

Curcumin nanoparticles and the therapeutic potential of curcumin for musculoskeletal disorders

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Abstract. – Musculoskeletal disorders (MSD) are a collection of degenerative conditions impacting the body's bones, joints, muscles, tendons, ligaments, and nerves. MSDs affect approximately 1.71 billion individuals worldwide and are a significant cause of disability. Curcumin is a polyphenolic compound with anti-inflammatory, antioxidant, and antitumor properties. In this review, we will discuss the research progress of structural analogs, derivatives, and nanomaterials that can improve the bioavailability of this natural drug. Curcumin may potentially retard the progression of osteoporosis, osteoarthritis, and rheumatoid arthritis. These effects may be related to curcumin's targeting of multiple signalling pathways.

Key Words:

Musculoskeletal, Curcumin, Nanomaterials, Osteoporosis, Osteoarthritis.

Introduction

Musculoskeletal disorders (MSD) are a group of degenerative conditions that affect the body's bones, joints, muscles, tendons, ligaments, and nerves. They result in extensive pain and inflammatory alterations restricting mobility, dexterity, and overall function. Multiple sclerosis is a significant cause of disability. Approximately 1.71 billion individuals worldwide suffer from MSD, with 441 million afflicted in high-income countries¹; this places a significant burden on healthcare systems. Osteoarthritis, rheumatoid arthritis (RA), fibromyalgia, sports injuries, and osteoporosis are the most prevalent MSDs, with health management, physiotherapy, medication, and surgery serving as their primary treatments. The purpose of health management is to

prevent the onset and progression of disease. It includes regular exercise, a healthy diet, quitting smoking, and avoiding repetitive strain injuries. Hot and cold packs, electrical stimulation, ultrasound, and strength training are used in physiotherapy to reduce pain and inflammation and enhance motor function². Nonsteroidal anti-inflammatory medications (NSAIDs) such as ibuprofen and naproxen, muscle relaxants, opioids, and corticosteroids can effectively alleviate MSD symptoms. However, they have significant side effects (e.g., gastrointestinal distress)³, so there is an urgent need to discover a safe and effective alternative drug that reduces the incidence of adverse events⁴.

Curcumin was discovered for the first time in India and Southeast Asia in the nineteenth century. It is a polyphenolic compound isolated from the rootstock of some *Zingiberaceae* and *Araceae* family plants⁵, with minimal toxicity and high tolerance. Curcumin has the chemical formula $C_{21}H_{20}O_6$, and its chemical structure and derivatives are depicted in Figure 1. It is a symmetrical molecule with o-methoxyphenol on either side and a seven-carbon keto-enol structure comprising two α and β -unsaturated carbonyl groups connected in the middle⁶. α and β -unsaturated carbonyl groups are Michael receptors that undergo nucleophilic addition and enhance antitumor effects⁷. The structure of curcumin also contains three active sites that can undergo oxidation by electron transfer and hydrogen abstraction, scavenging reactive oxygen species (ROS) and providing antioxidant activity⁶. Further studies⁸⁻¹⁵ of this polyphenolic compound have shown a variety of pharmacological effects such as antibacterial⁸, immunomodulation⁹, antioxidant¹⁰, anti-angiogenic¹¹, anti-inflammatory¹²,

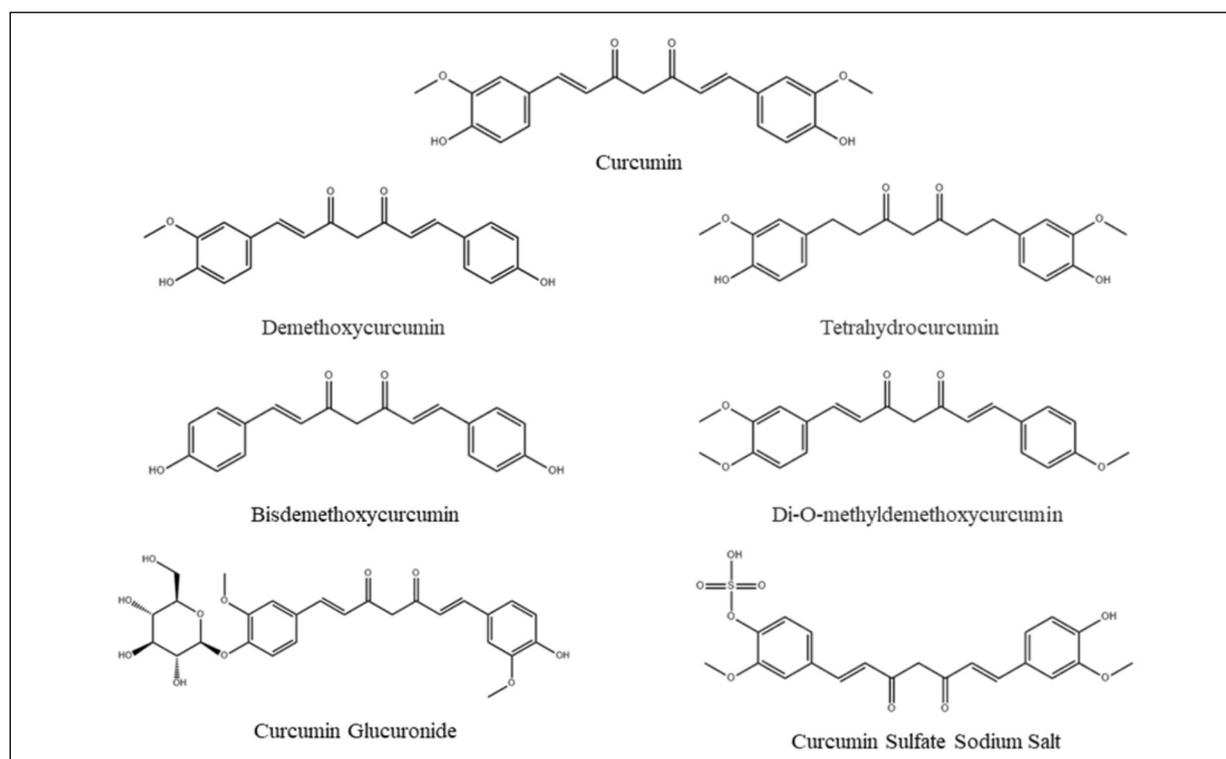


Figure 1. Chemical structures of curcumin and its derivatives.

analgesic¹³, chondroprotection¹⁴, antitumor¹⁵, the latter six of these bioactivities have the potential for the treatment of MSD.

In this review, we describe the current curcumin preparations, recapitulate the evidence on the protective effects of curcumin against musculoskeletal disorders in animals and humans, and explain the mechanisms of action of curcumin in the regulation of the musculoskeletal system.

Curcumin

Curcumin has extremely high safety as a drug. In the study by Ryan et al¹⁶, adult oral administration of curcumin at 6,000 mg/day for 7 weeks showed no toxic effects. Increasing the single oral dose of curcumin to 10,000 mg or 12,000 mg, which far exceeded the medicinal dose, resulted in mild headache and diarrhea in subjects¹⁷. Although the human body has good tolerance to curcumin, there are still some potential drawbacks that need to be considered: direct contact with the skin produces type 1 hypersensitivity reactions¹⁸, interference with iron absorption by chelation with iron¹⁹, poor water solubility, low bioavailability,

and inadequate curcumin concentrations in blood and tissues that are rapidly metabolized and eliminated, regardless of the route of administration. After intravenous injection of 10 mg/kg curcumin into rats, the maximum concentration in serum was only 0.36 µg/mL; after oral administration of 1.0 g/kg curcumin for 15 minutes, the concentration in rats' plasma was only 0.13 µg/mL, reaching a maximum concentration of 0.22 µg/mL after 1 hour. After 6 hours, it was undetectable in plasma. After intraperitoneal injection of 0.1 g/kg curcumin for 1 hour, it was discovered that there were significant differences in the distribution of curcumin in the organs, with the most extensive distribution in the intestine (117 µg/ml), followed by the kidney, blood, and liver, and a very low concentration in the brain (0.4 µg/ml)²⁰. In one human study²¹, the maximal detectable concentration of curcumin in the blood was only 11.1 nmol/mL when 3.6 g of curcumin was taken orally. Consequently, enhancing the water solubility and bioavailability of curcumin will be an important future research topic, in order to achieve this goal, curcumin's structural analogs and derivatives, curcumin β-cyclodextrin inclusion complex, curcumin phospholipid complex, curcumin nanoparticles,

and liposomal curcumin have been developed successively to address these issues.

Curcumin Structural Analogues and Derivatives

Tetrahydrocurcumin (THC)

Curcumin's metabolite, THC, is a white, odorless substance devoid of α,β -unsaturated carbonyl. Curcumin endures a reduction reaction during cellular metabolism. It is first converted to dihydro curcumin, then to THC, and finally, the conjugated bond in its seven-carbon chain is removed²².

THC has several potential health benefits, including reducing oxidative stress, insulin sensitivity, and inflammation. It can aid in preventing neurodegenerative diseases such as Alzheimer's and Parkinson's and has anticancer properties²³. THC has vigorous antioxidant activity. Somparn et al²⁴ proved that THC has a more muscular 2,2-Diphenyl-1-picrylhydrazyl (DPPH•) scavenging activity than curcumin. It inhibits the peroxidation of linoleic acid and the hemolysis of red blood cells induced by free radicals. Manjunatha et al²⁵ demonstrated that THC has a free radical scavenging activity of (79.8-86%) at lower concentrations (10-15 ppm), thereby protecting cells from free radical-induced damage. THC has also been studied for its potential benefits for cutaneous health. Xu et al²⁶ found that THC can ameliorate UV-induced skin aging *via* anti-inflammation, improvement of the extracellular matrix, and inhibition of melanogenesis. These effects may aid in reducing hyperpigmentation, diminishing age spots, and lightening the skin. THC has also been shown²⁷ to increase collagen and elastin to enhance skin elasticity, so its use as a new plant ingredient in the cosmetics industry is extremely promising.

