ISSN 2582 – 6050

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2024; 16(1):8-15

REVIEW ARTICLE

Curcumin Liposomal Formulations as Potential Therapeutics for Canine Osteoarthritis

Akhter Rasool[1]*, Puli Vishnu Vardhan Reddy[2], Keerthana Joshy B[1], Jan Mohd Muneeb[3]

[1]Department of Veterinary Gynecology and Obstetrics, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India, [2]Department of Veterinary Surgery and Radiology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, India, [3]Department of Animal Biotechnology, Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, India

Received: 10 December 2023; Revised: 22 January 2023; Accepted: 26 February 2024

ABSTRACT

Osteoarthritis (OA) is a multifaceted joint disorder affecting various structures, including articular cartilage, peri-articular bone, synovial joint lining, and connective tissues. This degenerative condition manifests as joint pain, stiffness, reduced mobility, and functional decline, impacting both dogs and humans globally. Risk factors include breed predispositions, joint diseases, higher body weight, and age. The current clinical approaches aim at symptom management and disease progression delay, with limited curative methods available. Nanoparticle (NPs)-based drug delivery systems, particularly curcumin liposomal formulations, show promise in OA treatment. Liposomes, lipid-based NPs, provide targeted drug distribution, extended-release, and enhanced retention in affected joints. Curcumin, a tetraterpenoid, exhibits anti-inflammatory, and antioxidant properties. Despite its efficacy, poor oral bioavailability led to the development of curcumin NPs to enhance therapeutic impact. Intra-articular administration of curcumin, especially in the form of curcumin monoglucuronide, addresses challenges associated with low hydrophilicity, demonstrating effectiveness in suppressing cartilage degeneration in OA. While non-encapsulated curcumin exhibits efficacy, its limited bioavailability prompts innovative approaches like curcumin NPs. The combination of curcumin with non-steroidal anti-inflammatory drugs or chondroprotective agents enhances anti-inflammatory effects, minimizing adverse reactions. Studies support curcumin's multifaceted therapeutic potential, promoting chondrogenic differentiation and inhibiting inflammatory mediators. This comprehensive review provides insights into canine OA treatment, emphasizing curcumin liposomal formulations as a promising avenue for informed decision-making in veterinary practice.

Keywords: Canine osteoarthritis, curcumin, liposomal formulations, pain management, therapeutics

INTRODUCTION

Osteoarthritis (OA) is a multifactorial and progressive joint disorder, influencing not only the articular cartilage but also other integral structures within the specific joint, including articular cartilage, peri-articular bone, synovial joint lining, and adjacent supporting connective tissues.[1] This degenerative condition presents with joint pain, stiffness, reduced mobility, and a progressive decline in joint function. OA is characterized not only by the gradual deterioration of cartilage but also by distinct features such as a narrowed synovial cavity, invasion into the subchondral bone, the formation of osteophytes, and inflammation in the synovial membrane and synovial fluid.[2] Significantly, OA emerges as a major contributor to pain, lameness, and morbidity across various species, impacting both dogs and humans

***Corresponding Author:**
Akhter Rasool,
E-mail: mirakhter1312@gmail.com

globally.[3-6] In canines, OA commonly arises due to diverse inciting factors, including coxofemoral (hip) joint dysplasia, elbow dysplasia, cranial cruciate ligament disease, and patella luxation.[5] The large weight-bearing joints, particularly the hip and knee, are most frequently affected by OA.[7] There are presently no fully satisfactory treatments for this incapacitating disease. The predominant standard of care centers around the management and alleviation of symptoms.[8,9] The current clinical treatments for OA predominantly focus on delaying disease progression, reducing pain, and improving joint mobility.[10] However, there is no definitive curative method presently available. Nevertheless, nanoparticle (NPs)-based drug delivery systems hold significant promise in the treatment of OA. This optimism stems from their capacity to achieve targeted drug distribution, prolong drug release, and augment drug retention within the affected joints. This paper aims to discuss treatment options for canine OA, with a particular focus on the curcumin liposomal formulation. The discussion will encompass both novel therapeutic approaches and existing treatments, providing comprehensive insights for informed decision-making in the management of canine OA.

