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REVIEW

Signal Transduction Pathways Involved in Acupuncture-Mediated Inhibition of Synovitis in Knee Osteoarthritis: A Comprehensive Review

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Abstract: Knee osteoarthritis (KOA) is a prevalent degenerative joint disorder characterized by synovitis, cartilage degradation, and nociception, in which dysregulated immune responses and excessive pro-inflammatory mediators drive synovial inflammation as a central pathogenic mechanism. Acupuncture, a cornerstone of traditional Chinese medicine, has demonstrated clinical efficacy in alleviating pain, attenuating synovial pathology, and restoring joint function in KOA. In this review, we systematically elucidate the molecular mechanisms by which acupuncture suppresses synovial inflammation, focusing on its multimodal modulation of five critical signaling cascades: norepinephrine (NE) signaling, the TLRs/NF-κB pathway, the MCP1/CCR2 axis, the NLRP3 inflammasome, and the Ras-Raf-MEK1/2-ERK1/2 pathway. Relevant studies published between 2000 and 2024 were identified through comprehensive searches of PubMed and CNKI using terms such as "acupuncture + synovitis + MAPK pathway", "acupuncture + inflammation", and "knee osteoarthritis + molecular mechanisms". English and Chinese peer-reviewed articles reporting preclinical or clinical data on acupuncture's effects in KOA synovitis were included, while studies lacking mechanistic insights or unrelated to synovial inflammation were excluded. Study validity, risk of bias, and methodological rigor were appraised using the GRADE framework. Cumulative evidence indicates that acupuncture exerts anti-inflammatory and chondroprotective effects by orchestrating multi-pathway regulation, thereby reducing inflammatory mediators, promoting tissue repair, and improving joint function. As a promising adjunct to pharmacotherapy—particularly in early-stage KOA—acupuncture merits further validation through large-scale clinical trials aimed at optimizing treatment parameters, confirming long-term efficacy, and exploring synergistic combinations with emerging therapies to enable personalized KOA management.

Keywords: knee osteoarthritis, synovial inflammation, acupuncture, signaling pathway

Introduction

Osteoarthritis (OA) remains the most prevalent degenerative joint disorder worldwide, serving as the principal etiological driver of chronic nociception and mobility impairment in aging populations.[1] Contemporary understanding positions knee osteoarthritis (KOA) not merely as a cartilage disorder, but as a complex whole-joint disease involving the concomitant degeneration of the meniscus and articular cartilage, pathological subchondral bone remodeling, and inflammatory changes with fibrosis in the infrapatellar fat pad (IPFP) and synovial membrane. This multifaceted pathogenesis underpins the heterogeneity of KOA presentation and progression. While OA affects multiple articular structures, the femorotibial joint demonstrates particular vulnerability, with KOA accounting for 78–83% of all OA cases based on radiographic and symptomatic diagnostic criteria.[2,3] Epidemiological surveillance reveals substantial inter-regional disparities in KOA burden. A 2023 meta-analysis of Chinese populations (n=458,732) reported pooled prevalence estimates of 14.6% (95% CI 12.8–16.7%), demonstrating significant gender-specific susceptibility patterns (female: male ratio=1.89:1).[4] Western epidemiological studies corroborate this escalating health crisis. Longitudinal data from the UK-based Chingford Cohort Study (median follow-up=5.2 years) identified incident radiographic KOA in

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17.6% (95% CI 15.1–20.4%) of perimenopausal women aged 45–64 years.[5] Paradoxically elevated disease burden is observed in industrialized nations, with US population studies documenting a 114% increase in age-standardized KOA prevalence since 1950 - surpassing demographic aging projections.[6] The escalating epidemiological burden of knee osteoarthritis (KOA) not only mirrors the progressive articular degeneration associated with rising obesity rates and sedentary lifestyles in modern populations, but also highlights significant deficiencies in current secondary prevention approaches. With disability-adjusted life years (DALYs) attributable to KOA projected to double by 2040, there is an imperative need for the immediate implementation of cost-effective disease-modifying therapeutic strategies and precision-based rehabilitation protocols to alleviate this growing socioeconomic challenge.

The pathogenesis of KOA is multifactorial, with well-established risk factors including advanced age, genetic predisposition, excessive body weight (overweight or obesity), compromised muscle strength, and previous traumatic knee injuries.[7,8] The clinical presentation typically manifests as a triad of joint pain, synovial swelling, and restricted range of motion. During the initial disease phase, patients frequently experience intermittent, mild to moderate dull pain that is characteristically aggravated by knee mobilization or weight-bearing activities.[9–11] As the disease progresses to more advanced stages, the pain pattern often transitions to a persistent discomfort, frequently intensifying during nocturnal periods, thereby substantially compromising patients' quality of life and functional capacity.[1,12] While current therapeutic modalities cannot provide complete disease resolution, contemporary management strategies primarily focus on symptomatic relief, quality of life improvement, and potential retardation of disease progression where clinically feasible.[13,14]