Encouragingly, THC can also prevent aging and prolong life. Kitani et al²⁸ fed mice with food supplemented with 0.2% THC, and the result was that the mice lived 11.7% longer than the control group. This may be related to THC increasing Sirtuin 2 (Sirt2)/forkhead box O1 (FOXO) signal transduction. When utilizing FOXO-null mutant flies, their lifetime was not increased²⁹. Inflammation is considered to be a contributing factor to many chronic diseases. Some studies³⁰ have shown that THC may be more effective than curcumin in reducing inflammation. It inhibits the activity of the cytokines cyclooxygenase (COX-1/COX-2), tumor necrosis factor (TNF- α), inter-

leukin (IL), leukotrienes (LT) and lipoxygenase (LOX), which LT is a group of inflammatory mediators produced by the metabolism of arachidonic acid (AA) *via* the 5-LOX pathway. LOX inhibitors such as zileuton are presently utilized to treat glucocorticoid-insensitive childhood asthma. THC has a potent LOX inhibitory effect at 1 $\mu\text{g/mL}$ and, therefore, has the potential to be used as a LOX inhibitor for asthma and is superior to curcumin.

THC has a higher performance than curcumin in some pharmacological properties. Compared to curcumin, THC is more stable, degrades more slowly, is more soluble in water and is more readily absorbed: its half-lives in cell culture media and plasma are 813 and 232 minutes, which are substantially longer than curcumin's 186 and 111 minutes³¹. In mice treated by oral gavage, intramuscular injection, and intraperitoneal injection, the plasma level of free tetrahydrocurcumin was also significantly higher in the THC group than in the curcumin group³².

Demethoxycurcumin (DMC) and Bidesmethoxycurcumin (BDMC)

DMC and BDMC are two of the three curcumin species extracted from turmeric, accounting for 4.5% and 25.8%, respectively³³. Compared to curcumin, DMC lacks only the methoxy group attached to the benzene ring, resulting in more excellent stability at physiological pH³⁴. Although DMC has provided antitumor³⁵, anti-inflammatory activity, and neuroprotection³⁶ and is beneficial in MSD³⁷, there is no comparative research data to prove whether the pharmacological actions of DMC and BDMC are superior to those of curcumin³⁸. Nonetheless, certain pharmacological properties of DMC and BDMC surpass those of curcumin.

DMC possesses potent antioxidant activity, and DMC and BDMC neutralize free radicals in lipid peroxidation much more effectively than curcumin. However, in chemical systems, curcumin is more effective than DMC and BDMC at scavenging free radicals²⁴. Curcumin's anti-inflammatory activity depends on the presence of methoxy in its molecule³⁹. Guo et al⁴⁰ demonstrated that the anti-inflammatory properties of DMC and BDMC were attributed to the inhibition of nuclear factor kappa-B (NF- κB) activity triggered by inhibition of inducible nitric oxide synthase (iNOS) and COX-2. At the same concentration, all effects of DMC were superior to those of BDMC, and methoxy enhanced the anti-inflammatory effect

of DMC. Sheu et al⁴¹ used DMC to treat carotid artery injury in rats and demonstrated that DMC downregulated the phosphoinositide 3-kinase (PK13)/protein kinase B (AKT) pathway, thereby inhibiting the migration of vascular smooth muscle cells (VSMC) and the formation of neointima after vascular injury, and is more potent than other curcuminoids. In terms of antifungal activity, Akter et al⁴² determined the DMC content of turmeric plants and compared its antifungal activity against *Fusarium Solani Sensu Lato* (FSSL). Antifungal activity increased with increasing DMC content in various species of turmeric, according to the results.

Curcumin Complex

Curcumin Cyclodextrin (CD) inclusion complex

CD is a glucose-containing cyclic oligosaccharide. The α -1,4 glycosidic bonds between the glucose units are not in a direct line; they are at an angle to each other and form a cone shape, which gives cyclodextrins their ring shape. CD has both hydrophilic and lipophilic exterior cavities. Encapsulating drug molecules in cyclodextrin cavities can increase their water solubility and absorption *in vivo*⁴³. The most common cyclodextrins are α -CD, β -CD and γ -CD, which contain six, seven and eight glucose units, respectively. The number of glucose units in a cyclodextrin molecule determines its cavity size and, consequently, its ability to form inclusion complexes with different types of molecules⁴⁴. The power of cyclodextrins to increase the solubility of curcumin in the order of hydroxypropyl (HP- β -CD) > Methyl- β -cyclodextrin (M- β -CD) > β -CD > γ -CD⁴⁵. Zheng et al⁴⁶ experimentally verified that the solubility of curcumin-HP- β -CD in H₂O, HCl (pH

1.2) and phosphate buffered solution (PBS) (pH 6.8) was 63.5, 60.1 and 52.9 times higher than that of natural curcumin, respectively, and the concentration in the brains of male mice increased by 38.7 times. The oral bioavailability ratio in rats was increased by 2.8-fold⁴⁵.

Curcumin phospholipid complex

Curcumin phospholipid complexes are manufactured by combining curcumin and phospholipids in a 1:1 ratio *via* the solvent evaporation method, the mechanical dispersion method, the supercritical fluid process, etc. Typically, the combined phospholipid is phosphatidylcholine⁴⁷. Phospholipids are amphiphilic molecules with a hydrophilic polar head containing nitrogen or phosphorus and a hydrophobic (lipophilic) lengthy hydrocarbon-based chain. Curcumin usually binds to the head of the phospholipid, positioning the water-labile β -diketone moiety into the lipid bilayer and shielding it from hydrolytic retro-Claisen fragmentation, the primary mechanism of degradation in water⁴⁸. The non-polar tail of the phospholipid creates a bilayer around the complex. This structure provides a protective barrier that facilitates the uptake and transport of curcumin across the cell membrane⁴⁹. Cuomo et al⁴⁸ demonstrated in a human study that the total absorption of curcumin lecithin formulation (Meriva) was approximately 29 times higher than that of natural curcumin. Liu et al⁵⁰ demonstrated that the maximum plasma drug concentration of curcumin phospholipid complex in rats was $C_{max}=600.93$ ng/ml, peak time $T_{max}=2.33$ h, and the area under the drug-time curve $AUC_{0-\infty}=8772.57$ (ng min/ml), while the sum of curcumin and tetrahydrocurcumin was $C_{max}=266.70$ ng/ml, $T_{max}=1.62$ h, $AUC_{0-\infty}=2,609.04$; thus, the

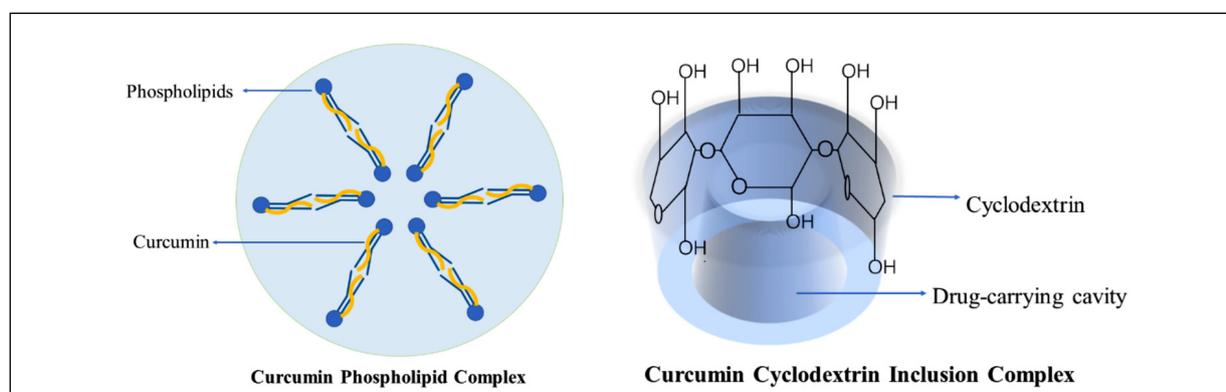


Figure 2. Curcumin complex.

phospholipid complex of curcumin significantly increased the bioavailability of curcumin in rats. Figure 2 shows curcumin cyclodextrin inclusion complex and curcumin phospholipid complex.

Nano Curcumin

Curcumin-loaded liposomes

Liposomes are spherical vesicle structures composed of lipid bilayers. The hydrophilic head faces outward towards the aquatic environment, and the hydrophobic tails face inward towards each other. In addition to the lipid bilayer, liposomes contain encapsulated water compartments, so hydrophilic and hydrophobic drugs can be encapsulated in these nanocarriers. Hydrophilic drugs are encapsulated in the middle, and lipophilic drugs are encapsulated in the lipid layer⁵¹. Improved biodegradability and biocompatibility, low toxicity, high durability, increased dissolution rate, controlled release/delivery, and the ability to target single cells are some of the pharmacological properties of liposomes⁵². The diameter of curcumin liposomes ranges between 25 nm and 1,000 nm, depending on the method of preparation used. The solvent injection method is utilized for the preparation of small unilamellar vesicles, reversed-phase evaporation for the preparation of giant unilamellar vesicles, thin-film dispersion and freeze-thaw method for the preparation of multilamellar vesicles, and the double emulsion method for the preparation of multivesicular liposomes⁵³. Finally, curcumin liposomes with high encapsulation efficiency and excellent stability were produced.

