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Review Article

Investigation of Plant-Based Treatments, Mechanisms of Action, and Related Molecular Pathways in Models of Monosodium Iodoacetate-Induced Knee Osteoarthritis: A Narrative Review

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Abstract

Objective: *The aim of this review is to systematically evaluate plant-based therapies used in monosodium iodoacetate (MIA)-induced knee osteoarthritis (OA) models in terms of experimental design, routes of administration, dosing strategies, and targeted molecular mechanisms.*
Method: *This study was designed as a narrative review. A total of 66 preclinical studies published in the PubMed database that examined the efficacy of plants or herbal products in MIA-induced knee OA models were evaluated. The studies were analyzed based on plant species, routes of administration, MIA doses, solvents used, sampling time points, and targeted molecular pathways.*
Findings: *The studies reviewed revealed that plant-based therapies exert their effects through multiple biological mechanisms, primarily through inflammation suppression, reduction of pain behaviors, and protection of the cartilage matrix. The most frequently targeted molecular pathways were NF-κB and MAPK signaling pathways, while antioxidant and anti-apoptotic effects were evaluated in a more limited number of studies.*
Conclusion: *Plant-based therapies in MIA-induced OA models show promising results at the preclinical level. However, heterogeneity in experimental design and molecular analyses necessitates further comprehensive and standardized studies to support the translational potential of these agents.*

Key words*: Disease Models, Monosodium Iodoacetate, Osteoarthritis, Phytotherapy,*

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Introduction

Knee osteoarthritis (OA) is a prevalent degenerative joint disease affecting approximately 23% of individuals over the age of 40 (1). According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2015, the prevalence of OA rose by 32.9% between 2005 and 2015, with knee OA accounting for approximately 15% of all musculoskeletal disorders worldwide (2) It is a chronic inflammatory disease consist of radiographic and histopathological changes of articular cartilage, synovial fluid, synovial membrane and bone (3). Quality of life is severely compromised by the pain and restricted mobility resulting from the disease (4)

Knee OA is managed through a spectrum of treatments, starting with pharmacological agents and escalating to surgical intervention in cases refractory to conservative care. Pharmalogical treatment of OA mainly consists of non-steroidal anti-inflammatory drugs (NSAIDS), intra-articular corticosteroids and analgesics, however these OA treatments have proven efficacy in relieving pain and inflammation, but fail to prevent progressive cartilage degradation (5). Edible or medicinal plants have been used in preclinical monosodium iodoacetate (MIA) animal models (6, 7). Treatments are given chronically or acutely (8, 9). Herbal studies have analysed OA pain and progression in MIA models by considering behavioral pain parameters, biochemical and histopathological changes (6, 10). Some herbs like turmeric contain anti-inflammatory compounds that reduce OA inflammation. Its active compound, curcumin, has a strong anti-inflammatory effect (11). Other herbal treatments contain antioxidants that support knee health. These herbs and foods like cashew and vigna angularis contain antioxidants that help body scavenge free radicals (7, 10). Additionally, apoptosis, is one of the many mechanisms that contribute to the pathophysiology of OA. Angelica dahurica exhibits anti-apoptotic activity in OA, mediated by its primary furanocoumarin constituent, imperatorin (12). Along with these treatments, OA pain is often focused on (13). These herbal interventions likely mitigate pain through their combined anti-inflammatory and analgesic mechanisms. Consequently, researchers have reported that the bioactive compounds present in these plants and herbal mixtures are anti-osteoarthritic by showing antioxidant (6) antinociceptive (14), anti-inflammatory (10) and anti-apoptotic effects (12-19).

Local chronic inflammation and pain are involved in the pathogenesis of OA and biomarkers of inflammation and pain have

been the focus in OA research (20). Evaluation of plants targeting pro-inflammatory, apoptotic, autophagic and pain potential biomarkers may be important in the development of effective drugs for the treatment of OA (21). In addition, elucidating the mechanisms of action of bioactive components in the pathogenesis of OA will provide comparable benefits. In the advanced stages of OA, surgical treatment methods such as arthroscopy and total knee arthroplasty are applied. Thus, these herbal treatments, having demonstrated the capacity to slow disease progression in preclinical models, may represent promising candidates for future clinical investigation.

Intra-articular administration of MIA in rats and mice serves as a model that mimics the pathogenesis of human OA by inducing comparable pain phenotypes, structural degeneration, and functional joint deficits By inhibiting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity (22). MIA interferes with glycolysis, a process that precipitates chondrocyte death and articular cartilage degradation. The method's minimal invasiveness and high reproducibility are key reasons for its widespread adoption (22). It can be effectively utilized as a method for assessing the efficacy of herbal constituents.

Given that the preclinical MIA model is well-suited for demonstrating the therapeutic potential of herbal interventions, this narrative review provides a comprehensive analysis of the existing literature. Our aim is to guide the development of new phytopharmacological strategies for targeting the pathophysiology and symptoms of OA.

Methods

This study was designed as a narrative review to provide a comprehensive overview of the existing preclinical literature regarding plant-based treatments in MIA-induced knee OA models, focusing on study design parameters, treatment efficacy, and molecular mechanisms.

Study Selection

In this study, 66 of the 422 peer-reviewed and published PUBMED articles that contain full-text articles investigating the evidence for the efficacy of plants and herbal products in animal models of MIA-induced knee OA were included. Inclusion criteria for publications in the study were MIA-induced knee OA in rats and mice, and the language of the publications in English. Publications of models with rabbits and models of hip and temporomandibular OA and duplicate results were excluded. Eight substances were determined as the subtitles plants, administration way of plants,

species, mia amount used, solvent, sacrifice time points after mia induction and pathways.

Plants in MIA-Induced Osteoarthritis Models

Analysis of the reviewed studies indicates that plant-derived interventions in MIA-induced OA primarily exert their effects by concurrently modulating inflammatory processes, cartilage matrix integrity, and pain-related outcomes. Evidence synthesized from the included studies indicates that formulations containing Commiphora (6), Boswellia (23-26), Curcuma (11, 23, 26, 27) and Ginger (23, 27, 28)(e.g., Manjarix (28), LI73014 (23), and Peedanil Gold (29) consistently attenuate key inflammatory mediators, including NF-κB signaling, pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), and downstream eicosanoid pathways, often resulting in reduced joint swelling and nociceptive behavior. Concurrently, several single-plant extracts—such as Phlomis umbrosa (14), Dipsacus asperoides (14), Alpinia oxyphylla (30), and Withania somnifera (31) alongside standardized polyherbal formulations (UP3005) (32) SHINBARO (33), and GCSB-5 (34), exert pronounced chondroprotective effects by suppressing matrix-degrading enzymes (MMP-2, -9, -13 and ADAMTS-4/5) and preserving essential extracellular matrix components like type II collagen, aggrecan, and SOX9. These structural benefits are frequently associated with functional improvements, including restored weight-bearing distribution and the attenuation of mechanical and thermal hyperalgesia, as evidenced in studies involving curcumin (26, 27, 35, 36), imperatorin (12), naringenin (37), and Capparis spinosa (38).

In addition to these primary effects, several agents—including annatto tocotrienols (39), salidroside (40), Morinda species (41, 42), and rosemary–peppermint essential oil formulations (43) modulated oxidative stress by reducing lipid peroxidation and nitric oxide levels while enhancing endogenous antioxidant defenses, thereby indirectly supporting cartilage integrity. Although investigated in fewer studies, regulation of chondrocyte apoptosis and autophagy emerged as a mechanistically relevant dimension, particularly for formulations such as BST106 (44), which influenced caspase activation and autophagy-related markers, suggesting a role in maintaining cellular homeostasis.

Taken together, this body of evidence indicates that plant-based interventions in MIA-induced models act through integrated, multi-level mechanisms, with the most robust effects observed in inflammatory suppression and extracellular matrix preservation.

