Review

A Brief Review of Drugs and Supplements Testing in Induced Osteoarthritis Murine Models: Methodologies and Findings

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ABSTRACT: Knee osteoarthritis (OA) is a complex, progressive disorder that involves the gradual breakdown of articular cartilage, alteration of the subchondral bone, synovial inflammation, and joint space limitation, ultimately leading to stiffness, pain, and impaired balance and mobility. At this moment there is no cure to stop the evolution of the disease, only symptomatic treatment. This fact is due to the lack of understanding of the underlying mechanisms, thus limiting the possibilities of developing disease-modifying drugs. This challenge arises from an incomplete understanding of the underlying mechanisms of disease, which limits the development of effective disease-modifying drugs due to the fact that human tissue samples are typically obtained in the advanced stages of the disease, usually when the patient is subjected to joint replacement surgery, making the study of early OA stages more difficult. For researchers, the murine animal model provides a useful tool for assessing the full evolution of the pathology and the study of the efficacy and safety of novel experimental drugs and supplements. The aim of our review is to present the diverse currently used murine models ranging from spontaneous to chemically and surgically induced OA and pharmacological results that were obtained on such models and are available for human use or represent a potential innovative therapy in the near future.

KEYWORDS: *Osteoarthritis, murine models, rat models, osteoarthritis therapy, pharmaceutical supplements.*

Introduction

Osteoarthritis (OA) is regarded as one of the most common rheumatic conditions.

Epidemiological studies have indicated that approximately one-third of the adult population presents radiological evidence of OA in joints such as the hand, knee, or hip.

The knee joint is the most frequently affected site, with OA prevalence rising progressively with advancing age [1].

Although knee OA was considered solely as a "wear-and-tear" condition of the articular cartilage due to aging, the underlying pathological implications are not yet fully understood, multiple factors such as inflammation, biomechanical changes, family history, innate immunity, trauma, and infections have also been incriminated in the evolution of the disease [2].

From a clinical standpoint, patients exhibit progressive joint stiffness, pain swelling, and restricted mobility which may lead to physiological and functional alterations that result in weakness, imbalance, and inability to fulfill activities of daily living [3].

In the initial stage of the disease, the articular cartilage exhibits focal fibrillation in regions subjected to maximal loading.

Chondrocytes, the only type of cells present at this level, undergo proliferation and hypertrophy in order to promote matrix synthesis while also releasing inflammatory mediators which further accelerates cartilage alterations.

With the progression of OA, significant matrix degradation takes place as proinflammatory cytokines continuously drive protease production.

These cytokines activate chondrocytes to release other additional cytokines and proteases, self-maintaining the process through autocrine and paracrine signaling mechanisms.

Chondrocyte apoptosis occurs in the later stages and results in an imbalance between the catabolism and synthesis of proteoglycans and collagen [4,5].

As a result, sulfated polysaccharides and cartilage fragments that stimulate synovial inflammation are released into the joint affecting other joint structures [5,6].

As the disease advances, it leads to the development of deep fissures and delamination in

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the cartilage, revealing the underlying calcified cartilage and subchondral bone.

The calcified cartilage region expands into the overlying hyaline cartilage, causing the duplication of the tidemark.

The process is initiated by the invasion of blood vessels and nerves, both sensory and sympathetic, into the osteochondral junction.

This leads to an alteration of the osteocyte canalicular network in the subchondral bone, resulting in osteocyte apoptosis.

Furthermore, osteophytes develop at the joint edges, and cysts form within the subchondral bone [7].

OA treatment is mainly symptomatic due to a lack of understanding of the underlying mechanisms thus limiting the possibilities of developing disease-modifying drugs.

Human tissue samples are usually collected through biopsy in advanced stages, usually during joint replacement surgery, making the study of early OA difficult.

As a result, researchers use preclinical *ex-vivo* and *in-vivo* animal models to examine early pathological changes.