Chen et al⁵⁴ selected soybean phospholipids (SPC), egg yolk phospholipids, and hydrogenated soybean phospholipids to formulate curcumin-loaded liposomes (Nanjing, Jiangsu Province, China). An *in vitro* skin penetration study⁵⁴ showed that curcumin-loaded SPC liposomes (C-SPC-L) most significantly promoted drug penetration and deposition, inhibiting B16BL6 melanoma cell proliferation the most among the three loaded liposomes. In 2020, Wu et al⁵⁵ produced curcumin liposomes using bovine milk and krill phospholipid (Ningbo, Jiangsu Province, China), with particle size and zeta potential of 163.1 ± 6.42 nm, -26.7 mv and 212.2 ± 4.1 nm, -15.23 mv. Compared with the two, bovine milk phospholipid liposomes were more stable under severe storage conditions, while krill phospholipid liposomes were more bioavailable. Moreover, they possessed compa-

table antioxidant and anti-hyperglycemic properties⁵⁵. In treating various malignancies, liposomal curcumin improves efficacy and tumor targeting, reduces overall systemic toxicity, and is simple to administer⁵⁶.

Curcumin nanoparticles

Curcumin nanoparticles are tiny particles smaller than 1,000 nm, which can improve the solubility and stability of curcumin, and enhance its absorption and distribution in the body. Methods for preparing curcumin nanoparticles include ionic gelation, self-assembly, and antisolvent precipitation methods⁵⁶. The ionic gelation technology is a method for synthesizing nanoparticles by utilizing electrostatic interactions between different ions, and chitosan is typically a polymer used with this technology. Chitosan cation (R-NH₃⁺) and sodium triphosphate anion (phosphate ion) are mixed with the polymer to create a structure resembling conventional gel⁵⁷. In 2022, Tian et al⁵⁸ synthesized berberine-curcumin self-assembled submicron particles (Beijing, China). They combined berberine and curcumin, and by high-speed stirring in the acidic solution, berberine became positively charged. In contrast, due to the phenolic hydroxyl group in the curcumin molecular structure, it became negatively charged in the aqueous solution and precipitated slowly. During the precipitation process, berberine and curcumin attract and interact with each other through electrostatic attraction, π - π stacking, and hydrophobic forces, resulting in two-dimensional crystal twinning, and mutual rotation through hydrophobic forces, forming a sphere with a three-dimensional structure⁵⁸. The working principle of liquid antioxidant precipitation is that when curcumin and aqueous antisolvent are mixed in the solution containing an organic solvent, a supersaturation effect occurs, and the adsorption of compound molecules leads to the nucleation and further growth of particles⁵⁹. These methods combine curcumin with other substances, such as polymers, to generate nanoparticles of a particular size and shape. Poly (lactide-co-glycolide acid) (PLGA), chitosan, metal, and mesoporous silica nanoparticles are the dominant carriers for curcumin nanoparticles⁶⁰.

PLGA is a commonly used polymer in nanomedicine, and its degradation products are lactic acid and hydroxyacetic acid, both of which are byproducts of human metabolic pathways and are, therefore, non-toxic. In addition, PLGA accelerates hydrolysis at acidic and alkaline pH, an antitumor property, as PLGA is more stable under

physiological conditions (pH 7.4). In contrast, in tumor tissue (pH 5.5), degradation is accelerated to facilitate the release of antitumor drugs⁶¹. Peng et al⁶² formulated curcumin PLGA nanoparticles and treated osteosarcoma cells at 2 µg/ml concentration for 24 hours. Fluorescence in the cytoplasm and nucleus increased under fluorescence microscopy, indicating that the amount of curcumin internalized into cells increased. This is due to nanoparticles' ability to enter cells *via* endocytosis, whereas isolated curcumin can only enter cells *via* passive diffusion⁶¹.

Chitosan is a linear polysaccharide produced by the deacetylation of chitin and it consists of glucosamine and N-acetyl glucosamine units linked by β-1,4 linkages. It is a natural polysaccharide containing cations with a high safety profile⁶³. Positively charged curcumin chitosan nanoparticles (CUR-CS-NP) have electrostatic interactions with negatively charged mucus glycoproteins, which prolong the contact duration between CUR-CS-NP and the colon mucus membrane. Compared to unbound curcumin, colon cancer cells absorb more CUR-CS-NP, and the effect of inhibiting cell viability is more robust⁶⁴.

Metal nanoparticles, as inorganic materials, have superior stability, high surface area and porosity, better drug loading capacity, bioavailability, drug release controllability, and resistance to most organic solvents compared to organic compounds⁶⁵. Common materials include gold, silver, titanium, zinc, and iron, among others. Some metal oxides, such as TiO₂, ZnO, and CuO, are negatively charged and capable of combining with curcumin, while also biodegradable and, therefore, relatively harmless for mammals⁶⁶. Song et al⁶⁷ modified silver nanoparticles with curcumin (Wuhan, Hubei, Chian) to produce silver/curcumin nanoparticles (cAgNPs). Comparatively to conventional silver nanoparticles, cAgNPs attach to the surfaces of *Bacillus subtilis* and *Escherichia coli*, producing a local high Ag⁺ environment while generating more reactive oxygen species under the synergistic effect of curcumin, resulting in membrane damage and increased bacterial mortality. This not only addresses the problem of curcumin's poor absorption but also combines the antibacterial effects of curcumin and silver nanoparticles⁶⁷. Dey and Sreenivasan⁶⁸ covalently conjugated curcumin onto the surface of gold nanoparticles (AuNPs) aided by a water-soluble polymer *via* a succinate linker (New Delhi, India) to produce curcumin succinate polymer gold nanoparticles (Ccm-SA-P1-AuNPs). Due to the

polyethylene glycol backbone of the Ccm-SA-P1-AuNPs molecule, the negatively charged Ccm-SA-P1AuNPs can largely avoid protein adsorption, thereby extending the duration for systemic circulation of the drug and enhancing its water solubility. Compared with free curcumin, Ccm-SA-P1-AuNPs have more significant cytotoxicity towards glioma cancer cells⁶⁸.

Mesoporous silica nanoparticles (MSN) as nanocarriers have properties such as many pores, a wide surface area, and an adjustable pore structure morphology. Functionalizing silica nanoparticles with different coating agents can better control the load⁶⁹. Bollu et al⁷⁰ synthesized two different silica-based (MSU-2 and MCM-41) curcumin-loaded mesoporous materials, V3 and V6 (Tarnaka, Hyderabad, India). In contrast to other silica-loaded curcuminoids, V3 and V6 release curcumin slowly and continuously under physiological conditions (pH = 7.4) and are more biocompatible in the Chinese hamster ovary cell line, while reducing the anti-apoptotic proteins epidermal growth factor receptor (EGFR) and B-cell lymphoma-2 (BCL-2), increasing reactive oxygen species (ROS) and subsequently exhibiting significant cytotoxicity in cancer cells⁷⁰. In the study by Pamukçu et al⁷¹ (Izmir, Turkey), curcumin was loaded onto hyperbranched polyethyleneimine-grafted mesoporous silica nanoparticles (F-MSN-PEI/Cur). F-MSN-PEI/Cur has more potent antimicrobial properties than pure curcumin; it reduces the total biomass in the biofilm matrix, inhibits biofilm formation, and eliminates immature biofilms. F-MSN PEI/Cur at 25 µg/ml can significantly reduce the cell viability of *Staphylococcus aureus*; at a maximal concentration of 400 µg/ml, only 20% of cell viability remained⁷². Figure 3 shows the curcumin-loaded liposomes, curcumin-chitosan nanoparticles, and curcumin-loaded MSN.

The Effects of Curcumin on Osteoporosis

Effects of Curcumin on Osteoporosis in Animal Studies

Osteoporosis is a metabolic bone disease characterized by decreased bone mass and deterioration of the microarchitecture of bone tissue, leading to increased bone fragility and fracture risk⁷³. Long-term steroid medication, hormonal changes and inadequate dietary intake are the most common causes of osteoporosis⁷⁴. Primary osteoporosis is associated with estrogen deficiency

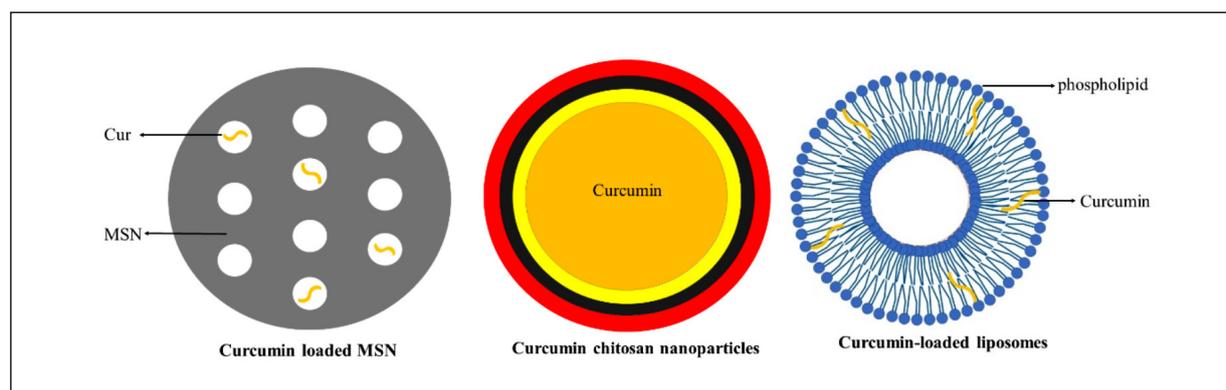


Figure 3. Curcumin nanoparticles and liposomal curcumin.

cy, and the decline in estrogen levels in women during menopause, or the decrease in estrogen and androgen levels in later years in men, can lead to a loss of bone mass and strength, resulting in osteoporosis⁷⁵. Patients with secondary osteoporosis typically suffer from diabetes or long-term glucocorticoid (GC) administration, which promotes osteoclast formation and accelerates bone degradation and loss⁷⁴. Consequently, ovariectomy (OVA) or glucocorticoids are animal models' most prevalent methods for inducing osteoporosis.