To facilitate a structured comparison of these experimental findings, the characteristics and outcomes of the included studies—including plant species, experimental design, administration protocols, and primary biological pathways—are consolidated in Table 1.

Table 1. Preclinical evidence on plant-derived compounds and formulations in MIA-induced osteoarthritis models: experimental design, treatment strategies, molecular pathways, and therapeutic outcomes.

Animal Species / Sex /Age (weeks) / Body weight (g)	MIA-induced OA model	Treatment (compound, dose, route, duration)	Pathway	Result	References
Sprague-Dawley rats / Male / 5 weeks	Intra-articular injection of MIA (50 µL of 40 mg/mL solution; equivalent to 2 mg MIA in 0.9% saline) into the knee joint (single dose; 26-G, 0.5-inch needle; under 2% isoflurane anesthesia)	A mixture of *Paeonia lactiflora* and *Commiphora myrrha* (HT083) administered via diet at 100 or 300 mg/kg/day for 24 days (AIN-93G-based diet); indomethacin 3 mg/kg/day as positive control (dietary administration); treatment initiated on the day of MIA injection	İnflammation and pain pathways	Serum IL-1β↑ weight-bearing capacities in MIA rats and decreasing writhing responses in mice	(6)
Wistar rats / Female / 150-200 g	Intra-articular injection (2 mg in 50 µL, 0.9% sterile saline)	Indomethacin (2 mg kg^{-1}, p.o., once daily, 4 weeks) vs. Manjarix (1000–62.5 mg kg^{-1}, p.o., once daily, 4 weeks)	Inflammation and Chondroprotective payhways	IL6, TNF-α, CTX-II HA, the pathological injury↓ MIA-induced pain behavior↓	(28)
Sprague-Dawley rats / 7 weeks / 280-300 g	Intra-articular injection (3 mg in 50 µL, 0.9% sterile saline; isoflurane anesthesia)	*Phlomis umbrosa* extract (200 mg kg^{-1}, p.o., once daily, 21 days; starting day 1 post-MIA)	Gene profiling publication (Wnt/β-catenin, OA pathway, and sonic hedgehog signaling activity)	MMP-9,MMP-13↓ ADAMTs4↓ ADAMTs5↓ COL2A1↑ *SOX-5,SOX-9* mRNAs↑ catenin beta-1 (Ctnnb1)↓	(14)
Wistar ST rats /	Intra-articular injection (1 mg	ALM16 (combined extract of	Pain pathways	Paw withdrawal threshold↓ OA lesions↓	(13)

6 weeks / 120-140 g	MIA in 50 µL, PBS; single dose; avertin anesthesia)	*Astragalus membranaceus* and *Lithospermum erythrorhizon*); ALM16 (100, 200, 400 mg kg^{-1}, p.o., once daily, 14 days; starting day 7 post-MIA)	Chondroprotective pathways	necrotic chondrocytes and cartilage erosion ↓	
Sprague Dawley rats / Male / 8-12 weeks / 140-230 g	Intra-articular injection (0.5 mg MIA in 50 µL; 10 mg mL^{-1}; left knee)	XGS (0.45 g, topical application to knee joint, once daily, 28 days; starting day 7 post-MIA)	Chondroprotective pathways Inflammation pathways	Inflammatory cytokines↓ matrix on cartilage tissue surfaces↑ Tnn, Col6a6, Igf1 and Lamb1 ↑ IL-6, MMP-3 and MMP-13 expression levels↓	(45)
Sprague Dawley rats /n200-250 g	Intra-articular injection (6 mg kg^{-1}, 50 µL; bilateral knees; single injection)	Psoralen (1 mg kg^{-1}, intra-articular injection; daily for 1 week, then once every 3 days for 1 week; starting day 14 post-MIA)	Chondroprotective pathways	Articular cartilage was more integrated with greatly organized chondrocytes and abundant cartilage matrix	(37)
Sprague Dawley rats / Male / 7 weeks / 190-210 g	Intra-articular injection (3 mg MIA in 50 µL, 0.9% NaCl; right knee; ketamine/xylazine anesthesia)	*Alpinia oxyphylla* extract (150–300 mg kg^{-1}, p.o.), Indomethacin (1 mg kg^{-1}, p.o.); once daily, 21 days; starting 3 days pre-MIA	Anti-nflammatory pathways Chondroprotective pathways	Cartilage degradation and bone resorption↓ Histomorphological changes↓ Osteocalcin level, urine DPD level↑ Serum levels of LTB4, IL-1β and IL-6↑ IL-6, TNF-α, iNOS, COX-2, MMP-2 and MMP-9 in cartilage↓	(46)
Sprague Dawley rats / Male / 5 weeks 7	Intra-articular injection (2 mg MIA in 50 µL; 40 mg mL^{-1}; knee joint; isoflurane anesthesia)	Aucklandia lappa Root Indomethacin (3 mg kg^{-1}, diet), *Aucklandia lappa* root extract (300 mg kg^{-1}, diet); 24 days	Pain pathways Iinflammatory pathways Chondroprotective pathways	Cartilage erosion↓ Sserum IL-1β↓	(15)
LEW/SSNHSD rats / Female/ 4 weeks / 120-130 g	Intra-articular injection (1 mg MIA in 50 µL, physiological saline; single dose; isoflurane anesthesia)	*Tribulus terrestris* extract (200–400 mg kg^{-1}, p.o.), Joins (200 mg kg^{-1}, p.o.), Celebrex (100 mg kg^{-1}, p.o.); once daily, 4 weeks	Inflammation pathways Chondroprotective pathways	NOS2, COX-2, TNF-α, IL-6↓ Phosphorylation of ERK↓ MMP-2, MMP-9↓ Cartilage damage↓	(47)
Sprague Dawley rats / Male / 2 month	Intra-articular injection: (MIA; 4 mg MIA in 50 µL, 0.9% NaCl single injection; right knee; day 0)	*Annatto tocotrienol* (50, 100, 150 mg kg^{-1}, p.o., once daily, 5 weeks; starting day 1 post-MIA; 6 days/week)	Chondroprotective pathways	Osteocalcin levels and osteoclast surface of subchondral bone↓ CTX-1↔ Serum hyaluronic acid↑	(39)
Sprague Dawley ratsc/ 14-16 weeks	Intra-articular injection (3 mg MIA in 50 µL saline; left knee;	*Spinacia oleracea* extract (250 and 500 mg kg^{-1} day^{-1}, p.o., once daily, 28	Inflammation pathways	GST, COMP and urinary CTX-II↓	(48)