RISK FACTORS ASSOCIATED WITH OA IN CANINE

Several major risk factors contribute to the development of OA, including breed predispositions and specific joint disease risks. Notably, certain breeds such as Rottweiler, Golden Retriever, and Labrador Retriever exhibit an increased susceptibility to cruciate ligament rupture.[11-15] Larger breeds, including Mastiffs, Boxers, Italian Corso dogs, German Shepherds, Golden and Labrador Retrievers, and Bernese Mountain dogs, are associated with higher prevalence rates of hip and elbow dysplasia.[15-19] In addition, higher body weight, leading to increased stress on weight-bearing joints, poses a heightened risk for OA, particularly in overweighed and larger breed dogs. Neutered individuals exhibit a significantly higher likelihood of developing joint diseases, and associations between neutering and weight gain have also been observed. Changes in gonadal hormones, which can indirectly impact joint protection, growth rates, and development, may contribute to this association.[19] While OA may initiate at any age, joint deterioration tends to escalate with age, emphasizing older age as a risk factor for conditions such as cruciate ligament rupture and OA.

MECHANISM OF PAIN AND CURRENT CLINICAL APPROACHES IN TREATING OA

Pain stands as the primary symptom of OA. It is crucial to identify the sources and mechanisms of pain in OA, as comprehending the underlying causes can aid in effectively targeting affected individuals with appropriate therapy. Furthermore, it has the potential to uncover alternative therapies aimed at reducing symptoms and improving overall joint function. Figure 1 outlines the fundamental mechanism of pain in OA, elucidating neuronal pathways associated with OA-induced pain and the intricate process of pain processing. This understanding serves as a valuable foundation for developing targeted interventions to alleviate pain and enhance the quality of life for patients suffering from OA.

The current clinical approaches predominantly emphasize symptomatic treatment and the delay of disease progression. The prevailing strategy for managing canine arthritis involves a comprehensive approach implemented by pet care providers. In addressing arthritis-associated pain, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly recommended, including Cox inhibitors such as carprofen and firocoxib, along with grapiprant, a non-Cox inhibitor, and a prostaglandin E EP4 receptor antagonist (PRA).[20-22] This comprehensive approach aims to effectively alleviate pain and discomfort associated with arthritis, constituting a holistic strategy for the management of canine joint health. It is imperative to acknowledge that NSAIDs, while effective, are not without potential side effects. The most prevalent adverse effects include gastrointestinal manifestations such as vomiting, diarrhea, and inappetence.

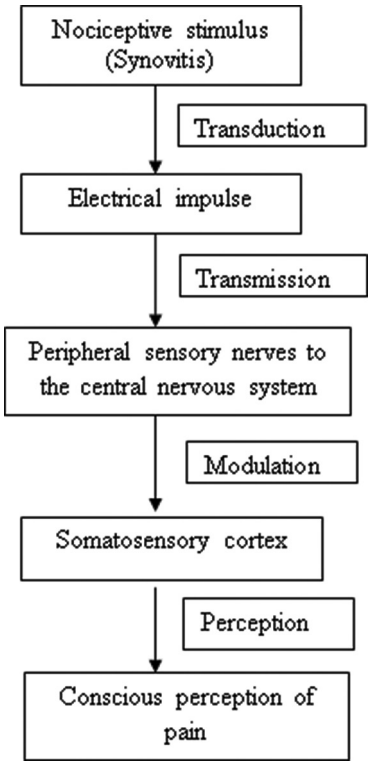

Figure 1: Stages of the pain pathway in osteoarthritis; Transduction involves the conversion of a nociceptive stimulus into an electrical impulse. Transmission denotes the transmission of this electrical impulse from peripheral sensory nerves to the central nervous system (CNS). Modulation encompasses the processing of the nociceptive stimulus by the CNS, including the involvement of the endogenous opioid system, as well as ascending input and descending inhibitory pathways. Perception is the interpretation of nociceptive inputs by the brain, particularly the somatosensory cortex, leading to the conscious perception of pain.[32]