To investigate the osteoprotective properties of curcumin, Chen et al⁷⁶ used dexamethasone (DEX) subcutaneously for 60 days to induce osteoporosis in rats. Subsequently, curcumin administration (100 mg/kg) for two months resulted in a significant increase in bone mineral density (BMD), bone alkaline phosphatase (B-ALP) and bone mechanical strength (ultimate load and stiffness of bone), a decrease in carboxy-terminal telopeptide (CTX) reduced, and an improvement in the microstructure of bone trabeculae⁷⁶. To further investigate the role of curcumin in primary osteoporosis, Kim et al⁷⁷ administered curcumin (9.5 mg/kg) by gavage through an esophageal cannula to mice after OVA, and after 8 weeks, compared with the control group, they showed significant higher femoral bone trabecular volume ratio (BV/TV), trabecular number (Tb. N), and femoral bone mineral density, as well as a reduction in serum collagen-type I fragments, which promoted bone resorption⁷⁷. Another study by French et al⁷⁸ found that ovariectomy alone decreased vertebral mineral content, bone mineral content, decreased vertebral spine BMD and increased osteocalcin and CTX levels in rats. When curcumin was administered to de-ovulated rats, these conditions were reversed, along with an

increase in femur size, resulting in an increase in femur compressive strength, producing beneficial alterations in osteoporotic bone turnover changes and an increase in bone strength⁷⁸.

In addition, Liang et al⁷⁹ studied the effects of curcumin on the biomechanical properties and microstructural enhancements of bone using a diabetic rat model. A high-sugar, high-fat diet and streptozotocin were used to induce diabetes in rodents, who were then treated with curcumin (110 mg/kg) for eight weeks. The results demonstrated a decrease in blood lipids (total cholesterol, triglycerides, and low-density lipoprotein) and fasting glucose levels, as well as significant improvements in maximal load, fracture load, elastic load and bone stiffness coefficients in the femur, and repair of bone trabecular microarchitecture in rats⁷⁹. Yang et al⁷³ discovered that curcumin may be an effective treatment for post-Alzheimer's osteoporosis. As a model for investigating osteoporosis, they chose transgenic mice (APP/PS1 mice) expressing a familial Alzheimer's disease (AD)-associated mutant human gene and orally administered curcumin (600 ppm) for three months. The analysis of bone histomorphometry revealed an increase in BMD, BV/TV, Tb. N, trabecular thickness (Tb. Th), and connectivity density (Conn.D), while trabecular separation (Tb. Sp) decreased. Simultaneously, the morphology of the proximal tibial metaphysis and shaft enhanced, and cortical thickness increased significantly⁷³. Various animal models⁷⁴ have demonstrated the effects of curcumin combined with other compounds. In a study, Partoazar and Goudarzi⁷⁴ created phosphatidylserine liposomes containing curcumin (PSLs-Cur) and induced osteoporosis in rats with methylprednisolone (MP) by administering PSLs-Cur (25 mg/kg) orally for three weeks. Compared to phospho-

tidylserine or curcumin alone, oral administration of PSL-Cur markedly improved serum markers (osteocalcin, B-ALP, Ca, and P) and bone mechanical strength. The PSL-Cur group also demonstrated a significant increase in the thickness and volume of cortical and trabecular bone mass; the thickness of the diaphysis and the bone marrow cavity also healed significantly⁷⁴.

Effects of Curcumin on Osteoporosis in Human Studies

There are fewer studies on the effects of curcumin on humans with osteoporosis, but several studies have examined its effects on human bone health. Kheiridoost et al⁸⁰ enrolled 120 postmenopausal women aged 50 to 65 with primary osteoporosis or osteopenia in a randomized controlled trial with triple blinding. The subjects were randomly assigned to receive a placebo, 80 mg of curcumin nanoparticles (CUR group), 1,000 mg of *Nigella sativa* oil (NS group), or 80 mg of nanomicelle curcumin plus 1,000 mg of *Nigella sativa* oil (CUR-NS group) for six months. The results showed an improvement in BMD and a significant reduction in Alkaline Phosphatase (ALP) in the CUR-NS group, with no significant differences in renal and hepatic biomarkers (urea, alanine aminotransferase, aspartate aminotransferase), and the combination was more effective and safer than treatment alone⁸⁰.

Similar results were obtained in another trial by Riva et al⁷⁵, in which the administration of 1,000 mg of curcumin orally for 6 months led to considerable increases in BMD in the subjects' heel, little finger, and upper jaw. In the same year, Hatefi et al⁸¹ conducted an oral trial with a higher dose of curcumin to investigate the effect of curcumin on bone loss in spinal cord injury patients. One hundred patients with spinal cord injuries were enrolled, and the intervention group received curcumin (110 mg/kg) for six months. Comparing pre- and post-study bone conversion parameters, carboxy-terminal telopeptide of type I collagen (sCTX) and procollagen type I N-terminal propeptide (PINP) were reduced in the curcumin group⁸¹. In conclusion, curcumin improves BMD in osteoporosis from all causes and has a good safety profile.

The Molecular Role of Curcumin in the Prevention of Osteoporosis

Curcumin regulates the production of osteoblasts

Osteoblasts are essential for the formation and maintenance of bone tissue. In healthy bones, os-

teoblast and osteoclast activity is strictly controlled to maintain a balance between bone formation and resorption⁸². In osteoporosis, however, the number and activity of osteoblasts are diminished, and the rate of bone resorption by osteoclasts exceeds the rate of bone formation by osteoblasts, resulting in a loss of bone mass and bone strength⁸³. During osteoblastogenesis, MSCs first undergo osteogenesis and become preosteoblasts. After that, the pre-osteoblasts undergo osteogenesis, during which cellular ALP activity (a marker of early osteoblast differentiation) and osteocalcin (OC) expression (a marker of late osteoblast cell differentiation) will be significantly enhanced, ultimately resulting in mineralization of the cellular matrix. During this process, the expression of osteoblast genes such as Runt-related transcription factor 2 (*Runx2*) and collagen, type I,1 (*Col1A1*) will be substantially increased⁸⁴. The classical Wnt/Frizzled/ β -catenin signalling pathway has also been shown⁸⁵ to play an essential role in osteoblast proliferation and differentiation. Low-density lipoprotein receptor-related protein 5 (LRP5) interacts with frizzled receptors and transduces signals *via* Wnt ligands, resulting in constitutively activated LRP5 mutations that can lead to increased bone density. Meanwhile, β -linked protein can act synergistically with bone morphogenetic protein 2 (BMP2) to promote osteoblast differentiation and bone formation.

Chen et al⁸⁶ utilized DEX to inhibit the proliferative capacity of osteoblasts, and treatment with curcumin led to significant upregulation of the expression levels of ALP, *Col1A1*, osteonectin, *Runx2* and osteocalcin, as well as the reactivation of the Wnt signalling pathway inhibited by DEX⁸⁶. In addition, curcumin inhibits osteoblast apoptosis regulation by decreasing the ratio of apoptosis-related proteins BCL2 associated X (*Bax*)/BCL-2, Cysteinyl aspartate-specific proteinase-3 (caspase-3) and cleaved Poly ADP-ribose polymerase (PARP) levels and activating Dex-induced extracellular signal-regulated kinase (ERK) signalling in osteoblasts⁷⁶. In another study by Li et al⁸⁴, curcumin (0.25 μ M) inhibited endogenous ROS production and attenuated H₂O₂-induced oxidative stress and apoptosis in osteoblasts by activating the Glycogen synthase kinase-3 beta (GSK3 β)/ Nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway. Two other studies^{87,88} have combined curcumin and *Fructus Ligustri Lucidi* (FLL) and hyaluronic acid-modified curcumin and alendronate (ALN) nanoparticles for co-delivery. The findings demonstrate that co-administration signifi-

cantly promoted the proliferation, differentiation and mineralization of the pre-osteoblast cell line (MC3T3-E1) cells compared to curcumin administration alone. This resulted in increased expression of bone morphogenetic proteins Runx2 and osteocalcin, as well as increased collagen deposition, which ultimately led to increased bone formation⁸⁸.

Curcumin regulates osteoclast production

Osteoclasts are multinucleated bone-resorbing cells that are formed by the fusion of monocytes/macrophages differentiated from bone marrow hematopoietic stem cells. It is present in stressed and injured bone tissue that requires remodeling. Osteoclast formation is dependent on the expression of monocyte/macrophage colony-stimulating factor (M-CSF) and TNF receptor superfamily members [receptor activator of nuclear factor- κ B ligand (RANKL) and osteoprotegerin (OPG)]. Osteoblasts express M-CSF constitutively, whereas RANKL is induced by bone resorption-stimulating factors such as hormones, growth factors, or cytokines. M-CSF binds to colony-stimulating factor-1 receptors (c-Fms) on osteoclast precursors and induces osteoclast precursor differentiation into mature osteoclasts⁴. RANKL is a transmembrane glycoprotein expressed on the surface of bone stromal cells. Osteoclast precursor cells express NF- κ B receptor activator (RANK), and RANKL interacts with RANK and leads to the recruitment of TNF receptor-associated factor (TRAF). The sequential recruitment of RANK to TRAF6 and NF- κ B-inducible kinase results in the activation of NF- κ B, and TRAF2 recruitment results in the activation of c-Jun N-terminal kinase (JNK), which promotes osteoclastogenesis and stimulates bone resorption by osteoclasts⁸⁹. In addition, M-CSF and RANKL play a crucial role in osteoclast differentiation and bone resorption by inducing the MAPK pathway and stimulating the expression of downstream molecules such as a nuclear factor of activated T cells 1 (NFATc1), tartrate-resistant acid phosphatase (TRAP), c-fos, and Cathepsin K⁹⁰. OPG inhibits osteoclastogenesis by inhibiting the interaction between RANKL and RANK, and parathyroid hormone and prostaglandin E₂ (PGE₂) cause an increase in RANKL and a decrease in OPG in osteoblasts⁸⁹.

