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Knee Osteoarthritis Preclinical Animal Models and Treatments Implementing a Traditional Chinese Medicine: A Systematic Comprehensive Review

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Abstract

knee osteoarthritis (KOA), a very common and crippling joint disease that has progressive articular cartilage degradation, subchondral bone remodeling, synovial inflammation, and osteophyte formation. Traditional Chinese Medicine (TCM), which includes multi-herb decoctions, traditional formulas, and bioactive monomeric chemicals, has become a prominent candidate for structural and symptomatic joint preservation because to the limited disease-modifying potential of current pharmaceutical therapy. Repeatable in vivo animal models are essential for the preclinical assessment and translational validation of TCM treatments. The current preclinical approaches for modeling KOA, including surgically induced, chemically induced, spontaneous aging, transgenic, non-human primate, big animal, and mechanical stress models, are summarized in this thorough study. Researchers systematically investigate the molecular and physiological pathways-such as anti-inflammatory signaling, extracellular matrix (ECM) homeostasis, chondrocyte anti-apoptosis, subchondral bone remodeling, and microRNA regulation-through which TCM interventions influence osteoarthritic pathogenesis. Additionally, for important TCM formulae and isolated monomeric substances, this article offers a systematic description of preclinical dosing, model choices, and quantitative results. Although TCM multi-target interventions successfully stop structural joint degeneration and suppress inflammatory cascades in preclinical animal models, standardized preclinical quality controls, sophisticated biomimetic delivery systems, and stringent, long-term human clinical trials are needed to translate these findings into clinical practice.

Keywords: Preclinical Methodology, Multi-Target Therapy, Traditional Chinese Medicine, Knee Osteoarthritis, Animal Models, Chondrocyte Protections, Translational Rheumatology.

Introduction

One of the main causes of chronic pain, physical disability, and a lower quality of life in middle-aged and older people worldwide is knee osteoarthritis (Hunter & Bierma-Zeinstra, 2019; Song et al., 2024). Osteoarthritis of the knee pathologically KOA is now considered to be a complex whole-joint disease with progressive extracellular matrix (ECM) erosion, subchondral bone sclerosis, low-grade synovial inflammation, subchondral bone marrow lesions, and meniscal degeneration rather than just a common wear-and-tear process of articular cartilage (Ji et al., 2019; Robinson et al., 2016). Short-term pain relief is the main goal of current conventional pharmacotherapies, which include acetaminophen, intra-articular corticosteroid injections, and (NSAIDs) non-steroidal anti-inflammatory medications (Hunter & Bierma-Zeinstra, 2019; Zhang et al., 2010Although such options are generally limited by systemic gastrointestinal, cardiovascular, and renal side effects during continuous use, and they frequently fail to stop structural joint degeneration (Ernst, 2002; Zhang et al., 2010). Therefore, finding efficient disease-modifying osteoarthritis medications (DMOADs) that maintain joint architecture continues to be a top priority in orthopedic research (Hunter & Bierma-Zeinstra, 2019; Karsdal et al., 2016).

Traditional Chinese Medicine (TCM) offers a rich repository of multi-component, multi-target therapeutic modalities (Sucher, 2006; Wang et al., 2020). Historically classified under the rubric of "Bi syndrome" (characterized by joint stiffness, pain, and qi/blood stagnation), TCM approaches KOA through holistic systemic regulation combined with local microenvironment modulation (Li & Zhang, 2019; Wang et al., 2020). Modern pharmacological investigations have increasingly confirmed that herbal formulations, classical decoctions, and purified botanical monomers (e.g., *icariin, curcumin, berberine, quercetin*) exert multi-faceted chondroprotective, anti-inflammatory, antioxidant, and anti-apoptotic properties (Li & Zhang, 2019; Wang et al., 2020; Zhou et al., 2020).

