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REVIEW

Recent Progress in Nano-TCM Active Ingredient Co-Delivery Systems for Inflammation-Mediated Diseases

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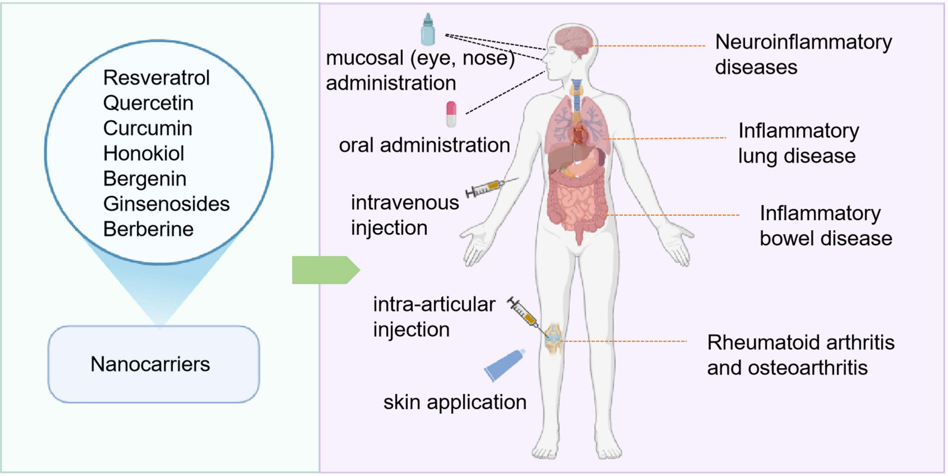
Abstract: Inflammation is a pivotal pathogenic factor in numerous diseases. Traditional Chinese medicine (TCM) has garnered significant attention due to its rich bioactive compounds with demonstrated anti-inflammatory and antioxidant activities. Nevertheless, clinical translation of TCM is often limited by poor pharmacokinetic properties, including low solubility, rapid clearance, and inadequate biomembrane permeability. Nanocarrier-based delivery systems have emerged as a promising strategy to overcome these limitations and enhance therapeutic outcomes. This review systematically summarizes: (1) the anti-inflammatory mechanisms of key TCM-derived compounds (resveratrol, quercetin, curcumin, honokiol, bergenin, ginsenosides, and berberine); (2) the classification and functional advantages of contemporary nanocarriers; and (3) recent advances in nanoengineered co-delivery systems for TCM active ingredients against inflammation-associated pathologies. Furthermore, we critically analyze persisting challenges and propose future directions to optimize nano-TCM platforms, offering new perspectives for targeted therapy of inflammatory diseases.

Keywords: traditional Chinese medicine, nanocarrier, nano-TCM co-delivery systems, inflammation-mediated diseases

Graphical Abstract



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Introduction

Inflammation is an essential protective response of the immune system to harmful stimuli, such as allergens or tissue injury. However, the uncontrolled activation of inflammation, driven by an overproduction of pro-inflammatory mediators and oxidative stress, is a major factor contributing to tissue damage and the development of various chronic diseases.[1] Inflammatory cells release reactive oxygen species (ROS), pro-inflammatory cytokines, transcription factors, and chemokines, which further amplify oxidative stress and disrupt the extracellular matrix, ultimately exacerbating the inflammatory response.[2,3] A growing body of evidence supports the therapeutic potential of targeting inflammation to alleviate the progression of a wide range of diseases.[4]