Bone marrow stromal cells (BMSC) and bone marrow-derived macrophages (BMMs) are the precursor cells of osteoclasts. Oh et al⁸⁹ found that curcumin (4 μ M) effectively reduced RANKL expression in IL1 α -stimulated BMSCs and inhibited

osteoclast formation. Gold nanoparticles (GNPs) have previously been reported to inhibit the formation of osteoclasts⁹¹. To investigate the effect of curcumin nano preparations on osteoclast genesis, Heo et al⁹² prepared β -cyclodextrin-coupled GNPs to form inclusion complexes with curcumin (CUR-CGNPs). They found that CUR-CGNPs substantially decreased osteoclast differentiation markers in BMMs, including c-fos, NFATc1 tartrate-resistant acid phosphatase (TRAP), and osteoclast-associated receptor (OSCAR) mRNA expression, compared to curcumin and GNP groups. In addition, CUR-CGNPs inhibit RANKL expression, thereby decreasing RANKL-induced F-actin ring formation and bone resorption activity⁹¹. In a recent study, Yang et al⁹⁰ coupled curcumin and poly amidoamine dendrimers (PADs) with hexachlorocyclotriphosphonitrile (HCCP) to form stable and homogeneous curcumin-loaded nanospheres (HCCP-Cur-PAD, HCP-NPs). It has been demonstrated that HCP-NPs can enter lysosomes *via* endocytosis. After entering BMMs cells, HCP-NPs were released and diffused to the nucleus. This resulted in decreased expression of RANKL and c-fos, NFATc1, TRAP, and actin ring, thereby inhibiting osteoclast formation. Simultaneously, the osteoclast-associated genes *histonectin K* and matrix metalloproteinase 9 (*MMP9*) inhibited osteoclast bone resorption⁹⁰.

A novel study by Liang et al⁹³, the C-C motif chemokine ligand 3 (CCL3) family are highly expressed in BMMs and serve a crucial role in osteoclast migration and differentiation. Subsequent *in vitro* and *in vivo* studies⁹³ demonstrated that curcumin (25 μ M) inhibited CCL3-induced osteoclast migration. Oral administration of curcumin (200 mg/kg/d for 4 weeks) significantly suppressed CCL3 serum levels in OVX mice, demonstrating that curcumin blocks the migration of BMMs and ultimately inhibits the formation of mature osteoclasts by decreasing the production of CCL3. These studies show the potential of curcumin to contribute to the prevention of osteoporosis. Table I summarizes the effects of curcumin on bone loss in animal, human and *in vitro* studies.

The effects of Curcumin on Osteoarthritis

Effects of Curcumin on Osteoarthritis in Animal Studies

The osteoarthritis pathology is characterized by focal loss of articular cartilage, subchon-

Curcumin nanoparticles and the therapeutic potential of curcumin for musculoskeletal disorders

Table 1. The effects of curcumin on bone loss in animal, human and *in vitro* studies.

Type of study	Type of model	Treatment, dose and duration	Findings	Reference
Animal	Glucocorticoid-induced osteoporotic rats	Curcumin (100 mg/kg) - oral, 2 months ultimate load↑, stiffness↑, trabecular thickness↑, CTX↓	BMD↑, B-ALP↑,	Chen et al ⁷⁶
Animal	Ovariectomy-induced osteoporotic mice	Curcumin (9.5 mg/Kg) - gavage, 8 weeks	BMD↑, BV/TV ↑, Tb.N.↑, Gpx↑, RANKL↓, NFAT2↓, ERK ↓, JNK↓, p38↓	Kim et al ⁷⁷
Animal	Ovariectomy-induced osteoporotic rats	Curcumin (1.5-15 mg/kg) - oral, 2 months	Bone mineral content↑, spine BMD↑, osteocalcin↓, CTX↓	French et al ⁷⁸
Animal	Diabetes-induced osteoporosis rats	Curcumin (110 mg/Kg) - gavage, 8 weeks	Total cholesterol↓, triglyceride↓, low-density lipoprotein↓ maximum load↑, breaking load↑, elastic load↑, bone rigidity coefficient↑, TGFβ1↑, TβRI↑, TβRII↑, Smad2/3↑	Liang et al ⁷⁹
Animal	APP/PS1 transgenic mice	Curcumin (600 ppm) - oral, 3 months	BMD↑, BV/TV↑, Tb.N↑, Tb.Th↑, Conn.D↑, Tb.Sp↓	Yang et al ⁷³
Animal	Methylprednisolone-induced osteoporotic rats	PSLs-Cur (25 mg/kg)	Bone strength↑, osteocalcin↑, Tb.Th↑, B-ALP↑, Ca↑, OPG↑, RANKL↓	Partoazar and Goudarzi ⁷⁴
Human	120 postmenopausal osteoporosis women	CUR-NS (80 mg+1,000 mg) - oral, 6 months	BMD↑, ALP↓	Kheiridoost et al ⁸⁰
Human	57 healthy low bone density adults	Curcumin (1,000 mg) - oral, 6 months	Bone mineral density with heel↑, small finger↑, upper jaw densities↑	Riva et al ⁷⁵
Human	100 Patients with Spinal Cord Injury	Curcumin (110 mg/kg) - oral, 6 months	BMD↑, sCTx↓, PINP↓, ALP↑, Col1A1↑, Runx2↑, osteocalcin↑, osteonectin↑, wnt↑, LRP5↑	Hatefi et al ⁸¹
Cell culture	Osteoblasts	Curcumin (2 μM)	Col1A1↑, Runx2↑, osteocalcin↑, osteonectin↑, p-GSK3β↑, Nrf2↑, Ros↓,	Chen et al ⁸⁶
Cell culture	MC3T3-E1 cells	Curcumin (0.25 μM)	Bax↓, Bcl-2↑, caspase 3↓, PARP↓	Chen et al ⁷⁶
Cell culture	MC3T3-E1 cells	Cur (50 μg)+FLL (70 μg)	ALP↑, Col1A1↑, Runx2↑, osteonectin↑, p-GSK3β↑, Nrf2↑, Ros↓,	Li et al ⁸⁴
Cell culture	MC3T3-E1 cells	HA-ALN/CUR-NPs	Calcium deposition↑, Runx2↑, ALP↑BMP-2↑	Bukhari et al ⁸⁷
Cell culture	MC3T3-E1 cells	HA-ALN/CUR-NPs	Runx2↑, BMP-2, osteocalcin↑, collagen deposition↑	Dong et al ⁸⁸
Cell culture	BMSC and whole bone marrow cells	Curcumin (4 μM)	RANKL↓	Oh et al ⁸⁹
Cell culture	Bone marrow-derived macrophages	CUR-CGNPs (10 μM)	c-fos↓, NFATc1↓, TRAP↓, OSCAR↓, RANKL↓	Heo et al ⁹¹
Cell culture	Bone marrow-derived macrophages	HCP-NPs (5-20 μg/ml)	RANKL↓, c-fos↓, NFATc1↓, TRAP↓, Cathepsin K↓, MMP9↓	Yang et al ⁹⁰
Cell culture	Bone marrow-derived macrophages	Curcumin (25 μM)	CCL3↓	Liang et al ⁹²

dral bone changes, and osteophyte formation, resulting in degenerative joint pain, stiffness, and limited range of motion. Because articular cartilage depends solely on its resident cells, the chondrocytes, for the maintenance of the extracellular matrix, impaired chondrocyte function and apoptosis are the most important pathogenic mechanisms in osteoarthritis⁹⁴. The Osteoarthritis Research Society International (OARSI)⁹⁵ devised the Mankin scoring system to classify the severity of osteoarthritic cartilage lesions. The evaluation consists of four categories: cartilage structure, chondrocyte periphery staining, spatial arrangement, and background staining intensity. The sum of the ratings for each type yields a total score between 0 (normal) and 14 (severe osteoarthritis). Curcumin has been shown⁹⁶ in animal models of osteoarthritis to mitigate osteoarthritis symptoms substantially. Jin et al⁹⁶ established a knee osteoarthritis model in rats with monoiodoacetate (MIA). After intravenous administration with 0.5% curcumin, the Mankin score of osteoarthritis rats was reduced, improving cartilage degeneration. Zhang and Zeng⁹⁷ treatment of osteoarthritis mice with intraperitoneal injections of curcumin (200 mg/kg) resulted in decreased Mankin scores, knee diameter, expression of synovial fluid inflammatory biomarkers IL-1 β , IL-6 and TNF- α , pain reductions, and increased paw reduction thresholds. Guan et al⁹⁸ used MIA to induce an experimental knee osteoarthritis (KOA) model in rats. After 2 weeks of oral treatment with 20 mg/kg curcumin and 100 mg/kg chondroitin sulfate, the knee joint's diameter decreased, the articular cartilage recovery improved, and synovial thickness reduced. The injured knee joint could be bent, and the edema reduced. Meanwhile, curcumin treatment also significantly increased superoxide dismutase (SOD) activity, downregulated MMP3 and cartilage oligomeric matrix protein (COMP) levels, and inhibited Toll-like receptors (TLR4) and COX-2 expression.

In addition, Feng et al⁹⁹ established a rat anterior cruciate ligament transection (ACLT) osteoarthritis model by surgery, followed by intraperitoneal injection of curcumin (50 mg/kg and 150 mg/kg) once daily for 8 weeks. The results showed that curcumin treatment reversed cartilage surface sclerosis and knee joint gap narrowing in a dose-dependent manner, improved chondrocyte and proteoglycan loss in ACLT rats, reduced apoptosis levels and inhibited osteoarthritis progression.