Severe complications, including gastrointestinal ulceration and renal toxicity, though rare, are documented.[23] Corticosteroids, recognized for their anti-inflammatory action, are considered to have analgesic effects in OA.[24] Methylprednisolone acetate is licensed for intra-articular (IA) use in dogs for inflammatory conditions. However, caution is advised due to contraindications, such as septic arthritis, and concerns about potential cartilage damage associated with long-term IA corticosteroid use.[25-27]

Apart from pain medication, complementary feed supplements containing chondroprotective agents are employed to promote and maintain joint health in dogs, with key components like chondroitin sulfate and glucosamine HCl playing a vital role in maintaining optimal joint function and mobility. Hyaluronic acid is also integrated to support synovial fluid, crucial for enhancing joint mobility and facilitating a smoother recovery process.[28] In addition, Omega-3 fatty acids are included for their beneficial properties.[29]

Mesenchymal stem cells (MSCs) exhibit the potential for differentiation into chondrocytes, facilitating the repair of OA lesions on injection into the affected site.[30] Platelet-rich plasma, enriched with growth factors, induces angiogenesis and chondrocyte proliferation, while mitigating processes such as chondrocyte apoptosis when injected into the IA space of the OA-affected joint.[31] However, it is noteworthy that there is a limited number of published clinical trials in dogs exploring these regenerative therapies.

CURCUMIN-ENCAPSULATED LIPOSOMES FOR MANAGING OA

OA is a localized rather than a systemic illness. The challenge lies in delivering a sufficient amount of medication to the designated site since cartilage lacks blood vessels, leading to low bioavailability. To address the issue, a novel transdermal drug delivery device capable of piercing the dermis and delivering drugs directly into the systemic circulation without traversing skin barriers can be employed.[33] NPs play a pivotal role as carriers for bioactive molecules and growth factors. They enable the targeted delivery of anti-inflammatory agents directly to the affected joint, thereby minimizing systemic exposure and potential side effects while increasing the concentration of therapeutic agents at the site of inflammation. Among NP options, lipid-based NPs stand out in the field of nanomedicine due to their biocompatibility, adaptability, and versatility in carrying a variety of therapeutic molecules, offering benefits such as prolonged circulation. Specifically, liposomes, spherical vesicles composed of a lipid bilayer, have exhibited promise in the context of OA treatment.[34] Liposomes are commonly prepared using methods such as sonication, repeated freeze-thaw cycles, hydration-extrusion, and microfluidic devices. The encapsulation of drugs into liposomes can be

achieved through passive loading, where drugs are mixed with lipids before vesicle formation, or through remote loading, leveraging transmembrane ion gradients.[35,36] Liposomal formulations exhibit the capability to encapsulate both hydrophilic and hydrophobic drug cargos. This characteristic contributes to an increased half-life for antioxidant medications, facilitates sustained drug release, and enhances lubrication. These properties make liposomes a potential avenue for delivering anti-inflammatory and disease-modifying medications to the affected joint in the treatment of OA.[37]

Curcumin (diferuloylmethane), a tetraterpenoid derived from Curcuma longa, has garnered attention for its reported anti-inflammatory, antioxidant, and anti-proliferative properties.[38-40] Widely studied for its therapeutic potential, curcumin has been utilized in the treatment of chronic inflammatory diseases such as arthritis.[41] Functioning as an antioxidant, direct scavenger of ROS, curcumin demonstrates the ability to mitigate oxidative stress, safeguard cells from oxidative damage, and actively contribute to the prevention and treatment of arthritis.[42] As mitochondrial function declines, there is an increase in the levels of matrix degradative enzymes, coupled with a decrease in the synthesis of extracellular matrix proteins such as collagen and proteoglycan. This imbalance leads to the progression of cartilage degradation, giving rise to OA pathologies such as cartilage matrix calcification and breakdown.[43,44] Curcumin, known for its antioxidant properties, plays a protective role against mitochondrial dysfunction and is recognized for its efficacy in preventing the advancement of pathological conditions.[45] Notably, a study observed that curcumin effectively alleviated inflammation, inhibited synovial vascular neovascularization, and suppressed abnormal fibroblast proliferation in arthritic rats. *In vitro*, experiments further revealed curcumin's inhibitory effect on osteoclastogenesis.[46] In the realm of osteogenesis, research has explored the impact of curcumin, demonstrating its potential to reduce bone resorption in osteoporotic rats.[47] These findings collectively underscore the multifaceted therapeutic potential of curcumin in addressing inflammatory and degenerative conditions, particularly within the context of arthritis.