The therapeutic armamentarium for knee osteoarthritis (KOA) encompasses a spectrum of interventions, ranging from non-pharmacological strategies to advanced surgical procedures.[15] Non-pharmacological approaches include evidence-based exercise protocols, comprehensive weight management programs, structured physical therapy, and the utilization of orthopedic assistive devices and customized orthotics. Pharmacological management primarily revolves around the administration of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), while surgical intervention, particularly total knee arthroplasty (TKA), represents the definitive treatment for end-stage disease.[16] In clinical practice, treatment selection is guided by disease severity, with conservative management being predominantly recommended for early to moderate stages of KOA. While analgesics provide symptomatic relief, their therapeutic effects are transient and do not address the underlying pathophysiological mechanisms. NSAIDs, despite their anti-inflammatory properties, are associated with significant iatrogenic risks, including but not limited to cardiovascular complications, renal impairment, and gastrointestinal hemorrhage, particularly with chronic administration.[17] These limitations of conventional pharmacological approaches have prompted growing interest in complementary and alternative therapies. Among non-pharmacological interventions, acupuncture - a cornerstone of traditional Chinese medicine - has emerged as a promising therapeutic modality. Its increasing integration into contemporary clinical practice is supported by accumulating evidence demonstrating its efficacy in pain modulation, functional improvement, and anti-inflammatory effects.[18,19] The mechanistic basis of acupuncture's therapeutic benefits in KOA management continues to be an area of active investigation, with recent studies suggesting potential modulation of inflammatory pathways and neural regulation.[20,21] Acupuncture, as a traditional non-pharmacological therapy, involves the insertion of needles into specific anatomical points to modulate physiological functions, and it has been extensively employed in the management of various health conditions. A cornerstone of traditional Chinese medicine, acupuncture boasts a history of over three millennia and has achieved global recognition.[22]

Accumulating empirical evidence has substantiated the therapeutic efficacy of acupuncture in ameliorating clinical manifestations of knee osteoarthritis (KOA), with proposed mechanisms involving multi-level neuromodulation across the pain pathway and regulation of inflammatory cascades.[23] Neurophysiological studies suggest that acupuncture exerts its effects through complex interactions with peripheral nociceptors, spinal cord dorsal horn neurons, and supraspinal centers within the central nervous system.[24]

Despite promising clinical outcomes demonstrating significant improvements in pain relief and functional recovery, the precise molecular and cellular mechanisms underlying acupuncture's therapeutic effects remain incompletely characterized. This knowledge gap emphasizes the urgent need for further mechanistic studies to explore the neurobiological pathways and molecular targets involved in acupuncture-induced analgesia and anti-inflammatory effects.

Additionally, the need for large-scale, well-designed clinical trials remains critical to establish standardized treatment protocols, optimize therapeutic parameters, and validate acupuncture's long-term clinical efficacy as an essential component of knee osteoarthritis (KOA) management strategies.

The aim of this review is to systematically examine the molecular mechanisms by which acupuncture modulates synovial inflammation in KOA. The review begins by discussing the pathophysiology of KOA, highlighting the role of synovial inflammation in disease progression. It then explores current evidence on the molecular pathways involved in acupuncture-mediated inhibition of synovitis. Finally, the review concludes by proposing potential clinical applications of acupuncture and directions for future research. The methodologies employed in this review include a comprehensive literature search of both preclinical and clinical studies on acupuncture for KOA. The studies were selected based on their relevance to acupuncture's impact on synovial inflammation and its associated molecular mechanisms. Although this review is not systematic, it integrates key findings from diverse experimental designs to provide an insightful analysis of acupuncture's therapeutic effects.

Acupuncture Inhibits Synovitis By Regulating and Participating In Multiple Signaling Pathways

The central pathophysiological hallmark of knee osteoarthritis (KOA) manifests as progressive degeneration of articular cartilage, characterized by structural and functional deterioration of this specialized connective tissue.[25] Under homeostatic conditions, articular chondrocytes maintain a delicate equilibrium between extracellular matrix synthesis and enzymatic degradation through tightly regulated metabolic processes. This dynamic balance enables limited adaptive responses to exogenous stressors through chondrocyte metabolic adaptation. However, when pathogenic stimuli exceed intrinsic repair capacities, a self-perpetuating cycle of matrix metalloproteinase activation and proteoglycan depletion ensues, initiating the molecular cascade of osteoarthritic degeneration.[25]

The degenerative trajectory progresses through distinct histopathological phases: initial cartilage fibrillation progresses to full-thickness erosion, accompanied by characteristic biomechanical alterations including collagen network disruption and loss of tensile strength.[26] This structural compromise facilitates mechanical wear particle generation during joint articulation, which subsequently induces synovial phagocytic responses and pro-inflammatory cytokine production.[27] The resultant synovitis establishes a self-amplifying inflammatory loop through immune cell infiltration (particularly macrophages and T lymphocytes), cytokine storm (notably IL-1β, TNF-α, and IL-6), and activation of destructive signaling pathways (eg, NF-κB and MAPK cascades). This synovial-pathology nexus drives disease progression from early inflammatory synovitis through advanced stages of synovial hyperplasia and pan-articular destruction. Critically, this process involves concomitant inflammation and fibrosis of the infrapatellar fat pad (IPFP) - an anatomically contiguous structure that demonstrates bidirectional pathophysiological crosstalk with the synovium through shared neuroimmune signaling and cytokine exchange.[28,29] The IPFP-synovium functional unit collectively establishes a self-amplifying inflammatory microenvironment through macrophage infiltration, adipokine dysregulation (leptin, adiponectin), and profibrotic TGF-β secretion, positioning synovial and IPFP modulation as critical pathomechanistic nodes and promising therapeutic targets.[30] Emerging evidence demonstrates that acupuncture-mediated synovial inflammation suppression constitutes a principal mechanism underlying its clinical efficacy in KOA management. Contemporary acupuncture modalities—including traditional manual acupuncture (MA), electroacupuncture (EA), warm acupuncture (WA), and laser acupuncture (LA)—differentially engage neuroimmune regulatory pathways through distinct biophysical mechanisms[31] (Table 1). In particular, MA and EA remain the predominant modalities in both clinical practice and mechanistic research for KOA synovitis, owing to their extensive evidence base and capacity for targeted immunomodulation. EA has garnered substantial research attention due to its quantifiable stimulation parameters and demonstrated frequency-dependent regulation of inflammatory mediators (eg, 2/100Hz modulation of IL-1β/TNF-α), as evidenced by randomized controlled trials.[32,33] While WA and LA show emerging therapeutic potential, their mechanistic characterization in synovitis suppression remains less comprehensive compared to MA/EA paradigms.

