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REVIEW

Advances in Electroacupuncture for Treatment of Knee Osteoarthritis: Mechanisms, Efficacy, and Future Directions

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Abstract: Knee osteoarthritis (KOA) is a common chronic degenerative joint disease marked by progressive cartilage loss, subchondral bone remodeling, and synovial inflammation, resulting in persistent pain, functional disability, and diminished quality of life. Electroacupuncture (EA), a modality combining traditional acupuncture with electrical stimulation, has gained attention as a non-pharmacological intervention for KOA. Growing evidence suggests that EA not only reduces pain and enhances joint mobility but also modulates diverse biological processes—such as neuroendocrine signaling, inflammatory cascades, cartilage metabolism, and local hemodynamics. Mechanistically, EA acts through multi-target mechanisms, including suppression of pro-inflammatory mediators, promotion of anti-inflammatory and chondroprotective factors, and regulation of critical signaling pathways such as NF-κB, MAPK, and Wnt/β-catenin. Additionally, EA engages central and peripheral neuromodulatory systems involving opioid, serotonergic, and cannabinoid receptors, underpinning its analgesic properties. Despite encouraging outcomes, current support derives predominantly from small-scale clinical trials with short follow-up periods, underscoring the necessity for large-scale, randomized controlled studies with rigorous designs to establish standardized protocols and validate long-term benefits. This review synthesizes contemporary understanding of EA's mechanisms and efficacy in KOA management, addressing ongoing challenges and outlining future directions for refining EA-based strategies within integrated treatment frameworks.

Keywords: knee osteoarthritis, electroacupuncture, analgesia, inflammation, cartilage repair, biological mechanisms

Introduction

Knee osteoarthritis (KOA) is a common degenerative joint disease, primarily characterized by the gradual destruction of articular cartilage, narrowing of the joint space, and the formation of bone spurs, often leading to pain, stiffness, and functional impairment.[1] According to global research, epidemiological data indicate that approximately 10% to 15% of adults are affected, with a higher incidence in the elderly population.[2] Due to its substantial morbidity and disability rates, KOA exerts dual physical and psychological impacts on patients and poses a significant burden on families and society.[3] The disease arises from an imbalance between joint tissue repair and degradation, with central pathological processes involving the degeneration and breakdown of articular cartilage, although the precise mechanisms remain incompletely understood.[4] Current knowledge of KOA pathogenesis encompasses genetic, biomechanical, inflammatory, and aging-related mechanisms.[5] Moreover, OA is a whole-joint disorder involving interactions among multiple tissues including cartilage, synovium, subchondral bone, ligaments, and menisci.[6] For instance, cartilage degradation products in OA activate synovial inflammation and reduce protective joint capacity, leading to abnormal stress on bone.[7] Activated synovium releases destructive cytokines that directly attack cartilage and worsen the joint environment.[8] Concurrently, subchondral bone sclerosis diminishes shock-absorbing functionality and exacerbates cartilage breakdown through biochemical crosstalk, while osteophyte formation further disrupts joint architecture.[9] Additionally, injuries to ligaments

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and menisci directly cause mechanical instability, abnormally increasing load on other joint tissues and accelerating wear.[3] Accumulating evidence suggests that the holistic nature of KOA implies that therapies targeting a specific tissue or systemic interventions (eg, weight loss) can produce beneficial ripple effects across the joint.[6] For example, inhibiting bone remodeling may reduce mechanical stress on subchondral bone and indirectly benefit cartilage;[10] potent anti-inflammatory interventions can simultaneously suppress synovitis and cartilage inflammation;[11] and weight loss alleviates loading on cartilage, bone, and synovium through both biomechanical and biochemical mechanisms.[12] Meniscal pathology may also ameliorate with treatment for KOA.[13]

Current management primarily involves non-steroidal anti-inflammatory drugs (NSAIDs), such as etoricoxib and celecoxib, which selectively inhibit prostaglandin synthesis to reduce joint swelling and pain through anti-inflammatory effects. However, issues including side effects, adverse reactions, and transient efficacy remain concerning.[14] Although glucosamine sulfate aims to support cartilage repair by replenishing cartilage matrix, delaying degradation, and restoring chondrocyte activity-thereby improving articular cartilage function-its effects are slow-onset, often requiring long-term use as an adjunct therapy.[15] In severe advanced cases, surgical options such as unicompartmental knee arthroplasty, total knee replacement, and high tibial osteotomy are available. Nonetheless, factors including high cost, prolonged recovery, and risk of complications limit their adoption.[16] Therefore, identifying safer and more effective treatment strategies remains a priority in clinical research.

Electroacupuncture (EA), an integrative modality combining traditional acupuncture with modern electrical stimulation, has a long history of use in clinical practice within traditional Chinese medicine. It is recognized for its effects in warming meridians, promoting Qi and blood circulation, reducing inflammation, and alleviating pain. Valued for its rapid onset, efficacy, cost-effectiveness, and favorable safety profile, EA enhances acupuncture effects through electrical stimulation of acupoints, improving local blood flow, relieving pain, and restoring joint function.[17] In recent years, EA has gained increasing attention in KOA management, with preliminary studies demonstrating promising outcomes in pain relief and functional improvement.[18,19] Research indicates that EA significantly alleviates muscular pain, joint stiffness, and numbness in KOA patients, while also enhancing immune function, contributing to its broad clinical application.[20] Furthermore, EA modulates chondrocyte proliferation and apoptosis, inhibits extracellular matrix (ECM) degradation, attenuates chondrocyte degeneration, and facilitates the repair of damaged cartilage, thereby effectively ameliorating clinical symptoms of KOA.[21]

The mechanisms underlying EA's efficacy in KOA involve synergistic multi-target and multi-pathway effects. It not only downregulates pro-inflammatory factors such as IL-1β, TNF-α, and MMPs but also upregulates protective factors including TGF-β and TIMP-1, thereby suppressing inflammatory responses and delaying cartilage matrix degradation.[22] Additionally, EA modulates signaling pathways such as MAPK, NF-κB, and PI3K/Akt, inhibiting inflammation and apoptosis at genetic and protein levels, promoting cartilage repair, and reducing osteophyte formation.[23] At the cellular level, EA helps maintain water metabolism balance by reducing aquaporin 3 (AQP3) expression[24] and regulates mitochondrial function and the Bcl-2/Bax ratio to inhibit apoptosis.[25] Moreover, EA improves peri-articular muscle strength and biomechanical balance, optimizes load distribution across the joint, and reduces abnormal stress on cartilage, thereby slowing degenerative processes.[26] In terms of analgesia, EA activates multiple pain regulatory systems including cannabinoid receptors (CB1R/CB2R), serotonin (5-HT) receptors, and μ/δ-opioid receptors, effectively inhibiting peripheral and central sensitization to pain.[27,28] Clinical studies confirm that EA monotherapy-particularly when using dense-sparse wave patterns and higher current intensities-outperforms manual acupuncture in alleviating pain and improving joint function, effects correlated with modulation of inflammatory cytokines such as TNF-α and IL-1β.[22] EA is also frequently combined with moxibustion, herbal medicine, pharmaceuticals, manual therapy, and physical interventions to form integrated treatment protocols. These combination strategies often yield superior outcomes in joint function and inflammatory markers compared to monotherapies.[29] Other mechanisms include regulation of the TLR4/NF-κB and Wnt/β-catenin pathways, inhibition of synovitis and cartilage degradation, and multi-level holistic effects achieved through modulation of pain-related factors and improved biomechanical equilibrium.[23] In summary, EA exerts multi-pathway, multi-target regulatory effects on inflammatory responses, signaling pathways, and cellular metabolism, effectively inhibiting cartilage degradation, promoting tissue repair, alleviating pain, and improving knee joint function. It represents a synergistic and mechanism-rich therapeutic approach for KOA.

Despite recent advances in both clinical and basic research on EA for KOA, a comprehensive synthesis of findings is lacking. This review aims to summarize the fundamental principles of EA, its clinical applications in analgesia and functional improvement, and elucidate its mechanisms-both in peripheral and central nervous systems for pain relief-and its chondroprotective effects mediated through suppression of inflammatory responses and retardation of joint degeneration.

Basic Principles and Techniques of EA

Definition and Operation Method of EA

EA is a new therapy that combines traditional acupuncture with electrical stimulation by introducing electric current into the acupuncture needles to enhance the efficacy of acupuncture. During EA treatment, after the needle is inserted into the acupoint and qi is obtained, a small amount of electric current that the human body could tolerate is applied to the needle, thereby stimulating the acupoint to achieve therapeutic effects. Its advantages include the combination of two types of stimulation, needling and electrical current, which could improve efficacy; the parameters of electrical stimulation, such as waveform, frequency, and intensity, are easier to control and have strong repeatability; EA replaces manual needling, saving labor and improving treatment efficiency, thus benefiting more patients.[30] The operation method of EA typically involves selecting appropriate acupoints, then using specialized EA equipment to insert the needle into the skin and apply low-frequency or high-frequency current through electrodes. During the operation, the practitioner needs to adjust the intensity, frequency, and waveform of the current based on the patient's specific condition and response to achieve the best therapeutic effect.[31] EA has a wide range of applications, commonly used in pain management, neurological rehabilitation, musculoskeletal diseases, and other treatments.[32] Research shows that EA could inhibit synovial inflammation, reduce inflammatory stimulation;[33] suppress cartilage degeneration, repair cartilage tissue;[5] regulate the expression of related pain receptors, exert analgesic effects;[28] thereby improving clinical symptoms such as limited activity due to knee joint pain and enhancing the quality of life of patients.