Although synthetic anti-inflammatory drugs are commonly prescribed, their use is often accompanied by significant adverse effects, raising concerns about their long-term safety. Nonsteroidal anti-inflammatory drugs (NSAIDs), the most widely used class of anti-inflammatory medications, are associated with serious gastrointestinal complications, including erosions, ulcers, bleeding, and perforations, affecting 1–2% of patients after three months of therapy.[5] Furthermore, NSAIDs have been linked to the development of small intestinal strictures, and aspirin, in particular, may induce platelet apoptosis, leading to thrombocytopenia. These issues highlight the limitations of conventional anti-inflammatory therapies and underscore the need for safer alternatives.[6] In contrast, TCM, with its rich array of bioactive compounds derived from natural sources, offers a promising alternative for the treatment of inflammatory diseases. TCM has garnered increasing attention in recent years, owing to its diverse pharmacological activities, including anti-inflammatory, anti-tumor, and immune-regulatory effects.[7] Many active ingredients from TCM can simultaneously target multiple molecular pathways, thereby enhancing therapeutic efficacy and modulating immune responses in a more comprehensive manner.[8–10] Despite its potential, the clinical application of TCM is limited by challenges such as poor solubility, unstable pharmacokinetics, non-specific side effects, and limited biofilm penetration of the active compounds. These obstacles have hindered the full therapeutic potential of TCM, highlighting the need for innovative approaches to improve the delivery and efficacy of TCM-based therapies.[11,12]

To improve the utilization of TCM, researchers have focused on the medical applications of nanocarriers. TCM has long been delivered through decoctions, pills, powders, pastes, and tinctures. However, these delivery methods often result in low absorption efficiency (eg, for polysaccharides and proteins), poor stability (prone to degradation by light and heat), and weak targeting (resulting in systemic distribution that may cause side effects in non-target organs). Additionally, the complex composition of TCM formulas delivered by traditional methods poses challenges in quality control.[13,14] In comparison to conventional drug delivery systems, nano-based TCM co-delivery systems offer superior safety and efficacy. These systems benefit from the inherent anti-inflammatory and antioxidant properties of the nanocarriers, as well as their specific physical/chemical targeting, and enhanced biocompatibility.[15,16] Lipid-based nanocarriers have gained attention due to their amphiphilicity, high stability, and excellent biocompatibility.[17] Polymeric nanoparticles have been widely studied for their high encapsulation efficiency.[18] Biomimetic nanocarriers, such as cell-based nanocarriers and exosomes, are recognized for their low immunogenicity, extended in vivo circulation time, and strong targeting ability.[19] Our review analyzes the anti-inflammatory mechanisms of various active components in TCM, introduces the classifications and properties of nanocarriers, and highlights the latest advancements in TCM delivery systems for treating inflammation-mediated diseases. It also discusses the advantages and unresolved issues of nanocarrier-based delivery of TCM, offering new perspectives for the development of this field.

Advantages and Limitations of TCM Active Ingredients in the Treatment of Inflammation-Mediated Diseases

Resveratrol

Resveratrol, a natural polyphenolic compound, demonstrates a wide range of biological activities, including free radical scavenging, regulation of antioxidant enzyme expression and activity, anti-inflammatory, anti-aging, anti-glycation, anti-cancer, neuroprotective, and cardioprotective effects.[20,21] In high-fat diet-induced obesity (DIO) mice, resveratrol exhibits potent anti-inflammatory and antioxidant properties,[22] alleviating allergic asthma by inhibiting JNK and NF-κB signaling pathways.[23] Furthermore, resveratrol effectively reduces insulin resistance and macrophage infiltration in adipose tissue, improving inflammation in both the peripheral and central nervous systems of DIO mice.[24] Recent studies have shown that the anti-inflammatory effects of resveratrol are linked to SIRT1 activation. For instance, resveratrol modulates the SIRT1/NF-κB signaling pathway to suppress the expression of pro-inflammatory factors such as COX-2, IL-1, and IL-6, thereby alleviating colitis.[25] Additionally, resveratrol has demonstrated therapeutic effects on osteoarthritis (OA) and vasculitis.[26,27] Despite its high absorption rate, the low solubility, poor stability, short half-life, and rapid metabolism of resveratrol contribute to its low bioavailability, which limits its clinical application.[28]