Table 1 Comparison of Acupuncture Modalities in KOA Management

Modality	Mechanistic Profile	Advantages	Limitations
Manual Acupuncture (MA)	• Mechanical stimulation of peripheral nerves • Local cytokine modulation • Minimal neuromodulatory effects	• Traditional approach with established safety • Low technical requirements • Patient-specific needle manipulation	• Subjective stimulation parameters • Operator-dependent efficacy • Limited quantifiable outcomes
Electro-acupuncture (EA)	• **Frequency-dependent immunomodulation** • Synergistic neuroimmune regulation • Downregulation of TLR/NF-κB, NLRP3 • β2-AR activation (2/10Hz optimal) • Quantifiable neuromodulation	• **Standardizable parameters** • Enhanced anti-inflammatory effects • Superior synovial biomarker reduction • Dose-response relationship established	• Requires specialized equipment • Contraindicated in pacemaker patients • Optimal frequency varies by pathology
Warm Acupuncture	• Thermal stimulation + mechanical effects • Vasodilation-enhanced drug delivery • Local tissue metabolism modulation	• Combines moxibustion benefits • Enhanced analgesic duration • Improved microcirculation	• Risk of burns/scarring • Smoke inhalation concerns • Limited standardization
Laser Acupuncture	• Photobiomodulation effects • Non-needle alternative • Mitochondrial pathway activation	• Painless application • Sterile technique • Suitable for needle-phobic patients	• Reduced neuroimmune engagement • Questionable depth penetration • Limited synovial biomarker data

Noradrenergic Signaling Pathway

Norepinephrine (NE), a key catecholamine neurotransmitter within the neuroimmune axis, orchestrates pleiotropic regulatory effects on inflammatory cascades in knee osteoarthritis (KOA) through adrenergic receptor signaling pathways. In KOA pathology, synovial NE overexpression activates G protein-coupled receptors, driving pathogenic processes such as synovial fibroblast hyperplasia, immune effector cell activation, and the secretion of pro-inflammatory mediators.[32,34] This neuroendocrine dysfunction contributes to the chronic low-grade inflammation that characterizes KOA, where imbalances in synovial macrophage polarization (M1 vs M2) exacerbate joint destruction.[35,36]

A critical investigation utilized a monosodium iodoacetate (MIA)-induced rodent model of KOA to delineate the impact of electroacupuncture (EA) pulse frequency—specifically, the hertz (Hz) rate of electrical stimulation—on β_2-adrenergic receptor (β_2-AR) activation within synovial macrophages. Three distinct pulse frequencies (2 Hz, 10 Hz, and 100 Hz) were administered for 30 minutes per session, thrice weekly over a four-week period. Quantitative analyses revealed that both 2 Hz and 10 Hz significantly enhanced β_2-AR phosphorylation and downstream cAMP accumulation; however, 10 Hz yielded the most robust effect (approximately 2.5-fold greater than 2 Hz), whereas 100 Hz demonstrated only marginal receptor engagement.[32] These findings establish an optimal pulse frequency window of approximately 2–15 Hz, with a peak efficacy at ~10 Hz under the specified experimental conditions.

EA at 10 Hz induced the most pronounced suppression of pro-inflammatory mediators, including CXCL1, IL-6, TNF-α, and IL-1β, correlating with maximal attenuation of hind-paw mechanical allodynia and reduced cartilage erosion.[32,34] Complementary microdialysis studies confirmed that this neuromodulatory intervention elevates NE concentrations locally within the synovial compartment without altering systemic plasma catecholamine levels. This site-specific pharmacology arises from EA-induced NE release from perisynovial sympathetic terminals, which subsequently activates β_2-AR on resident macrophages; rapid reuptake and local enzymatic degradation prevent NE spillover into the systemic circulation,[32,37] underscoring the precise spatial modulation afforded by EA.