/ 180-200 g	single dose; ketamine/xylazine anesthesia)	days; starting day 3 post-MIA)	Chondroprotective pathways	IL1-β,TNF-α, Col-10, MMP-1, MMP-3,MMP-13↓Sox 9 and Col-2↑	
Sprague Dawley rats / Male / 200-220 g	Intra-articular injection (2.5 mg MIA in 25 µL, 0.9% NaCl; right knee; single dose; diethyl ether anesthesia)	SHINBARO (six-herb standardized formulation; *Ledebouriellae Radix*, *Achyranthis Radix*, *Acanthopanacis Cortex*, *Cibotii Rhizoma*, *Glycine Semen*, *Eucommiae Cortex*), SHINBARO treatment via intra-articular (2–20 mg kg^{-1}) or oral (20–200 mg kg^{-1}) administration once daily for 21 days; diclofenac (5 mg kg^{-1}, p.o.) as comparator	Inflammation pathways Chondroprotective pathways	The serum PGE2↓ Anti-type II collagen↓ Right knee joint cartilages of iNOS, COX-2↓ (TNF)-α, (IL)-1β) NF-κB↓	(33)
Sprague Dawley rats /Male / 6 weeks / 130-190 g	Intra-articular injection (3 mg MIA in 50 µL, 0.9% NaCl; left knee; single dose)	LI73014F2 (standardized formulation of *Terminalia chebula*, *Curcuma longa*, and *Boswellia serrata* in a 2:1:2 ratio; standardized to ~1.8% gallic acid, 3.5% curcuminoids, and 0.9% AKBA) LI73014F2 (25–100 mg kg^{-1}) or ibuprofen (20 mg kg^{-1}) once daily for 3 weeks; vehicle: 0.5% CMC-Na	Inflammation pathways Chondroprotective pathways	Synovial fluid IL-1β↓ COX-2, PGE2, 5-LOX, LTB4, IL-1β, IL-6, TNF-α↓	(23)
Sprague Dawley rats / Male / 7 weeks / 230-270 g	Intra-articular injection (3 mg MIA in 50 µL, normal saline; single dose; knee joint)	Oral treatment with indomethacin (2.5 mg kg^{-1} day^{-1}) or PN-G formulations (PN-G 104, PN-G 312, PN-G 936; 312–936 mg kg^{-1} day^{-1}) from day 7 to day 26 post-induction.	Inflammation pathways Pain pathways	Interleukin-6 (IL-6) and interleukin-1 beta (IL-1β)↓ joint inflammation↓ Cartilage Oligomeric Matrix Protein (COMP)↓	(29)
Wistar rats / Male / 8-12 weeks / 140-230 g	Intra-articular injection (3 mg MIA in 50 µL, normal saline; single dose; right knee joint)	YH23537: Notoginseng Radix and Rehmanniae Radix Preparata Extract Combination YH23537 (oral administration,	Pain pathways Chondroprotective pathways	Metalloproteinase-3, nitrotyrosine, IL-1β and IL-6 increased in OA joints.↓ Metalloproteinase (TIMP)-1 and TIMP-3 in IL-1β-stimulated human OA chondrocytes.↑	(16)

		once daily for 24 days; starting day 4 post-MIA)		NF-κBp65 and HIF-2α in the joint tissues↓	
Sprague Dawley rats /Male / 30 days	Intra-articular injection (1 mg MIA in 50 µL; 20 mg mL^{-1}; single dose; knee joint)	*Ageratum conyzoides* L. leaves extract (40–160 mg/200 g b.w., p.o., day 29–49 post-MIA)	Inflammation pathways Chondroprotective pathways	Serum TNF-α and MMP-9↓number of leukocytes, lymphocytes and udem volume↓inflammation and cartilages degradation↓	(17)
Sprague Dawley rats / Male / 180-220 g	Intra-articular injection (1 mg MIA in 50 µL; 20 mg mL^{-1}; single dose; knee joint)	Hei-Shun-Pian (Processed Aconitum carmichaeli Debeaux Lateral Root With Peel) dHsp (14 g kg^{-1}, p.o., once daily, 28 days; starting day 0 post-MIA)	Pain pathways Chondroprotective pathways	Joint pain ,articular degeneration↓ Col10, Mmp2, Sox5, Adamts4/5/9 ↓ Col2 expression in rat cartilage ↑	(49)
Wistar rats / Male / 6-8 weeks / 195-225 g	Intra-articular injection (0.3 mg MIA in 25 µL saline; single dose; right knee; ketamine/xylazine anesthesia)	*Curcuma longa* extract or curcuminoids (22.5–90 mg kg^{-1}, p.o.) or tramadol (10 mg kg^{-1}, p.o.) as a single dose on day 5 post-MIA	Pain pathways	MMP-3 and MMP-7↓ Anti-nociceptive effect↑	(11)
Wistar rats / Male / 270-280 g	Intra-articular injection (4 mg MIA in 50 µL saline; single dose; right knee joint)	Grape seed proanthocyanidin extract (100 or 300 mg kg^{-1}, p.o., three times per week, 4 weeks; starting post-MIA)	Pain pathways Chondroprotective pathways	MIA-induced pain and histologic Changes↓nitrotyrosine and MMP13↓	(50)
Sprague Dawley rats / Male / 5 weeks / 180-240 g	Intra-articular injection (3 mg kg^{-1} MIA in 50 µL, 0.9% saline; single dose; right knee joint; isoflurane anesthesia)	*Schisandrae Fructus* extract (100 mg kg^{-1}, p.o., once daily for 3 weeks)	Inflammation pathways Chondroprotective pathways	Serum PGE2, NO, IL-1β, IL-6 and TNF-α↓ Cartilage oligomeric matrix protein (COMP) and C-telopeptide of type II collagen (CTX-II) iNOS, COX-2 ↓ MMP-13↓, CTX-II, COMP (immuno)↓	(51)
Wistar rats / Male and Female / 12 weeks / 200-220 g	Intra-articular injection (2 mg MIA in 25 µL sterile normal saline; single dose; left knee joint; ketamine/xylazine anesthesia)	Topical nanoemulsion/essential oil gels or solution (1 mL, once daily for 14 days); diclofenac gel 1% as reference	Pain pathways Chondroprotective pathways	All the treatments improve the cartilage change induced by MIA injection and reduce the joint pain. SOD and GPx↑ MDA↓	(43)
Sprague Dawley rats / Male / 7 weeks	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; right	*Litsea japonica* Fruit Fleshe extract (25–100 mg kg^{-1}, p.o.) or indomethacin (1 mg	Pain pathways	Serum levels of IL-1β↓, IL-6, leukotriene B4 (LTB4), 5-LOX ↓, Osteocalcin↓	(52)

	knee joint; ketamine/xylazine anesthesia)	kg^{-1}, p.o.), administered for 1 week prior to MIA	Chondroprotective pathways	The urine levels of deoxypyridinoline (DPD)↓ Gelatinase A (MMP-2), gelatinase B (MMP-9), and COX-2 in cartilage↓	
Wistar rats / Male / 140-175 g	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; right knee joint	*Entada pursaetha* extract (30–300 mg kg^{-1}, p.o.) or etoricoxib (10 mg kg^{-1}, p.o.) once daily for 21 days	Pain pathways Chondroprotective pathways	Mechanical, heat, cold hyperalgesia↓ Horizontal and vertical movements↑ Cartilage structure↓	(53)
Sprague Dawley rats / 12 weeks / 210-215 g	Intra-articular injection (1.0 mg MIA in 50 µL physiologic saline; single dose; left knee joint; isoflurane/ketamine/xylazine anesthesia)	Withaferin A (WFA) (10 mg kg^{-1} day^{-1}, p.o., once daily for 28 days post-MIA; vehicle: gum acacia)	Inflammation pathways Chondroprotective pathways	SOX9,COL2↑AGGRECAN, BMP2↑ IL-1β, TNF-α↓ MMP1, MMP13, MMP3↓ µ-CT analysis↑cartilage erosion↓	(31)
Sprague Dawley rats / Male / 7 weeks	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; right knee joint; ketamine/xylazine anesthesia)	*Schisandra chinensis* leaf extracts (150 or 300 mg kg^{-1}, p.o., once daily; 3 days pre-MIA to 21 days post-MIA; vehicle: 0.5% CMC); indomethacin (1 mg kg^{-1}, p.o., same schedule)	Pain pathways Inflammation pathways	IL-6, ↓IL-1β↓, TNF-α↔, (MMP)-2 MMP-9 ↓ Osteocalcin ↓ Deoxypyridinoline (DPD), İNOX,COX2↓ IL-6,IL-1B,COX-2,İNOS,MMP-2,MMP-9,GAPDH (pcr)	(54)
Sprague Dawley rats / Male / 7 weeks / 190-210 g	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; left knee joint; ketamine/xylazine anesthesia)	*Mollugo pentaphylla* L. extract (75, 150, 300 mg kg^{-1}, p.o., once daily; 3 days pre-MIA to 11 days post-MIA; vehicle: 5% CMC in saline) or indomethacin (1 mg kg^{-1}, p.o., same schedule)	Pain pathways Chondroprotective pathways Inflammation pathways	IL-1β TNF-α and IL- 6 ↓ synthesis of MMP-2, MMP-9 and COX-2 ↓ MPE attenuated the severity of MIA-induced OA in rats.	(18)
Wistar rats / Female / 12 weeks	Intra-articular injection (2 mg MIA in 30 µL sterile saline; single dose; right knee joint; ketamine anesthesia)	*Vigna angularis extract* (50 or 100 mg kg^{-1}, p.o., once daily for 4 weeks post-MIA; vehicle: saline)	Chondroprotective pathways Inflammation pathways	Synovial fluid IL-6 and TNF-a↓ Articular cartilage from degeneration and necrosis↓	(55)
Sprague-Dawley rats / Male / 200-220 g	Intra-articular injection (3 mg MIA in 50 µL physiological saline; single dose; left knee	GCSB-5, a Herbal Formulation (Ledebouriellae Radix, Achyranthis Radix, Acanthopanacis	Chondroprotective pathways Inflammation pathways	Serum TNF-α↓, IL-1β↔, and IL-10 ↑ COX-2 and iNOS↓, TNF-α, IL-1β, IL-10↓ (PCR)	(34)