Differences Between EA and Traditional Acupuncture

EA and AM exhibit distinct differences in the management of KOA, particularly in their modes of stimulation and mechanisms of action. EA delivers continuous electrical current to specific acupoints (eg, ST34, ST35, SP10), providing consistent and quantifiable stimulation parameters. This approach more effectively modulates pain pathways and inflammatory responses, with notable efficacy in suppressing pro-inflammatory cytokines such as TNF-α and IL-1β.[22,34,35] In contrast, AM relies on manual needle manipulation (eg, lifting, thrusting, and rotating) to elicit the deqi sensation. Its effects are oriented more toward systemic regulation of Qi and blood, functional recovery, and particularly excel in alleviating joint stiffness and improving long-term functional capacity.[36–38]

In terms of clinical efficacy, EA demonstrates superior short-term analgesic effects and enhancement of joint mobility, attributable to its ability to promote the release of endogenous opioids and activate descending pain inhibitory pathways.[39–41] While AM may exhibit less immediate pain relief compared to EA, it offers unique advantages in ameliorating depressive symptoms, enhancing quality of life, and improving functional mobility-particularly in patients with deficiency patterns such as kidney and marrow insufficiency in KOA.[42–44] Furthermore, AM emphasizes pattern-based acupoint selection and highly individualized treatment strategies, aligning with the holistic principles of Traditional Chinese Medicine.[45,46]

From the perspectives of applicability and patient tolerance, EA's adjustable electrical parameters make it more suitable for individuals tolerant to stronger stimulation. It also integrates readily with modern rehabilitation therapies, such as extracorporeal shockwave treatment, forming comprehensive therapeutic regimens.[47,48] Conversely, AM is often better suited for patients sensitive to electrical stimulation or those presenting with complex deficiency patterns. It demonstrates sustained benefits in long-term symptom management and relapse prevention.[38,43,49] Thus, in clinical practice, the choice or combination of EA and AM should be tailored to the patient's specific condition], syndrome pattern, and treatment goals to optimize therapeutic outcomes (Table 1).

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Table 1 Efficacy Comparison Between EA and AM in the Treatment of KOA

NO.	gEA (n)	AM (n)	Acupoint	Assessment Items	Conclusion	References
1	40	40	EA: GB34 (Yanglingquan), ST36 (Zusanli); AM: EX-LE4 (Waixiyan), EX-LE5 (Neixiyan), ST36 (Zusanli), BL23 (Shenyu), ST34 (Liangqiu), SP10 (Xuehai)	Symptoms, TCM symptom score, HSS score	EA quickly reduces local inflammation, eases symptoms, and improves knee joint function.	[34]
2	45	45	ST36 (Zusanli), ST35 (Dubi), SP9 (yinlingquan), ST34 (Liangqiu), SP10 (Xuehai), BL23 (Shenyu), EX-LE4 (Waixiyan), EX-LE5 (Neixiyan)	WOMAC score	EA effectively relieves pain, while AM is better at reducing joint stiffness.	[36]
3	30	30	BL11 (Dazhu), ST36 (Zusanli), ST34 (Liangqiu), SP10 (Xuehai), BL23 (Shenyu), EX-LE4 (Waixiyan), EX-LE5 (Neixiyan)	WOMAC score, VAS score	EA is better for pain relief, while AM alleviates joint stiffness; overall, EA is more effective.	[37]
4	35	35	BL11 (Dazhu), ST36 (Zusanli), SP10 (Xuehai), BL23 (Shenyu), EX-LE5 (Neixiyan), GB34 (Yanglingquan), GB39 (Xuanzhong)	WOMAC score, VAS score, TCM symptom score	AM could relieve pain, maintain or improve joint function, and prevent the progression of OA.	[38]
5	30	30	LI4 (Hegu) and LR3 (Taichong) bilaterally, and ST36 (Zusanli), ST35 (Dubi), (Xiyan) and SP10 (Xuehai)	Pain severity, Functional impairment, Peak isometric strength, Pain pressure threshold	No significant difference in immediate effects of AM vs EA on pain, strength, and mobility in KOA patients.	[39]
6	31	31	ST34 (Liangqiu), SP10 (Xuehai), EX-LE5 (Neixiyan), EX-LE4 (Waixiyan), GB34 (Yanglingquan), ST36 (Zusanli), SP9 (yinlingquan)	VAS score, HAMD score, Lysholm score, KOOS score	AM can alleviate depression, reduce knee pain, and improve function in early to mid-stage OA.	[42]
7	40	40	ST36 (Zusanli), ST34 (Liangqiu), SP10 (Xuehai), EX-LE5 (Neixiyan), ST35 (Dubi), SP9 (yinlingquan),	WOMAC score, Severity of illness index, clinical efficacy	EA reduces swelling and pain, while AM relieves stiffness and enhances quality of life.	[45]
8	37	37	Dubi (ST 35), Neixiyan (EX-LE4), Xuehai (SP 10), Zusanli (ST 36), Yanglingquan (GB 34)	WOMAC score, illness severity index and systematic efficacy	EA relieves pain effectively, while AM alleviates joint stiffness; EA's effectiveness surpasses AM's.	[46]
9	28	30	ST34 (Liangqiu), ST35 (Dubi), ST36 (Zusanli), Heding, Neixiyan, GB33 (Xiyangguan), GB34 (Yanglingquan), SP9 (Yinlingquan), SP10 (Xuehai), LR7 (Xiguan), LR8 (Ququan) and ah shi points	WOMAC score, VAS score, inflammatory factor, Cartilage degradation markers.	EA and AM improved pain relief and functionality in mild to moderate KOA patients over 8 weeks.	[22]
10	30	30	ST34 (Liangqiu), ST35 (Dubi), ST36 (Zusanli), Heding,Neixiyan, GB33 (Xiyangguan), GB34 (Yanglingquan), SP9 (Yinlingquan), SP10 (Xuehai), LR7 (Xiguan), LR8 (Ququan)	WOMAC score, SF-12 score, VAS score	The treatments in both groups are equally effective.	[49]
11	29	30	ST36 (Zusanli), EX-LE5 (Neixiyan), ST35 (Dubi), SP9 (yinlingquan), ST34 (Liangqiu), SP10 (Xuehai)	Symptoms, HSS score, SF-12 score	AM could lower inflammation, relieve pain, and improve knee joint function.	[50]
12	30	30	SP10 (Xuehai), BL23 (Shenyu), ST36 (Zusanli), SP9 (yinlingquan)	Overall effective rate	The EA's effective rate (96.67%) is much higher than the AM's (80%).	[51]

Abbreviations: EA, Electroacupuncture; AM, acupuncture and moxibustion; TCM, Traditional Chinese Medicine.

Relationship Between Stimulation Parameters of EA and Effects

EA exerts its therapeutic effects in KOA through carefully selected stimulation parameters, each playing a distinct role in neuromodulation and clinical efficacy. A data mining study showed that the two most commonly connected acupoints for EA are Neixiyan-Dubi and Liangqiu-Xuehai (Figure 1), with the most frequently used stimulation parameters being sparse wave, dense wave, 2 Hz, 2/100 Hz, tolerable intensity, 30 min/session, treated once every other day, for a total treatment duration of 4 weeks.[52] The waveform and frequency are particularly significant: dilatational waves (eg, 2/100 Hz) are most commonly employed for their ability to simultaneously activate multiple opioid receptors and reduce neural adaptation, thereby enhancing analgesic and anti-inflammatory outcomes.[47,52,53] In contrast, low-frequency continuous waves (2–5 Hz) predominantly activate μ-opioid pathways to alleviate pain, while higher frequencies (15–100 Hz) are more effective in reducing muscle spasms and modulating local inflammation.[54–56] The selection of appropriate waveform and frequency thus directly influences neurotransmitter release and subsequent pain modulation.

Current intensity and treatment scheduling are equally critical in achieving optimal results. Intensity must be individualized to a patient's tolerance level, typically ranging between 2–5 mA, as stronger yet tolerable stimulation has been associated with more pronounced and sustained analgesia through enhanced Aδ and C-fiber engagement.[57–59] Regarding treatment regimen, a session duration of 20–30 minutes applied 3 times per week over 4–6 weeks has been consistently adopted in clinical protocols to balance efficacy and practicality.[60–62] Intensive treatment within this window facilitates cumulative biological effects-including reduced pro-inflammatory cytokines and improved functional mobility-without compromising patient adherence.[59,63]

The interplay of these parameters ultimately determines the effectiveness of EA in managing KOA. Longer treatment courses (≥4 weeks) with adequate session frequency are necessary to address chronic pain mechanisms, such as central sensitization and synovitis, and to promote longer-lasting functional improvements.[58,59] Tailoring parameters to specific clinical presentations-for instance, using higher frequencies for acute inflammatory pain and lower frequencies for chronic dysfunction-can further optimize outcomes.[64,65] Future studies should focus on stratified patient analyses to establish phenotype-specific parameter recommendations, advancing toward personalized EA applications in osteoarthritis therapy (Table 2).