Quercetin

Quercetin, a polyphenolic flavonoid predominantly found in fruits and vegetables, exhibits anti-inflammatory, antioxidant, and autophagy-inducing properties. Consequently, it has been investigated for the prevention and treatment of cancer, cardiovascular diseases, chronic inflammation, oxidative stress, and neurodegenerative disorders.[29] In vitro studies demonstrate that quercetin inhibits TNF-α-induced inflammation in macrophages and adipocytes by modulating MAPK (JNK and ERK) and nuclear factor-kappa B(NF-κB) pathways.[30] In vivo, it alleviates experimentally induced hepatitis and interstitial nephritis by suppressing macrophage M1 polarization.[31,32] In OA animal models, quercetin acting as a SIRT1 agonist activates the AMPK signaling pathway to suppress inflammation and apoptosis in chondrocytes,[33] while promoting cartilage repair through M2 polarization of synovial macrophages.[34] Conversely, quercetin has also been shown to reduce excessive extracellular matrix accumulation in renal interstitial cells by inhibiting M2 polarization via antagonism of the TGF-β1/Smad2/3 signaling pathway.[31] Given these complex effects on macrophage polarization, further studies are required to elucidate its precise mechanisms of action. Additionally, quercetin significantly reduces plasma histamine levels and serum IgE concentrations, thereby alleviating peanut-induced allergic responses in rats.[35] However, its high first-pass elimination rate—resulting in rapid excretion within 24 hours—and inherent hydrophobicity limit its bioavailability and therapeutic potential.[36,37]

Curcumin

Curcumin, a polyphenolic compound extracted from the rhizome of Curcuma longa (turmeric), exhibits regulatory effects on inflammation, oxidative stress, and various cellular processes including proliferation, differentiation, and survival.[38] Recent studies have demonstrated that the anti-inflammatory properties of curcumin are primarily mediated through the modulation of several key signaling pathways, such as NF-κB, peroxisome proliferator-activated receptor gamma (PPAR-γ), and Toll-like receptor (TLR)/myeloid differentiation protein 2 (MD2) pathways. For example, curcumin mitigates colitis and rheumatoid arthritis by inhibiting IκB kinase (IKK) activity and IκB-α phosphorylation, thereby blocking NF-κB pathway activation,[39,40] In addition, upregulation of PPAR-γ expression has been shown to attenuate inflammation and reduce ROS production.[41] Acting as a PPAR-γ agonist, curcumin suppresses angiotensin II–induced inflammation in vascular smooth muscle cells.[42] Moreover, aberrant activation of TLR signaling complexes serves as an upstream trigger of inflammatory responses. Curcumin and its analogs competitively bind to MD2, thereby inhibiting the TLR4-MD2 complex and reducing the secretion of pro-inflammatory cytokines. This mechanism has been implicated in the amelioration of acute lung injury (ALI) and sepsis.[43] Furthermore, curcumin modulates macrophage polarization by inhibiting M1 phenotypes while promoting M2 polarization, contributing to its immunomodulatory effects.[44,45] Despite its broad therapeutic potential, the clinical application of curcumin remains limited due to its low water solubility, poor bioavailability, rapid metabolic degradation, and fast systemic elimination.[46]

Honokiol

Honokiol is a natural polyphenolic compound extracted from the bark and leaves of Magnolia species belonging to the Magnoliaceae family. It exhibits low toxicity and a broad spectrum of biological activities, including anti-inflammatory, antioxidant, anti-tumor, anti-obesity, and neuroprotective effects.[47] The anti-inflammatory effects of honokiol are closely associated with the activation of SIRT3, a mitochondrial deacetylase that plays a crucial role in maintaining mitochondrial function and redox homeostasis.[48,49] For instance, honokiol alleviates osteoarthritis by targeting the SIRT3–COX4I2 axis, thereby reprogramming mitochondrial respiratory chain complexes.[48] Additionally, honokiol regulates the differentiation of T helper 17 (Th17) cells by activating SIRT3, which in turn inhibits the STAT3/RORγt signaling

