth factor activates the MAPK and NFkappaB pathways that converge on Elk-1 to control production of matrix metalloproteinase-13 by human adult articular chondrocytes. J Biol Chem 282: 31409-31421, 2007.
128. Pi Y, Zhang X, Shao Z, Zhao F, Hu X and Ao Y: Intra-articular delivery of anti-Hif-2α siRNA by chondrocyte-homing nanoparticles to prevent cartilage degeneration in arthritic mice. Gene Ther 22: 439-448, 2015.
129. Hirata M, Kugimiya F, Fukai A, Saito T, Yano F, Ikeda T, Mabuchi A, Sapkota BR, Akune T, Nishida N, *et al*: C/EBPβ and RUNX2 cooperate to degrade cartilage with MMP-13 as the target and HIF-2α as the inducer in chondrocytes. Hum Mol Genet 21: 1111-1123, 2012.
130. Otero M, Plumb DA, Tsuchimochi K, Dragomir CL, Hashimoto K, Peng H, Olivotto E, Bevilacqua M, Tan L, Yang Z, *et al*: E74-like factor 3 (ELF3) impacts on matrix metalloproteinase 13 (MMP13) transcriptional control in articular chondrocytes under proinflammatory stress. J Biol Chem 287: 3559-3572, 2012.
131. Iwasa K, Hayashi S, Fujishiro T, Kanzaki N, Hashimoto S, Sakata S, Chinzei N, Nishiyama T, Kuroda R and Kurosaka M: PTEN regulates matrix synthesis in adult human chondrocytes under oxidative stress. J Orthop Res 32: 231-237, 2014.
132. Zhang Q, Lai S, Hou X, Cao W, Zhang Y and Zhang Z: Protective effects of PI3K/Akt signal pathway induced cell autophagy in rat knee joint cartilage injury. Am J Transl Res 10: 762-770, 2018.
133. Vetrano M, Ranieri D, Nanni M, Pavan A, Malisan F, Vulpiani MC and Visco V: Hyaluronic acid (HA), platelet-rich plasm and extracorporeal shock wave therapy (ESWT) promote human chondrocyte regeneration in vitro and ESWT-mediated increase of CD44 expression enhances their susceptibility to HA treatment. PLoS One 14: e0218740, 2019.
134. Wang CJ, Weng LH, Ko JY, Sun YC, Yang YJ and Wang FS: Extracorporeal shockwave therapy shows chondroprotective effects in osteoarthritic rat knee. Arch Orthop Trauma Surg 131: 1153-1158, 2011.
135. Wang CJ, Hsu SL, Weng LH, Sun YC and Wang FS: Extracorporeal shockwave therapy shows a number of treatment related chondroprotective effect in osteoarthritis of the knee in rats. BMC Musculoskelet Disord 14: 44, 2013.
136. Cheng JH, Chou WY, Wang CJ, Siu KK, Peng JM, Wu YN, Lee MS, Huang CY, Ko JY and Jhan SW: Pathological, morphometric and correlation analysis of the modified mankin score, tidemark roughness and calcified cartilage thickness in rat knee osteoarthritis after extracorporeal shockwave therapy. Int J Med Sci 19: 242-256, 2022.
137. Chou WY, Cheng JH, Wang CJ, Hsu SL, Chen JH and Huang CY: Shockwave targeting on subchondral bone is more suitable than articular cartilage for knee osteoarthritis. Int J Med Sci 16: 156-166, 2019.
138. Wang CJ, Sun YC, Siu KK and Wu CT: Extracorporeal shockwave therapy shows site-specific effects in osteoarthritis of the knee in rats. J Surg Res 183: 612-619, 2013.
139. Wang CJ, Huang CY, Hsu SL, Chen JH and Cheng JH: Extracorporeal shockwave therapy in osteoporotic osteoarthritis of the knee in rats: An experiment in animals. Arthritis Res Ther 16: R139, 2014.
140. Yilmaz V, Karadaş Ö, Dandinoğlu T, Umay E, Çakçı A and Tan AK: Efficacy of extracorporeal shockwave therapy and low-intensity pulsed ultrasound in a rat knee osteoarthritis model: A randomized controlled trial. Eur J Rheumatol 4: 104-108, 2017.
141. Cheng JH, Yen KT, Chou WY, Jhan SW, Hsu SL, Ko JY, Wang CJ, Kuo CA, Wu SY, Hsu TC and Hsu CC: Autologous adipose-derived mesenchymal stem cells combined with shockwave therapy synergistically ameliorates the osteoarthritic pathological factors in knee joint. Pharmaceuticals (Basel) 14: 318, 2021.