Studies have substantiated the chondroprotective potential of curcumin through gene expression profile analysis *in vitro*, particularly in chondrocytes. In addition, curcumin treatment has demonstrated a significant reduction in synovitis. When administered orally or topically, curcumin exhibited a notable deceleration or delay in the initiation and progression of OA in mice. This was evident through reduced cartilage erosion, proteoglycan loss, synovitis, subchondral plate thickness, and degradation of Type II collagen.[48]

Despite the significant efficacy of non-encapsulated curcumin administered orally in slowing OA progression, its therapeutic effectiveness may be limited due to its relatively poor oral bioavailability, with low hydrophilicity and conjugation in the intestinal tract.[49,50] To overcome this limitation, researchers have developed curcumin NPs utilizing a novel polymeric NP carrier.[51] This innovative approach aims to enhance the bioavailability of curcumin, potentially amplifying its therapeutic impact in the context of OA management. To overcome the limitations associated with oral curcumin ingestion, IA administration, a prevalent drug delivery method in OA therapies, has been employed. This approach delivers a concentrated therapeutic dose of curcumin directly into the joint, demonstrating efficacy in suppressing articular cartilage degeneration and synovial inflammation in an OA rat model.[52-54] Given the low hydrophilicity of curcumin, the use of curcumin monoglucuronide (CMG), a conjugated form, in IA administration addresses this challenge. CMG can be absorbed into the deep layer of the cartilage, maximizing its pharmacological effects. Notably, CMG exhibits 10-fold lower antioxidative activity than unconjugated, free-form curcumin.[55] However, for CMG to execute its antioxidative activity, it must undergo metabolism to free-form curcumin *in vivo*, a process facilitated by the important hydrolase enzyme, β-glucuronidase.[56] This enzyme is released from neutrophils, injured cells at inflammation sites, and cells in bone.[57,58] Enhanced β-glucuronidase secretion in the articular cartilage, synovium, and synovial fluid during inflammation and OA further supports the deconjugation of CMG to free-

form curcumin in the OA joint, resulting in the suppression of articular cartilage degeneration.[59-61] Moreover, curcumin exhibits anti-inflammatory properties by suppressing cytokines such as TNF-α, IL-1β, and IL-6. It also inhibits the production of pro-inflammatory mediators and matrix-degrading enzymes, namely metalloproteinase (MMP)-3 and MMP.[62] In addition, curcumin promotes the chondrogenic differentiation, proliferation, and migration of MSCs.[63,64]

The combination of curcumin with NSAIDs or chondroprotective agents, such as Omega-3 or glucosamine, holds the potential to enhance anti-inflammatory and analgesic pharmacological effects while minimizing adverse reactions associated with oral NSAIDs,[65] In one study, the combined administration of curcumin and omega-3 was found to be more effective in pain regulation and inhibiting cartilage destruction compared to a single administration of curcumin or NSAIDs.[66] Similarly, a co-micronized formulation of N-palmitoyl-D-glucosamine (PGA) together with curcumin (PGA-cur) significantly reduced clinical and histopathological signs of inflammation and pain.[67,68] It protected articular cartilage against degeneration and decreased pro-inflammatory cytokines.[69] However, the underlying mechanism for this enhanced effect is not yet clear, emphasizing the need for further validation through additional clinical and basic research in the future.

Based on the aforementioned findings, numerous treatment options are presently available for managing OA in dogs. IA administration of liposomally encapsulated curcumin, combined with chondroprotective agents, shows promise in effectively alleviating chronic orthopedic pain and mitigating clinical signs associated with OA in dogs.