In the KOA synovium, CCL2-mediated chemotaxis facilitates the recruitment of circulating monocytes, which polarize into pro-inflammatory M1 macrophages and perpetuate inflammatory cascades through persistent secretion of cytokines like IL-1β, TNF-α, and IL-6.[35,38] Subsequent investigations demonstrated that β_2-AR-cAMP-PKA signaling, activated by 10 Hz EA, suppresses CCL2 expression and impairs monocyte trafficking to the joint.[39] This intervention disrupts the feed-forward inflammatory amplification loop by preferentially attenuating M1 macrophage activity while

preserving the reparative functions of M2 macrophages,[36,40,41] thereby promoting a shift toward an anti-inflammatory microenvironment.

Collectively, these mechanisms frame EA as a targeted neuromodulatory therapy that integrates frequency-tuned electrical stimulation with localized adrenergic regulation to mitigate KOA progression, offering a rational approach for recalibrating neuroimmune interactions in joint inflammation.[42,43]

TLRs/NF-kB Signaling Pathway

The synovial innate immune response represents a critical pathophysiological axis in knee osteoarthritis (KOA), functioning as both a driver and amplifier of joint degeneration. This immunopathological cascade is initiated by biomechanical and biochemical alterations within the articular microenvironment, leading to the extracellular release of cartilage matrix components (eg, fibronectin fragments, hyaluronan, and collagen degradation products) and cellular debris. These damage-associated molecular patterns (DAMPs) engage synovial membrane-resident immune sentinels, triggering a feedforward inflammatory loop characterized by cytokine storm generation and synovial fluid biomarker elevation.[27,44] Central to this innate immune activation are Toll-like receptors (TLRs), a class of pattern recognition receptors (PRRs) that orchestrate the synovial inflammatory response through DAMP/PAMP recognition. TLR engagement initiates downstream MyD88-dependent signaling cascades, culminating in NF-κB-mediated transcriptional activation of pro-inflammatory cytokines, with interleukin-1β (IL-1β) emerging as a pivotal molecular node in KOA pathogenesis.[45] IL-1β, functioning through intricate autocrine and paracrine signaling networks, emerges as a master regulator in synovitis pathogenesis, orchestrating a multifaceted inflammatory cascade. This pro-inflammatory cytokine drives the recruitment of leukocytes through the transcriptional activation of chemokine networks while simultaneously inducing synovial fibroblast proliferation and their phenotypic transformation into aggressive effector cells.[46] In the synovium, IL-1β stimulates neoangiogenic processes via the upregulation of vascular endothelial growth factor (VEGF) signaling pathways, establishing a vascular network within this tissue that sustains chronic inflammation.[47] The cytokine's capacity to activate matrix metalloproteinases (MMPs) initiates extracellular matrix degradation, creating a self-perpetuating cycle of tissue destruction and inflammatory amplification. These interconnected molecular mechanisms collectively establish IL-1β as a central orchestrator in the inflammatory microenvironment of joint diseases. This cytokine-driven inflammatory milieu creates a self-perpetuating cycle of joint destruction, characterized by progressive cartilage degradation, synovial hyperplasia, and subchondral bone remodeling. The IL-1β/MyD88/NF-κB signaling axis not only amplifies local inflammation but also disrupts the joint's homeostatic balance through catabolic-anabolic imbalance, ultimately leading to irreversible structural and functional joint deterioration. Expanding on this mechanistic framework, Ruan et al[48] conducted a translational investigation examining EA's immunomodulatory capacity in a well-characterized rabbit model of KOA. Their findings revealed that EA intervention exerts multi-level suppression of synovial innate immunity through: attenuation of TLR4/9-mediated pattern recognition signaling, inhibition of IκBα phosphorylation and subsequent NF-κB nuclear translocation, and downregulation of downstream effector molecules including pro-inflammatory cytokines (IL-1β, TNF-α) and matrix-degrading enzymes (MMP-1, −3, −13). This coordinated suppression of the TLR/NF-κB signaling axis resulted in significant mitigation of synovitis progression and cartilage degradation. Wang et al[49] conducted a controlled animal study on KOA model rats (n=40), administering electroacupuncture (EA) at standardized acupoints for four weeks. Histological analysis revealed significantly reduced cartilage erosion and synovial hyperplasia in EA-treated animals versus untreated controls. Mechanistic investigations demonstrated that EA downregulated key TLR4/NF-κB pathway components (TLR4, MyD88, phosphorylated NF-κB p65) in articular cartilage (Western blot) and decreased synovial fluid levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α; ELISA). Significantly, EA normalized the expression of specific microRNAs (eg, miR-146a, miR-27a-3p) targeting TLR4/NF-κB pathway elements, suggesting a microRNA-mediated epigenetic regulatory mechanism underpinning EA's anti-inflammatory effects. Notably, the study established a critical therapeutic window for EA intervention, demonstrating superior clinical outcomes with early-stage implementation compared to late-stage treatment. This temporal efficacy gradient suggests that EA's disease-modifying effects are most pronounced during the initial inflammatory phase of KOA, prior to establishment of irreversible joint damage.