	joint; diethyl ether anesthesia)	Cortex, Cibotii Rhizoma, Glycine Semen, Eucommiae Cortex) GCSB-5 (300 or 600 mg kg^{-1}, p.o., once daily for 2, 7, or 28 days post-MIA; vehicle: saline) or diclofenac (5 mg kg^{-1}, p.o., same schedule)		NF-κB ↓and Cytosolic IκB-α↓	
Sprague Dawley rats / Female / 225 ± 5 g	Intra-articular injection (3 mg MIA in 50 µL physiological saline; single dose; left knee joint; diethyl ether anesthesia)	*Vernonia amygdalina*, bitter leaf extract (150–300 mg kg^{-1}, p.o., 8 weeks) or diclofenac (5 mg kg^{-1}, p.o.)	Pain pathways Chondroprotective pathways Inflammation pathways	Prostaglandin E2, IL-1β, Matrix metalloproteinases (MMP-13 and MMP-3) levels, and serum CTX-II (C-terminal cross-linked telopeptide type II collagen ↑ (IL-1β, PTGS2, nuclear factor κβ, and TNF-α) and metallopeptidase (ADAMTS5) (TIMP3)↓	(8)
Balb-C mice / 10 weeks / 20 ± 5 g	Intra-articular injection (0.1 mg MIA; single dose; left knee joint)	*Elaeagnus angustifolia* L. extract (32 mg kg^{-1}, p.o., once daily for 28 days; starting day 14 post-MIA) or quercetin (20 mg kg^{-1}, p.o., same schedule)	Chondroprotective pathways	Blood MMP-3↔ MMP-13↓ tibial and femoral bones ↑ cartilage damage ↓	(56)
Sprague Dawley rats / Male / 5 weeks / 200-210 g	Intra-articular injection (3 mg MIA in 50 µL, 0.9% sterile saline; single dose; right knee joint; isoflurane anesthesia)	*Litsea japonica* fruit extract (50, 100, 200 mg kg^{-1}, p.o., once daily for 3 weeks post-MIA; vehicle: saline) or indomethacin (2 mg kg^{-1}, p.o., same schedule)	Inflammation pathways	MMP-2, MMP-3, MMP-7, MMP-9, MMP-13, TIMP-1, and TIMP-2 in the articular cartilage (pcr)↓ IL-6, IL-1β, and TNF-α serum ↓	(57)
Wistar rats / Male / ~ 250 g	Intra-articular injection (1.5 mg MIA in 50 µL, 0.9% sterile saline; single dose; right knee joint; ketamine/xylazine anesthesia)	*Sida tuberculata* extract (1.5, 5, or 15 mg mL^{-1}, p.o., once daily for 14 days post-MIA) or sodium diclofenac (10 mg kg^{-1}, p.o., once daily for 14 days)	Pain pathways Inflammation pathways	Pain decrease, lower neutrophil activity in the knee, and increased blood serum activity Lipid peroxidation, on protein carbonyl content, superoxide dismutase (SOD) and on total no-protein thiol content (NPSH)↓ Decrease in mechanical hyperalgesia	(58)
C57BL/6 mice /	Intra-articular injection (500 µg	Amurensin H (10 or 20 mg kg^{-1} body	TLR4/Syk/ NF-κB	Amurensin H exerts chondroprotective effects	(59)

Male / 20-22 g	MIA; joint capsule; control: 10 µL sterile saline)	weight, p.o., once daily; starting day 14 post-MIA)	signals (in cell culture)	by attenuating oxidative stress, inflammation and matrix degradation via the TLR4/Syk/NF-κB pathway.	
Sprague Dawley rats / Male / 7 weeks	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; right knee joint; ether anesthesia)	*Dipsacus asperoides* extract (200 mg kg^{-1}, p.o., once daily for 3 weeks) or *Phlomis umbrosa* extract (200 mg kg^{-1}, p.o., once daily for 3 weeks) or indomethacin (1 mg kg^{-1}, p.o., once daily for 3 weeks)	Pain pathways Chondroprotective pathways Inflammation pathways	Serum levels of TNF-α, IL-1β↓ MMP-2, MMP-9, MMP-13 in Knee Joint Tissues↑ Cartilage destruction.↓	(14)
Sprague Dawley rats / Male / 6 weeks / 160-180 g	intra-articular injection (0.8 mg MIA in 50 µL saline solution into the left knee joint using 26 G needle)	UP3005, a Botanical Composition Containing Two Standardized Extracts of Uncaria gambir and Morus alba (500 mg/kg once daily for 6 weeks p.o.) or Diclofenac (10 mg/kg p.o)	Pain pathways Chondroprotective pathways	UP3005 resulted in almost a complete inhibition in proteoglycans degradation, Reductions of 16.6% (week 4), 40.5% (week 5), and 22.0% (week 6) in pain sensitivity, statistically significant improvements in articular cartilage matrix integrity, Minimal visual subchondral bone damage, and statistically significant increase in bone mineral density when compared to the vehicle control with MIA.	(32)
Sprague Dawley rats / Male / 8 weeks / 180-220 g	Intra-articular injection (0.5 mg MIA in 50 µL physiological saline; 10 mg/mL; single dose; knee joint)	Saponin fraction from Clematis chinensis Osbeck roots (SFC; 50, 100, 200 mg kg^{-1}, p.o., once daily for 28 days) or diclofenac (4 mg kg^{-1}, p.o., once daily for 28 days)	Chondroprotective pathways	SFC (50, 100, 200 mg/kg) dose-dependently reduced cartilage injury and PG degradation induced by MIA	(60)
Sprague Dawley rats / Male / 160-180 g	Intra-articular injection (1 mg MIA; single dose; right knee joint; isoflurane anesthesia)	Huoxuezhitong capsule consists of Angelica sinensis (Oliv.) Diels, Panax notoginseng (Burkill) F. H. Chen ex C. H., Boswellia sacra, Borneol, Eupolyphaga sinensis Walker, Pyritum. HXZT (0.5 or 1.0 g kg^{-1} day^{-1}, p.o., once daily for 5 weeks; starting day	PI3K/ Akt/ NF-κB pathway	Blood PGE2, IL-1β and TNF-α↓ Rat knee joint NFκB (p50) and p-PI3K protein expression ↓ Cartilage destruction ↓	(61)