CONCLUSION

Drug delivery systems utilizing various NPs offer significant advantages in the treatment of OA. The key benefits include extended drug release, increased drug retention within joints, and enhanced therapeutic efficacy through functional regulatory strategies. These advantages pave the way for lower therapeutic doses, reduced administration frequency, high pharmacological efficacy, and minimized off-target toxicity. The use of curcumin liposomal formulations addresses challenges related to low bioavailability and allows for precise targeting and sustained drug release in the complex joint environment. Despite these promising developments, certain limitations persist. The optimal dosage and administration frequency of curcumin require careful consideration, emphasizing the need for further research to determine the most effective treatment protocols. Challenges, including regulatory approval, scale-up production, and long-term safety assessments, must be addressed to facilitate the widespread implementation of these innovative drug delivery systems in clinical practice. While NP-based drug delivery systems show great promise, continued exploration and refinement are crucial to unlocking their full potential in the effective management of OA.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: A disease of the joint as an organ. Arthritis Rheum 2012;64:1697-707.
2. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, *et al*. Osteoarthritis. Lancet 2015;386:376-87.
3. Brown DC, Boston RC, Farrar JT. Comparison of force plate gait analysis and owner assessment of pain using the Canine Brief Pain Inventory in dogs with osteoarthritis. J Vet Intern Med 2013;27:22-30.
4. Knazovicky D, Helgeson ES, Case B, Gruen ME, Maixner W, Lascelles BD. Widespread somatosensory sensitivity in naturally occurring canine model of osteoarthritis. Pain 2016;157:1325-32.
5. Anderson KL, O'Neill DG, Brodbelt DC, Church DB, Meeson RL, Sargan D, *et al.* Prevalence, duration and risk factors for appendicular osteoarthritis in a UK dog population under primary veterinary care. Sci Rep 2018;8:5641.
6. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine 2020;29-30:100587.