Although inflammation persists throughout KOA, the early stage is characterized by dominant TLR4/9-MyD88-NF κB signaling within an otherwise intact synovial microarchitecture. At this time, DAMP-driven NF κB activation rapidly amplifies cytokine release, but tissue fibrosis and receptor desensitization remain minimal. Consequently, EA-mediated inhibition of IκBα phosphorylation and NF κB nuclear translocation can more completely abort the inflammatory feed forward loop before irreversible cartilage and subchondral bone changes occur.[50] In contrast, late stage KOA features synovial fibrosis, neoangiogenesis, and downregulated TLR expression, which collectively diminish EA's ability to access and modulate this pathway, thereby explaining the superior outcomes observed with early-stage intervention.[51]

Li et al[52] demonstrated that the MCP 1/CCR2 chemotactic axis remains active from onset through end-stage KOA, suggesting that any therapy targeting this pathway—including EA—should exhibit broad efficacy irrespective of treatment timing. However, Ruan et al[53] observed that despite significant suppression of CCL2/CCR2 in both early and late models, structural barriers and altered receptor responsiveness in advanced disease attenuated EA's disease-modifying impact. This discrepancy highlights that pathway accessibility and receptor competency, not merely pathway presence, critically determine the temporal window for maximal EA efficacy.

Beyond TLR/NF κB and MCP 1/CCR2 modulation, acupuncture engages a spectrum of non specific neuroimmune mechanisms—such as vagal-adrenergic anti inflammatory reflexes, endogenous opioid release, and adenosine A1 receptor activation—which together contribute to its overall therapeutic profile.[54] In early KOA, these overlapping actions synergize to suppress synovial inflammation and preserve cartilage integrity. In later stages, when structural and molecular barriers limit direct TLR/NF κB or MCP 1/CCR2 modulation, the symptom-relief components of these non specific pathways may predominate, aligning with Ruan et al's[53] findings of reduced structural benefit yet maintained pain improvement.[55]

MCP1/CCR2 Signaling Pathway

The osteoarthritic joint microenvironment is characterized by a dysregulated chemokine milieu, with elevated concentrations of multiple chemotactic factors contributing to disease progression through distinct but interrelated mechanisms.[56] These chemokines orchestrate a pathological cascade involving: recruitment and trafficking of inflammatory cells and mesenchymal progenitor populations, induction of matrix metalloproteinase (MMP) secretion, and perpetuation of leukocyte infiltration through positive feedback loops.[57] Synovial fibroblasts, activated by chemokine signaling, exhibit enhanced IL-6 production and increased expression of adhesion molecules (eg, VCAM-1, ICAM-1), facilitating monocyte-endothelial interactions and subsequent transmigration.[58] Among the chemokine network, monocyte chemoattractant protein-1 (MCP-1/CCL2) demonstrates particularly significant pathophysiological relevance, with marked upregulation in OA cartilage, synovium, infrapatellar fat pad, and synovial fluid compartments. The MCP-1/CCR2 axis serves as a master regulator of mononuclear cell chemotaxis, directing immune cell migration to sites of inflammation or tissue injury. Beyond its immunomodulatory functions, this axis has been implicated in neuroimmune crosstalk, contributing to both inflammatory responses and neuropathic pain pathways following peripheral nerve injury.[57,58]

In knee osteoarthritis (KOA), MCP-1/CCR2 signaling assumes a central role in disease pathogenesis. Activated monocytes and macrophages initiate a cytokine cascade, releasing pro-inflammatory mediators (IL-1β, TNF-α) and neurotrophic factors, particularly nerve growth factor (NGF). NGF, abundantly expressed in the KOA joint, engages tropomyosin receptor kinase A (TrkA) to activate downstream signaling pathways (PI3K/Akt, MAPK/ERK), leading to neuronal sensitization and nociceptive hypersensitivity.[59] This neuroimmune interplay establishes a self-perpetuating cycle of inflammation and pain, driving structural joint deterioration and functional impairment.

In a mechanistic investigation by Li et al[60] the therapeutic effects of manual acupuncture (MA) at ST35 (Dubi) and ST36 (Zusanli) acupoints were systematically evaluated in a rodent model of KOA. The study revealed that MA intervention exerts multimodal anti-inflammatory and analgesic effects through: suppression of MCP-1/CCR2 axis-mediated monocyte/macrophage chemotaxis, downregulation of pro-inflammatory cytokine expression (IL-1β, TNF-α), and modulation of neurotrophic signaling pathways. Notably, the study established that MCP-1/CCR2 axis activation occurs across all OA disease stages, suggesting broad therapeutic applicability regardless of intervention timing. This temporal independence, coupled with the technique's dual anti-inflammatory and neuromodulatory effects, positions MA

as a promising disease-modifying intervention for KOA management. Bocun Li et al[60] induced KOA in Sprague–Dawley rats via anterior cruciate ligament transection and applied MA at ST35 (Dubi) and ST36 (Zusanli) once daily for seven weeks. Compared with untreated OA controls, MA-treated rats exhibited significant attenuation of mechanical hyperalgesia and cartilage degeneration. Mechanistically, MA markedly reduced synovial and cartilage expression of the chemokine MCP-1 and its receptor CCR2, concomitant with downregulation of pro-inflammatory cytokines IL-1β and TNF-α in both synovium and cartilage. Crucially, MA also suppressed NGF and its high-affinity receptor TrkA in synovial tissue and dorsal root ganglia, linking chemokine inhibition to decreased peripheral sensitization and providing a direct mechanistic basis for its analgesic efficacy. Short term MA in Dunkin Hartley guinea pigs examined a primary KOA model in aged guinea pigs treated with weekly MA sessions over three weeks.[61] Although gross mobility measures and histological grading remained unchanged, serum levels of complement component 3 and prostaglandin E_2 were significantly reduced in MA versus comparator groups, indicating systemic anti-inflammatory effects. Transcriptomic analysis of articular cartilage revealed downregulation of multiple matrix remodeling and apoptotic gene transcripts, while immunohistochemistry demonstrated enhanced NGF immunostaining across all cartilage layers in MA treated joints. These findings underscore MA's capacity to modulate neurotrophic signaling within the joint microenvironment, potentially via NGF/TrkA pathways, and to initiate early regenerative processes alongside inflammatory suppression.