		2 post-MIA; vehicle: 0.5% CMC-Na) or diclofenac (2.5 mg kg^{-1} day^{-1}, p.o., same schedule)			
Sprague Dawley rats / Male / 12 weeks / 250-290 g	Intra-articular injection (2 mg MIA in 50 µL, 0.9% saline; single dose; knee joint)	Imperatorin (5 mg kg^{-1} day^{-1}, p.o., once daily for 6 weeks; starting 2 weeks post-MIA; vehicle: 0.5% CMC-Na)	NLR family pyrin domain-containing 3 inflammasome cascade	NLRP3↓, caspase-1↓, ASC↓,caspase 1 p10↓ TGF-β1, VEGF and TIMP-1↓ Serum IL-1β and IL-18↓ IMP ameliorated synovitis and synovial fibrosis	(12)
Sprague Dawley rats / Male / 6 weeks	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; knee joint)	Scopoletin (coumarin)- and epicatechin (flavonoid)-rich *Morinda citrifolia* extract (p.o., once daily for 28 days)	Inflammation pathways Oxidative pathways	Serum MMP1↓, MMP3↔, and MMP13↓ Serum pro -collagen type II N and C terminal (PIINP, PIICP), procollagen type I N terminal (PINP), C telopeptide type II collagen (CTXII)↑, nitric oxide (NO)↓, tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β IL-6, IL-10, TNF-α, PTGS2/COX2, and PTGER2↓ gly -cosaminoglycan and nitric oxide release from the cartilage, ıl-1b↓	(41)
BALB/c nude mice Male / 5 weeks	Intra-articular injection (5 mg kg^{-1} MIA in physiological saline; single dose; knee joint)	*Saussurea lappa* extract (1.0, 1.5, 2.0, 2.5, 3.0 mg kg^{-1}, i.p., once daily for 20 days; starting day 2 post-MIA; vehicle: physiological saline)	NF-κB Pathway	IL-1β/-6 and TNF-α in serum ↓ IL-6, TNF-α, and IL-1β in cartilage ↓ cartilage P2X7R and MMP-13↓ Subtance P and PGE2 in cartilage↓ p-IκBα↓ p-NF-κBp65, NF-κBp65↓ in articular cartilage	(62)
Sprague Dawley rats / Male/ 6 weeks / 170-200 g	Intra-articular injection (3 mg MIA in 100 µL, 0.9% saline; single dose; right knee joint)	*Caragana sinica* root extract (200 or 400 mg kg^{-1}, p.o., once daily for 4 weeks post-MIA; vehicle: distilled water) or indomethacin (1 mg	MAPK/NF-κB signaling pathway	Serum Nitric Oxide↓ and PGE2↓, MMP-3, 9, and 13↓ COX-2↓ Serum aggrecan, GAGs↑	(63)

		kg^{-1}, p.o., same schedule)			
Sprague Dawley rats / Female / 12 weeks	Bilateral ovariectomy followed by intra-articular injection (3 mg MIA in 50 µL saline; single dose; right knee joint; 26 G needle)	*Ficus deltoidea* extract (200 or 400 mg kg^{-1}, p.o., once daily for 28 days; starting 14 days post-MIA; vehicle: deionized water) or diclofenac (5 mg kg^{-1}, p.o., same schedule)	Inflammation pathways	Osteocalcin and osteoprotegerin↑ Collagen type I breakdown product CTX-I↓ and receptor activator of nuclear kappa-beta ligand RANKL↓ NFKB,IL-6,IL-1B↓	(64)
Sprague Dawley rats / Male	Intra-articular injection (2 mg MIA in 25 µL saline; single dose; knee joint; isoflurane anesthesia)	*Capparis spinosa* root powder and extracts (DEC, EtH_2O, CH_2Cl_2, H_2O-Res), p.o. acutely on 14.day of MIA p.o.; vehicle: 1% CMC (dose empirically selected)	Pain pathways	Capparis spinosa root powder and its different extracts are able to acutely relieve pain in rat models of OA	(38)
Sprague Dawley rats / Male / 200-230g	Intra-articular injection (3 mg MIA in 25 µL sterile saline; single dose; knee joint)	Cashew (*Anacardium occidentale* L.) Nuts (100 mg kg^{-1}, p.o., three times per week for 21 days; starting day 3 post-MIA; vehicle: saline)	Inflamation pathways Chondroprotective pathways	Serum GSH↑, GPX↑,MDA↓,CAT↑,SOD↓ Interleukin-1beta (IL-1β), tumor necrosis factor alpha (TNF-α)↓, nerve growth factor (NGF)↓, and matrix metalloproteinase-1-3-9 (MMP-1 MMP-3 MMP-9)↓ collagen degradation and cartilage abnormalities↓	(10)
Sprague Dawley rats / Male / 190-260 g	Intra-articular injection (2 mg MIA in 50 µL sterile saline; single dose; right knee joint; via infrapatellar ligament)	Salidroside (10, 50, or 100 mg kg^{-1}, i.v.; sterile saline vehicle; first dose at 0 h post-MIA, then every 12 h until 30 h post-MIA)	Inflammation pathways Chondroprotective pathways Oxidative pathways	TNF-α↔, IL-1β↓, IL-6↓, CXCL1)↓, and chemokine (C–C motif) ligand 2 (CCL2)↓, PGE2↓, ROS,RNS,4-HNE↓,MPO↓,NO ↓in synovial fluid TNF-a,IL-1B,IL-6,Ccl2,CxCl1,NOs2,Nos3,Ptgs2,Rela,NFKB (pcr)↓ Lökosit,nötrofil,lenfosit,makrofaj,total protein↓	(40)
Sprague Dawley rats / Female /12 weeks / 240 ± 10 g	Bilateral ovariectomy followed by intra-articular injection (3 mg MIA in 50 µL saline; single dose; right knee joint; 26 G needle)	Comparison of diclofenac with apigenin-glycosides rich *Clinacanthus nutans* extract (200 or 400 mg kg^{-1}, p.o.; deionized water vehicle; once daily for 4 weeks, starting 2 weeks	Inflammation pathways Chondroprotective pathways	Serum Interleukin 1 beta (IL-1β)↓,procollagen type II Nterminal propeptide (PIINP)↑, Osteocalcin, procollagen type I N-terminal propeptide (PNP)↓, NF-κβ, IL-1β ↓and COX-2↓,MMP-13↓ Cartilage erosion, bone loss↓	(65)