Existing *ex-vivo* models do not account for the crucial inter-tissue interactions required for disease progression, and the variability in anatomy, size, biomechanics, and histology across animal models hinders their translation to human systems. [8].

Current OA research predominantly utilizes in vivo models, which provide a clear framework for defining disease susceptibility and progression, and they are instrumental in identifying the etiological factors driving OA.

The knowledge derived from these preclinical studies is crucial for developing early-stage therapeutic interventions [9].

Although there are minor structural and range-of-motion differences, joint anatomy remains highly conserved across animal species and humans.

The rat is extensively utilized in OA research due to its diverse modeling options, practical handling, and limited spontaneous cartilage degeneration associated with age.

Chemically induced models, such as monosodium iodoacetate (MIA), are frequently employed in rats to assess the analgesic and anti-inflammatory properties of potential OA therapies, rendering the rat an ideal model for comprehensive toxicity and efficacy studies [10].

By using the rat for inducing experimental models of OA, distinct biological pathways have been evaluated in order to find effective drugs or pharmaceutical supplements.

Among the studied therapies, traditional drugs such as anti-inflammatory agents, pharmaceutical supplements, and newer-designed drugs targeting OA mediators have shown promising results [11].

The aim of this study is to present the various types of murine models of knee osteoarthritis (OA) and the drugs and pharmaceutical supplements tested for their therapeutic potential.

Material and Methods

To review the current literature on various OA murine models and the drugs and supplements tested on them, articles of all types, involving animals, as well as human subjects or cell cultures, and published in English, were analyzed.

The databases explored included PubMed, Google Scholar, ScienceDirect, Scopus, and Springer Link, using combinations of relevant keywords such as "osteoarthritis," "OA murine models," "cartilage degeneration," "synovial inflammation," "analgesic treatment," "chondroprotective agents," and "OA dietary supplements."

From a total of sixty studies concerning animal models of OA, after applying the exclusion/inclusion criteria (Figure 1) twenty-five studies were defined as eligible to the scope of our study.

Similarly, fourteen studies were included in our review, from a total of forty-five that were analyzed, considering the exclusion/inclusion criteria.

Our focus concerned papers that provided insights into the development and progression of OA in murine models, as well as the therapeutic effects of various drugs and new potentially efficient supplements tested on these models.

This literature review aimed to address the following research questions: “What are the advantages and disadvantages of using the murine OA model?”, “Which are the main models used for inducing OA in murine?”, “What is the current understanding of these models’ effectiveness in drug and new supplement testing?” and “What is known about the mechanisms by which tested drugs and supplements influence OA symptoms or progression in these models?”

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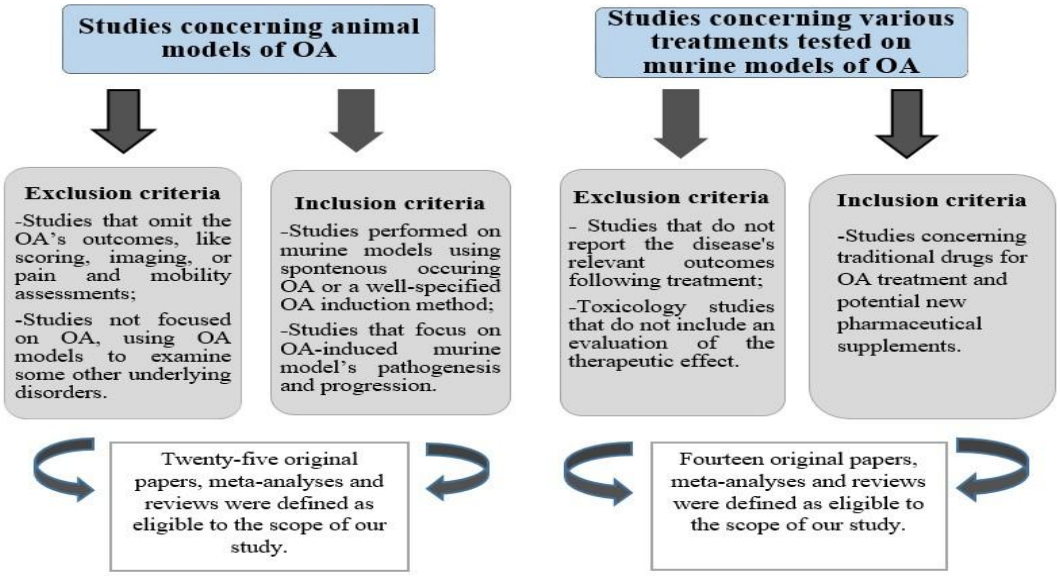