It takes rigorous, repeatable, and pathophysiologically relevant in vivo animal models to translate these plant remedies into evidence-based clinical treatments (Gregory et al., 2012; Little & Hunter, 2013). While every experimental strategy reflects different aspects of human KOA, from rapid post-traumatic cartilage erosion to chronic, age-dependent joint wear, choosing the right animal model is essential (Gregory et al., 2012; McCoy, 2015). This review gives a thorough examination of animal modeling techniques, describes the molecular pathways that TCM interventions target, offers a structured comparative table of preclinical dosing and results, critically assesses the quality of preclinical methodology and clinical trial data, and describes the translational difficulties associated with integrating TCM into contemporary clinical rheumatology

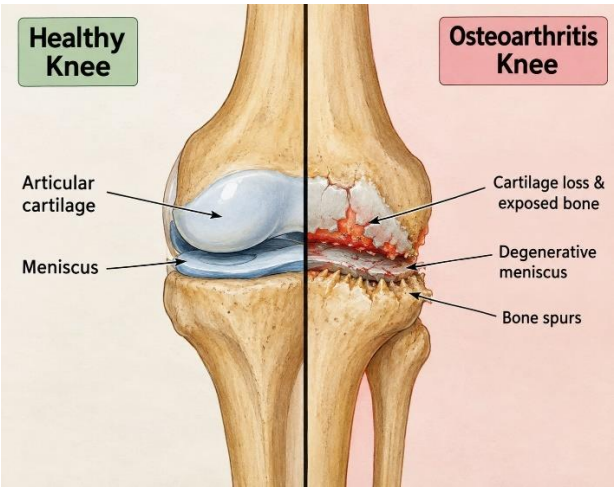


Figure 1. Comparison of healthy and osteoarthritic knee joints.

Methodology and Search Strategy

A systematic literature search was conducted using PubMed, Web of Science, EMBASE, and the China National Knowledge Infrastructure (CNKI) databases to find pertinent primary research and methodological literature published before late 2026. Medical Subject Headings (MeSH) and free-text phrases were merged in search strings such as ("knee osteoarthritis" OR "osteoarthritis, knee") AND ("animal model" OR "surgical model"). OR "MIA" OR "DMM" OR "ACLT") AND ("traditional Chinese medicine" OR "herbal medicine" OR "decoction" OR "monomer" OR "phytomedicine").

Inclusion criteria specified:

- Initial preclinical in vivo research using proven KOA animal models to assess TCM formulations, botanicals, or derived monomeric chemicals
- Methodological articles describing KOA animal modeling methods
- To evaluate translational alignment, clinical trials, systematic reviews, and meta-analyses examining TCM therapies in human KOA
- Peer-reviewed journal articles with precise methodological guidelines, dosage recommendations, and measurable structural or biochemical results.

Exclusion criteria comprised:

- Exclusively in vitro cell research without animal validation in vivo
- Research without appropriate control groups or precise dosage instructions
- Non-peer-reviewed commentary, editorials, and conference abstracts.

This review analyzed and synthesized 45 primary research articles, systematic reviews, and methodological benchmark publications.

Comprehensive Overview of KOA Animal Models

Animal models are essential for understanding the pathophysiology of KOA and assessing new treatment options (Gregory et al., 2012; Little & Hunter, 2013). Physiological relevance, model reproducibility, experimental schedule, and cost must all be carefully considered when choosing a model (McCoy, 2015; Percie du Sert et al., 2020).

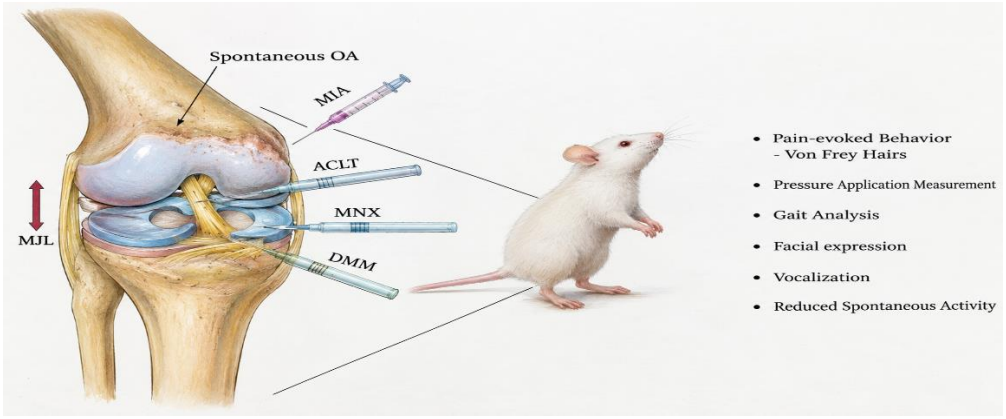


Figure 2. Experimental models of osteoarthritis and pain assessment methods.