		post-MIA / 4 weeks post-OVX) Diclofenac (5 mg kg^{-1}, p.o.; once daily for 4 weeks)			
Wistar rats / Male / 6 weeks / 140-230 g	Intra-articular injection (3 mg MIA in 50 µL, 0.9% saline; single dose; knee joint)	Combination of probiotic complex + rosavin + zinc + celecoxib (p.o.; once daily for 13 days), *Hijikia fusiforme* extract (p.o.; once daily for 26 days)	Inflammation pathways Pain pathways	Cartilage destruction,pain↓ TNF-α, IL-6↓, MMP3↓,Tımp3, IL-10 in joints ↑ (pcr) MMP3 and TIMP3↓TNF-α and IL-6↓	(66)
Sprague Dawley rats / Male / 6 weeks / 200-250 g	Intra-articular injection (3 mg MIA in 50 µL sterile 0.9% saline; single dose; knee joint; 27 G needle)	*Rose Hip* extract: 500 mg/kg bw, p.o., once daily for 26 days, *Hijikia fusiforme* (20% ethanol extract): 250 or 500 mg/kg bw, p.o., once daily for 26 days (Administered starting 3 days after arrival / acclimatization)	Biochemical pathways for cartilage	Collagen type I, II, aggrecan, and TIMPs expression (pcr)↑ MMP-3 and 7, NO and PGE2↓	(67)
Sprague Dawley rats / Female / 230-250 g	Intra-articular injection (1 mg MIA in 50 µL sterile 0.9% saline; single dose; knee joint)	Intraperitoneal administration curcumin (i.p.), once daily for 14 days, starting 2 weeks after MIA induction	TLR4 /MyD88/NF-κB signal pathway	Synovial fluid cytokine expression (IL-6,IL-1β, and TNF-α) levels↓ TLR4 receptor↑ MyD88, p-IκBα, NF-κB, TNF-α, IL-1β, and IL6 expression↓	(35)
Wistar albino rats / Male / 200 ± 30 g	Intra-articular injection (2 mg MIA in 50 µL sterile saline; single dose; right knee joint; infra-patellar ligament; under light isoflurane anesthesia)	Herbal formula (Zingiber officinale + Curcuma longa, 1:1 hydroethanolic extract), orally administered at 200 or 400 mg/kg/day for 30 days (starting post-MIA)	Inflammation pathways Chondroprotective pathways	Serum level of COMP↓ Blood hyaluronic acid (HA)↓ BLood myeloperoxidase (MPO)↓ Blood Interleukin-1 beta (IL-1β)↓ Blood malondialdehyde (MDA) ↓ Superoxide dismutase (SOD)↑	(27)
Wistar rats / Male / 220-240 g	Intra-articular injection (2 mg MIA in 30 µL; right knee joint; single dose; 26.5 G needle; under	Naringenin (20 or 40 mg/kg), orally administered by gavage once daily, starting 2 days post-MIA; vehicle:	Pain pathways	MMP-3 expression↓ Erosion of cartilage↓ Pain alleviation	(68)

	isoflurane anesthesia)	5% DMSO; dose volume: 300 µL			
Sprague Dawley rats / Male / 6 weeks	Intra-articular injection (3 mg MIA in 50 µL sterile 0.9% saline; single dose; knee joint)	*Morinda elliptica* extract, orally administered at 200 or 400 mg/kg/day for 28 days; diclofenac 5 mg/kg/day (p.o.) as positive control	Inflammation pathways Oxidative pathways	Serum MMP1, MMP3, MMP13↓, PIINP, PIICP↔, procollagenTypeI N terminal (PINP)↑, C telopeptide Type II collagen (CTXII)↓, NO↓, tumornecrosis factor alpha (TNF-α)↔, IL-1β↓ Cartilage TIMP1 and TIMP2↑ ADAMTS4↓	(42)
Sprague Dawley rats / 200-220 g	Intra-articular injection (2 mg MIA in saline; single dose)	*Chrysanthemum zawadskii* var. *latil obum* extract 50, 100, 200 mg/kg, p.o., once daily for 28 days	Inflammation pathways	Weight changes↑ Horizontal and vertical sizes in edema of Knee joints↑ Less synovial membrane damage Pro-inflammatory factors↓ MMP-13, MMP-1, MMP-9, MMP-3, expressions↓ MMP-2 and MMP-8↔SOX9↑ADAMTS-4 and ADAMTS-5↓ ACAN↑ and COL2A1↑	(69)
Spague Dawley rats / 140–170, 190–220 g	Intra-articular injection (50 µL of MIA solution, 60 mg/mL in 0.9% saline; single dose; right knee joint; infrapatellar ligament; 26 G, 0.5-inch needle; under Zoletil™ + Rumpun™ anesthesia)	WIN-34B (Lonicera japonica Thunb and Anemarrhena asphodeloides BUNGE), (100, 200, or 400 mg/kg), Joins (400 mg/kg), or celecoxib (100 mg/kg), orally administered once daily for 14 days; vehicle: 0.5% CMC in distilled water	Pain pathways Inflammation pathways	Hind paw weight distribution↓	(70)
Sprague Dawley rats / Male / 12 weeks / 180-220 g	Intra-articular injection (50 µL of MIA solution, 60 mg/mL in saline; single dose; right knee joint; under sodium pentobarbital anesthesia)	Fraxetin, orally administered at 5 mg/kg/day for 4 weeks (post-MIA induction)	Chondroprotective pathways	The progress of cartilage erosions, defects, and destruction in rats was alleviated by fraxetin treatment, indicating that fraxetin slowed the progress of cartilage destruction in OA rats.	(71)
Sprague Dawley rats / Female / 12 weeks / 210-215 g	Intra-articular injection (3 mg MIA in 50 µL saline; single dose; left knee joint; under ketamine–xylazine anesthesia)	Caviunin glycoside from *Dalbergia sissoo* extract DSE, orally administered by gavage at 250 or 500 mg/kg/day for 28 days, starting 1 day post-MIA	Chondroprotective pathways Inflammation pathways	Serum CTX-I, CTX-II, COMP, IL-1β, ↓ MMP-3 and 13 cartilage ↓ Sox9, Col2A1, Aggrecan, MMP-1↓	(72)

Sprague Dawley rats / Male / 7 weeks	Intra-articular injection (3 mg MIA in 50 µL of 0.9% saline; single dose; right knee joint; under ketamine–xylazine anesthesia)	*Saposhnikovia divaricata* ethanol extract (200 mg/kg) or indomethacin (2 mg/kg), orally administered; treatment initiated 1 week prior to MIA injection and continued for 4 weeks	Inflammation pathways Chondroprotective pathways	Serum IL-1β, IL-6, TNF-α, and PGE2↓ mRNA levels of COX-2, iNOS, IL-1β, IL-6, and TNF-α in the knee joint tissues↓	(73)
Sprague Dawley rats / Male / 8 weeks	Intra-articular injection (3 mg MIA in 50 µL of 0.9% saline; single dose; right knee join)	*Pinus densiflora* root extract powder orally administered at 100, 300 and 500 mg/kg/day for 6 weeks before 3 weeks of MIA induction	Inflammation pathways Chondroprotective pathways	Cartilage erosion↓ Serum interleukin-1β, prostaglandin E2, and TNF-a, IL-6, NO, MMP1,MMP3, MMP13 levels↓ Cartilage volume↓ antinociceptive effects↑	(74)
Wistar rats / Male / 6 weeks / 140-230 g	Intra-articular injection of 3 mg MIA in 50 µL saline into the right knee joint (single dose; 26.5-G needle; via patellar ligament; under isoflurane anesthesia)	Eupatilin, orally administered at 100 mg/kg/day; vehicle: 10% DMSO	Pain pathways Chondroprotective Properties	The expression of interleukin-1β (IL-1β), interleukin-6 (IL-6), nitrotyrosine and inducible nitric oxide synthase (iNOS) in cartilage↓ antinociceptive effects↑	(75)
Wistar albino rats / Male / 240-250 g	Intra-articular injection of 0.3 mg MIA in 25 µL of 0.9% saline into the right knee joint (single dose; infrapatellar ligament; 27-G needle; under anesthesia); left knee injected with saline	Turmerosaccharides-rich or -less fractions (22.5–90 mg/kg, single oral dose on day 5 post-MIA) vs tramadol 10 mg/kg	Pain pathways	Significant analgesic effect	(11)
Sprague Dawley rats / Male / 200-220 g	Intra-articular injection of 2 mg MIA in 50 µL saline into the right knee joint (single dose	BST106 (ethanol extract of *Chrysanthemum zawadskii* var. latilobum), orally administered at 50, 100, or 200 mg/kg/day for 28 days	Apoptotic pathways Autopaghy pathways Chondroprotective pathways	Serum MMP-2 and MMP-13↓ Serum cartilage oligomeric matrix protein ↑ Cleaved caspase-8, cleaved caspase-3, and cleaved PARP↑ Swelling and limping were attenuated TNFR1, Bax, cytosolic cytochrome C and cleaved	(19)