OA=Osteoarthritis

Figure 1. Flowchart of the exclusion and inclusion criteria for studies defined as eligible to the scope of our study.

The search, conducted between August and November 2024, provided an overview of the experimental approaches and outcomes related to OA treatment strategies in animal models, highlighting the value of these models in understanding OA pathology and therapeutic interventions.

Various types of murine models used to assess OA

The initial models were developed primarily to investigate the structural aspects of OA, particularly cartilage degeneration, rather than its symptomatic manifestations.

The use of animal models in disease research addresses challenges that arise when studying human subjects.

However, rodent models have certain limitations.

These include variables such as sex and age differences, as well as translational limitations, including differences in weight-bearing, articular cartilage physiology, and gait patterns compared to humans.

Despite these challenges, animal models remain one of the most valuable research perspectives, providing critical insights into the molecular mechanisms underlying OA progression and development [12].

Some advantages and disadvantages of these models are presented in Table 1.

Table 1. An overview of the main advantages and disadvantages of using an animal model of OA [13].

Advantages of using animal models of OA	Disadvantages of using animal models of OA
• Tissue samples can be collected across various stages of the disease, allowing a detailed analysis of OA development and the effectiveness of potential treatments at different points in disease progression.	• There are biomechanical differences between human and animal joints, alongside species-specific variations in cartilage repair processes and thickness, which may limit the accuracy of findings.
• Researchers can precisely determine the onset of OA or identify specific initiating events, enabling a clearer understanding of disease progression.	• The rapid OA progression observed in smaller animals can lead to misleading drug efficacy results.
• Genetic models offer insights into the role of particular genes and molecular pathways involved in OA.	• Differences in species, age, OA induction methods, and drug delivery further complicate model comparisons, making it challenging to standardize findings across studies.
• These models allow control over causative and environmental factors, contributing to consistent phenotypic outcomes with expected molecular responses to experimental treatments.	• Early-stage OA lacks clear symptoms, complicating detection and measurement, while diverse symptoms like pain, limping, and joint stiffness vary between cases, and symptom severity often does not correlate with OA progression.

OA=Osteoarthritis

Murine models of OA are generally categorized into three types: **spontaneous**, **chemically induced**, and **surgically induced**.

Each of these models has distinct characteristics that allow researchers to explore different aspects of OA pathology and potential therapeutic strategies [8].

Spontaneous OA naturally develops in the knee joints of various mouse strains.

Additionally, mutant and transgenic mouse models have been discovered and thoroughly characterized.

This type of OA has also been observed in other species, including Syrian hamsters, guinea pigs, and nonhuman primates.

In these animals, both naturally occurring and transgenically induced OA progress slowly, resulting in longer timelines for drug testing and studies on disease evolution.

However, the pathology and pathogenesis observed, particularly in spontaneous models, are likely similar to those found in the most common, slowly progressive forms of human OA [14].

Moreover, these models necessitate extended development periods and exhibit increased variability in outcomes, resulting in higher study costs associated with prolonged animal housing and the potential need for larger sample sizes to attain sufficient statistical power.

Rats are generally considered less suitable as models for the study of naturally occurring OA, as they exhibit a limited tendency to develop spontaneous OA [15].

Rodent and rabbit models are characterized by spontaneous intrinsic cartilage healing, a phenomenon not observed in larger animal models or humans.