7. Hochberg MC, Hunter DJ, Felson DT. Osteoarthritis. BMJ 2006;332:639-42.
8. Zhang RX, Ren K, Dubner R. Osteoarthritis pain mechanisms: Basic studies in animal models. Osteoarthritis Cartilage 2013;21:1308-15.
9. Rainbow R, Ren W, Zeng L. Inflammation and joint tissue interactions in OA: Implications for potential therapeutic approaches. Arthritis 2012;2012:741582.
10. Arden NK, Perry TA, Bannuru RR, Bruyère O, Cooper C, Haugen IK, *et al.* Non-surgical management of knee osteoarthritis: Comparison of ESCEO and OARSI 2019 guidelines. Nat Rev Rheumatol 2021;17:59-66.
11. Taylor-Brown FE, Meeson RL, Brodbelt DC, Church DB, McGreevy PD, Thomson PC, *et al.* Epidemiology of cranial cruciate ligament disease diagnosis in dogs attending primary-care veterinary practices in England. Vet Surg 2015;44:777-83.
12. Adams P, Bolus R, Middleton S, Moores AP, Grierson J. Influence of signalment on developing cranial cruciate rupture in dogs in the UK. J Small Anim Pract 2011;52:347-52.
13. Grierson J, Asher L, Grainger K. An investigation into risk factors for bilateral canine cruciate ligament rupture. Vet Comp Orthop Traumatol 2011;24:192-6.
14. Nečas A, Zatloukal J, Kecova H, Dvořák M. Predisposition of dog breeds to rupture of the cranial cruciate ligament. Acta Vet Brno 2000;69:305-10.
15. Whitehair JG, Vasseur PB, Willits NH. Epidemiology of cranial cruciate ligament rupture in dogs. J Am Vet Med Assoc 1993;203:1016-9.
16. Coopman F, Verhoeven G, Saunders J, Duchateau L, van Bree H. Prevalence of hip dysplasia, elbow dysplasia and humeral head osteochondrosis in dog breeds in Belgium. Vet Rec 2008;163:654-8.
17. Hou Y, Wang Y, Lu X, Zhang X, Zhao Q, Todhunter RJ, *et al.* Monitoring Hip and Elbow Dysplasia achieved modest genetic improvement of 74 dog breeds over 40 years in USA. PLoS One 2013;8:e76390. Erratum in: PLoS One 2013;8.
18. Lavrijsen IC, Heuven HC, Meij BP, Theyse LF, Nap RC, Leegwater PA, *et al.* Prevalence and co-occurrence of hip dysplasia and elbow dysplasia in Dutch pure-bred dogs. Prev Vet Med 2014;114:114-22.
19. Witsberger TH, Villamil JA, Schultz LG, Hahn AW, Cook JL. Prevalence of and risk factors for hip dysplasia and cranial cruciate ligament deficiency in dogs. J Am Vet Med Assoc 2008;232:1818-24.
20. Aragon CL, Hofmeister EH, Budsberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. J Am Vet Med Assoc 2007;230:514-21.
21. Sundar Dhilip Kumar S, Houreld NN, Abrahamse H. Therapeutic potential and recent advances of curcumin in the treatment of aging-associated diseases. Molecules 2018;23:835.
22. Lin CR, Amaya F, Barrett L, Wang H, Takada J, Samad TA, *et al*. Prostaglandin E2 receptor EP4 contributes to inflammatory pain hypersensitivity. J Pharmacol Exp Ther 2006;319:1096-103.
23. Monteiro-Steagall BP, Steagall PV, Lascelles BD. Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. J Vet Intern Med 2013;27:1011-9.
24. Johnston SA, Budsberg SC. Nonsteroidal anti-inflammatory drugs and corticosteroids for the management of canine osteoarthritis. Vet Clin North Am Small Anim Pract 1997;27:841-62.
25. Chunekamrai S, Krook LP, Lust G, Maylin GA. Changes in articular cartilage after intra-articular injections of methylprednisolone acetate in horses. Am J Vet Res 1989;50:1733-41.
26. Farquhar T, Todhunter RJ, Fubini SL, Burton-Wurster N, Lust G. Effect of methylprednisolone and mechanical loading on canine articular cartilage in explant culture. Osteoarthritis Cartilage 1996;4:55-62.
27. Murphy DJ, Todhunter RJ, Fubini SL, Vernier-Singer M, Straubinger RK, Lust G. The effects of methylprednisolone on normal and monocyte-conditioned medium-treated articular cartilage from dogs and horses. Vet Surg 2000;29:546-57.
28. Akmal M, Singh A, Anand A, Kesani A, Aslam N, Goodship A, *et al.* The effects of hyaluronic acid on articular chondrocytes. J Bone Joint Surg Br 2005;87:1143-9.
29. Moreau M, Troncy E, Del Castillo JR, Bédard C, Gauvin D, Lussier B. Effects of feeding a high omega-3 fatty acids diet in dogs with naturally occurring osteoarthritis. J Anim Physiol Anim Nutr (Berl) 2013;97:830-7.
30. Scharstuhl A, Schewe B, Benz K, Gaissmaier C, Bühring HJ, Stoop R. Chondrogenic potential of human adult mesenchymal stem cells is independent of age or osteoarthritis etiology. Stem Cells 2007;25:3244-51.
31. Collins T, Alexander D, Barkatali B. Platelet-rich plasma: A narrative review. EFORT Open Rev 2021;6:225-35.
32. Yamaoka TT, Auckburally A. Adjunctive analgesics. Vet Nurse 2014;5:474-81.
33. Waghule T, Singhvi G, Dubey SK, Pandey MM, Gupta G, Singh M, *et al.* Microneedles: A smart approach and increasing potential for transdermal drug delivery system. Biomed Pharmacother 2019;109:1249-58.
34. Rao AK, Tiwari R, Sharma N, Gupta N, Rajput D, Samanthula KS, *et al*. Innovative nanomedicine approaches in osteoarthritis therapy: A systematic review. YMER Digit 2023;22:322-50.
35. Yang J, Zhu Y, Wang F, Deng L, Xu X, Cui W. Microfluidic liposomes-anchored microgels as extended delivery platform for treatment of osteoarthritis. Chem Eng J 2020;400:126004.
36. Mwangi TK, Bowles RD, Tainter DM, Bell RD, Kaplan DL, Setton LA. Synthesis and characterization of silk fibroin microparticles for intra-articular drug delivery. Int J Pharm 2015;485:7-14.
37. Ji X, Yan Y, Sun T, Zhang Q, Wang Y, Zhang M, *et al.* Glucosamine sulphate-loaded distearoyl phosphocholine liposomes for osteoarthritis treatment: Combination