Classification and Characteristics of KOA Animal Models

Preclinical models are essential for mapping disease pathways and assessing novel therapeutics. The model chosen will depend on whether the study aims to evaluate rapid pain responses, long-term age-related degeneration, or acute post-traumatic change

Model Category	Specific Model	Primary Mechanism	Key Advantages	Limitations
Surgical	ACLT / DMM	Mechanical instability & post-traumatic OA	Predictable progression; closely mimics human trauma	Requires surgical skill; localized to traumatic OA
Chemical	MIA Injection	Chondrocyte metabolic inhibition & rapid cell death	Rapid onset; excellent for pain/analgesic testing	Severe, non-physiological chemical destruction
Spontaneous	Hartley Guinea Pigs	Natural, age-dependent joint wear	High physiological relevance to primary human KOA	High housing costs; lengthy study duration

Table 1. Comparison of animal models of knee osteoarthritis.

Surgical Models (Post-Traumatic Osteoarthritis)

Through acute structural instability or altered weight-bearing distribution, surgical models impair joint mechanics and cause post-traumatic osteoarthritis (PTOA), (Gregory et al., 2012; Hayami et al., 2006).

Anterior Cruciate Ligament Transection (ACLT)

Anteroposterior instability results from the surgical removal of the anterior cruciate ligament in ACLT (Hayami et al., 2006; Bendele, 2001). Within 4-8 weeks following surgery, this mechanical destabilization causes low-grade synovial inflammation, osteophyte production, subchondral bone remodeling, and progressive localized cartilage loss (Bendele, 2001; Stoop et al., 2001). ACLT is frequently used in research with rats, rabbits, and dogs (Hayami et al., 2006; Stoop et al., 2001). However, compared to primary human KOA, the joint deterioration might be quite severe and quick (Gregory et al., 2012; Bendele, 2001).

Destabilization of the Medial Meniscus (DMM)

DMM causes mild medial meniscal displacement by surgically transecting the medial meniscotibial ligament (MMTL), (Glasson et al., 2007; Culley et al., 2015). The sluggish progression of human PTOA is mirrored in the gradual, very repeatable illness course that DMM produces in mouse models (Glasson et al., 2007; Loeser et al., 2013). Because of its consistency and minimal background variability, DMM is frequently used for mice genetic knockouts; yet, it necessitates excellent surgical precision under magnification (Culley et al., 2015; Loeser et al., 2013).

Medial Meniscectomy (MMX) and Partial Meniscectomy

Peak mechanical contact stresses on the medial tibial plateau are significantly increased by direct excision of the medial meniscus, whether complete or partial (Janusz et al., 2002; Kamekura et al., 2005). MMX is helpful for short-term intervention screening in rats and rabbits because it quickly speeds up articular cartilage fibrillations and subchondral bone sclerosis (Janusz et al., 2002; Appleyard et al., 2003).

Ovariectomy (OVX) Combined with Joint Injury

Surgical ovariectomy is paired with modest joint instability (such as a meniscal rupture or ACLT) to simulate postmenopausal osteoarthritis (Hoegh-Andersen et al., 2004; Sniekers et al., 2008). Systemic estrogen deficiency increases cartilage loss and speeds up subchondral bone turnover, offering a unique setting for researching postmenopausal KOA treatments (Hoegh-Andersen et al., 2004; Ma et al., 2007).

3.2 Chemically Induced Models

Toxic or enzymatic substances are injected intra-articularly in chemical models to interfere with chondrocyte metabolism or matrix structural integrity (Gregory et al., 2012; Guingamp et al., 1997).

Monosodium Idoacetate (MIA)

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity in chondrocytes is inhibited by intra-articular MIA injection, which suppresses glycolysis and causes fast chondrocyte death (Guingamp et al., 1997; Combe et al., 2004). MIA causes strong neurogenic inflammation, subchondral bone exposure, and widespread dose-dependent cartilage necrosis (Combe et al., 2004; Li et al., 2021). MIA is frequently used to screen for analgesic drugs and anti-inflammatory natural items because of its quick onset, predictability, and noticeable pain behavior, even though it does not reflect the mechanical etiology of primary human KOA. (Guingamp et al., 1997; Li et al., 2021).