However, curcumin's water solubility and bio-

availability are weak. Kang et al¹⁰⁰ designed an acid-activatable curcumin polymer (ACP) that can rapidly release curcumin under acidic conditions in order to enhance the therapeutic efficacy of curcumin. Compared to the same concentration of natural curcumin, ACP micelles treatment resulted in smooth joint surfaces, the structural integrity of cartilage, robust expression of proteoglycan, aggrecan, and collagen, as well as more pronounced inhibition of TNF- α and IL-6 β . Chen et al¹⁰¹ loaded curcumin into small extracellular vesicles (sEV-CUR) and injected 10 μ L (1×10^9 p/mL) of sEV-CUR every two weeks into the right knee cavity of ACLT-induced osteoarthritis animals. Mice treated with ACLT for four weeks had lower Mankin scores, indicating decreased synovial inflammation, oxidative stress, chondrocyte apoptosis, and osteoarthritis-related pain.

Effects of Curcumin on Osteoarthritis in Human Studies

Regarding the effect of curcumin on knee osteoarthritis pain, Lopresti et al¹⁰² designed a randomized, double-blind, placebo-controlled study. This study enrolled 101 patients between the ages of 45 and 70 with KOA, activity-related knee pain, and morning stiffness lasting less than 30 minutes. These subjects were divided into treatment and placebo groups and received 500 mg of standardized curcumin extract (Curcugen[®], Perth, WA 6150, Australia) or a placebo twice per day for eight weeks. Curcumin significantly decreased the Knee Injury and Osteoarthritis Outcome Score (KOOS) compared to the placebo and demonstrated greater improvement than the placebo in the timed up-and-go test, the 6-minute walk test, and the Japanese Orthopaedic Association Score for Osteoarthritic Knees (JOA), as well as reducing the use of pain medication in 37% of subjects¹⁰¹. Henrotin et al¹⁰³ conducted another study in which 150 patients aged 45 to 80 years with primary osteoarthritis diagnosed according to the American College of Rheumatology (ACR) clinical radiology criteria were divided into three groups: the bio-optimized *Curcuma longa* extract (B-oCL) low-dose group, the B-oCL high dose group and the placebo group. Efficacy analyses showed that serum levels of the global assessment of disease activity (PGADA) and the osteoarthritis biomarker sColl2-1 were reduced in patients treated with curcumin, and a daily intake of 186.6 mg/day of BCL reduced knee pain in patients with symptomatic osteoarthritis of the knee¹⁰³. The following year in Iran, Atabaki et al¹⁰³ re-

cruited 30 osteoarthritis patients (aged 40-55 years) based on ACR criteria. They were divided into two groups: one received 80 mg of Sinacurcumin® (Mashhad, Iran), and the other group received a placebo. After three months, the treatment group demonstrated a significant reduction in knee pain, the visual analog scale (VAS), C-reactive protein (CRP), cluster of differentiation 4 (CD4) and CD8 T cell frequencies, Th17 cell and B cell frequencies, and a significant increase in Treg cells compared to the placebo group. The authors speculated that the immunomodulatory effects of curcumin on T and B cell numbers and function might be beneficial for patients with osteoarthritis¹⁰⁴.

The Molecular Role of Curcumin in the Prevention of Osteoarthritis

Inhibits the formation of inflammatory factors IL-1 β and TNF

Local joint injury caused by trauma or overuse permits the release of inflammatory factors as a cause of osteoarthritis¹⁰⁵. Among these cytokines, IL-1 β and TNF are the most important; IL-1 β is associated with cartilage degeneration, whereas TNF promotes the inflammatory response. Patients with osteoarthritis have elevated levels of IL-1 β and TNF in their synovial fluid, synovial membrane, subchondral bone, and cartilage, which inhibits the synthesis and expression of proteoglycan, link protein, and type II collagen in their chondrocytes¹⁰⁶. In chondrocytes, IL-1 β induces typically nuclear translocation of NF- κ B¹⁰⁷. NF- κ B is a family of dimeric transcription factors that are indispensable for coordinating inflammatory responses and innate and adaptive immunity. NF- κ B is typically activated by classical signalling pathways to generate NF- κ B dimers, which, in conjunction with TNF, Toll-like receptors (TLR), etc., recruit the κ B inhibitor kinase (IKK) complex and result in the activation of the IKK complex. Activation of the IKK complex results in the ubiquitination and proteasome-dependent degradation of the inhibitor of NF- κ B (I κ B), releasing NF- κ B into the nucleus and activating downstream gene transcription¹⁰⁸, and subsequently mediates inflammatory effects.

Csaki et al¹⁰⁷ treated IL-1 β -induced human chondrocytes with 50 μ M curcumin or 50 μ M resveratrol and showed decreased expression of Cox-2, MMP-3, MMP-9, vascular endothelial growth factor (VEGF) and the regulatory death-associated protein cysteine-aspartic pro-

tease 3 (caspase3) and increased expression of SRY-Box Transcription Factor 9 (Sox-9), which is essential for cartilage matrix gene expression. Curcumin treatment alone completely inhibited IL-1 β -induced IKK activation; resveratrol blocked the degradation and ubiquitination of I κ B α , a natural inhibitor of NF- κ B¹⁰⁷. Buhrmann et al¹⁰⁹ cultivated chondrocytes into 3D-alginate, placed in an *in-vivo*-like osteoarthritic environment model and treated with different concentrations of curcumin. Elevated expression of Sox-9, which in turn inhibited the NF- κ B pathway, led to a decrease in osteoarthritic environment-related catabolic factors (MMP-9, Cox-2, caspase 3), increased chondrocyte survival-related factors (collagen II, β 1-integrin, and CSPG), thereby protecting human chondrocytes¹⁰⁹. Recently, sEV-CUR was manufactured by Xu et al¹⁰¹, which increased the number of mice chondrocytes and extracellular matrix synthesis-related marker aggrecan proteoglycan *in vitro*. It inhibited the expression of chondrocyte catabolic markers aggrecanase (ADAMTS5) and MMP13, inflammatory factors (IL-1 β and TNF α), exerting a powerful protective effect against osteoarthritis¹⁰¹. In addition, Wang et al¹¹⁰ formulated hyaluronic acid/chitosan nanoparticles (HA/cNPs) for the delivery of curcumin and determined that a drug dosage of 38.44% was optimal. Using HA/cNP (30 μ g/ml) effectively reversed joint surface injury and promoted chondrocyte proliferation in rats with arthritis by decreasing MMP-1 and MMP-13 protein levels and I κ B α phosphorylation¹¹⁰.

Regulation of chondrocyte apoptosis through caspase 3 expression

Apoptosis is a genetically controlled process of programmed cell death that is essential for removing damaged or unwanted cells from the body and controlling cell proliferation. Caspase 3 is a cysteine protease that, once activated, cleaves many cellular substrates, including structural proteins such as actin and laminin, as well as proteins involved in DNA repair and cell survival, leading to terminal cell death¹¹¹. Caspases are activated mainly by extrinsic and intrinsic pathways. The extrinsic pathway binds to death receptors on the cell surface through death ligands (e.g., TNF- α and Fas ligands), allowing the recruitment of caspase 8 and activation of downstream caspase 3. The intrinsic pathway, also known as the mitochondrial pathway, consists of DNA damage, oxidative stress, and oncogene activation that inhibits the *BCL*-

2 anti-apoptotic gene and activates the *BAX* pro-apoptotic gene, which increases the permeability of the outer mitochondrial membrane and subsequently releases cytochrome c from the mitochondria into the cytoplasm, where it binds to Apaf-1 and forms the apoptosome, activating caspase 9 and caspase 3 to cause apoptosis¹¹².

Zhao et al¹¹³ used sodium nitroprusside (SNP) to induce apoptosis in rabbit chondrocytes and investigated the anti-apoptotic effect of curcumin (0-20 μ M). Curcumin reversed SNP-induced chondrocyte apoptosis and NO production, decreased the expression of caspase 3, BCL/Bax and loss of mitochondrial membrane potential ($\Delta\Psi_m$), and increased the expression of collagen II in rabbit chondrocytes¹¹³. In osteoarthritis induced by anterior cruciate ligament transection (ACLT) surgery in rats, immunoreactivity of MMP-3, caspase 3, vascular endothelial growth factor (VEGF) and Runt-related transcription factor 2 (RUNX2) was significantly increased in the articular cartilage region. An intra-articular injection of 20-40 μ M chemically modified curcumin (CMC2.24) can reverse these trends and chondrocyte apoptosis by inhibiting the NF- κ B/hypoxia-inducible factor (Hif-2 α) axis¹¹⁴. In addition to this, Xu et al¹⁰¹, developed small extracellular vesicles containing curcumin (sEV-CUR). In ACLT-induced mice and Tert-butyl hydroperoxide (TBHP)-induced chondrocytes, sEV-CUR had greater anti-apoptotic effects than free curcumin and sEV. Moreover, the protein expression of MMP-13, the oxidative stress marker 8-OHdG, a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) and caspase 3 were significantly reduced after sEV-CUR treatment¹⁰¹.

Overall, these findings demonstrate the potential of curcumin to modulate articular cartilage degradation and apoptosis to treat osteoarthritis. Table II summarizes the effects of curcumin on osteoarthritis *in vivo* and *in vitro* studies.