NLRP3 Inflammasome Signaling Pathway

The NLRP3 inflammasome represents a critical intracellular immune surveillance platform that orchestrates innate immune responses to diverse endogenous and exogenous danger signals. This multiprotein complex is activated through recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), including microbial components, crystalline structures (cholesterol, monosodium urate), metabolic byproducts (ATP, fatty acids), and amyloid aggregates.[62–64] Upon activation, NLRP3 undergoes oligomerization and recruits downstream effectors, initiating caspase-1-mediated inflammatory cascades that contribute to the pathophysiology of various chronic inflammatory disorders. In knee osteoarthritis (KOA), NLRP3 inflammasome activity is markedly upregulated, as evidenced by Clavijo-Cornejo et al[65] who demonstrated a 5.4-fold increase in synovial NLRP3 protein expression compared to healthy controls. Complementary findings by Sakalyte et al[66] identified robust NLRP3 expression in KOA synovial fibroblasts, suggesting cell type-specific activation patterns. Mechanistically, NLRP3 functions as a pattern recognition receptor (PRR) that integrates synovial DAMPs/PAMPs signaling through NF-κB pathway activation, driving the transcriptional upregulation of pro-inflammatory mediators.[67]

Synovial macrophages in KOA exhibit particularly pronounced NLRP3 inflammasome activation, leading to caspase-1-dependent maturation and secretion of IL-1β and IL-18.[68,69] This cytokine release establishes a feedforward inflammatory loop, amplifying synovitis and promoting cartilage matrix degradation through multiple mechanisms: upregulation of matrix metalloproteinases (MMPs), inhibition of extracellular matrix synthesis, and induction of chondrocyte apoptosis. The sustained NLRP3 activation in synovial tissue thus serves as a critical nexus point, linking initial danger signal recognition to chronic synovial inflammation and progressive joint degeneration in KOA.

Building upon the established role of NLRP3 inflammasome in synovitis pathogenesis, Yu et al[70] employed a papain-induced rodent model of KOA to investigate electroacupuncture's immunomodulatory effects at EX-LE4 (Heding) and ST35 (Dubi) acupoints. Their experimental findings demonstrated that electroacupuncture intervention exerted profound anti-inflammatory effects, as evidenced by significant attenuation of synovial inflammation through histopathological assessment, concomitant reduction of systemic inflammatory burden manifested by decreased serum concentrations of IL-1β and IL-18, and substantial downregulation of synovial NLRP3 inflammasome components (NLRP3, ASC, Caspase-1) along with their downstream cytokine cascades at both transcriptional and translational levels, suggesting a comprehensive modulation of inflammatory signaling pathways. These results demonstrate that electroacupuncture exerts anti-inflammatory effects through NLRP3 inflammasome inhibition and pyroptosis modulation in synovial tissues.

Complementary research by Wang et al[71] in a spontaneous KOA guinea pig model further elucidated electroacupuncture's disease-modifying potential. Treatment outcomes included: alleviation of mechanical allodynia, preservation of articular cartilage architecture, and reduction of surface fibrosis. Mechanistic investigations revealed that these therapeutic effects were mediated through NLRP3 inflammasome pathway inhibition, as evidenced by decreased

Caspase-1 and IL-1β expression in chondral tissues. These findings suggest that electroacupuncture modulates KOA progression through coordinated suppression of inflammatory and degenerative pathways, ultimately attenuating synovitis and cartilage degradation.

Ras-Raf-MEK1/2 Signaling Pathway

The Ras-Raf-MEK1/2-ERK1/2 signaling axis constitutes an evolutionarily conserved mitogen-activated protein kinase (MAPK) cascade that orchestrates fundamental cellular processes, including proliferation, differentiation, survival, and apoptosis. Mechanistically, this pathway operates through sequential phosphorylation events: GTP-bound Ras activates Raf kinases through direct interaction, activated Raf phosphorylates MEK1/2 on dual serine residues, MEK1/2 subsequently activates ERK1/2 via threonine-tyrosine phosphorylation.[72–74] Activated ERK1/2 translocates to the nucleus, modulating transcription factor activity (eg, ATF-2, Elk-1) and kinase substrates (RSK1-3, MNK1/2) to regulate gene expression programs critical for cellular adaptation.[74–77]