142. Zhou Q and Chen J: A critical overview of systematic reviews and meta-analyses of extracorporeal shockwave therapy for knee osteoarthritis. Asian J Surg 47: 2975-2984, 2024.
143. Ma H, Zhang W, Shi J, Zhou D and Wang J: The efficacy and safety of extracorporeal shockwave therapy in knee osteoarthritis: A systematic review and meta-analysis. Int J Surg 75: 24-34, 2020.
144. Choi IJ, Jeon JH, Choi WH and Yang HE: Effects of extracorporeal shockwave therapy for mild knee osteoarthritis: A pilot study. Medicine (Baltimore) 102: e36117, 2023.
145. Wang YC, Huang HT, Huang PJ, Liu ZM and Shih CL: Efficacy and safety of extracorporeal shockwave therapy for treatment of knee osteoarthritis: A systematic review and meta-analysis. Pain Med 21: 822-835, 2020.
146. Zhong ZY, Liu B, Liu G, Chen J, Li Y, Chen J, Liu X and Hu Y: A randomized controlled trial on the effects of low-dose extracorporeal shockwave therapy in patients with knee osteoarthritis. Arch Phys Med Rehabil 100: 1695-1702, 2019.
147. ISMST: ESWT Guidelines. International Society for Medical Shockwave Treatment, 2023. https://shockwavetherapy.org/ismst-guidelines. Accessed August 15, 2026.
148. Imamura M, Alamino S, Hsing WT, Alfieri FM, Schmitz C and Battistella LR: Radial extracorporeal shock wave therapy for disabling pain due to severe primary knee osteoarthritis. J Rehabil Med 49: 54-62, 2017.
149. Neogi T: The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 21: 1145-1153, 2013.
150. Bliddal H and Christensen R: The treatment and prevention of knee osteoarthritis: A tool for clinical decision-making. Expert Opin Pharmacother 10: 1793-1804, 2009.
151. Berkman ND, Lohr KN, Morgan LC, Kuo TM and Morton SC: Interrater reliability of grading strength of evidence varies with the complexity of the evidence in systematic reviews. J Clin Epidemiol 66: 1105-1117.e1, 2013.
152. Chen L, Ye L, Liu H, Yang P and Yang B: Extracorporeal shock wave therapy for the treatment of osteoarthritis: A systematic review and meta-analysis. Biomed Res Int 2020: 1907821, 2020.
153. Avendaño-Coy J, Comino-Suárez N, Grande-Muñoz J, Avendaño-López C and Gómez-Soriano J: Extracorporeal shockwave therapy improves pain and function in subjects with knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials. Int J Surg 82: 64-75, 2020.
154. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P and Schünemann HJ; GRADE Working Group: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336: 924-926, 2008.
155. Li W, Pan Y, Yang Q, Guo ZG, Yue Q and Meng QG: Extracorporeal shockwave therapy for the treatment of knee osteoarthritis: A retrospective study. Medicine (Baltimore) 97: e11418, 2018.
156. Jensen MP, Turner JA and Romano JM: What is the maximum number of levels needed in pain intensity measurement? Pain 58: 387-392, 1994.
157. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J and Stitt LW: Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15: 1833-1840, 1988.
158. Ko NY, Chang CN, Cheng CH, Yu HK and Hu GC: Comparative effectiveness of focused extracorporeal versus radial extracorporeal shockwave therapy for knee osteoarthritis-randomized controlled study. Int J Environ Res Public Health 19: 9001, 2022.
159. Schmitz C, Császár NB, Milz S, Schieker M, Maffulli N, Rompe JD and Furia JP: Efficacy and safety of extracorporeal shock wave therapy for orthopedic conditions: A systematic review on studies listed in the PEDro database. Br Med Bull 116: 115-138, 2015.
160. Foldager CB, Kearney C and Spector M: Clinical application of extracorporeal shock wave therapy in orthopedics: Focused versus unfocused shock waves. Ultrasound Med Biol 38: 1673-1680, 2012.
161. Speed CA: Extracorporeal shock-wave therapy in the management of chronic soft-tissue conditions. J Bone Joint Surg Br 86: 165-171, 2004.
162. Mayer-Wagner S, Ernst J, Maier M, Chiquet M, Joos H, Müller PE, Jansson V, Sievers B and Hausdorf J: The effect of high-energy extracorporeal shock waves on hyaline cartilage of adult rats in vivo. J Orthop Res 28: 1050-1056, 2010.