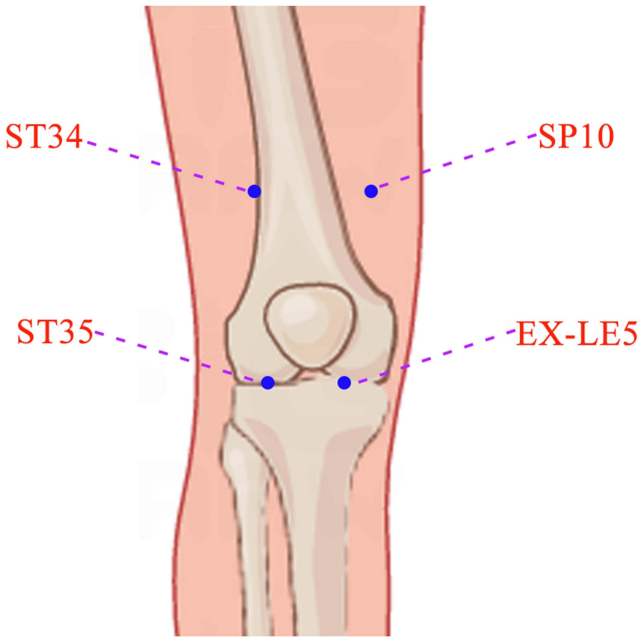

Figure 1 The Two Top Commonly Connected Acupuncture Points (lateral: "Liangqiu" (ST34) and "Dubi" (ST35), medial: "Xuehai" (SP10) and "Neixiyan" (EX-LE5)).

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Table 2 Parameters of EA Treatment for KOA

NO.	Waveform	Frequency	Current	Session Time	Treatment Frequency	Duration	References
1	Dilatational wave	15 Hz	5-10 mA	30 min	Once daily, 6 sessions a week	6 w	[66]
2	Continuous wave	2 Hz	Tolerable	30 min	Once daily, 6 sessions a week	2 w	[55]
3	Continuous wave	5 Hz	Tolerable	20 min	3 times a week	4 w	[36]
4	Dilatational wave	60 Hz	Tolerable	30 min	Once daily	2 w	[67]
5	Low frequency	10-30 Hz	Tolerable	30 min	3 times a week	3 w	[68]
6	Dilatational wave	2 Hz	Tolerable	30 min	Once daily, 6 sessions a week	3 w	[69]
7	Continuous wave	2 Hz	Tolerable	30 min	Once daily	3 w	[70]
8	Continuous wave	2 Hz	Tolerable	30 min	Once daily, 5 sessions a week	4 w	[71]
9	Dilatational wave	15 Hz	Tolerable	30 min	Once daily, rest for 1 d after 10 sessions	30 d	[72]
10	Continuous wave	2 Hz	Tolerable	20 min	Once daily	10 d	[73]
11	Dilatational wave	2 Hz/100 Hz	Tolerable	45 min	Once every other day	30 d	[53]
12	Continuous wave	2-4 Hz	Tolerable	30 min	Once daily, 5 sessions a week	3 w	[74]
13	Continuous wave	2 Hz	Tolerable	30 min	Twice a week	5 w	[60]
14	Continuous wave	2 Hz	2mA	20 min	Once every other day	6 w	[64]
15	Continuous wave	2 Hz	2mA	30 min	Once daily (post-operation)	2 d	[75]
16	Continuous wave	2 Hz	High:2 mA - 5 mA Low:0 mA- 0.5 mA	30 min	Once daily, 6 sessions a week	2 w	[58]
18	Modified square wave	100 Hz	Tolerable	30 min	Once a week	10 w	[76]
19	Continuous wave	5 Hz	Tolerable	30 min	Once every other day	8 w	[46]
20	Continuous wave	4 Hz/20 Hz	1-2 mA	30 min	Once daily, 5 sessions a week	4 w	[77]
21	Continuous-wave	8 Hz	Tolerable	30 min	Once daily, Treat for 15 d, rest for 5, then treat another 15	35 d	[63]
22	Dilatational wave	50 Hz	Tolerable	20 min	Twice a week	6 w	[78]
23	Biphasic pulse	3 Hz	Tolerable	20-25 min	Once daily	10 d	[79]

24	Continuous-wave	2 Hz/100 Hz	Tolerable	30 min	Once daily	10 d	[80]
25	Continuous-wave	2/100 Hz	Tolerable	20 min	3 times a week, once every other day	30 d	[81]
26	Dilatational wave	2 Hz	Tolerable	20 min	Once daily	4 w	[82]
27	Continuous wave: 5 min Dilatational wave: 20 min	5 Hz	Tolerable	30 min	3 times a week,once every other day	8 w	[61]
28	Continuous-wave	1 Hz	Tolerable	30 min	Once every other day	4w	[19]
29	Dilatational wave	2 Hz	Tolerable	30 min	Once daily	2 w	[83]
30	Continuous wave	2 Hz	Tolerable	20 min	3 times a week	4 w	[62]
31	Continuous wave	2/100 Hz	0.1–1 mA	30 min	3 sessions a week, once every other day	8 w	[84]
32	Dilatational wave	3/100 Hz	Tolerable	30 min	Once daily, 5 sessions a week	4 w	[85]
33	Dilatational wave	5Hz	Tolerable	30 min	Once daily, 3 sessions a week	4 w	[42]
34	Dilatational wave	2/100 Hz	Tolerable	30 min	Once daily, 5 sessions a week	6 w	[47]
35	Dilatational wave	100Hz	Tolerable	30 min	Once daily, 6 sessions a week	3 w	[35]
36	Continuous-wave	5Hz	Tolerable	30 min	Once daily, 5 sessions a week	4 w	[50]
37	Dilatational wave	2/100 Hz	Tolerable	30 min	Once daily, 3 sessions a week	8 w	[34]
38	Dilatational wave	2/100 Hz	0.2 mA	30 min	Once daily, 5 sessions a week	8 w	[39]
39	Dilatational wave	2/100 Hz	Tolerable	30 min	Once every other day	4 w	[86]
40	Continuous-wave	20Hz	Tolerable	20 min	Once every other day	4 times	[87]
41	Continuous-wave	2Hz	High:2 mA - 5 mA Low:0 mA- 0.5 mA	30 min	Once daily, 5 sessions a week	2 w	[59]

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The Impact of EA on KOA Pain

Physiological Basis of Pain Mechanisms

KOA is a common degenerative joint disease with a complex pain mechanism involving various physiological and biochemical pathways. Chronic pain is one of the main symptoms in KOA patients, primarily consisting of peripheral nociceptive pain and central sensitization pain.[88] In terms of joint injury and inflammation, the pain in KOA mainly originates from damage to the articular cartilage, synovial inflammation, and sensitization of peripheral nerves. The degeneration of articular cartilage and osteophyte formation could lead to increased mechanical load within the joint, stimulating nerve endings and releasing inflammatory mediators such as prostaglandins and cytokines, which further promote the activation of pain receptors.[89] In terms of signaling molecules and pathways, interactions among the nerve growth factor (NGF)/TrkA signaling pathway, calcitonin gene-related peptide (CGRP), CCL2/CCR2 signaling pathway, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), NLRP3 inflammasome, and Wnt/β-catenin signaling pathway play a role in the generation and maintenance of OA pain, affecting both the peripheral and central nervous systems. For example, NGF is produced in joint tissues through the upregulation of cytokines like TNF, leading to sensitization of the nervous system.[90] CGRP is expressed in nociceptive neurons and participates in pain signal transmission.[91] The CCL2/CCR2 signaling pathway plays a central role in OA pain behavior.[92] TNF-α and IL-1β, as pro-inflammatory cytokines, are critical but have limited clinical treatment effects.[93] The NLRP3 inflammasome is involved in the production of active IL-1β,[94] while abnormal activation of the Wnt/β-catenin signaling pathway is associated with chronic pain.[95] A review confirmed that EA produces a greater analgesic effect than manual acupuncture (MA) for different types of pain.[96] Studies have found that EA could effectively reduce the levels of inflammatory mediators in the joint by modulating local inflammatory responses and promoting blood circulation, thereby alleviating pain.[97]

EA treatment could upregulate the expression of miR-214 in OA knee cartilage, which may participate in the expression of proteins involved in apoptosis and pain transmission by inhibiting its downstream targets, thus exerting therapeutic effects.[98] EA combined with extracorporeal shock wave (ESW) therapy could significantly reduce the levels of inflammatory factors such as nitric oxide (NO), interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinase-3 (MMP-3) in joint synovial fluid, while increasing the levels of superoxide dismutase (SOD) and transforming growth factor-beta1 (TGF-β1). These changes help reduce joint inflammatory responses, improve joint microcirculation, relieve muscle spasms, and positively impact joint mobility.[48] Additionally, the mechanism of action of EA may also be related to the regulation of the central nervous system, as EA stimulation could activate analgesic pathways in the spinal cord and brain, inhibit spinal dorsal horn afferent neurons, reduce the transmission of pain signals, and promote the release of endogenous analgesic substances such as endorphins and brain-derived neurotrophic factor (BDNF).[40]

Clinical Evidence of EA's Analgesic Effects

In recent years, the effectiveness of EA in managing KOA pain has been supported by an increasing number of clinical studies. A randomized controlled trial showed that patients in the EA treatment group had significantly better pain scores and functional assessments than the control group, with effects lasting for several weeks.[99] Another study indicated that EA could effectively improve joint function in KOA patients and reduce the need for traditional analgesics, thereby lowering the risk of drug-related side effects.[100] Furthermore, different parameter settings for EA (such as frequency and intensity) have also been shown to significantly impact pain relief, with appropriate parameter selection enhancing treatment effects.[101] In a large cohort study based on KOA patients, it was found that the β-diversity of the gut microbiome was significantly correlated with knee joint WOMAC scores, and the abundance of streptococci was significantly related to the severity of knee joint effusion, indicating that gastrointestinal microbiota directly contribute to pain and inflammation associated with knee osteoarthritis.[102] Overall, existing clinical evidence suggests that EA, as a non-invasive treatment method, has a good effect on pain relief in patients with knee osteoarthritis.