Papain and Collagenase Injections

Proteolytic enzymes (such as papain or bacterial collagenase) administered intra-articularly break down type II collagen fibers and proteoglycans in the articular cartilage matrix (van der Kraan et al., 1990; Murat et al., 2007). Enzymatic models are appropriate for the short-term assessment of matrix-protective phytomedicines because they cause fast cartilage breakdown without necessitating surgical entrance (van der Kraan et al., 1990; Zheng et al., 2019).

Spontaneous, Genetic, and Aging Models

Hartley Guinea Pigs

In terms of histological progression, subchondral bone sclerosis, and biomarker expression, Dunkin-Hartley guinea pigs spontaneously develop age-dependent KOA that closely mirrors primary human osteoarthritis (Bendele & Hulman, 1988; Xu et al., 2021). Joint lesions often appear at 6 months of age and worsen over the course of 12 to 18 months (Bendele & Hulman, 1988; Huebner et al., 2002). Hartley guinea pigs are a useful model for assessing non-traumatic, age-related primary KOA interventions despite their high housing expenses and lengthy delays (Xu et al., 2021; Huebner et al., 2002).

Transgenic and Knockout Mouse Models

Molecular cascades can be precisely dissected using genetically modified mice (e.g., inducible chondrocyte-specific knockouts) (Little et al., 2009; Glasson et al., 2005). Knockout strains clarify whether particular TCM drugs depend on parallel functioning processes or target specific molecular pathways (Glasson et al., 2005; Tan et al., 2020).

Less Common and Emerging Models

Non-Human Primates (NHPs)

As they age, cynomolgus monkeys and rhesus macaques spontaneously develop KOA (Chateauvert et al., 1989; Zhang et al., 2022). NHPs and humans are quite similar in terms of anatomy, biomechanics, and genetics (Chateauvert et al., 1989). NHP models have been used in recent research to investigate systemic gut-joint axis changes and cutting-edge biotherapies (Zhang et al., 2022; Pritzker & Chateauvert, 1992). However, NHP use is limited to specialist late-stage translational research due to ethical concerns, long life spans, and significant financial expenditures (Chateauvert et al., 1989; Pritzker & Chateauvert, 1992).

Large Animal Models

Compared to small rodents (less than 0.1 mm in mice), large animals (Dogs, Sheep, Goats, and Horses) offer joint sizes and articular cartilage thicknesses (1-3 mm) that are significantly closer to humans (Gregory et al., 2012; Aigner et al., 2010). For assessing intra-articular injections, hydrogel delivery systems, surgical cartilage repair, and biomechanical load restoration, canine ACLT or caprine meniscectomy models are useful (Aigner et al., 2010; McIlwraith et al., 2012).

Strenuous Exercise and Mechanical Overload Models

Rodents' knee joints are repeatedly impacted by high-intensity, extended treadmill jogging, which causes low-grade cartilage wear, chondrocyte microtrauma, and increased intra-articular inflammatory cytokines (Pap et al., 1998; Poulet et al., 2011). This non-invasive model is perfect for researching joint weariness brought on by exercise and early preventative measures (Pap et al., 1998; Ni et al., 2014).

Pharmacological Mechanisms of TCM Interventions in KOA

Key pathological processes implicated in joint degradation are modulated by TCM therapies through multi-component, multi-target networks (Wang et al., 2020; Sucher, 2006)

TCM multi-Target Pathomechanisms

Anti-Inflam (NF-κB/MAPK)	ECM Anabolic Preservation	Apoptosis & ROS Defenses	Subchondral Bone Remodel

Downregulation of Inflammatory Pathways and Cytokine Cascades

One of the main causes of KOA development is synovial inflammation (Ji et al., 2019; Robinson et al., 2016). Nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling cascades are triggered when pro-inflammatory cytokines, mainly interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), bind to chondrocyte cell-surface receptors (Robinson et al., 2016; Wang et al., 2020). Inflammatory mediators such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), prostaglandin E2 (PEG-2), and nitric oxide (NO) are

upregulated when these pathways are activated (Wang et al., 2020; Zhou et al., 2020).