of sustained drug release and improved lubrication. Biomater Sci 2019;7:2716-28.
38. Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D, *et al*. Oral bioavailability of curcumin: Problems and advancements. J Drug Target 2016;24:694-702.
39. Gong X, Jiang L, Li W, Liang Q, Li Z. Curcumin induces apoptosis and autophagy inhuman renal cell carcinoma cells via Akt/mTOR suppression. Bioengineered 2021;12:5017-27.
40. Deng H, Wan M, Li H, Chen Q, Li R, Liang B, *et al.* Curcumin protection against ultraviolet-induced photo-damage in Hacat cells by regulating nuclear factor erythroid 2-related factor 2. Bioengineered 2021;12:9993-10006.
41. Kloesch B, Becker T, Dietersdorfer E, Kiener H, Steiner G. Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes. Int Immunopharmacol 2013;15:400-5.
42. Sanderson RO, Beata C, Flipo RM, Genevois JP, Macias C, Tacke S, *et al.* Systematic review of the management of canine osteoarthritis. Vet Rec 2009;164:418-24.
43. Cillero-Pastor B, Rego-Pérez I, Oreiro N, Fernandez-Lopez C, Blanco FJ. Mitochondrial respiratory chain dysfunction modulates metalloproteases -1, -3 and -13 in human normal chondrocytes in culture. BMC Musculoskelet Disord 2013;14:235.
44. Johnson K, Jung A, Murphy A, Andreyev A, Dykens J, Terkeltaub R. Mitochondrial oxidative phosphorylation is a downstream regulator of nitric oxide effects on chondrocyte matrix synthesis and mineralization. Arthritis Rheum 2000;43:1560-70.
45. Trujillo J, Granados-Castro LF, Zazueta C, Andérica-Romero AC, Chirino YI, Pedraza-Chaverrí J. Mitochondria as a target in the therapeutic properties of curcumin. Arch Pharm (Weinheim) 2014;347:873-84.
46. Xu Z, Shang W, Zhao Z, Zhang B, Liu C, Cai H. Curcumin alleviates rheumatoid arthritis progression through the phosphatidylinositol 3-kinase/protein kinase B pathway: An *in vitro* and *in vivo* study. Bioengineered 2022;13:12899-911.
47. Liang Y, Zhu B, Li S, Zhai Y, Yang Y, Bai Z, *et al.* Curcumin protects bone biomechanical properties and microarchitecture in type 2 diabetic rats with osteoporosis via the TGFβ/Smad2/3 pathway. Exp Ther Med 2020;20:2200-8.
48. Zhang Z, Leong DJ, Xu L, He Z, Wang A, Navati M, *et al.* Curcumin slows osteoarthritis progression and relieves osteoarthritis-associated pain symptoms in a post-traumatic osteoarthritis mouse model. Arthritis Res Ther 2016;18:128.
49. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm 2007;4:807-18.
50. Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2007;853:183-9.
51. Tar M, Cabrales P, Navati M, Adler B, Nacharaju P, Friedman AJ, *et al*. Topically applied NO-releasing nanoparticles can increase intracorporal pressure and elicit spontaneous erections in a rat model of radical prostatectomy. J Sex Med 2014;11:2903-14.
52. Zhou Y, Ming J, Deng M, Li Y, Li B, Li J, *et al*. Chemically modified curcumin (CMC2.24) alleviates osteoarthritis progression by restoring cartilage homeostasis and inhibiting chondrocyte apoptosis via the NF-κB/HIF-2α axis. J Mol Med (Berl) 2020;98:1479-91.
53. Henrotin Y, Malaise M, Wittoek R, de Vlam K, Brasseur JP, Luyten FP, *et al*. Bio-optimized Curcuma longa extract is efficient on knee osteoarthritis pain: A double-blind multicenter randomized placebo controlled three-arm study. Arthritis Res Ther 2019;21:179.
54. Yan D, He B, Guo J, Li S, Wang J. Involvement of TLR4 in the protective effect of intra-articular administration of curcumin on rat experimental osteoarthritis. Acta Cir Bras 2019;34:e201900604.
55. Choudhury AK, Raja S, Mahapatra S, Nagabhushanam K, Majeed M. Synthesis and evaluation of the anti-oxidant capacity of curcumin glucuronides, the major curcumin metabolites. Antioxidants (Basel) 2015;4:750-67.
56. Ozawa H, Imaizumi A, Sumi Y, Hashimoto T, Kanai M, Makino Y, *et al.* Curcumin β-D-glucuronide plays an important role to keep high levels of free-form curcumin in the blood. Biol Pharm Bull 2017;40:1515-24.
57. Marshall T, Shult P, Busse WW. Release of lysosomal enzyme beta-glucuronidase from isolated human eosinophils. J Allergy Clin Immunol 1988;82:550-5.
58. Kunihiro AG, Luis PB, Brickey JA, Frye JB, Chow HH, Schneider C, *et al*. Beta-glucuronidase catalyzes deconjugation and activation of curcumin-glucuronide in bone. J Nat Prod 2019;82:500-9.
59. Fawthrop F, Hornby J, Swan A, Hutton C, Doherty M, Dieppe P. A comparison of normal and pathological synovial fluid. Br J Rheumatol 1985;24:61-9.
60. Chang H, Israel H. Analysis of inflammatory mediators in temporomandibular joint synovial fluid lavage samples of symptomatic patients and asymptomatic controls. J Oral Maxillofac Surg 2005;63:761-5.
61. Nakahata A, Ito A, Nakahara R, Kishimoto A, Imaizumi A, Hashimoto T, *et al.* Intra-articular injections of curcumin monoglucuronide TBP1901 suppresses articular cartilage damage and regulates subchondral bone alteration in an osteoarthritis Rat model. Cartilage 2021;13:153S-167.
62. Liacini A, Sylvester J, Li WQ, Huang W, Dehnade F, Ahmad M, *et al.* Induction of matrix metalloproteinase-13 gene expression by TNF-alpha is mediated by MAP kinases, AP-1, and NF-kappaB transcription factors in articular chondrocytes. Exp Cell Res 2003;288:208-17.
63. Mathy-Hartert M, Jacquemond-Collet I, Priem F, Sanchez C, Lambert C, Henrotin Y. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. Inflamm Res 2009;58:899-908.