Additionally, rodents maintain open physes and continue endochondral ossification throughout their lifespan [16].

A study that investigated cartilage degeneration in Wistar and Fischer 344 rats found that young adult Wistar rats exhibited minimal cartilage degeneration in the knees, while aged rats of the same strain showed a higher incidence of lesions, ranging from mild superficial staining loss to more severe damage, including frayed, fibrillated cartilage and chondrocyte loss.

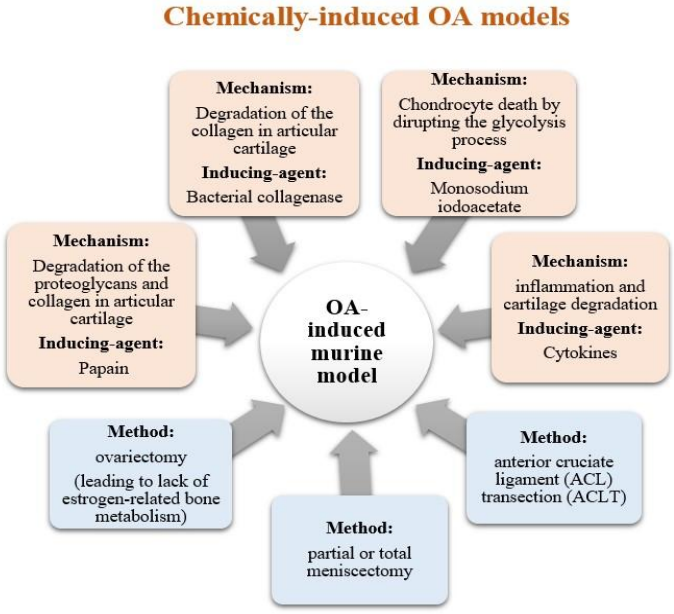
In contrast, the Fischer 344 strain displayed more frequent and severe lesions, with all young adults showing some degree of degeneration.

Aged Fischer 344 rats had more advanced lesions than their Wistar counterparts.

Although the severity of the lesions did not reach end-stage OA levels seen in humans, both strains proved useful for studying age-related cartilage degeneration.

Wistar rats, with milder, later-onset degeneration, are suitable for prophylactic studies, while Fischer 344 rats, which develop earlier and more severe degeneration, are better suited for therapeutic intervention and cartilage repair studies [17].

However, the chemically and surgically-induced OA models have a more precise and impressive mechanism or method (Figure 2).



OA=Osteoarthritis

Figure 2. Mechanisms or methods of chemically and surgically-induced OA murine models.

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Chemical-induced OA models utilize intra-articular injections of various destabilizing agents, usually delivered through the patellar ligament.

These agents include iodoacetate, papain, collagenase, steroids, cytokines, and immunotoxins [8,12].

Chemical models of OA exhibit a distinct pathophysiological mechanism and differ significantly from post-traumatic OA.

Furthermore, chemical models are less invasive than surgical models, and their ease of induction and high reproducibility make them especially suitable for short-term experimental studies [18].

Papain is a proteolytic enzyme that induces collagen and proteoglycan degradation, disrupting the integrity and microarchitecture of cartilage in affected joints.

At low doses, it rapidly generates osteoarthritis-like conditions, making it a suitable method for inducing OA in experimental models.

The histological lesions it produces closely resemble those observed in the early stages of natural osteoarthritis in humans [19].

Previous studies have demonstrated that a concentrated papain injection (0.2mL) can induce osteoblast activity, chondrocyte death, and fibrillation, within 5 days post-induction in the knee joints of mice.

After 14 days, total cartilage necrosis and osteophyte formation were recorded, with only a few remaining chondrocytes, while fibrillation and clustering became less frequent.

Another study performed on the same experimental model reported that 15 days post-injection, the joints exhibited an irregular surface, edema, fibrillation, and hypocellularity, with the degree of degeneration increasing over time, and more pronounced osteoarthritic alterations observed at 4 weeks [20].