Advantages and Challenges of EA in Pain Management

The advantages of EA in pain management mainly lie in its non-pharmacological nature and lower risk of side effects. Compared to traditional drug treatments, EA not only effectively alleviates pain but also improves patients' quality of life and reduces drug dependence.[49] Additionally, the therapeutic effects of EA are often relatively long-lasting, allowing patients to continue enjoying good pain control after treatment.[39] However, EA still faces some challenges in practical application, including insufficient standardization of treatment and the influence of individual differences. Different patients may respond significantly differently to EA, and how to develop personalized EA treatment plans requires further research.[31] Moreover, although the efficacy of EA has received some clinical evidence support, verifying its long-term effects and safety in large, multi-center randomized controlled trials remains an important direction for future research.[37]

Research on EA for Improving Knee Joint Function

Selection of Functional Assessment Indicators

The selection of functional assessment indicators is fundamental to evaluating EA efficacy in KOA, with pain intensity scales serving as the primary endpoint for analgesic effect. The Visual Analog Scale (VAS) is most widely employed due to its sensitivity in capturing subjective pain perception.[103] Studies consistently demonstrate that EA leads to more significant and rapid VAS reductions compared to AM, a difference attributed to its sustained electrical stimulation and stronger activation of endogenous opioid pathways.[34,37,46] While AM also alleviates pain, its effects on VAS are often more gradual, reflecting its reliance on manual needle manipulation and holistic regulatory mechanisms rather than targeted neuromodulation.

For evaluating physical function, joint-specific scales such as the WOMAC and HSS provide nuanced insights into domain-specific improvements.[104,105] The WOMAC, in particular, is valuable for its ability to dissect outcomes into pain, stiffness, and physical function subscales. EA consistently shows superior performance in enhancing physical function-such as walking and stair climbing-linked to its anti-inflammatory and neuromuscular modulation effects.[36,41,49] In contrast, AM frequently demonstrates comparable or even greater efficacy in reducing joint stiffness, suggesting a stronger influence on local soft tissue compliance and microcirculation through biomechanical needle manipulation.[36,37]

Beyond pain and joint-specific metrics, broader patient-reported outcomes such as the SF-12 and KOOS quality-of-life scales capture the holistic impact of treatment.[106] These tools reveal distinctive strengths of AM, particularly in improving mental health components and overall well-being, which align with its traditional focus on systemic balance and Qi regulation.43,45 In cases of deficiency patterns like kidney and marrow insufficiency, AM shows pronounced benefits in alleviating secondary symptoms such as fatigue and mood disturbances, underscoring the importance of pattern-specific evaluation in traditional Chinese medicine interventions.[38,50]

Incorporating psychological and syndrome-specific instruments-such as the Hamilton Depression Scale (HAMD) or TCM symptom scores-enables a more comprehensive efficacy profiling. These assessments highlight therapeutic dimensions beyond conventional orthopaedic metrics, emphasising AM's role in addressing comorbidity and personalised dysfunction.[42,45] A multimodal evaluation strategy is thus essential, as it clarifies that EA excels in biomechanical pain and functional recovery, whereas AM offers broader benefits in stiffness, mental well-being, and holistic regulation. Future clinical trials should adopt integrated assessment protocols to fully elucidate the complementary strengths of EA and AM (Tables 1 and 3).

Summary and Analysis of Clinical Trial Results

Clinical trials directly comparing EA and AM provide robust evidence for their efficacy in treating KOA, yet reveal distinct therapeutic profiles shaped by their mechanisms and application. Meta-analyses of these studies consistently confirm that both interventions are significantly superior to sham acupuncture or wait-list controls, but they excel in different clinical domains. EA demonstrates pronounced advantages in rapid analgesia and objective functional improvement, largely attributable to its quantifiable, intensity-dependent neurostimulation that effectively modulates pain

Table 3 The Impact of EA on Pain and Knee Joint Function in Patients with KOA

NO.	EA Group	Control	Conclusion	References
1	EA	MA	Both treatments enhance knee function; EA for KOA is especially effective for pain relief.	[39]
2	EA	MA	EA treatment effectively reduces pain and improves function in KOA patients for at least 26 weeks.	[41]
3	EA	MA	Eight weeks of EA and MA enhance pain relief and function in mild to moderate KOA patients, partly through changes in TNF-α, IL-1β, and IL-13.	[49]
4	EA	MA, Moxibustion	Three methods reduce knee pain and disability in KOA: moxibustion, EA, and MA.	[59]
5	EA	NWM, TDP	Therapies relieve pain and stiffness, improving health in KOA patients.	[43]
6	Dilatational, Continuous, and Discontinuous wave group		All EA types may relieve KOA symptoms by raising TGF-β1 in joint fluid, aiding cartilage repair.	[107]
7	EA	Relaxing-needling	The Relaxing-needling is as effective as EA for KOA but better at relieving pain and improving mobility.	[88]
8	Strong EA (> 2 mA)	Weak EA (< 0.5 mA), sham-EA	EA requires two weeks to impact pain in KOA patients; stronger EA reduces pain more effectively than weaker or sham treatments.	[59]
9	EA	Needle Knife Group	Both treatments for KOA are effective, but needle knife therapy is superior to EA in pain relief and knee function improvement.	[60]
10	EA	Sham-EA	EA has the potential to alleviate pain in KOA patients by influencing levels of plasma cortisol and β-endorphins.	[108]
11	Strong, Weak and Sham-EA group		Strong EA effectively reverses acute pain to chronic by repairing Diffuse Noxious Inhibitory Controls (DNIC).	[76]
12	EA	MA	EA and MA produce comparable immediate effects on pain, muscle strength, and mobility in individuals with KOA.	[46]
13	Arthroscope +EA	Arthroscope	EA significantly improves arthroscopic surgery outcomes for KOA, offering longer-lasting benefits and better knee function than surgery alone.	[109]
14	EA	Sham-EA	EA effectively treats joint pain from aromatase inhibitors in breast cancer patients and lowers serum C-reactive protein.	[110]
15	EA	AM	EA focuses on pain relief and has a greater therapeutic effect than AM.	[54]
16	EA	Sham-EA	The relief of pain after EA may significantly improve gait performance in patients with KOA	[111]
17	EA	Sham-EA	Plasma β-endorphin levels rose significantly in EA, while cortisol levels fell; EA effectively reduces pain, stiffness, and disability in KOA patients.	[80]
18	Before EA	After EA	Patients showed improved VAS scores, lower limb function, and reduced IL-1β and TNF-α levels after EA.	[112]
19	EA	MA	EA improves KOA symptoms and releases β-endorphin.	[113]
20	EA	Oral medication	EA improves clinical symptoms and knee mobility in KOA patients, surpassing oral diclofenac sodium.	[82]
21	EA	Hydrotherapy	Combining EA, hydrotherapy, and education reduces pain and enhances quality of life.	[44]

Abbreviations: EA, Electroacupuncture; MA, Manual acupuncture; NWM, Needle Warming Moxibustion; TDP, Teding Dianci Pu; AM, acupuncture and moxibustion; KOA, knee osteoarthritis.

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pathways and local inflammation.[41,49,59] In contrast, AM shows sustained benefits in enhancing joint flexibility, reducing stiffness, and improving quality of life, aligning with its holistic approach to regulating Qi and blood circulation.[36,37,43]

A detailed analysis of outcome measures clarifies this divergence. In studies utilizing the VAS and WOMAC pain subscale, EA frequently achieves greater and faster reduction in pain scores. This is mechanistically linked to its ability to elicit strong endogenous opioid release and suppress pro-inflammatory cytokines (eg, TNF-α, IL-1β), particularly when higher current intensities (2–5 mA) and mixed frequencies (2/100 Hz) are applied.[40,59] Conversely, AM, while effective for pain relief, often yields more gradual analgesia but excels in the WOMAC stiffness subscale and functional mobility tests. Furthermore, EA has also been found to improve joint function by modulating inflammatory responses, a mechanism that may be related to the regulation of the Wnt/β-catenin signaling pathway.[114] This suggests its mode of action-relying on deqi sensation and manual manipulation-may more effectively influence periarticular soft tissue compliance and proprioceptive function.[37,46,111]

The long-term and holistic outcomes further differentiate these modalities. Trials incorporating quality-of-life measures such as SF-12 or KOOS reveal that AM often leads to greater improvement in mental health components and overall well-being, especially in patients with underlying deficiency patterns like kidney and marrow insufficiency.[42–44] EA, particularly when combined with modern rehabilitation techniques like extracorporeal shockwave therapy, shows strong performance in restoring muscle strength and biomechanical function, as quantified by isokinetic testing and performance-based assessments.[48,61,115] Furthermore, the sustainability of treatment effects favors EA in some studies; its modulation of central sensitization leads to prolonged analgesic periods, whereas AM's benefits on stiffness and functional adaptation appear to accumulate over a longer treatment course.[38,41,58] (Tables 1 and 3).