Phosphorylation is suppressed by TCM formulations (like *Du-Huo-Ji-Sheng-Tang, Juan-Bi-Tang*) and monomers (like *berberine, curcumin, and quercetin*), which prevents NF-κB p65 nuclear translocation and downregulates the expression of downstream catabolic genes (Wang et al., 2020; Chen et al., 2017; Zhang et al., 2019).

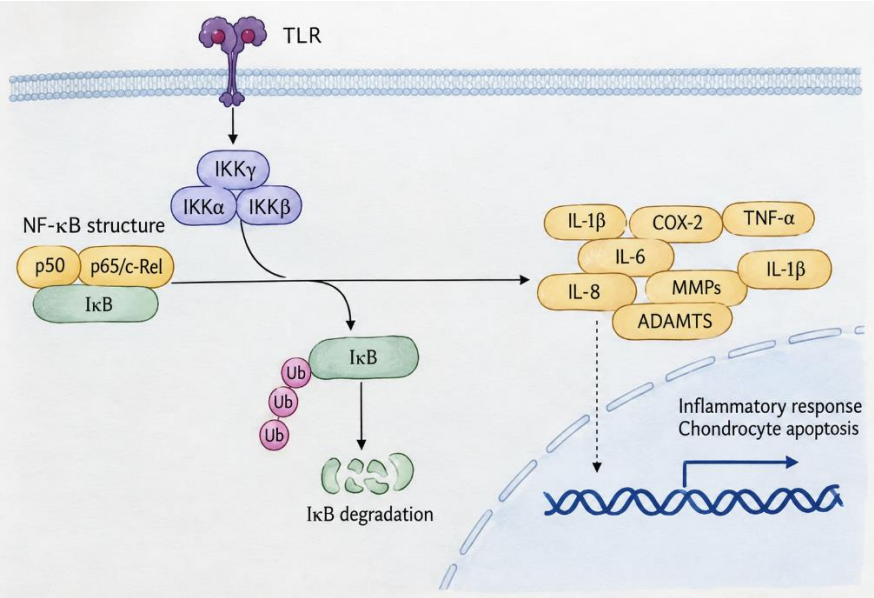


Figure 3. NF-κB signaling pathway in osteoarthritis.

Regulation of Extracellular Matrix (ECM) Synthesis and Degradation

The homeostatic balance between catabolic enzyme degradation and anabolic ECM synthesis is essential for cartilage integrity (Ji et al., 2019; Troeberg & Nagase, 2012). Major catabolic enzymes that break type II collagen and aggrecan include matrix metalloproteinase-13 (MMP-13), MMP-3, and a disintegrin and metalloproteinase with thrombospondin motifs 4 and 5 (ADAMTS-4/5) (Troeberg & Nagase, 2012; Fosang & Little, 2008).

TCM treatments increase the expression of collagen type II and aggrecan by upregulating anabolic transcription factors, particularly SRY-box transcription factor 9 (SOX9) (Wang et al., 2020; Liu et al., 2020). Concurrently, substances like icariin and baicalin modulate the TGF-β/Smad and Wnt/β-catenin signaling pathways to downregulate MMP-13 and ADAMTS-5 levels (Liu et al., 2020; Chen et al., 2018).

4.3 Suppression of Chondrocyte Apoptosis and Oxidative Stress

DNA damage, caspase-dependent apoptosis, and chondrocyte mitochondrial dysfunction are all driven on by excessive intra-articular reactive oxygen species (ROS) (Blanco et al., 2011; Qiu et al., 2018). Loss of chondrocytes impairs cartilage's ability to regenerate itself (Ji et al., 2019; Blanco et al., 2011).

The nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant pathway is activated by bioactive monomers (such as *resveratrol, astragalin, and epimedium flavonoids*), increasing the activity of superoxide dismutase (SOD) and reducing the buildup of malondialdehyde (MDA) (Qiu et al., 2018; Lei et al., 2017). Furthermore, TCM drugs maintain chondrocyte survival by upregulating anti-apoptotic Bcl-2 and decreasing pro-apoptotic Bax and caspase-3 expression (Lei et al., 2017; Zhang et al., 2018).