Bacterial collagenase was first utilized for inducing an OA-induced model in a study that involved young C57BL/6 mice.

Although presented minimal cartilage lesions, this model caused joint destabilization by damaging surrounding structures, such as ligaments and menisci.

These changes eventually give rise to osteoarthritic conditions in the joints, closely mirroring the spontaneous osteoarthritis observed in C57BL/6 and other mouse strains.

The intra-articular administration of collagenase in young mice (10 weeks old) induces joint changes similar to those seen in spontaneous osteoarthritic older animals, but within a significantly shorter time frame of just a few weeks [21,22].

In a study employing an OA rabbit model, intra-articular injection of collagenase (0.5-2.0mg) induced dose-dependent OA-like changes, with 1.0mg being sufficient to maintain these changes for up to 6 weeks.

Unlike the higher doses of papain (4-12mg) typically used in similar models, collagenase required a lower dose to produce comparable effects.

This may be attributed to collagenase's greater substrate specificity for collagen, a primary cartilage component, making it potentially more effective than papain for inducing OA-like alterations [23].

Research conducted using rat models has demonstrated that the collagenase-induced OA model not only mimics the mechanistic interplay between inflammation and mechanical degradation but also shows critical characteristics of human OA.

These characteristics include cartilage degeneration, an increase in synovial lining cells, synovial fibrosis, and bone remodeling.

Additionally, by adjusting the dosage of a collagenase 290U/mg solution, the severity of the model can be easily influenced.

Doses of 500 and 1000 U typically result in a mild OA phenotype, while a more severe phenotype can be achieved by extending the duration of the experiment.

It is advisable to avoid doses exceeding 1000U, as they may cause significant adverse effects.

Even with a 1000U dose, the occurrence of early cartilage degeneration raises important questions regarding the model's relevance for studying OA [21].

One of the most commonly used models for studying OA is the monosodium iodoacetate (MIA) model in rats. MIA is administered through intra-articular injection, and it is an inhibitor of glyceraldehyde-3-phosphate dehydrogenase, therefore disrupting the glycolysis process.

This leads to chondrocyte death and triggers an inflammatory response characterized by the infiltration of immune cells, such as monocytes and neutrophils, peaking around day 3.

By day 7, the inflammation begins to subside, followed by progressive degradation of cartilage and subchondral bone.

The damage peaks between days 10 and 14, resulting in full-thickness cartilage damage,

formation of osteoclasts, and various vascular changes.

Low doses of MIA (0.1 or 0.2mg) cause reversible cartilage damage and synovitis, while higher doses (greater than 0.5mg) result in irreversible bone erosion.

An interesting observation is that for pain relief, a biphasic response is noted: non-steroidal anti-inflammatory drugs (NSAIDs) are effective in alleviating early inflammation, while later stages of neuropathic pain respond better to morphine or gabapentin.

This biphasic nature facilitates comprehensive pharmacological testing, making the model valuable for screening potential OA treatments [13,24-26].

A less commonly used model, likely due to its high cost, involves the use of cytokines.

Recombinant human TNF-alpha (rhTNFα), which closely resembles rat TNFα, has been reported to induce osteoarthritis (OA) in rat models.

Intra-articular injections of TNFα lead to a rapid but temporary degradation of cartilage proteoglycans, resulting in a mild and reversible OA effect.

This characteristic makes TNFα useful for quick in vivo screening of chondroprotective drugs.

Moreover, it's important to note that both TNFα and interleukin-1 beta (IL-1β) trigger inflammation and cartilage degradation in rats.

However, IL-1β is often favored because it also causes bone resorption and is generally considered to be more potent [27,28].

A common technique for inducing OA involves a surgical procedure in which a surgeon creates an injury, leading to the gradual development of OA in the targeted joint [29].

Surgical models offer the benefits of repeatability, along with a quick onset and progression of OA.

However, this rapid progression makes them less suitable as models for spontaneous OA.