In conclusion, the collective evidence from clinical trials advocates for a tailored and integrated treatment strategy. EA serves as a powerful tool for controlling inflammatory pain and facilitating rapid functional recovery, ideal for patients with acute exacerbations or significant pain-related disability. AM offers a multifaceted approach addressing stiffness, psychological distress, and overall well-being, making it suitable for chronic management and patients with systemic imbalance. Future research should prioritize standardized protocol reporting and head-to-head trials that employ a comprehensive battery of outcomes to fully define the roles of each modality within personalized KOA treatment algorithms.

EA: Biological Mechanisms

EA is a therapeutic approach that combines traditional acupuncture with electrical stimulation, demonstrating promising efficacy in recent years for pain management, inflammation modulation, and cartilage protection. Research into its biological mechanisms has deepened, revealing the multifaceted roles in neuromodulation, inflammatory responses, and chondroprotection.

Neuromodulation Mechanisms

EA activates the peripheral nervous system by stimulating specific acupoints, thereby regulating central nervous system responses. This mechanism primarily involves the release of neurotransmitters and the activation of neural pathways. Peripheral pain sensation originates from local tissues in the knee joint, while central pain sensation arises from the central nervous system, namely the spinal cord and brain. The specific mechanisms of central pain disorders include central sensitization in the spinal cord and disruptions in ascending and descending pathways from the brain to the spinal cord. Pain occurrence in KOA patients is related to an imbalance in the function or structure of ascending and descending pathways, mainly manifested at the spinal and brain levels.[116] EA treatment could modulate the descending pain control system. Signals from the descending pain pathways originate from the anterior cingulate cortex, hypothalamus, and amygdala, reaching the spinal dorsal horn through the periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM), enhancing or inhibiting nociception directly or indirectly.[117]

The descending pathways include both pain and analgesic mechanisms, with the analgesic mechanisms mediated by 5-HT, endogenous opioids, and others. Low-frequency (2 Hz) and high-frequency (100 Hz) EA could mediate analgesia through the body's μ and δ opioid receptors and κ receptors, respectively,[118] with the analgesic effect of low-frequency EA being more significant than that of high-frequency.[56] Additionally, EA could upregulate the expression of 5-HT2A

receptors in the dorsal spinal cord of mice with knee osteoarthritis, and it could also increase the expression of GABAA receptors and KCC2, a protein that controls the inhibitory function of GABAA receptors.[119] Injecting 5-HT1 and 5-HT3 receptor antagonists could reduce the analgesic effect of EA.[120] Pro-inflammatory factor TNF-α enhances the expression and activity of MMPs, increasing the destructive power of inflammatory cells, thereby destroying joint cartilage, degrading cartilage matrix, and promoting further inflammation. Anti-inflammatory cytokine IL-10 promotes the synthesis of cartilage proteoglycans, protects joint cartilage, prevents the degeneration of joint cartilage, and further alleviates the condition of KOA. Studies have shown that 2 Hz low-frequency EA could upregulate IL-10 levels and downregulate TNF-α levels,[65] which is important for maintaining the balance of pro-inflammatory/anti-inflammatory cytokines in cartilage tissue, reducing spinal nociceptive sensitization, delaying OA progression, and relieving pain. Other studies have shown that 1 Hz/15 Hz also alleviates synovial inflammation and referred pain behavior in rats with KOA by activating local sympathetic noradrenergic signals.[121] Other neuromodulation mechanisms of EA treatment for KOA are shown in Table 4 and Figure 2.

Regulation of Inflammatory Responses

EA exerts its anti-inflammatory effects in KOA through sophisticated regulation of multiple signaling pathways, which collectively mitigate synovitis, reduce cartilage degradation, and alleviate pain. The clinical efficacy of EA is closely associated with its ability to simultaneously target various inflammatory cascades, rebalancing the joint microenvironment from a catabolic, inflammatory state toward a more homeostatic, reparative condition. The following analysis elaborates on key inflammatory pathways modulated by EA and links these mechanisms to observed clinical outcomes.

The NF-κB and MAPK pathways are central regulators of inflammatory responses in KOA. EA significantly inhibits NF-κB activation, reducing nuclear translocation of p65 and downstream production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[23,131–133] This suppression correlates clinically with reduced joint swelling, pain relief, and improved mobility. Similarly, EA dampens MAPK signaling-particularly p38 and JNK phosphorylation-leading to decreased expression of matrix-degrading enzymes like MMP-13 and ADAMTS5.[134–136] Patients receiving EA show lower levels of MMPs and slower radiographic progression, underscoring how these molecular effects translate into cartilage preservation and functional improvement.

EA effectively inhibits the NLRP3 inflammasome, a key complex involved in the cleavage and activation of IL-1β.[131,137,138] By reducing the expression of NLRP3, ASC, and caspase-1, EA limits pyroptosis-a highly inflammatory form of cell death-and decreases IL-1β levels in synovial fluid. This mechanism is particularly relevant for patients with significant synovitis and effusion. Clinically, EA-treated individuals exhibit not only reduced pain and swelling but also improved joint function, reflecting the role of NLRP3 in driving symptom severity and structural damage.

Beyond inhibiting inflammation, EA promotes tissue repair through growth factor pathways. EA upregulates TGF-β1, which enhances the synthesis of collagen and proteoglycans while counteracting IL-1β-induced inflammation.[139–141] Additionally, EA modulates BMP-2/Smad1/5/8 signaling, stimulating chondrogenesis and inhibiting aberrant subchondral bone remodeling.[142,143] Studies have found that EA could improve intestinal function in rats with irritable bowel syndrome, indicating its potential in regulating intestinal inflammation.[144] These anabolic effects contribute to the long-term benefits of EA, including sustained functional improvement and delayed disease progression, particularly in patients with early to moderate KOA.

EA also impacts upstream innate immune receptors. It suppresses TLR4 and its adaptor MyD88, thereby inhibiting NF-κB activation and cytokine production.[145,146] Moreover, EA enhances SIRT1 expression, which deacetylates HMGB1 and mitigates its pro-inflammatory effects.[147,148] These actions lead to reduced synovitis and lower levels of systemic inflammatory markers, which are associated with pain reduction and improved quality of life in KOA patients.

EA's regulation of inflammatory responses in KOA is multi-targeted and synergistic. By concurrently inhibiting NF-κB, MAPK, NLRP3, and TLR4/MyD88 pathways while promoting TGF-β and BMP-2-mediated repair, EA addresses both inflammatory symptoms and structural deterioration. These mechanisms explain its efficacy in reducing pain, improving joint function, and modifying disease progression, supporting its use as a complementary strategy for KOA management. Further research should focus on optimizing EA parameters to maximize these anti-inflammatory and pro-reparative effects. Other studies on the regulation of inflammatory responses by EA are shown in Figure 3 and Table 5.

Table 4 The Neuromodulatory Mechanisms of EA in KOA

NO.	Function	Mechanisms	Classification	References
1	Significantly reduced pain and improved behavioral scores	Regulate central DA, NE, 5-HT, β-EP, and L-ENK for analgesia; inhibit IL-1β to delay KOA progression.	Central	[122]
2	Improved gait and knee function	Increase type II motor units and enhance neuromuscular conduction to improve knee function in KOA.	Peripheral	[123]
3	Reduce inflammation and improve pain behavior	Reduce CD11b+ cells and M1 macrophages, inhibit TNF-α and IL-6, decrease synovial cytokines, alleviate nerve injury, and relieve spontaneous and touch-evoked pain.	Peripheral	[124]
4	Activate sympathetic noradrenaline signaling to manage inflammation	Increase norepinephrine in synovium, inhibit TNF-α, IL-1β, IL-6, reduce cryptogenic nerve denervation, alleviate inflammatory pain and cartilage damage, and suppress IL-6 overexpression via CXCL1-CXCR2 axis in macrophages.	Peripheral	[121]
5	Regulate pain threshold, monoamine neurotransmitter release	Regulate serotonin and catecholamine levels to reduce joint cartilage damage and pain.	Central	[125]
6	EA and H-TENS have similar pain control effects.	Stimulate nerve fibers to affect pain transmission and promote analgesia.	Peripheral, Central	[115]
7	Increase neurotransmitter release and cellular membrane potential	Inhibit spinal signals for analgesia, activate sympathetic fibers, enhance endogenous opioid release, affect membrane potentials, and alter cellular functions, including pain perception.	Peripheral, Central	[126]
8	Inhibit pain signals, enhance neurotransmitter release	Stimulating large-diameter fibers activates spinal inhibitory neurons, reducing pain transmission and promoting endogenous opioid release, mediating pain regulation and altering blood flow.	Peripheral, Central	[127,128]
9	Low-frequency EA reduces pain perception via receptor pathways	2 Hz EA might reduce chronic OA pain by targeting 5-HT1, 5-HT3, and muscarinic receptors.	Central	[120]
10	Inhibit pain signals and boost analgesic neurotransmitters	Promote endorphins, lower cortisol, and alleviate KOA pain.	Central	[80]
11	Reduce pain factors and alleviate spinal hyperalgesia	Reduce pain factors in KOA rats, lower spinal hyperalgesia, and alleviate KOA pain.	Central	[129]
12	Pain relief through central nervous system control	Reduce IL-17 and IL-17R in spinal tissue to relieve OA pain.	Central	[130]

Abbreviations: EA, Electroacupuncture; KOA, knee osteoarthritis; H-TENS, High-Frequency Transcutaneous Electrical Nerve Stimulation.