The Effects of Curcumin on RA

Effects of Curcumin on RA in Animal Studies

RA is a common chronic autoimmune disease characterized by inflammation and joint damage due to a breakdown in self-tolerance that causes the immune system to attack the synovial membranes of the joints¹¹⁵. For rheumatoid arthritis, Dai et al¹¹⁶ treated rats with bovine

type II collagen to induce arthritis. After 21 days, curcumin (200 mg/kg) was administered by gavage daily for three weeks. The rats showed reduced hind paw edema volume and decreased arthritis scores, and histopathology showed that inflammatory cell infiltration and synovial hyperplasia were suppressed¹¹⁶. The following year, Wang et al¹¹⁷ induced an attack of arthritis in rats reinjecting bovine type II collagen seven days after the initial injection and observed a significant improvement in joint edema, bone/chondral destruction, synovial hyperplasia and vascular opacity formation after ten days of oral administration of curcumin (200 mg/kg)¹¹⁷. To overcome the low oral bioavailability of curcumin, Zheng et al¹¹⁸ formulated curcumin into oil-water nanoemulsions (CM-NS) with a diameter of 150 nm, and by treating Freund's complete adjuvant-induced arthritic rats with oral CM-NS (50 mg/kg) for 2 consecutive weeks, the levels of TNF- α and IL-1 β in synovial fluid and serum were significantly decreased, and the intense inflammatory cell dip consisting of lymphocyte plasma cells, macrophages and neutrophils, was improved considerably¹¹⁸. Since anti-inflammation and joint lubrication are required to treat RA, Fan et al¹¹⁹ constructed a novel anti-RA drug consisting of hyaluronic acid/curcumin (HA/Cur) nanomicelles with a diameter of 164 nm. HA/Cur nanomicelles (336 g/mL) injected intra-articularly into the ankle joint of rats with type II collagen-induced arthritis improved joint surface blurring and soft tissue enlargement, decreased foot edema, and protected cartilage from RA-induced damage by substantially reducing the coefficient of friction between cartilage surfaces thanks to hyaluronic acid¹¹⁹.

Effects of Curcumin on RA in Human Studies

Curcumin has had limited human studies but still shows great potential in the prevention and treatment of RA in humans. Amalraj et al¹²⁰ designed a randomized, double-blind, double-dose, placebo-controlled study in which 36 RA patients with a mean age between 35 and 40 years were enrolled. These subjects were randomly assigned in a ratio of 1:1:1 to receive capsules containing 250 mg low-dose curcumin, 500 mg high-dose curcumin, or 500 mg placebo twice daily. After three months, the visual analog scale (VAS) and disease activity score 28 (DAS28) were significantly improved in the low and high-dose curcumin treatment groups, the values of

Curcumin nanoparticles and the therapeutic potential of curcumin for musculoskeletal disorders

Table II. Effects of curcumin on osteoarthritis in animal, human and *in vitro* studies.

Type of study	Type of model	Treatment, dose and duration	Findings	Reference
Animal	MIA induced osteoarthritic rats	Curcumin (0.5%) - i.a. injection, once	Mankin scores↓, OARSI scores↓, cartilage degeneration↓MMP-13↓, COL-II↑, PINK1↑, p62↑, Beclin1↑, LC3B↑	Jin et al ⁹⁵
Animal	Anterior cruciate ligament transection rats	Curcumin (50 or 150 mg/kg) - i.p. injection, 8 weeks	Caspase3↓, CHOP↓	Feng K et al ⁹⁸
Animal	MIA induced osteoarthritic rats	Curcumin (200 mg/kg) - i.p. injection, 2 weeks	Mankin scores↓, knee swelling↓, knee diameter↓, knee pain↓, inflammatory biomarkers (IL-6, IL-1β, TNF-α)↓, TLR4↓, NF-κB↓	Zhang and Zeng ⁹⁶
Animal	MIA induced osteoarthritic mice	ACP (2.5 or 5 mg/kg) - i.m. injection, 4 weeks	Proteoglycan↑, aggrecan↑, collagen↑, TNF-α↓, IL-1β↓	Kang et al ⁹⁹ Xu et al ¹⁰⁰
Animal	ACLT induced osteoarthritic mice	sEV CUR (10 μL) - intra-articular injections, 4 weeks	Mankin scores↓, 8-OHdG↓, caspase3↓, aggrecan↑, collagen II↑	Guan et al ⁹⁷
Animal	MIA induced osteoarthritic rats	Curcumin (20 mg/kg) chondroitin sulfate (100 mg/kg) – oral, 2 weeks	Mankin Scores↓, knee diameter↓, knee space↓, thickness of the synovium↑, collagen II↑, SOD↓, MMP-3↓, TLR4↓, cox-2↓, p-p65/p65↓	Lopresti et al ¹⁰¹
Human	101 adults with knee osteoarthritis	Curcuminoids extract (500 mg) - oral, 8 weeks	KOOS Knee Pain Subscale Score↓, knee pain ratings↓, JOA score↑	Henrotin et al ¹⁰² Atabaki et al ¹⁰³
Human	150 adults with knee osteoarthritis	B-oCL (2×2 or 2×3 capsule/day) - oral, 3 months	sColl2-1↓, PGADA↓, knee pain↓	
Human	30 adults with knee osteoarthritis	Sinacurcumin (80 mg) – oral, 3 months	VAS↓, CRP↓, CD4+ and CD8+ T cells↓, Th17 cells↓, B cells↓, Treg cells↑	
Cell culture	IL-1β-stimulated rat articular chondrocytes	Curcumin (10 μM)	ROS↓, Ca2+↓, IL-1β↓, ΔΨm↑, intercellular ATP levels↑, PINK1↑, Parkin↑	Jin et al ⁹⁵
Cell culture	Tert-Butyl hydroperoxide-induced rat articular chondrocytes	Curcumin (20 μM)	Caspase3↓, PARP↓, CHOP↓, GRP78↓, ATF4↓, p-PERK/PERK↓, p-eIF2α/eIF2α↓, Bcl2↑, SIRT1↑	Feng et al ⁹⁸
Cell culture	TBHP-induced mice articular chondrocytes	sEV-CUR (1×10 ⁹ p/mL)	Aggrecan↑, collagen↑, ADAMTS5↓, MMP13↓, IL-1β↓, TNFα↓	Xu et al ¹⁰⁰
Cell culture	IL-1β-stimulated human articular chondrocytes	Curcumin (50 μM) or resveratrol (50 μM), Curcumin (50 μM) and resveratrol (50 μM),	Bcl2↑, Bcl-xL↑, TRAF1↑, caspase-3↓, Cox-2↓, MMP-3↓, MMP-9↓, VEGF↓, IKK activation↓, collagen II↑, Sox-9↑	Csaki et al ¹⁰⁶
Cell culture	3D-chondrocytes in osteoarthritic environment	Curcumin (1,2,5,10 μM)	Sox9↑, collagen II↑, β1-integrin↑, CSPG↑, MMP-9↓, Cox-2↓, Caspase 3↓	Buhrmann et al ¹⁰⁸
Cell culture	IL-1β-stimulated rat articular chondrocytes	HA/cNP (30 μg/ml)	collagen II↑, I-κBα↑, MMP-1↓, MMP-13↓	Wang et al ¹⁰⁹
Cell culture	SNP-stimulated rabbit articular chondrocytes	Curcumin (0-20 μM)	ΔΨm↑, Bcl2↑, collagen II↑, Caspase 3↓, Bax↓, MMP-13↓	Zhao et al ¹¹²

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) were decreased, and there was a statistically significant improvement in joint swelling and joint tenderness¹²⁰. The following year, Javadi et al¹²¹ divided 65 RA patients into two groups and gave each group capsules containing either curcumin nanomicelles (40 mg) or a placebo. After the intervention, the within-group DAS-28, Tender joint count (TJC) and swollen joint count (SJC) in the curcumin nanomicelle and placebo groups decreased significantly compared to the baseline¹²¹. In 2010, Stavropoulos-Kalinoglou et al¹²² found that obesity is associated with an increased risk of developing RA, with obese RA patients exhibiting greater inflammatory activity and a lower quality of life. Pourhabibi-Zarandi et al¹²³ enrolled 48 women with RA between 20 and 70 years in a randomized, double-blind, placebo-controlled clinical trial. Subjects were treated with curcumin (500 mg once daily) for eight weeks. In addition to decreased CRP and ESR, the homeostatic model assessment for insulin resistance (HOMA-IR), triglyceride, and adiposity index decreased significantly. Curcumin consumption may be an effective strategy for women with RA to modulate metabolic factors, inflammation, and adiposity¹²³.

The Molecular Role of Curcumin in the Prevention of RA

The initial histological features of RA are characterized by synovial epithelium hyperplasia, excessive angiogenesis, and the accumulation of mononuclear cells in the synovium¹²⁴. Normal synovium contains mesenchymal-derived fibroblast-like synoviocytes (FLS) and macrophages. Macrophages are central effectors of synovitis by releasing cytokines (e.g., TNF- α and IL), reactive oxygen intermediates, nitrogen intermediates, prostaglandins and matrix-degrading enzymes production, phagocytosis and presentation of antigens¹²⁵. In rheumatoid arthritis, the membrane lining expands. FLS presents a semi-autonomous phenotype characterized by promoting the expression of disease-related cytokines and chemokines, adhesion molecules, and MMPs, leading to local cartilage destruction and chronic inflammation of the synovium¹²⁶.