Instead, these models are often viewed as better representations of post-traumatic osteoarthritis (PTOA) in humans, despite the accelerated disease progression, possibly due to continued use of the destabilized limb.

PTOA is a common result of joint injury, contributing to approximately 12% of all OA cases.

Trauma to joint structures, particularly involving anterior cruciate ligament (ACL) and/or meniscal tears or ruptures can alter the integrity of articular cartilage, initiating processes that typically lead to PTOA over a 10-to 15-year period.

The pathogenesis of PTOA is marked by progressive degeneration of articular cartilage and is further characterized by synovial inflammation, meniscal alterations, and associated bone remodeling [30].

Some argue that the rapid onset of lesions after surgery may reduce responsiveness to treatments, with certain models even recommending “pretreatment” with the desired therapeutic compound.

Additionally, responses to therapy can vary depending on the specific mechanism of injury [15].

Surgical-induced animal models for osteoarthritis have predominantly involved sheep, dogs, rabbits, and mice.

Common approaches include partial or total meniscectomy and anterior cruciate ligament (ACL) transection (ACLT), frequently applied in sheep, rabbits, and dogs.

More intensive models, though less commonly used, combine ligament injury with meniscectomy, particularly in rabbits [31].

The ACLT model was the first widely recognized and remains the most commonly used surgical model in OA research today.

The basis for using this model is that an ACL injury leads to joint instability, which then triggers the onset of PTOA.

This model replicates the degradation of articular cartilage secondary to ACL rupture.

Compared to meniscectomy, OA lesions in the ACLT model develop more gradually, making it more suitable for use in pharmaceutical studies.

The success of the procedure is typically assessed using the anterior drawer test [32].

The use of this method in the laboratory rat first implies anesthesia and placing the animal in a supine position.

Following the removal of the fur and local disinfection, a medial parapatellar incision is performed.

The patella is laterally displaced with the joint in hyperextension, and the ACL is transected with the knee flexed using micro scissors.

Subsequently, the joint is irrigated with sterile saline, the patella is repositioned, and both the capsule and skin are closed using absorbable and monofilament sutures, respectively.

In sham surgeries, only patellar luxation and saline irrigation are performed.

Postoperative analgesia should be provided [33].

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The use of medial meniscectomy in the laboratory rat implies performing a unilateral medial meniscal tear that rapidly produces cartilage degeneration characterized by proteoglycan and chondrocyte loss, osteophyte formation, and cell cloning.

The model involves severing the medial collateral ligament below its attachment point to the meniscus subsequently causing the shift of the meniscus toward the femur when the knee joint space is opened.

The incision is performed at the narrowest point of the meniscus without interfering with the tibial surface.

By 3-6 weeks post-surgery, tibial cartilage degeneration becomes severe in focal areas, with osteophyte formation and surrounding matrix alterations.

In order to do pharmaceutical testing, pre-dosing may be needed due to the rapid disease evolution.

Consistent surgical technique ensures reliable lesions, although the procedure is technically challenging due to the small joint space and highly vascularized tissue in the medial knee region [34].

More aggressive, though less commonly used, osteoarthritis models have been created by combining ligament injury with total meniscectomy in rabbits.

Regarding the use of this protocol on a laboratory rat, the experimental model requires a medial incision on the medial aspect of the knee joint.

Subsequent to the quadriceps muscle anterior retraction, the collateral ligament is exposed and transected approximately 3mm from the joint line and later retracted.

After the medial meniscus extraction, the ligament, quadriceps, and skin are sutured [31].

A meta-analysis of sixteen animal studies across various species which included rats, mice, guinea pigs, rabbits, sheep, and miniature pigs investigated the effects of ovariectomy (OVX), a procedure that replicates postmenopausal hormonal conditions (due to lack of estrogen-related bone metabolism), commonly used as a model for both osteoporosis and osteoarthritis.