64. Buhrmann C, Mobasheri A, Matis U, Shakibaei M. Curcumin mediated suppression of nuclear factor-κB promotes chondrogenic differentiation of mesenchymal stem cells in a high-density co-culture microenvironment. Arthritis Res Ther 2010;12:R127.
65. Zhang R, Zhang Q, Zou Z, Li Z, Jin M, An J, *et al.* Curcumin supplementation enhances bone marrow mesenchymal stem cells to promote the anabolism of articular chondrocytes and cartilage repair. Cell Transplant 2021;30:096368972199377.
66. Jhun J, Lee D, Na HS, Cho KH, Lee SY, Lee JS, *et al*. Curcumin and omega-3 ameliorate experimental osteoarthritis progression in terms of joint pain and mitochondrial dysfunction. Preprint; 2023.
67. Della Rocca G, Schievano C, Di Salvo A, Conti MB, Della Valle MF. Palmitoyl-glucosamine co-micronized with curcumin for maintenance of meloxicam-induced pain relief in dogs with osteoarthritis pain. BMC Vet Res 2023;19:37.
68. Gugliandolo E, Peritore AF, Impellizzeri D, Cordaro M, Siracusa R, Fusco R, *et al.* Dietary supplementation with palmitoyl-glucosamine co-micronized with curcumin relieves osteoarthritis pain and benefits joint mobility. Animals (Basel) 2020;10:1827.
69. Cordaro M, Siracusa R, Impellizzeri D, D'Amico R, Peritore AF, Crupi R, *et al.* Safety and efficacy of a new micronized formulation of the ALIAmide palmitoylglucosamine in preclinical models of inflammation and osteoarthritis pain. Arthritis Res Ther 2019;21:254.