163. Kang S, Gao F, Han J, Mao T, Sun W, Wang B, Guo W, Cheng L and Li Z: Extracorporeal shock wave treatment can normalize painful bone marrow edema in knee osteoarthritis: A comparative historical cohort study. Medicine (Baltimore) 97: e9796, 2018.
164. Zhang YF, Liu Y, Chou SW and Weng H: Dose-related effects of radial extracorporeal shock wave therapy for knee osteoarthritis: A randomized controlled trial. J Rehabil Med 53: jrm00144, 2021.
165. Şah V: The short-term efficacy of large-focused and controlled-unfocused (Radial) extracorporeal shock wave therapies in the treatment of hip osteoarthritis. J Pers Med 13: 48, 2022.
166. Schofer MD, Hinrichs F, Peterlein CD, Arendt M and Schmitt J: High- versus low-energy extracorporeal shock wave therapy of rotator cuff tendinopathy: A prospective, randomised, controlled study. Acta Orthop Belg 75: 452-458, 2009.
167. Schulz KF, Altman DG and Moher D: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. J Pharmacol Pharmacother 1: 100-107, 2010.
168. Lee JK, Lee BY, Shin WY, An MJ, Jung KI and Yoon SR: Effect of extracorporeal shockwave therapy versus intra-articular injections of hyaluronic acid for the treatment of knee osteoarthritis. Ann Rehabil Med 41: 828-835, 2017.
169. Lequesne MG, Mery C, Samson M and Gerard P: Indexes of severity for osteoarthritis of the hip and knee. Validation-value in comparison with other assessment tests. Scand J Rheumatol Suppl 65: 85-89, 1987.
170. Roles NC and Maudsley RH: Radial tunnel syndrome: Resistant tennis elbow as a nerve entrapment. J Bone Joint Surg Br 54: 499-508, 1972.
171. Irrgang JJ, Snyder-Mackler L, Wainner RS, Fu FH and Harner CD: Development of a patient-reported measure of function of the knee. J Bone Joint Surg Am 80: 1132-1145, 1998.
172. Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, Richmond JC and Shelborne KD: Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 29: 600-613, 2001.
173. Chen TW, Lin CW, Lee CL, Chen CH, Chen YJ, Lin TY and Huang MH: The efficacy of shock wave therapy in patients with knee osteoarthritis and popliteal cyamella. Kaohsiung J Med Sci 30: 362-370, 2014.
174. Lee JH, Lee S, Choi S, Choi YH and Lee K: The effects of extracorporeal shock wave therapy on the pain and function of patients with degenerative knee arthritis. J Phys Ther Sci 29: 536-538, 2017.
175. Lizis P, Kobza W and Manko G: Extracorporeal shockwave therapy vs. kinesiotherapy for osteoarthritis of the knee: A pilot randomized controlled trial. J Back Musculoskelet Rehabil 30: 1121-1128, 2017.
176. Xu Y, Wu K, Liu Y, Geng H, Zhang H, Liu S, Qu H and Xing G: The effect of extracorporeal shock wave therapy on the treatment of moderate to severe knee osteoarthritis and cartilage lesion. Medicine (Baltimore) 98: e15523, 2019.
177. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H and Carr AJ: Osteoarthritis. Lancet 386: 376-387, 2015.
178. Charlier E, Deroyer C, Ciregia F, Malaise O, Neuville S, Plener Z, Malaise M and de Seny D: Chondrocyte dedifferentiation and osteoarthritis (OA). Biochem Pharmacol 165: 49-65, 2019.
179. Sanchez-Lopez E, Coras R, Torres A, Lane NE and Guma M: Synovial inflammation in osteoarthritis progression. Nat Rev Rheumatol 18: 258-275, 2022.
180. van der Worp H, van den Akker-Scheek I, van Schie H and Zwerver J: ESWT for tendinopathy: Technology and clinical implications. Knee Surg Sports Traumatol Arthrosc 21: 1451-1458, 2013.
181. Renz H and Rupp S: Effects of shock waves on chondrocytes and their relevance in clinical practice. Arch Orthop Trauma Surg 129: 641-647, 2009.
182. Jin Y, Meng Z, Qin Z, Zhu J, Hong L, Shao W, Hu Z, Zhang Y, Gu X and Xu B: Mechanisms of extracorporeal shock wave therapy in burn scar repair: Advances in immunoactivation-based scar remodeling research. Regen Ther 30: 182-194, 2025.

Copyright © 2026 Chen et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.