				caspase-8, cleaved caspase-9 protein↑ Levels of LC3-II, an autophagosome marker, and p62, an autophagy substrate↑ beclin-1 and Atg5-12 complex, phagophore-related proteins,↔ LAMP-2 and Rab7, lysosomal membrane proteins, and the lysosomal protease cathepsin B protein expression↓	
Sprague Dawley rats / Male / 7 weeks / 170-200 g	Intra-articular injection of 3 mg MIA in 50 µL of 0.9% saline into the right knee joint (single dose; patellar ligament; under tiletamine–zolazepam anesthesia); left knee injected with saline	5-Loxin®, (standardized *Boswellia serrata* extract), (100 or 200 mg/kg/day, p.o.) or indomethacin (2 mg/kg/day, p.o.); oral administration for 4 weeks (2 mL/day/animal)	Inflammation pathways Chondroprotective pathways Pain pathways	Joint pain through inhibition↓ Serum cyclooxygenase (COX)-2 and 5-lipoxygenase (LOX)↓ MMP-2, MMP-3, and MMP-13 gene expression in the cartilage tissue↓ MMP-9↔ Srostaglandin (PG) E2 and leukotriene (LT) B4 levels.↓	(25)
Sprague Dawley rats / Male / 7 weeks	Intra-articular injection of 3 mg MIA in 50 µL of 0.9% saline into the right knee joint (single dose; under anesthesia)	*Peucedanum japonicum* extract (200 mg/kg), orally administered once daily; treatment initiated 1 week prior to MIA injection and continued for 4 weeks	İnflammation pathways Pain pathways Chondroprotective pathways	Levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, leukotriene B4 (LTB4) and 5-lipoxygenase (5-LOX) in serum↓ (IL-1β, IL-6, TNF-α, COX-2, and iNOS) in the knee joint ↓ Caspase-3 (CASP3; rutin, chlorogenic acid, and isoquercitrin), caspase-7 (CASP7; rutin and chlorogenic acid), and cytochrome P450 2D6 (CYP2D6; xanthotoxin and isoimperatorin) (Compound-target gene network linking) Hind paw weight bearing distribution attenuated	(76)
Wistar rats /	Intra-articular injection of 3 mg MIA into the	BDMC-curcumin + AKBA-Boswellia + Ashwagandha	Chondroprotective pathways	TNF-α, IL-1β, IL-10, COMP, and CRP in the serum↓	(26)

Female / 8 weeks	right knee joint (single dose; infrapatellar ligament; under ketamine (50 mg/kg) and xylazine (10 mg/kg) anesthesia)	(JHF): Turmeric extract standardized to 96% total curcuminoids (including 24% BDMC), *Boswellia serrata* extract standardized to 85% AKBA, and *Withania somnifera* extract standardized to 20% withanolide glycosides; orally administered at 100–200 mg/kg for 4 weeks, starting 2 weeks post-MIA	Inflammation pathways Oxidative pathways	Lipid peroxidation but increased SOD, GSH-Px, and CAT activities MMP-3, COX-2, and LOX-5↓	
Wistar rats / Male / 300-450 g	Intra-articular injection of MIA (0.25 mg MIA in 25 µL of 0.9% saline; single dose)	Sesamol dissolved in saline and orally administered at 30 mg/kg body weight, twice weekly for 2 weeks	NF-KB Signaling	MMP-1 and -9 Expression in Cartilages of MIA-Induced OA in Rats↓	(77)
Sprague Dawley rats / Male / 12 weeks / 175-200 g	Intra-articular injection of MIA (1 mg MIA in 50 µL of 0.9% saline; single dose into the infrapatellar ligament of the right knee)	10 mg/kg Gingkolide C (dissolved in a sterile saline solution containing 2% Tween-80) orally once a day for 4 consecutive weeks following MIA induction.	Innate immune–inflamatuvar pathway Nrf2/NQO1 pathway	articular cartilage structure ↑ pain-related behavioral assays ↑	(78)

Routes of administration

The application method of the herbal treatments applied to the MIA-induced knee OA model was mostly carried out orally. In these studies, oral gavage was used in 59 articles, and intra-articular injection was used in 3 articles. Intraperitoneal administration was performed in one study. In one study, intravenous administration was performed. External application was performed in 2 studies. When the application days of the plants are analyzed, acute and chronic applications are observed. Although acute dose (single dose) was used in 3 studies, applications up to 56 doses (once a daily) were carried out. The dose applied in most of the articles was included in 22 articles with 28 doses. 8 articles choosed 21 doses. 14 dose administrations are included in 7 articles. 24 doses were included in 5 articles. 42 doses were applied in 2 articles. There are also articles using 3,5,7,9,12,13,26 and 30 doses.

Species

MIA-induced models of knee osteoarthritis are commonly performed in rats. The most used rat breed was Sprague Dawley in 44 articles among 66 articles. Wistar rats were used in 15 articles. Balb-C mice were used in 2 articles, and C57BL/6 mice in 1 article. In addition, Wistar/ST and LEW/SSNHSD rats were used in each article.

MIA dosage

MIA is a chemical agent that is frequently used in research to understand the pathogenesis of OA in rodents and to treat this disease (79). However, the dose and method of administration of MIA in rodents such as mice and rats may vary according to rodent species, age and sex. The amount of MIA used in the article 66 articles varied. In 31 publications, 3 mg MIA was injected into the intra-articular area of the right/left knee through the patellar ligament. While 2 mg MIA was injected in 12 articles, 1 mg MIA was injected in 7 articles. 0,5 mg, 0.3 mg and 4 mg MIA were injected in 2 articles. Different amounts of MIA were used in the remaining single articles.

Solvent

The type and amount of solvent used in MIA-induced OA models may vary depending on the purpose of the study. MIA is dissolved in solvent before it is injected into the right or left intra-articular space. 50 µL of 0,9% saline was used as solvent in 48 of 66 articles. In 7 articles, 25 µL of 0,9% saline was used as the solvent. In 2 articles, 50 and 30 µL of PBS were used. While the dose used in 5 articles is unclear, it is stated to be saline. 50 µL was used in 1 article, but the solvent type is unclear. 10, 30 and 100 µL 0,9% saline was used as the solvent in another articles.

Sacrifice time points After MIA Induction

Some of the plant-based treatments used in the studies were given before the induction of MIA, while some were given after the induction in plant studies. Animal sacrification after MIA induction in plant studies is usually performed between 21 and 42 days. However the earliest sacrification day is 30 hours after MIA induction. While 28 days after MIA induction in 17 articles were applied. In addition to 21 days in 16 articles were applied. 7 articles were completed after 42 days. While 6 articles were completed after 14 days, 15 days and 29 days were selected for 3 articles. 35 days in 2 articles were applied. The remaining 8 articles were completed after 5,6,7,11,27,37,50 and 56 days.

Molecular Mechanisms and Signaling Pathways

The initiation and progression of OA are governed by a complex network of signaling cascades that regulate chondrocyte survival, matrix homeostasis, and inflammatory responses. While the majority of studies in this review focused on phenotypic outcomes, a subset of articles (n=7) provided mechanistic insights into how plant-based interventions modulate these specific molecular targets. (12, 35, 59, 61-63, 77).

The NF-κB and MAPK Inflammatory Axis: The Nuclear Factor Kappa B (NF-κB) pathway represents the most frequently targeted mechanism in the reviewed MIA models. In OA pathophysiology, NF-κB activation acts as a key mediator, driving the expression of catabolic enzymes (MMP-1, MMP-3, MMP-13) and pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) (77). Several herbal interventions demonstrated efficacy by suppressing this axis. For instance, Ma et al. reported that Amurensin H exerts chondroprotective effects via the TLR4/Syk/NF-κB signaling pathway. By inhibiting TLR4 activation, the treatment reduced the downstream expression of inflammatory mediators, thereby preserving cartilage structure (59). Similarly, Zhang et al. observed that curcumin administration downregulated the MyD88/NF-κB axis, leading to significant reductions in IL-6, IL-1β, and TNF-α in both cartilage tissue and synovial fluid (35). This pathway often functions in concert with Mitogen-Activated Protein Kinases (MAPKs). Min et al. suggested that Caragana sinica root extract modulates OA pathology by inhibiting the MAPK/NF-κB signaling cascade (63). Furthermore, sesamol was shown to inhibit the phosphorylation of ERK and p38 MAPK, subsequently preventing NF-κB nuclear translocation and decreasing MMP-9 and MMP-13 expression in chondrocytes (77).