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pathway, leading to decreased expression of IL-17 and interleukin-21 (IL-21), and ultimately reducing intestinal inflammation in colitis models.[50] Furthermore, honokiol exerts anti-colitic effects through modulation of the PPARγ/NF-κB, AMP-activated protein kinase (AMPK), and nuclear factor erythroid 2–related factor 2/heme oxygenase-1 (NRF2/HO-1) signaling pathways.[51] Recent findings also suggest that honokiol can activate SIRT1, expanding its regulatory effects on cellular stress responses.[52] Moreover, honokiol has been shown to attenuate lung inflammation by regulating AMPK and superoxide dismutase 2 (SOD2) signaling pathways.[53,54] Taken together, these findings highlight honokiol as a promising therapeutic candidate for inflammation-related diseases. However, its clinical application is substantially hindered by poor physicochemical properties, including low aqueous solubility, instability, and rapid metabolic degradation. These factors result in an oral bioavailability of approximately 5%, significantly limiting its therapeutic potential.[55,56]

Bergenin

Bergenin, an isocoumarin compound derived from *Bergenia* species, exhibits diverse biological activities, including anti-inflammatory, antioxidant, antiviral, antifungal, and organ-protective effects.[57] As a SIRT1 agonist, bergenin alleviates asthma by modulating the NF-κB pathway in macrophages, thereby suppressing the expression of IL-1β, IL-5, IL-6, and MMP-9.[58] Additionally, it mitigates OA by regulating macrophage M1/M2 polarization.[59] PPAR-γ, an upstream regulator of SIRT1, can be activated by bergenin, leading to upregulated SIRT1 expression. This mechanism reduces oxidative stress and inflammation, offering therapeutic benefits for colitis and Alzheimer's disease-related dementia.[60,61] Furthermore, bergenin's anti-inflammatory effects are associated with the PI3K/AKT signaling pathway.[62] However, its clinical application is hindered by low water solubility, poor permeability, and limited biofilm penetration,[63] as well as instability and susceptibility to degradation in neutral and alkaline environments.[64] These limitations contribute to its low bioavailability, necessitating higher doses to achieve effective therapeutic blood concentrations.[65]

Ginsenosides

Ginsenosides (G), the primary bioactive constituents of ginseng, regulate diverse cellular processes by interacting with cell membranes, kinases, and transcription factors.[66] Specifically, G-Rb1, G-Rb2, G-Rd, G-Re, G-Rg1, G-Rg3, Rh1, and compound K (CK) exhibit potent anti-inflammatory effects in vivo and in vitro by suppressing the activity of IL-1 receptor-associated kinase (IRAK-1), NF-κB, and MAPK signaling pathways.[67–73] Notably, G-Rb2,[74] G-Rc,[75] G-Rg1,[76] G-Rg3 exert anti-inflammatory actions via SIRT1 activation.[77] For example, G-Rg3 mitigates microglial inflammation by modulating the SIRT1/NRF2/NF-κB and AMPK/PI3K/AKT pathways.[78] Given that mitochondrial dysfunction is a key driver of inflammation,[79] G-Rg3 further ameliorates inflammatory responses by enhancing mitochondrial biogenesis through AMPK-mediated mitophagy and upregulation of PGC-1α and related genes.[80,81] Additionally, G-Rg6 suppresses TLR4-mediated systemic inflammation,[82] while G-Rh1 modulates the ERK and STAT (STAT1/STAT3) pathways to attenuate inflammation.[83] However, the therapeutic potential of ginsenosides is limited by their susceptibility to degradation or transformation in gastric acid and intestinal bacteria, with metabolites potentially inhibiting the absorption of parent compounds. Although their lipophilicity aids biofilm penetration, poor oral absorption and low bioavailability remain major challenges (Figure 1).[66,84]

Berberine

Berberine (BBR), an isoquinoline alkaloid derived from various medicinal plants, exhibits potent anti-inflammatory properties. BBR and its derivatives demonstrate therapeutic efficacy in inflammatory diseases affecting the gut, lungs, skin, and bone.[85,86] Mechanistically, BBR suppresses the expression of pro-inflammatory genes (eg, IL-1β, IL-6, and iNOS) by activating the AMPK signaling pathway and inhibiting MAPKs phosphorylation in macrophages.[87] Its anti-inflammatory effects further involve modulation of the Nrf2 and NF-κB pathways.[88] Notably, BBR significantly inhibits IgE production, highlighting its potential in managing food allergies. This immunomodulatory effect is linked to BBR's ability to suppress IκB phosphorylation and regulate gut microbiota composition.[89,90] Despite demonstrating multiple beneficial pharmacological activities against various diseases, the therapeutic application of berberine is substantially