While eleven studies demonstrated OVX-related impacts on cartilage-such as changes in mechanical properties, alterations in composition, and signs of deterioration, including erosion, fibrillation, and even complete cartilage loss-four studies reported no such effects.

Specifically, OVX did not alter OA severity scores or incidence in mice.

In STR/ort mice, which are prone to spontaneous OA, neither OVX nor orchiectomy (ORX) influenced OA development or the distribution of cleaved aggrecans.

It is important to mention that several of these studies used very young, sexually immature animals.

Additionally, in rabbits, OVX did not affect collagen content or glycosaminoglycan in knee cartilage, though this study only investigated short-term effects [35].

Drugs and novel pharmaceutical supplements tested in OA rat models

When it comes to drugs, paracetamol is one of the most administered painkillers in the world, in the mouse model proving an analgesic effect with a central mechanism of action, but also a sedative action at a high dose of 400mg/kg body weight [36].

A study using the MIA rat model assessed the corticosteroid dexamethasone, along with the traditional nonselective NSAIDs, such as diclofenac, nabumetone, and ibuprofen, for their therapeutic impact on knee OA lesions.

Results from the study indicated that both the NSAIDs and the corticosteroid demonstrated positive effects on disease progression within this model, proving their potential as effective interventions in preclinical OA management.

Drug treatment significantly reduced damage scores, which were assessed by measuring cartilage thickening, osteophyte appearance, and cartilage erosions, as well as other parameters elevated due to joint-destructive processes.

Significantly, the reduction in osteophyte formation seen in drug-treated rats likely contributed to a decrease in glycosaminoglycan (GAG) synthesis and overall GAG levels in these animals, indicating a potential mechanism by which these drugs alleviate joint degeneration [37].

As mentioned above, the rat MIA model was also used to illustrate that NSAIDs are effective in managing early inflammation that appears in the model progression.

In contrast, it has been observed that later stages of neuropathic pain tend to respond more favorably to treatments such as morphine or gabapentin [26].

In the rat meniscectomy model, treatment with the symptomatic slow-acting drug diacerein, an anthraquinone derivative that inhibits cytokine production by the synovial membrane and chondrocytes and reduces the bioactivity of IL-1 receptors, was also reported.

The study compared the effects of diacerein with those of the widely used supplement glucosamine.

Diacerein was administered at a dose of 50mg/kg/day, and glucosamine at 240mg/kg/day, with both doses adjusted to account for the higher metabolic rates in rats compared to humans.

Findings indicated that prophylactic administration of diacerein resulted in a notably lower degree of articular stiffness than glucosamine in the context of experimentally induced osteoarthritis.

Histological analyses showed that while both diacerein and glucosamine exhibited similar chondroprotective effects, diacerein's impact on joint flexibility was more pronounced, suggesting its potential superiority in reducing joint rigidity in this model [38,39].

Additional studies involving the surgical meniscal tear and the MIA knee OA rat models have shown that broad-spectrum matrix metalloproteinase inhibitors (MMPIs) can significantly reduce cartilage degradation.

The studies used an oral dose of MMPIs comprised between 25mg/kg twice daily (b.i.d) and 35mg/kg b.i.d, and both of them have shown promising results for using this class of pharmaceuticals in the management of OA disease [40,41].

A study investigated the effects of estrogen and levormeloxifene-a selective estrogen-receptor modulator (SERM) on ovariectomized rats.

The selected doses for the drugs were 0.1mg/kg of estrogen, while for the SERM agent, two different doses were tested: 0.2mg/kg/day and 5mg/kg/day.

The results demonstrated that both treatments effectively suppressed the increase in knee cartilage turnover, mitigated the progression of cartilage lesions, and normalized biomarker levels associated with bone and cartilage metabolism.

However, even at a high dose (5mg/kg/day), the SERM agent was less effective than estrogen treatment in reducing bone resorption [42].

The pharmaceutical supplements are also worth mentioning as their effectiveness was demonstrated in several studies involving the animal models described.

Probably the most popular supplement is represented by glucosamine hydrochloride or sulfate.