The PI3K/Akt and NLRP3 Pathways: The PI3K/Akt pathway plays a dual role, regulating both cell survival and inflammatory responses. Ju et al. demonstrated that Huoxuezhitong (HXZT) capsules delayed OA onset by modulating the PI3K/Akt/NF-κB axis. The study indicated that HXZT inhibited pathway-mediated mRNA production of inflammatory cytokines in LPS-induced cells, thereby preventing synovitis and cartilage destruction (60).

Additionally, the NLRP3 inflammasome has emerged as a critical target for synovial inflammation. Zhang et al. provided evidence that imperatorin, a furanocoumarin derivative, alleviates synovitis and synovial fibrosis by inhibiting HIF-1α/NLRP3 signaling, effectively blocking the cascade responsible for cytokine overproduction (12).

Wnt/β-catenin and Pathway Limitations: The Wnt/β-catenin signaling pathway is crucial for maintaining cartilage homeostasis, with aberrant activation often leading to chondrocyte hypertrophy and osteophyte formation. Chun et al. utilized gene profiling to demonstrate that Phlomis umbrosa root extract exerted its observed effects by modulating Wnt/β-catenin signaling, alongside reducing MMP-9 and MMP-13 levels (14). Despite these pathway-specific findings, the overall mechanistic landscape of MIA-based herbal studies remains incompletely characterized, highlighting the need to evaluate the limitations of current molecular evidence.

Limitations of Current Mechanistic Evidence: It is important to acknowledge that the depth of mechanistic analysis in the current MIA-based herbal literature remains limited. Only a small fraction of studies (approx. 10%) investigated defined signaling pathways. Notably, critical pathways implicated in subchondral bone remodeling and cartilage repair, such as TGF-β/Smad signaling, are largely absent from the reviewed studies. This represents a significant gap in the literature. Future research must move beyond descriptive phenomenology to include comprehensive molecular analyses of these broader disease-modifying pathways to improve the translational relevance of botanical treatments.

Orthopaedic and Translational Implications of MIA-Based OA Models

Knee OA is a multifactorial orthopaedic disorder characterized by progressive cartilage degeneration, subchondral bone remodeling, synovial inflammation, and functional impairment. In preclinical research, the MIA-induced OA model has been widely used due to its technical simplicity and reproducibility (13, 14, 24,

80); however, its orthopaedic and translational relevance requires careful interpretation.

From a structural perspective, MIA injection induces rapid chondrocyte death through inhibition of glycolysis, leading to thinning of articular cartilage, extracellular matrix (ECM) degradation, and increased expression of matrix metalloproteinases (37, 71). Several plant-based interventions reviewed in this study demonstrated preservation of cartilage thickness, reduced proteoglycan loss, and partial protection against ECM breakdown (10, 19, 23, 44, 61). In addition, some studies reported secondary effects on subchondral bone remodeling, including changes in osteocalcin levels, bone resorption markers, and microarchitectural parameters, suggesting potential effects beyond cartilage alone (81).

Functionally, MIA-induced OA is characterized by marked pain-related behaviors (25, 37), including weight-bearing asymmetry, reduced limb loading, altered gait patterns, and mechanical hyperalgesia. These functional impairments are commonly used as primary outcome measures in MIA-based studies and are particularly sensitive to anti-inflammatory and analgesic interventions. Many of the plant-based treatments summarized in this review showed significant improvement in weight distribution and nociceptive thresholds, indicating effective modulation of pain-related outcomes.

However, an important limitation of the MIA model from an orthopaedic standpoint is the dissociation between pain-dominant endpoints and long-term structural disease progression (81). While pain relief and short-term functional improvement are clinically relevant, they do not necessarily correlate with cartilage preservation, joint stability, or delayed need for surgical intervention in human OA. Clinical orthopaedic decision-making, including indications for joint-preserving procedures or total knee arthroplasty, is largely driven by irreversible structural damage, biomechanical dysfunction, and radiographic progression rather than pain alone.

Therefore, although MIA-based models are valuable for screening analgesic and anti-inflammatory effects of plant-derived compounds, their ability to predict disease-modifying or structure-modifying outcomes remains limited. Translational interpretation of findings from MIA-induced OA models should be made with caution, particularly when extrapolating preclinical results to clinical orthopaedic management or surgical decision thresholds.

Limitations of the MIA-Induced Osteoarthritis Model

Despite its widespread use in preclinical OA research, the MIA-induced model has important limitations that must be acknowledged when interpreting experimental outcomes and translational relevance.

The MIA model represents a chemically induced form of OA characterized by rapid inhibition of chondrocyte glycolysis (81), leading to acute chondrocyte death and subsequent cartilage degeneration. This mechanism differs fundamentally from the slowly progressive, multifactorial pathogenesis of human OA, which typically develops through age-related degeneration, mechanical overload, joint instability, or post-traumatic injury.

In contrast to surgical models of OA, such as anterior cruciate ligament transection (ACLT) or destabilization of the medial meniscus (DMM), which more closely mimic biomechanical joint instability and progressive structural remodeling, the MIA model primarily induces cartilage damage through direct metabolic toxicity (82). As a result, MIA-induced OA does not fully recapitulate the complex interactions between cartilage, subchondral bone, ligaments, and menisci that characterize clinical OA.

Another important limitation of the MIA model is its strong bias toward pain-dominant phenotypes. Behavioral pain responses, including weight-bearing asymmetry and mechanical hyperalgesia, develop rapidly and often precede or outweigh structural joint changes. Consequently, therapeutic interventions that effectively reduce inflammation or nociceptive signaling may produce marked improvements in pain-related outcomes without necessarily exerting sustained disease-modifying or structure-preserving effects (83).

From a translational and orthopaedic perspective, this dissociation between pain relief and long-term structural preservation limits the predictive value of the MIA model for evaluating interventions intended to slow disease progression, prevent joint collapse, or delay surgical intervention. Therefore, while the MIA model is valuable for investigating inflammatory mechanisms and analgesic efficacy, its limitations should be carefully considered when extrapolating preclinical findings to human OA or clinical orthopaedic management.

Conclusion

The MIA-induced knee OA model is widely used in preclinical research to investigate inflammatory mechanisms, pain-related outcomes, and potential therapeutic

interventions. The studies summarized in this review demonstrate that a variety of plant-based and herbal formulations can attenuate inflammatory responses, reduce pain-related behaviors, and partially preserve cartilage integrity in MIA-induced OA models.

However, it is important to emphasize that the evidence discussed in this review is exclusively preclinical and derived from heterogeneous animal studies with substantial variation in experimental design, dosing regimens, outcome measures, and duration of follow-up. As such, no direct extrapolation to clinical efficacy, optimal dosing, or therapeutic recommendations for human knee OA can be made.

Furthermore, pharmacokinetic properties, long-term safety profiles, and regulatory considerations of the reviewed plant-based interventions have not been systematically evaluated within the context of these studies. Consequently, the potential role of these compounds in clinical OA management remains unestablished.

Future research should focus on well-designed preclinical studies incorporating standardized outcome measures, comprehensive molecular analyses, and clinically relevant structural endpoints, followed by rigorously controlled clinical investigations to determine safety, efficacy, and translational relevance.

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