4.4 Subchondral Bone Remodeling and Microvascular Homeostasis

Joint pain and structural deterioration are largely caused by subchondral bone turnover, microfractures, and abnormal H-type vascular angiogenesis (Li et al., 2013; Hu et al., 2021). The RANKL/RANK/OPG signaling pathway is modulated by traditional TCM formulae that target "Kidney-nourishing" qualities (such as *You-Gui-Wan and Shen-Qi-Wan*), preventing excessive osteoclastogenesis and lowering subchondral bone turnover (Hu et al., 2021; Zhang et al., 2019). The normal biomechanical load distribution over the articular cartilage above is maintained by this microstructural stability (Li et al., 2013; Zhang et al., 2019).

4.5 Regulation of Non-Coding RNAs and Epigenetics

Recent research emphasizes the part long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) play in the pathophysiology of osteoarthritis (Endisha et al., 2018; Zu et al., 2019). It has been demonstrated that some TCM substances alter functional miRNA networks (Endisha et al., 2018). For example, *icariin* suppresses the translation of ADAMTS-5 by upregulating miR-140, a chondrocyte-

protective miRNA (Zu et al., 2019; Miyaki et al., 2010). By downregulating miR-34a, other botanical extract monomers reduce inflammatory signals and chondrocyte senescence (Endisha et al., 2018; Abou-heif et al., 2020).

5. Comprehensive Summary of TCM Formulas and Bioactive Compounds

The fundamental preclinical studies assessing significant TCM classical formulations, herbal extracts, and pure monomeric chemicals across several KOA animal models are summarized in the following structured table, which also includes information on particular dose, administration routes, and important measurable outcomes.

Compound	Animal Model	Species & Sample Size	Dosing Regimen & Route	Quantitative Outcomes & Biological Mechanisms	Reference
Juan-Bi-Tang (JBT)	DMM	Male C57BL/6 Mice (*n*=36)	1.5 g/kg/day or 3.0 g/kg/day gavage for 6 weeks	Lowered Mankin scores; decreased serum PGE2 and COMP; inhibited MAPK (p38/JNK) phosphorylation in articular cartilage.	Wang et al. (2020); Zhang et al. (2019)
Shen-Tong-Zhuan-Tong-San	MIA	Male Sprague-Dawley Rats (*n*=30)	3.2 g/kg/day gavage for 4 weeks	Reduced mechanical allodynia and thermal hyperalgesia; downregulated spinal cord c-Fos and synovial COX-2 expression.	Li et al. (2021)
Icariin	DMM	Male C57BL/6 Mice (*n*=40)	10 mg/kg/day or 20 mg/kg/day IP injection for 8 weeks	Prevented cartilage matrix degradation; upregulated miR-140; inhibited ADAMTS-5 and MMP-13 expression in chondrocytes.	Zu et al. (2019)
Curcumin	ACLT	Male Sprague-Dawley Rats (*n*=36)	50 mg/kg/day or 100 mg/kg/day gavage for 8 weeks	Decreased OARSI score; inhibited NF-κB p65 nuclear translocation; reduced caspase-3 apoptotic cells in cartilage.	Zhang et al. (2018)
Berberine	MIA	Male Wistar Rats (*n*=32)	20 mg/kg/day or 50 mg/kg/day gavage for 4 weeks	Significantly reduced weight-bearing asymmetry; suppressed intra-articular IL-1, TNF-α, iNOS, and NO production.	Zhou et al. (2020)
Quercetin	MMX	Male Sprague-Dawley Rats (*n*=35)	25 mg/kg/day or 50 mg/kg/day gavage for 6 weeks	Protected chondrocyte mitochondria; activated Nrf2/HO-1 pathway; decreased MDA and elevated SOD activity.	Qiu et al. (2018)
Resveratrol	ACLT	Male New Zealand White Rabbits (*n*=24)	10 μmol/L Intra-articular injection weekly for 6 weeks	Prevented chondrocyte apoptosis; upregulated SIRT1 expression; suppressed p53 and Bax acetylation in articular cartilage.	Lei et al. (2017)
Baicalin	DMM	Male C57BL/6 Mice (*n*=30)	30 mg/kg/day IP injection for 6 weeks	Decreased subchondral bone loss and cartilage erosion; downregulated Wnt/β-catenin pathway targets (Cyclin D1, *c*-Myc).	Liu et al. (2020)
Paeoniflorin	Papain injection	Male Sprague-Dawley Rats (*n*=30)	20 mg/kg/day or 40 mg/kg/day gavage for 4 weeks	Reduced synovial inflammatory cell infiltration; decreased serum TNF-α and IL-6; inhibited p38 MAPK pathway.	Zheng et al. (2019)
Astragalin	MIA	Male C57BL/6 Mice (*n*=32)	10 mg/kg/day or 20 mg/kg/day IP injection for 4 weeks	Attenuated MIA-induced joint pain; suppressed NF-κB activation; decreased MMP-1 and MMP-13 gene expression.	Tan et al. (2020)