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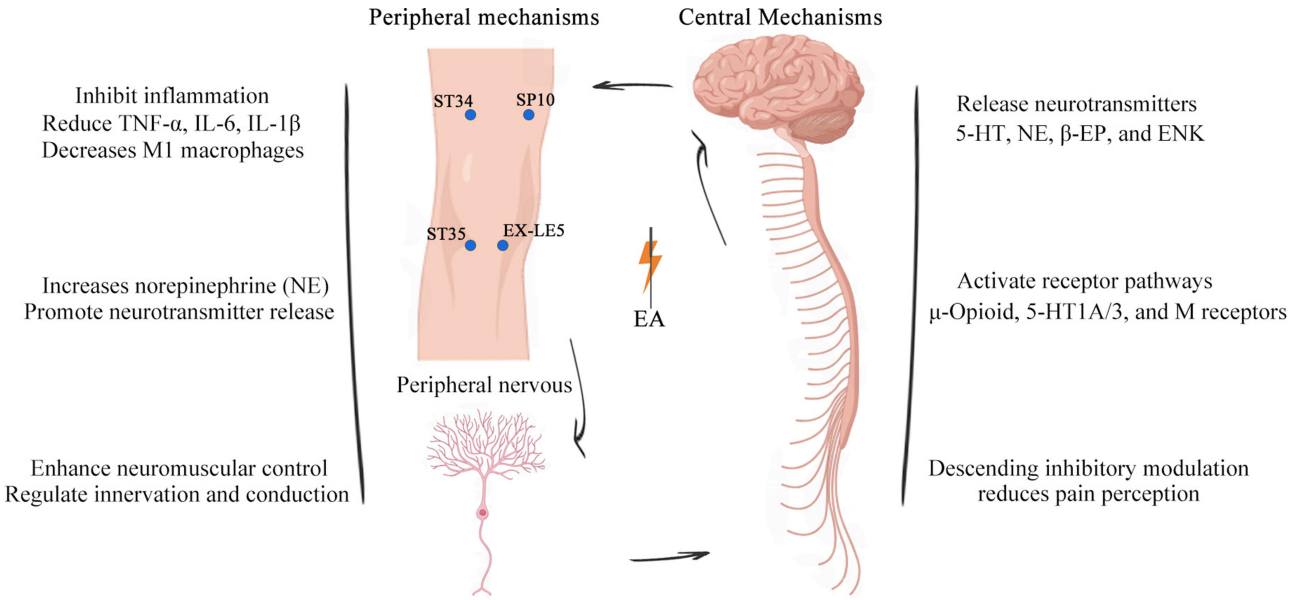

Figure 2 Mechanisms of EA in alleviating KOA Pain (By Figdraw). EA alleviates KOA pain through synergistic peripheral and central mechanisms. Peripherally, it suppresses inflammation by downregulating pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), reduces M1 macrophage infiltration, elevates norepinephrine levels, and enhances neuromuscular control. Centrally, it facilitates the release of neurotransmitters including 5-HT, NE, β-EP, and ENK, activates μ-opioid receptor signaling pathways, and engages descending pain inhibitory systems, ultimately leading to effective analgesia, attenuated inflammatory responses, and improved motor function and affective state.

Mechanisms of Cartilage Protection

Beyond its potent anti-inflammatory effects, EA plays a crucial role in directly preserving articular cartilage structure and function in KOA. This protection is achieved through multi-faceted mechanisms that promote anabolic metabolism, inhibit catabolic processes, enhance chondrocyte survival, and regulate subchondral bone remodeling. These actions collectively slow cartilage degeneration and contribute to long-term joint integrity, which is fundamental to sustaining clinical efficacy beyond mere symptom relief.

EA actively stimulates pathways responsible for cartilage matrix synthesis and chondrocyte viability. By activating the Wnt/β-catenin signaling pathway in a controlled manner, EA upregulates anabolic factors and transcription factors like SOX9, which are essential for the production of type II collagen and aggrecan.[114,141,142] Conversely, it avoids detrimental overactivation of Wnt signaling, which is associated with osteophyte formation. Furthermore, EA enhances the BMP-2/Smad1/5/8 pathway, promoting chondrogenic differentiation and repairing cartilage defects.[143,144] Clinically, this translates to improved cartilage morphology on imaging and better scores on joint structure-related evaluation tools, indicating a true disease-modifying potential.

A key mechanism for cartilage preservation is the inhibition of excessive chondrocyte apoptosis. EA modulates several critical anti-apoptotic pathways.[161] It activates the PI3K/Akt signaling pathway, leading to increased expression of the anti-apoptotic protein Bcl-2 and decreased expression of the pro-apoptotic protein Bax.[26,150] This balance protects chondrocytes from cytokine-induced death. Additionally, EA reduces endoplasmic reticulum (ER) stress and subsequent apoptosis by downregulating markers like GRP78 and CHOP.[164,165] By promoting mitochondrial homeostasis and mitigating oxidative stress, EA helps maintain chondrocyte viability, which is crucial for preventing the decline in cellularity that characterizes OA progression. This cytoprotective effect underpins the long-term sustainability of clinical improvements in pain and function.

EA exerts protective effects on the osteochondral unit by modulating bone metabolism. It influences the RANKL/RANK/OPG pathway, a central regulator of osteoclast activity. EA treatment increases the expression of osteoprotegerin (OPG), a decoy receptor for RANKL, thereby inhibiting excessive osteoclastogenesis and preventing subchondral bone resorption.[16,152] This helps maintain the mechanical support for overlying cartilage and reduces pathological crosstalk

between bone and cartilage. The stabilization of subchondral bone structure is a critical factor in slowing the overall progression of KOA, contributing to preserved joint space and reduced pain during weight-bearing activities.

EA enhances cellular quality control mechanisms by activating autophagy and mitophagy-processes that clear damaged organelles and proteins. Through upregulation of the Pink1-Parkin signaling pathway, EA promotes the clearance of dysfunctional mitochondria, reducing oxidative stress and preventing apoptosis in chondrocytes.[162] This is particularly important in the stressed, nutrient-deficient environment of the OA joint. Furthermore, EA-mediated inhibition of the NLRP3 inflammasome is also linked to enhanced autophagy, creating a feedback loop that further suppresses inflammation and cell death.[138] By bolstering these innate cellular repair processes, EA helps chondrocytes withstand metabolic and inflammatory insults, thereby preserving tissue integrity and delaying degeneration.

The cartilage-protective mechanisms of EA are comprehensive, targeting anabolic-catabolic imbalance, cell survival, subchondral bone homeostasis, and cellular waste clearance. By synergistically promoting matrix synthesis (via Wnt/β-catenin, BMP-2), inhibiting apoptosis (via PI3K/Akt), regulating bone turnover (via OPG/RANKL/RANK), and enhancing autophagy, EA addresses the fundamental pathophysiology of KOA. These actions underpin its ability to not only alleviate symptoms but also potentially modify disease progression, offering a compelling non-pharmacological strategy for preserving joint structure and function. Future research should focus on standardizing EA protocols that maximize these chondroprotective effects for different stages of KOA. Other mechanisms of cartilage protection regulated by EA are shown in Figure 3 and Table 5.

Clinical Applications and Future Research Directions of EA

Current Status and Limitations of Clinical Applications

As a therapeutic approach that combines traditional acupuncture with modern EA technology, EA has gradually gained recognition in clinical applications in recent years. It is mainly used in pain management, neurological rehabilitation, disease treatment, and other fields. Studies have shown that EA could work by regulating the nervous system, promoting