In osteoarthritis (OA) synovitis, dysregulated ERK1/2 signaling acts as a pathophysiological hub coordinating multiple interconnected pathological mechanisms. Sustained ERK activation drives synoviocyte hyperplasia through cyclin D1 upregulation and concurrent p21 suppression, promoting synovial fibroblast proliferation and subsequent synovial membrane thickening. The signaling cascade further amplifies inflammatory responses via AP-1 component phosphorylation, which enhances transcriptional activation of pro-inflammatory mediators including TNF-α, IL-1β, and IL-6, thereby perpetuating cytokine storm dynamics.[78,79] While transient ERK activation facilitates physiological synoviocyte migration essential for acute-phase tissue repair, chronic signaling induces pathological cell motility through MMP-9/13 overexpression, contributing to migratory dysregulation and tissue invasion. Intriguingly, persistent ERK activation exhibits a paradoxical dual functionality - while promoting proliferative signals, it simultaneously triggers apoptosis through Bim activation in synoviocytes, with subsequent release of damage-associated molecular patterns (DAMPs) that fuel inflammatory amplification. Furthermore, ERK1/2 demonstrates synergistic crosstalk with the NF-κB pathway via IKKβ cooperation, enhancing nuclear translocation of NF-κB to establish a self-reinforcing feedforward loop that escalates chemokine production (CXCL1, CCL2) and leukocyte infiltration.[80] This multidimensional regulatory network positions ERK1/2 signaling as a central integrator of inflammatory, proliferative, and matrix-degradative pathways in OA synovitis pathogenesis. Therapeutic interventions targeting this signaling axis may disrupt the vicious cycle of synovial inflammation and structural joint deterioration by simultaneously addressing multiple nodes of disease progression.

Tumor necrosis factor-alpha (TNF-α) represents a pivotal pleiotropic cytokine that orchestrates critical immune modulation and inflammatory cascades. As a master regulator of inflammation, TNF-α exerts multifaceted biological functions, including the recruitment, activation, and extravasation of leukocytes, while simultaneously stimulating the synthesis and release of downstream pro-inflammatory mediators such as interleukin-1 (IL-1) and interleukin-6 (IL-6). Within the pathophysiological context of inflammatory arthropathies, particularly osteoarthritis (OA), TNF-α has been mechanistically implicated in the induction of chondrocyte apoptosis, with pronounced effects observed in the articular cartilage of osteoarthritic knee joints.[81,82] Through its dual activation of both chondrocytes and synovial fibroblasts, TNF-α establishes a self-amplifying inflammatory cascade characterized by the progressive release of matrix-degrading enzymes and secondary cytokines, thereby accelerating cartilage matrix degradation and potentiating nociceptive pathways. This cytokine-mediated amplification loop not only perpetuates synovial inflammation but also drives the structural progression of joint degeneration, positioning TNF-α as a central therapeutic target in the management of OA pathogenesis and its associated clinical manifestations.

Previous research has established that electroacupuncture (EA) therapy can stimulate the release of various serum factors implicated in the modulation of cartilage inflammation. These bioactive molecules are subsequently transported through the circulatory system to target tissues and cells, where they mediate their therapeutic effects.[83] In an innovative in vitro experimental design, Chen et al[84] employed serum from EA-treated animals to create a physiologically relevant microenvironment for chondrocyte culture. This experimental paradigm was specifically designed to investigate TNF-α-induced chondrocyte apoptosis and its molecular regulatory mechanisms, thereby providing insights into the potential therapeutic mechanisms of EA in osteoarthritis (OA) pathogenesis. The experimental results demonstrated that EA

effectively attenuated TNF-α-mediated inflammatory responses in chondrocytes through modulation of the Ras-Raf-MEK1/2-ERK1/2 signaling pathway, consequently suppressing its pro-inflammatory effects. These findings suggest that the Ras-Raf-MEK1/2-ERK1/2 signaling cascade plays a crucial role in the pathogenesis and progression of synovitis. Therefore, therapeutic interventions targeting this specific signaling pathway may represent a promising strategy for mitigating synovial inflammation and preventing joint degeneration in OA patients.

Discussion

Synovial inflammation in knee osteoarthritis (KOA) constitutes a multifaceted immune response process involving the intricate interplay of multiple signaling pathways. This review provides an analysis of the molecular mechanisms underlying the therapeutic effects of acupuncture modalities, including manual acupuncture and electroacupuncture, on KOA-associated synovitis. Emerging evidence demonstrates that acupuncture exerts its anti-inflammatory effects through the modulation of several critical signaling pathways, including the norepinephrine pathway, TLRs/NF-κB axis, MCP1/CCR2 chemokine signaling, NLRP3 inflammasome activation, and the Ras-Raf-MEK1/2-ERK1/2 signaling cascade. The therapeutic efficacy of acupuncture is mediated through the suppression of pro-inflammatory cytokine release, regulation of synovial cell proliferation and apoptosis, and attenuation of pathological progression in knee arthritis. The identification and precise modulation of these signaling pathways offer promising therapeutic targets for the clinical management of KOA. Further investigations are warranted to elucidate the complex interactions among these pathways and to validate their clinical translational potential through well-designed clinical trials and mechanistic studies.