Compound	Animal Model	Species & Sample Size	Dosing Regimen & Route	Quantitative Outcomes & Biological Mechanisms	Reference
Naringin	Hartley Guinea Pigs	Male Guinea Pigs (*n*=20)	40 mg/kg/day gavage for 12 weeks	Delayed spontaneous cartilage degeneration at 9 months of age; elevated Collagen II staining; reduced subchondral sclerosis.	Xu et al. (2021)
Ginsenoside Rb1	ACLT	Male Wistar Rats (*n*=36)	10 mg/kg/day or 20 mg/kg/day gavage for 8 weeks	Inhibited chondrocyte pyroptosis; downregulated NLRP3 inflammasome activation, caspase-1, and IL-18 cleavage.	Sun et al. (2021)

Table 2. Natural compounds and their therapeutic effects in experimental osteoarthritis models.

Clinical Evidence and Human Translation

Thorough analysis of synthesis information from clinical trials, randomized controlled trials (RCTs), and systematic reviews is necessary to determine whether preclinical animal findings translate to human treatment efficacy (Chen et al., 2016; Yang et al., 2017).

Clinical Translation Landscape

Demonstrated Clinical Benefits	**Clinical Limitations**
Lower WOMAC Pain NSAID-Sparing effects High Safety Profile Improved Mobility	Short Follow-up Periods (<12 weeks) Small RCT Sample Sizes Blinding Hurdles

Clinical Trial Outcomes

In patients with primary KOA, several double-blind, randomized controlled clinical trials have assessed traditional TCM formulations (Chen et al., 2016; Wang et al., 2018). When compared to placebo or baseline, traditional decoctions, most notably *Du-Huo-Ji-Sheng-Tang* (DHJST), have shown statistically significant improvements in functional mobility scores and reductions in the pain and stiffness subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Chen et al., 2016; Teekachunhatean et al., 2004).

Oral TCM decoctions often show synergistic effects when used in addition to standard conservative therapy (such as physical therapy or oral NSAIDs), increasing global clinical response rates and decreasing NSAID dependence (Chen et al., 2016; Wang et al., 2018).

Systematic Reviews and Meta-Analyses

Chinese herbal medication offers clinical benefits for managing KOA symptoms, especially with regard to pain alleviation, joint swelling decrease, and functional recovery, according to summaries of systematic reviews (Yang et al., 2017; Liu et al., 2021). Importantly, adverse event rates are similar to or lower than those of oral NSAID control groups, according to clinical safety analyzes, indicating a positive safety profile (Yang et al., 2017). Minor gastrointestinal discomfort (such as moderate nausea and loose stools) that goes away with dose adjustment is the most commonly reported mild side effect (Chen et al., 2016; Yang et al., 2017).

Translational Gaps

The quality of data across clinical trials is still inconsistent despite a favorable clinical signal (Yang et al., 2017; Zhang et al., 2015). A large portion of the current clinical evidence is categorized as "low" to "moderate" quality based on GRADE criteria ratings (Yang et al., 2017). Main clinical limitations include:

- Single-center trials with small sample sizes.
- Insufficient double-blinding descriptions (because of different herbal scents and tastes).
- Short follow-up periods (usually 4-12 weeks), which are inadequate to demonstrate actual disease-modifying cartilage preservation in human subjects (Yang et al., 2017; Zhang et al., 2015).