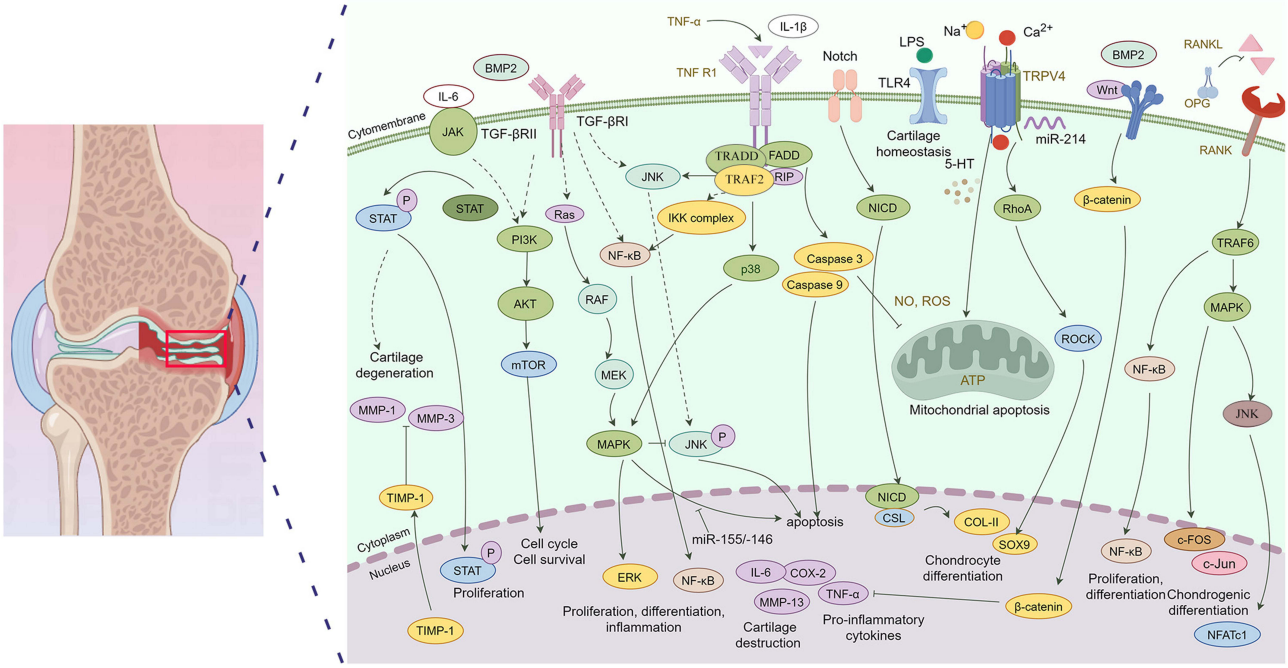

Figure 3 Mechanisms of EA in Treating KOA through Inhibition of Inflammatory Responses and Cartilage Repair (By Figdraw). Pro-inflammatory factors such as TNF-α and IL-1β induce inflammatory responses, expression of matrix-degrading enzymes (eg, MMPs), and apoptosis by activating the NF-κB and MAPK pathways (including JNK/p38). In contrast, the BMP2/Wnt pathway promotes chondrogenic differentiation (upregulation of SOX9) via Smad1/5/8 and β-catenin; however, its overactivation can lead to hypertrophy and degeneration. The Notch pathway inhibits differentiation and synergizes with NF-κB to exacerbate inflammation. TGF-β counteracts inflammation through Smad2/3 and promotes matrix synthesis (eg, upregulation of COL-I and TIMP-1) to maintain homeostasis. Additionally, miRNAs (eg, miR-146a exerting anti-inflammatory effects and miR-155 promoting inflammation) and oxidative stress (via ROS/Caspase) further fine-tune this balance. The interplay among these pathways determines chondrocyte fate: an imbalance favoring inflammatory and catabolic signals leads to degeneration, whereas reparative and anabolic signals support homeostasis. These findings suggest that effective therapeutic strategies may require multi-target interventions, such as suppressing NF-κB while enhancing TGF-β/BMP2 signaling.

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Table 5 Related Pathways and Mechanisms of EA Treatment for KOA

Classification	Mechanisms		References
Inflammatory factor	Matrix metalloproteinase (MMP)	Downregulating MMP-13, reducing inflammation factors and preventing cartilage degradation.	[149]
		Inhibiting MMP-1, MMP-3 and promoting TIMP-1 expression in cartilage, protecting Type II collagen, and reducing cartilage destruction.	[150]
		Reducing inflammatory factors in synovial fluid, improving knee function and alleviating pain.	[151]
		Inhibiting the expression of MMP-1 and MMP-3 through TIMP-1, repairing cartilage in KOA rats.	[152]
	Interleukin (IL) tumor necrosis factor-α (TNF-α)	EA combined with acupoint delays KOA progression by reducing the levels of IL-6, TNF-α, and IL-1β.	[153]
		Inhibiting IL-1β and IL-6 expression in lipopolysaccharide-induced chondrocytes, alleviating the inflammatory response of chondrocytes.	[154]
		Reducing IL-1 and TNF-α in osteoarthritis dogs' serum inhibits inflammation and decreases Substance P to alleviate pain and improve knee function.	[155]
		Reducing TNF-α level, more rapidly alleviating inflammatory stimulation, relieving knee pain and swelling.	[22]
	Transforming growth facto-β (TGF-β)	Increasing TGF-β1 in synovial fluid, inhibiting secretion of inflammatory cytokines to promote cartilage repair.	[107,156]
		Activating both the JAK-STAT and TGF-β pathways simultaneously to delay the degeneration of articular cartilage.	[139]
		Increasing TGF-β1 in synovial fluid and Smad3 expression in chondrocytes promotes the proliferation of chondrocytes and the repair of damaged cartilage.	[139,157]
		EA with rehabilitation therapy improves KOA by raising TGF-β1 and reducing inflammatory factors like IL-6 and TNF-α, alleviating pain and enhancing joint function.	[140]
		EA combined with triptolide could delay mouse KOA through the TGF-β signaling pathway.	[158]
		Up-regulating TGF-β1 expression in OA cartilage promotes cartilage repair.	[141]

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Signal pathway	p38 MAPK signal pathway	Inhibiting p38 MAPK phosphorylation and inflammatory factors like COX-2 promotes chondrocyte proliferation and cartilage matrix synthesis.	[134]
		Inhibiting p38 MAPK, JNK, and ERK1 regulates MMP-13 mRNA to prevent cartilage degeneration.	[135]
		EA improves cartilage degeneration, inhibits inflammation, and reduces apoptosis by regulating the miR-155/-146α-mediated MAPK signaling pathway.	[136]
		The Tendon-soothing maneuver combined with EA might alleviate synovial inflammation by activating the p38 MAPK/NF-κB signaling pathway, thereby affecting the activity of inflammatory factors.	[137]
		Deep needling combined with EA could reduce ASIC1 expression and the phosphorylation level of p38 MAPK, inhibit apoptotic factor p53 expression, reduce chondrocyte apoptosis, and alleviate chondrocyte injury.	[138]
	Nuclear factor-κB (NF-κB) signal pathway	Downregulate TNF-α expression, enhance the activity of NF-κB signaling, and inhibit chondrocyte apoptosis.	[132]
		Activate NF-κB signal pathway to reduce MMPs and inflammation, delaying cartilage degeneration.	[23]
	Wnt/β-catenin signal pathway	Activate Wnt/β-catenin signaling in OA cartilage to promote chondrocyte proliferation.	[139]
		Activate Wnt/β-catenin signaling to increase MMP-13 expression and reduce inflammatory factors like IL-1β, inhibiting cartilage matrix degradation and improving cartilage structure.	[114]
		Inhibit the Wnt/β-Catenin pathway, reduce interleukin levels, and suppress cartilage degeneration.	[140]
		Activate the Wnt signaling pathway to inhibit chondrocyte apoptosis and repair damaged cartilage.	[141]
		Activate Wnt-7B/β-catenin signaling to reduce inflammation, improve subchondral bone damage, alleviate pain.	[142]
	BMP-2 signal pathway	Downregulating BMP-2/Smad1 in rabbit KOA cartilage inhibits osteophyte formation and delays KOA progression.	[143]
		Up-regulate BMP-2 in OA cartilage and activate Wnt4 and Wnt14 to promote chondrocyte differentiation.	[144]
	Hippo signal pathway	Upregulate YAP to regulate cartilage damage and activate Hippo YAP signaling to promote chondrocyte proliferation.	[145]
	bFGF signal pathway	Regulate cartilage matrix balance to enhance self-repair or increase fibrous tissue for faster cartilage repair.	[146]
	PTHrP-Ihh signal pathway	Regulate the PTHrP-Ihh signaling axis and related factors to restore cartilage balance and enhance self-repair.	[147,148]
	Notch signal pathway	Up-regulate Notch1 and JAG1 to enhance the Notch pathway's reparative role in osteoarthritis.	[149]
	PI3K/Akt signal pathway	Regulate PI3K/Akt pathway to increase Bcl-2, decrease Bax, IL-1β and TNF-α, delaying cartilage degeneration.	[150]
		Regulate PI3K/Akt to reduce inflammation, decrease chondrocyte apoptosis, and delay KOA progression.	[26]
	RhoA/ROCK signal pathway	Up-regulate Rac1 and Cdc42 in OA cartilage, inhibit RhoA/ROCK pathway, and promote type II collagen and Sox9 expression, and chondrocyte differentiation.	[151]

(*Continued*)

Table 5 (Continued).