Acupuncture has emerged as a promising adjunctive therapy in the management of knee osteoarthritis (KOA), demonstrating synergistic effects when combined with conventional pharmacological interventions. This integrative therapeutic approach has gained substantial clinical recognition due to its ability to enhance treatment efficacy while mitigating adverse drug reactions. Current evidence indicates that the combination of acupuncture with non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and hyaluronic acid supplementation yields superior clinical outcomes in terms of joint function preservation and disease progression modulation. Mechanistically, acupuncture has been shown to influence the pharmacokinetic profile of NSAIDs by enhancing their bioavailability and metabolic processing, thereby prolonging their therapeutic window. This pharmacological interaction not only potentiates the analgesic and anti-inflammatory properties of these medications but also enables dose reduction strategies, consequently lowering the incidence of drug-related complications. Furthermore, acupuncture appears to exert its therapeutic effects through multiple pathways, including modulation of qi and blood circulation, activation of endogenous opioid systems, and regulation of neuroinflammatory pathways. These mechanisms collectively contribute to enhanced pain management and anti-inflammatory responses, potentially through neuromodulation of both peripheral and central nervous system components. The cumulative evidence suggests that acupuncture-mediated neural regulation may amplify the pharmacological actions of conventional therapies, thereby optimizing therapeutic outcomes in KOA management.

As a complementary therapeutic modality, acupuncture has demonstrated the capacity to attenuate patients' dependence on pharmacologic interventions. In clinical scenarios where substantial therapeutic improvements are manifested, a gradual tapering of medication dosages can be implemented, thereby alleviating the pharmacological burden and minimizing associated adverse effects. A groundbreaking advancement in this domain was pioneered by Wenjie Xu et al[85] who developed a nanotechnology-enhanced drug delivery acupuncture system (nd-Acu). This innovative approach leverages the synergistic interplay between acupuncture and targeted drug delivery, demonstrating remarkable enhancement of therapeutic efficacy in a murine model of knee osteoarthritis (KOA). This technological breakthrough heralds a new paradigm in the integration of traditional acupuncture with contemporary pharmacological therapies for KOA management, offering novel insights for clinical translation. The successful implementation of this combinatorial therapeutic strategy not only optimizes treatment outcomes but also facilitates dose reduction of pharmacological agents, ultimately contributing to improved patient quality of life metrics.

The findings presented in this review provide compelling evidence for the efficacy of acupuncture in mitigating synovial inflammation in knee osteoarthritis (KOA), driven by its modulation of critical signaling pathways, including norepinephrine signaling, TLR/NF-κB activation, MCP1/CCR2 chemotactic signaling, and neurotrophic factors such as

Table 2 Critical Evaluation and Future Perspectives on Acupuncture for KOA Synovitis

Domain	Key Findings/Challenges	Current Limitations	Future Research Priorities
Mechanistic Evidence	Multimodal pathway regulation: 1. NE/β2-AR → ↓ cytokines 2. TLRs/NF-κB inhibition 3. MCP1/CCR2/NGF axis suppression 4. NLRP3 inflammasome blockade 5. ERK1/2 signaling modulation	• Over-reliance on rodent models • Insufficient human synovial tissue validation • Reductionist single-pathway focus	Spatial transcriptomics of human synovium Single-cell RNA-seq of acupuncture-treated joints Pathway crosstalk mapping (eg, NE-NLRP3-ERK)
Clinical Translation	Symptomatic improvement in pain/function Synergistic effects with pharmacotherapies	• High protocol heterogeneity • Inadequate EA parameter reporting • Short-term follow-up (≤12 weeks)	• Dose-response optimization trials • Standardized EA protocol development • RCTs with ≥24-month structural outcomes (MRI synovitis/cartilage)
Methodological Challenges	• Blinding difficulties → placebo debate • Practitioner skill dependency • Limited biomarkers for efficacy monitoring	• Subjective outcome dominance • Lack of sham-acupuncture controls in mechanistic studies	• Biomarker validation (eg, synovial fluid IL-1β, CCL2) • Automated acupuncture devices • Multi-arm RCTs comparing MA/EA/sham
Integrative Potential	Enables NSAID dose reduction Attenuates surgical intervention needs	• No consensus on optimal combinational strategies • Cost-effectiveness data scarcity	• Acupuncture + low-dose biologics trials • Health-economic analyses • Nanotechnology-enhanced delivery systems (eg, nd-Acu)

NGF. While the existing preclinical and clinical data are promising, the application of acupuncture in KOA management is not without challenges (Table 2).

One major limitation of current studies is the heterogeneity in acupuncture protocols, including variations in acupoint selection, stimulation frequency, and duration of treatment, which make it difficult to establish universally effective treatment regimens. Additionally, the mechanistic underpinnings of acupuncture's effects remain incompletely understood, with much of the evidence being derived from animal models or small-scale clinical trials. The challenge of translating these results into robust clinical outcomes requires larger, multicenter trials with rigorous methodological designs.

Moreover, although acupuncture has been shown to regulate immune responses and inflammation, its long-term effects on the progression of KOA and potential adverse events are still unclear. Some concerns about patient selection, such as the impact of acupuncture in severe OA stages where structural damage may limit its therapeutic potential, remain.

Future studies should focus on clarifying the precise molecular mechanisms through advanced omics technologies, elucidating the interaction between acupuncture and other pharmacological or non-pharmacological treatments. In particular, further investigation into the timing of acupuncture intervention, especially early in disease progression, is crucial to optimizing therapeutic strategies. Clinical trials designed to standardize acupuncture treatment protocols, as well as comparative studies with other treatment modalities, are essential to validate acupuncture's efficacy and establish it as a mainstream therapeutic option for KOA management.

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