Limitations

There are a number of intrinsic difficulties in connecting preclinical animal models with clinical rheumatology:

Anatomical and Biomechanical Discrepancies: When compared to bipedal humans, quadrupedal animals have very different joint biomechanics, cartilage thicknesses (<0.1 mm in mice vs. 2-3 mm in humans), and load distribution patterns (Gregory et al., 2012; McCoy, 2015). The restricted ability of human articular cartilage to regenerate may not be fully reflected in the rapid cartilage repair seen in small rodents (McCoy, 2015; Aigner et al., 2010).

Etiological Disconnect in Chemical Models: Within days, chemically generated models such as MIA result in acute neurogenic pain and fast, severe chondrocyte necrosis (Guingamp et al., 1997; Combe et al., 2004).

The gradual, low-grade inflammatory and biomechanical etiology typical of primary human KOA is circumvented by this rapid chemical injury (Guingamp et al., 1997; Yang et al., 2017).

Complex Herbal Formulations: Numerous active phytochemicals can be found in traditional TCM decoctions (Sucher, 2006; Heinrich et al., 2020). It is still technically difficult to pinpoint the exact bioavailable metabolites that enter the intra-articular joint region following oral consumption (Heinrich et al., 2020).

Poor Oral Bioavailability of Pure Monomers: When taken orally, purified monomeric substances (such as quercetin, resveratrol, and curcumin) often have low intra-articular bioavailability, quick systemic metabolism, and poor aqueous solubility (Wang et al., 2020; Lei et al., 2017). Overcoming pharmacokinetic barriers requires the development of tailored delivery technologies, such as intra-articular injectable hydrogels, liposomes, or polymeric nanoparticles (Wang et al., 2020; Evans et al., 2018).

Future Research Directions

Future studies should concentrate on five key areas in order to get over present translational obstacles and establish TCM as an evidence-based DMOAD option:

Adoption of Standardized Quality and Reporting Guidelines: To ensure batch reproducibility, preclinical animal research should strictly adhere to ARRIVE principles and report complete HPLC/LC-MS chemical fingerprints of herbal decoctions (Percie du Sert et al., 2020; Heinrich et al., 2020).

Integration of Advanced Omics and Systems Biology: High-resolution mapping of how TCM formulae affect particular chondrocyte subpopulations, synovial macrophages, and subchondral bone osteoblasts will be possible through the use of single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and metabolomics (Ji et al., 2019; Endisha et al., 2018).

Development of Biomimetic Nanocarriers: By extending the intra-articular retention period of pure botanical monomers, intra-articular drug delivery platforms-such as temperature-sensitive hydrogels, hyaluronic acid conjugates, and exosome-based vehicles-can maximize local therapeutic concentrations while preventing systemic toxicity (Wang et al., 2020; Evans et al., 2018).

Standardization of Preclinical Animal Selection: When using an animal model, researchers should consider certain therapeutic processes (e.g., using DMM for delayed matrix erosion, MIA for pain and neuro-inflammation, or OVX+ACLT for postmenopausal subchondral bone loss) (Gregory et al., 2012; Guingamp et al., 1997).

Rigorously Designed, Long-Term Clinical Trials: To demonstrate actual disease-modifying joint preservation in people, multi-center, large-scale, double-blind RCTs with longer follow-up periods (12-24 months) incorporating quantitative MRI joint structural assessments (e.g., cartilage volume, bone marrow lesion score) are required (Chen et al., 2016; Yang et al., 2017).

Conclusion

For understanding the pathophysiology of knee osteoarthritis and assessing new treatment options, in vivo animal models continue to be essential resources. Non-traumatic aging models (Hartley guinea pigs) best represent chronic primary human KOA, but surgically induced models (ACLT, DMM) successfully capture post-traumatic joint mechanics and chemical models (MIA) offer quick platforms for pain screening. A comprehensive, multi-target treatment approach is provided by traditional Chinese medicine, which can suppress chondrocyte death, maintain extracellular matrix integrity, downregulate inflammatory cascades, and stabilize subchondral bone remodeling. Research at the nexus of TCM and contemporary rheumatology holds great promise for providing efficient disease-modifying treatments for knee osteoarthritis by fusing standardized animal modeling techniques with biomimetic delivery systems, cutting-edge omics technology, and superior clinical trial designs.

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