Classification	Mechanisms		References
	RANKL/RANK/OPG signal pathway	Increase OPG content, activate OPG/RANK/RANKL pathway, and delay osteoporosis and cartilage degeneration.	[152]
		Activate RANK/RANKL/OPG pathway to inhibit trabecular bone loss and protect cartilage in OVX rats.	[16]
	Ras-Raf-MEK-ERK signal pathway	Regulate genes and proteins in the Ras-Raf-MEK-ERK pathway to reduce cartilage degeneration in KOA.	[153,154]
		Reduce mRNA expression of Ras, Raf, MEK1/2, and ERK1/2 in cartilage, inhibit chondrocyte apoptosis from inflammation, and delay cartilage degeneration.	[155]
		Inhibit Ras, Raf, and ERK to promote chondrocyte proliferation and differentiation, delaying cartilage degeneration.	[156]
	HIF-1α/Sox9 signal pathway	Activate HIF-1α/Sox9 pathway to reduce MMP-13, boost cartilage formation, and delay OA degeneration.	[157]
	JNK signal pathway	Inhibit the JNK signaling pathway to reduce chondrocyte apoptosis.	[136]
	TLR4 signal pathway	Downregulate key factors in the TLR4/NF-κB pathway to reduce IL-6 and TNF-α, decrease cartilage destruction, and delay KOA progression in rats.	[145]
		Suppress TLR4/MyD88/NF-κB pathway to improve knee joint synovitis in KOA rats and reduce effusion.	[146]
		Activate TLR4/NF-κB pathway, inhibit synovial inflammatory responses, and delay the progression of KOA.	[158]
		Inhibit innate immune response mediated by TLRs, reduce inflammatory factors and MMPs expression.	[33]
	NLRP3 inflammasome	Inhibit NLRP3 inflammasome and reduce pyroptosis to protect cartilage tissue and delay KOA progression.	[131]
		Inhibit NLRP3 inflammasome activation, reduce caspase-1 and IL-1β in cartilage, alleviate allodynia, prevent cartilage fibrosis, improve cartilage structure, and delay OA.	[137]
		Promote autophagy in chondrocytes, inhibit NLRP3 and MMP-13, reduce inflammation, delay chondrocyte injury and apoptosis, improve metabolism, and treat KOA.	[138]
		Regulate the NF-κB p65/NLRP3 pathway to reduce inflammatory factors and improve cartilage structure.	[133]
	Sirt1 signal pathway	Activate the SIRT1/HMGB1 signaling pathway to improve synovial inflammatory damage in KOA rats.	[147]
		Promoting SIRT1 expression inhibits cartilage degradation and improves subchondral bone microstructure.	[148]
	cGAS/STING signal pathway	Downregulate cGAS/STING to reduce inflammation and delay cartilage degeneration in KOA rats.	[159]

Aquaporins, mitochondria	Aquaporins 3 (AQP3)	Reduce AQP3 mRNA in chondrocytes to inhibit water transport, matrix degradation, and cartilage destruction.	[160]
	Mitochondria and apoptosis pathway	Downregulate Cytochrome C, Apaf-1, Caspase-9, and Caspase-3 in OA chondrocytes to prevent mitochondrial pathway-induced apoptosis.	[161]
		Regulating SNP reduces NO production, slowing mitochondrial membrane potential decline and lowering permeability, inhibiting apoptosis.	[25]
		Enhance chondrocyte mechanics, activate Pink1-Parkin signaling, regulate mitochondrial autophagy, inhibit cartilage matrix degradation, and prevent degeneration.	[162]
		Regulate mitochondrial apoptosis to inhibit chondrocyte apoptosis.	[163]
	Endoplasmic Reticulum Stress-induced apoptosis pathway	Inhibit stress response factors expression such as Chop, JNK, and Bcl-2, block ERS, and delay chondrocyte apoptosis.	[164]
		ROS damage, fibrosis, and endoplasmic reticulum stress in KOA rat synovial tissue, reducing inflammation.	[165]
Biomechanics	Abnormal biomechanics	Enhance muscle function in KOA patients, adjust the biomechanical environment of cartilage, and utilize mechanisms like anti-inflammatory effects, improved circulation, and pain relief.	[166]
Others	Noradrenaline signaling pathway	Activate β2AR in the synovium, inhibit CXCL1-CXCR2 IL-6 overexpression, and reduce inflammatory pain.	[121]
	miRNA	Increasing miR-214 alleviates pain and prevents chondrocyte apoptosis by inhibiting BAX and TRPV4.	[167]
	Glucolysis	Enhance microcirculation and oxygen levels to reduce cartilage hypoxia, and adjust glycolytic metabolism in chondrocytes for cartilage repair.	[18]
	Macrophage M2 polarization	Promote M2 macrophage polarization in aged OA rats' cartilage and bone to reduce cartilage degradation and inhibit osteoporosis, preserving joint integrity.	[168]
	Lipid metabolism and gut microbiota	Regulate lipid metabolism and gut microbiota to prevent the loss of joint cartilage in obese rats.	[169]

Abbreviations: EA, Electroacupuncture; KOA, knee osteoarthritis; SNP, sodium nitroprusside; NO, Nitric Oxide; TIMP-1, Tissue Inhibitor of Metalloproteinases 1; ASIC-1, Acid-sensing ion channel; YAP, Yes-associated protein; ROS, Reactive Oxygen Species.

blood circulation, and improving local metabolism. However, there are still some limitations to the clinical application of EA. Firstly, the variability in individual responses to treatment poses challenges for the standardization of EA. Secondly, research on the optimal stimulation parameters (such as frequency, intensity, and duration) of EA is insufficient, and there is a lack of unified clinical guidelines. Additionally, the long-term effects and safety of EA still need further verification, especially in specific populations such as the elderly and patients with chronic diseases. Therefore, although EA shows potential in clinical practice, its application still needs to be continuously improved with the support of scientific research.

Hotspots and Trends in Future Research

The hotspots in future research on EA mainly focus on mechanism exploration, personalized treatment, and new application fields. Firstly, the mechanisms of action of EA still need further research. Recent studies have shown that EA may exert therapeutic effects by regulating neurotransmitters, affecting inflammatory responses, and promoting nerve regeneration, among other pathways.[170] Secondly, with the development of precision medicine, personalized EA treatment will become an important trend. Researchers are exploring how to develop personalized EA treatment plans based on the specific conditions of patients (such as pathological types, genetic characteristics, etc.) to improve efficacy.[171] Additionally, the application of EA in new fields is also attracting attention, such as in the management of cancer-related symptoms, mental health, and sports injury rehabilitation.[172] These research directions will not only promote the scientific development of EA but also provide new treatment options for clinical practice.

In conclusion, the application prospects of EA in treatment of KOA are broad. With further verification of its effectiveness and safety, EA is expected to become an important component of KOA management. Future research should not only continue to explore the efficacy of EA but also pay attention to its combined application with other treatment methods, aiming to provide more comprehensive treatment plans for KOA patients through multidisciplinary integration.

Abbreviations

5-HT, 5-Hydroxytryptamine; AKT, Protein Kinase B; APC, Anaphase-Promoting Complex; ATP, Adenosine Triphosphate; BAD, BCL2-Associated Agonist of Cell Death; BMP2, Bone Morphogenetic Protein 2; C-FOS, FBJ Osteosarcoma Oncogene; Caspase-3, Cysteine-ASPartic protease-3; Caspase-9, Cysteine-ASPartic protease-9; c-Jun, v-jun avian sarcoma virus 16 oncogene homolog; COL-I, Collagen Type I; COX-2, cyclooxygenase – 2; CSL, CBF1/Suppressor of Hairless/LAG-1; ERK, Extracellular signal-Regulated Kinase; FADD, Fas-Associated Death Domain; GSK-3β, Glycogen Synthase Kinase-3 beta; HES/HEY, Hairy and Enhancer of Split/HES-related with YRPW motif, IKK complex, Inhibitor of NF-κB Kinase complex; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; IRAK, Interleukin-1 Receptor-Associated Kinase; JAK, Janus Kinase; JNK, c-Jun N-terminal Kinase; LRP, LDL-Receptor-related Protein; MAPK, Mitogen-Activated Protein Kinase; MEK, MAPK/ERK Kinase; MMP-1, Matrix Metalloproteinase-1; MMP-3, Matrix Metalloproteinase-3; MMP-13, Matrix Metalloproteinase-13; mTOR, mechanistic Target Of Rapamyc; MyD88, Myeloid Differentiation primary response 88; NF-κB, Nuclear Factor - kappa B; NFATc1, Nuclear Factor of Activated T-cells, cytoplasmic 1; NICD, Notch IntraCellular Domain; NO, Nitric Oxide; OPG, Osteoprotegerin; PI3K, Phosphatidylinositol 3-Kinase; PTEN, Phosphatase and Tensin Homolog; QcOx-2, Quiescin sulfhydryl oxidase 2; RANK, Receptor Activator of Nuclear factor κB; RANKL, Receptor Activator of Nuclear factor κB Ligand; RhoA, Ras Homolog gene family, member A; RIP, Receptor-Interacting Protein; ROCK, Rho-associated Coiled-coil-containing protein Kinase; ROS, Reactive Oxygen Species; SOCS1, Suppressor Of Cytokine Signaling 1; SOX9, SRY-Box Transcription Factor 9; STAT, Signal Transducer and Activator of Transcription; TGF-β1, Transforming Growth Factor-beta 1; TGF-βRI, Transforming Growth Factor-beta Receptor I; TGF-βRII, Transforming Growth Factor-beta Receptor II; TIMP-1, Tissue Inhibitor of Metalloproteinases-1; TLR4, Toll-Like Receptor 4; TNF-α, Tumor Necrosis Factor-alpha; TNF-R1, Tumor Necrosis Factor Receptor 1; TRADD, TNFRSF1A-Associated via Death Domain; TRAF2, TNF Receptor-Associated Factor 2; TRAF6, TNF Receptor-Associated Factor 6; TRPV4, Transient Receptor Potential Vanilloid 4; Wnt, Wingless-type; MMTV integration site family.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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