In an ACLT rat model, 1000mg/kg/day glucosamine hydrochloride showed structure-modifying effects by decreasing cartilage damage.

It maintained proteoglycan content, inhibited type II collagen degradation, and enhanced the synthesis of type II collagen within the cartilage [43].

Nevertheless, considering the wide variety of this category, our priority is concerned with newer pharmaceutical supplements that have shown promising results in the OA rat models.

In a recent study of MIA-induced knee OA in a rat animal model, a 300 mg/kg oral daily dose of nicotinamide riboside (NR), a precursor of nicotinamide adenine dinucleotide (NAD+), was demonstrated to alleviate specific oxidative stress markers such as the catalase (CAT), the malondialdehyde (MDA) and the myeloperoxidase (MPO) levels, and reduce histological lesions associated with the disease [44].

Another novel discovered adjuvant therapeutic option is represented by the salicylic acid-functionalized iron oxide nanoparticles (SaIONPs).

An oral daily dose of 1mL of SaIONPs suspension was efficient in alleviating histological lesions in a rat model of MIA-induced knee OA.

Also, the results demonstrated that SaIONPs effectively reached targeted sites, providing chondroprotective effects by reducing cellularity changes, and proteoglycan depletion.

Additionally, SaIONPs reduced MDA and TNF-α levels, suggesting their therapeutic potential, though further studies are necessary to clarify dose-response relationships [45].

Among the various categories, flavonoids also represent a noteworthy area of interest.

In the MIA OA rat model, apigenin and eupatilin, flavonoids with known antioxidant, anti-inflammatory, and anti-cancer properties have also demonstrated promising roles in rheumatic disease management.

Research findings performed in this model indicated that a dose of 0.2mg apigenin-equivalent/kg orally administered is similar to diclofenac in minimizing inflammation and it effectively reduced cartilage erosion, bone loss, and catabolic factors, as well as decreased the expression of pro-inflammatory cytokines.

In a similar context, an oral dose of 100mg/kg eupatilin administered daily, lowered the Mankin score, reflecting a reduction in osteoarthritis severity, by attenuating cartilage degradation and reducing osteoclast numbers in the subchondral bone of the rat model.

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Additionally, eupatilin downregulated the expression of matrix metalloproteinase (MMP)-13, IL-1β, IL-6, inducible nitric oxide synthase (iNOS), and nitrotyrosine in the OA model compared to the control [46-48].

Additionally, two other flavonoids, genistein and morin, have been shown to be beneficial in the ACLT OA rat model.

In this animal model, oral administration of 20mg/kg/day genistein led to an increase in collagen and GAG content compared to the control, along with a reduction in tumor necrosis factor (TNF)-α and IL-1 levels.

Similarly, oral administration of 50mg/kg/day morin was found to suppress cartilage degradation.

Moreover, extensive in vitro and in vivo studies demonstrate that morin possesses very low toxicity and is well-tolerated, even with prolonged administration [46,49,50].

Conclusion

In conclusion, the murine models are an important tool for advancing the understanding and treatment of OA, providing a platform for preclinical studies that simulate the progression and therapeutic responses of the disease as it manifests in humans.

While it is challenging to replicate all aspects of human OA in a single model, the wide variety of models enables researchers to select the most appropriate one for the scope of their study.

A domain that benefits from these models is represented especially by the drug discovery field and the testing of pharmaceutical supplements.

These models help researchers to evaluate toxicological profiles, and establish appropriate dosing, efficacy, and side effects, all of which are essential for conducting subsequent human trials.

However, it is important to note that the doses must be adjusted appropriately, considering that the murine have higher metabolic rates, and among other limitations that must be considered, differences in biomechanics, and cartilage repair processes between animals and humans can also limit the direct applicability of findings.

Therefore, animal models of OA are ethically managed and scientifically valid tools that continue to support the development of safe and effective therapies for OA in humans.

Conflict of interest

None to declare.

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