To investigate the anti-RA potential of curcumin, Xu et al¹²⁷ designed an *in vivo* and *in vitro* study to observe the effects of curcumin on a mouse model of collagen-induced arthritis (CIA) and primary RA fibroblast-like synoviocytes

(RA-FLS). We found that curcumin (50 μ M) reversed TNF- α -induced RA-FLS proliferation and induced cell apoptosis. Secondly, curcumin inhibits cell migration and invasion by reducing the expression of MMP-2 and MMP-9 proteins. In *in vivo* experiments, curcumin bound to AKT1 and inactivated the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, reducing the concentrations of TNF- α , IL-6 and IL-17 in the synovial tissue of CIA mice and improving RA progression¹²⁷. Similar results were obtained in a study by Park et al¹²⁴, where curcumin inhibited COX-2 and prostaglandin E₂ and caused apoptosis of RA-FLS by decreasing BCL-2 expression and increasing BAX, caspase-3, caspase-9 expression¹²⁴. Recently, Manca et al¹²⁸ loaded curcumin in hyaluronan-immobilized phospholipid vesicles called hyalurosomes. In *in vitro* experiments, curcumin-loaded hyalurosomes were able to downregulate the cellular inhibitor of apoptosis proteins (cIAP1) and cIAP2 while causing a decrease in IL-6 and IL-15 and ROS production to treat anti-rheumatoid arthritis¹²⁸. In the same year, to study the toxicity and anti-inflammatory mechanisms of curcumin on macrophages in synovial membranes, Yan et al¹²⁹ combined prednisolone (PD) with curcumin and human serum albumin (HSA) in the nanoparticle system (N-PD/CU) to treat activated macrophages, and demonstrated that proinflammatory cytokines (TNF- α , IL-1 β , IL-6, IL-10) were significantly inhibited and the release of anti-inflammatory IL-10 was increased¹²⁹.

These results suggest that curcumin has potential for the treatment of rheumatoid arthritis. Table III summarizes the effects of curcumin on RA *in vivo* and *in vitro* studies.

Discussion

This article reviews curcumin as a drug for treating musculoskeletal disorders, as well as structural analogs, derivatives, and nanocarrier pharmaceuticals that enhance their bioavailability and water solubility. Tetrahydrocurcumin, a metabolite of curcumin in which the alpha- and beta-unsaturated carbonyl groups have been removed, is more soluble in water than curcumin and has twice the half-life of curcumin in plasma. DMC lacks a methoxy group and, as a result, has less antioxidant activity than curcumin, but this does not prevent it from having potent antifungal activity. Cyclodextrins have a hydrophilic exteri-

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Table III. Effects of curcumin on RA in animal, human and *in vitro* studies.

Type of study	Type of model	Treatment, dose and duration	Findings	Reference
Animal	Bovine type II collagen induced RA rats	Curcumin (200 mg/kg) gavage, 3 weeks	Inflammatory cell infiltration↓, synovial hyperplasia↓, hind paw edema volume↓, arthritic scores↓, Akt1↓, mTOR↓, p70S6K ↓, IL-1β↓, TNF-α↓, MMP-1↓, MMP-3↓,	Dai et al ¹¹⁵
Animal	Collagen-induced arthritis rats	Curcumin (100 or 200 mg/kg) - oral, 10 days	Arthritis scores↓, edema↓, bone/cartilage destruction↓, synovial hyperplasia↓, pannus formation↓, TNF-α↓, IL-17↓, IL-1β↓	Wang et al ¹¹⁶
Animal	Freund's adjuvant-induced arthritis rats	CM-NS (50 mg/kg) - oral, 2 weeks	Arthritis scores↓ paw swelling↓, NF-κB↓, TNF-α↓, IL-1β↓	Zheng et al ¹¹⁷
Animal	Collagen-induced arthritis rats	HA/Cur nanomicelles (336 μg/ml) - i.a. injection	Paw edema↓, swelling of soft tissue↓, friction coefficient↓, VEGF↓	Fan et al ¹¹⁸
Human	36 adults with RA	Curcuminoids (250 mg, 500 mg) - oral, 12 weeks	Swollen joints↓, tender joints↓, VAS↓, DAS28↓, CRP↓, ESR↓, RF↓	Amalraj et al ¹¹⁹
Human	65 adults with RA	Curcumin nanomicelle (40 mg) - oral, 12 weeks	DAS28↓, TJC↓, SJC↓	Javadi et al ¹²⁰
Human	48 women with RA	Sinacurcumin (500 mg) – oral, 8 weeks	ESR↓, CRP↓, HOMA-IR↓, triglyceride↓, Obesity index ↓,	Pourhabibi-Zarandi et al ¹²²
Cell culture	Human RA-FLS	Curcumin (50 μM)	TNF-α↓, IL-17↓, IL-6↓MMP-2↓, MMP-9↓, p-PI3K/PI3K↓, p-AKT/AKT↓	Xu et al ¹²⁶
Cell culture	Human RA-FLS	Curcumin (25-100 μM)	COX-2↓, prostaglandin E2↓, Bcl-2↓, BAX↑, caspase-3↑, caspase-9↑	Park et al ¹²³
Cell culture	Human RA-FLS	Curcumin loaded hyalurosomes	IAP1↓, IAP2↓, IL-6↓, IL-15↓, ROS↓	Manca et al ¹²⁷
Cell culture	Macrophages	N-PD/CU	TNF-α↓, IL-1β↓, IL-6↓, IL-10↑	Yan et al ¹²⁸

or and a lipophilic cavity, and the encapsulation of curcumin molecules in the cyclodextrin cavity results in an increase of 60-fold in water solubility and 2.8-fold in bioavailability ratio. Curcumin is typically bonded to the head of the phospholipid in the curcumin phospholipid complex, thereby localizing the water-unstable β -diketone fraction within the lipid bilayer. This structure provides a protective barrier that facilitates the uptake and transport of curcumin across the cell membrane, allowing the curcumin phospholipid complex to be assimilated 29 times more in the human body than natural curcumin.

Curcumin nanoparticles are typically less than 1,000 nm in size and comprise liposomes, PLGA, chitosan, metal and mesoporous silica particles. Liposomes are spherical vesicle structures consisting of lipid bilayers. The hydrophilic heads face outwards towards the aqueous environment, the hydrophobic tails face inwards towards each other, and the cysts contain encapsulated water compartments in the center. Curcumin is encapsulated in the lipid layer, enhancing its efficacy and targeting. The degradation products of PLGA, lactic acid and hydroxyacetic acid are by-products of the human metabolic pathway and have non-toxicity. Also, PLGA particles are more stable under physiological conditions (pH 7.4), whereas hydrolysis is accelerated in tumor tissue (pH 5.5), allowing curcumin to be delivered to cells *via* endocytosis. By binding to negatively charged histones with the positive charge it conveys, chitosan can prolong the duration of action of curcumin. Together, silver nanoparticles and curcumin can sterilize and enhance the cytotoxicity against tumor cells in a synergistic manner. As a nanocarrier, mesoporous silica nanoparticles (MSN) have numerous pores, a wide surface area, and a morphology-adjustable pore structure. By functionalized silica nanoparticles with various coating agents, the dosage can be more precisely controlled, and Cur-MSN can release curcumin slowly and continuously under physiological conditions.

Numerous studies on curcumin have demonstrated that it can potentially treat skeletal muscle disorders *via* various mechanisms. Curcumin prevents bone loss in osteoporosis by increasing the production of osteoblasts and osteoprotegerin and decreasing osteoclasts *via* Runx2, RANK/RANKL. In animal models of ovariectomy, glucocorticoid, and diabetes-induced osteoporosis, curcumin significantly increased bone density and enhanced the microstructure

of bone trabeculae to increase bone mechanical strength. Curcumin treatment for osteoarthritis can reduce the inflammatory factors IL-1 β and TNF in the joint cavity by inhibiting the NF- κ B pathway, slow the degradation of cartilage and extracellular matrix, and inhibit chondrocyte apoptosis by decreasing apoptotic genes such as *BAX*, *caspase-3*, and *caspase-9*. Curcumin alleviates RA by inhibiting the proliferation and invasion of mesenchymal-derived fibroblast-like synovial cells (FLS), thereby reducing synovial proliferation and angiogenesis, and also inhibits the progression of the disease by modulating the accumulation of monocytes in the synovium and reducing the release of inflammatory factors. In addition, curcumin slows down the inflammatory response by decreasing the production of ROS, which in turn protects beneficial skeletal osteoblasts and chondrocytes.

According to a summary of animal studies^{75,83-89}, Curcumin can ameliorate osteoporosis by modulating RUNX2, Wnt/ β -catenin, GSK3 β -Nrf2, RANKL, NF- κ B, and MAPK signalling pathways. It also affects NF- κ B, RUNX2, and PI3K/AKT to treat arthritis and rheumatoid arthritis^{113,126}. However, there are very few human studies on curcumin, with the majority of studies involving small numbers of patients, significant individual differences, and approximately the same dose for subjects of varying weights. Laboratory tests on subjects are also more limited, generally limited to blood sampling and CT examinations to analyze inflammatory factors and bone. It is also challenging to assess the safety of curcumin in humans; therefore, additional extensive animal studies are required to investigate the signalling pathways through which curcumin acts and the therapeutic effects of curcumin nanomaterials on musculoskeletal disorders.

Conclusions

In curcumin nanomedicine, compared to natural curcumin, the solubility of the drug is increased exponentially. In MSD, curcumin promotes the production of osteoblasts and osteoprotegerin and reduces osteoclasts through Runx2, RANK/RANKL to treat osteoporosis. In osteoarthritis, curcumin reduces the production of inflammatory factors IL-1 β and TNF in the joint cavity and slows down cartilage apoptosis and extracellular matrix degradation by inhibiting apoptotic genes such as *NF- κ B* pathway, *BAX*,

caspase-3, *caspase-9*. Meanwhile, curcumin inhibits the proliferation and invasion of FLS, reduces synovial proliferation and angiogenesis, and slows down the progression of RA by regulating the accumulation of monocytes in the synovium and reducing the release of inflammatory factors.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and Informed Consent

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Authors' Contribution

Haoyue Wu: Conceptualization, Data curation, Formal analysis, Writing - original draft. Haotao Yu: Writing - review and editing. Bing Kang: Investigation, Data curation. Yingying Xuan: Visualization. Data curation. Haoqiang Zhang: Resources, Supervision. Xusheng Li: Project administration, Supervision.

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