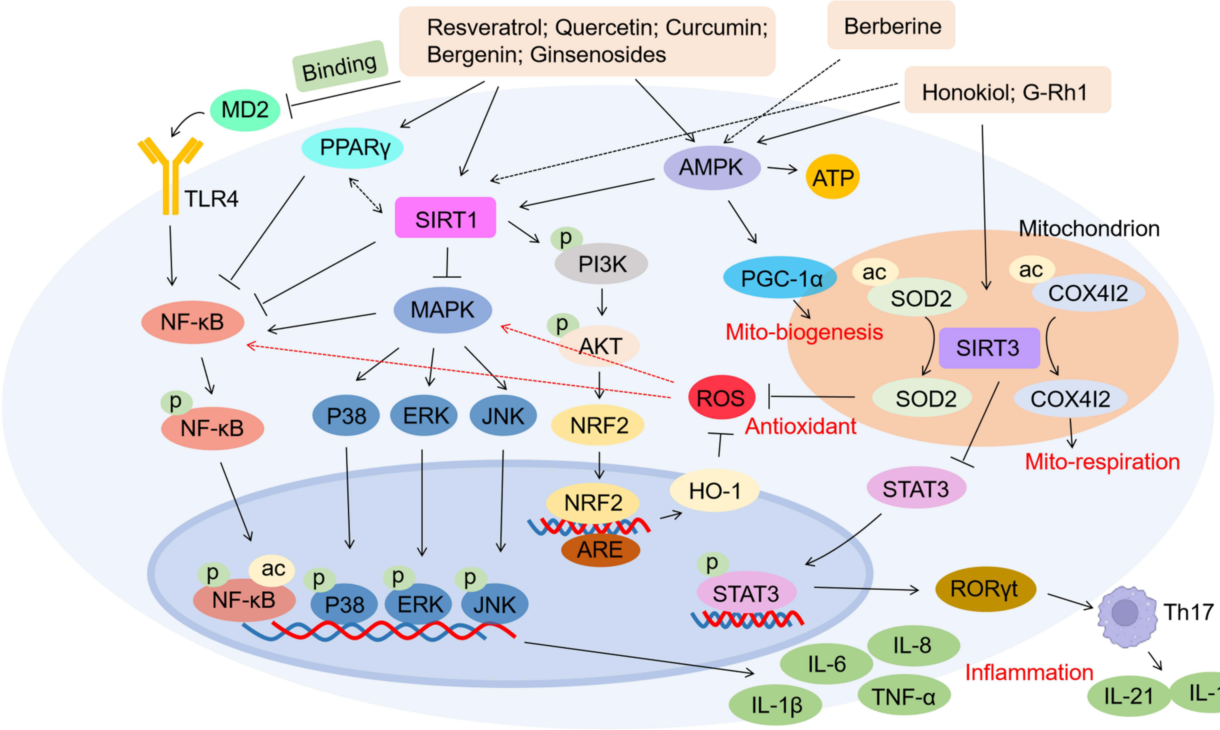

Figure 1 The anti-inflammatory molecular mechanisms of TCM active ingredients. Resveratrol, quercetin, curcumin, bergenin, and ginsenosides exert anti-inflammatory effects by targeting membrane receptors (TLR4, MD2), nuclear regulators (PPARγ, SIRT1), and AMPK, thereby suppressing pro-inflammatory NF-κB, MAPK, and PI3K/AKT signaling pathways while mitigating oxidative stress and promoting mitochondrial biogenesis. Additionally, honokiol, as a SIRT3 agonist, modulates immune responses by inhibiting Th17 cell differentiation through suppression of the STAT3/RORγt pathway.

limited by several pharmacokinetic challenges, including poor oral bioavailability, low gastrointestinal absorption, and extensive first-pass elimination.[91,92]

Advantages of Nano-TCM Active Ingredient Co-Delivery Systems

Improve the Bioavailability of TCM Active Ingredients

Most TCM preparations suffer from poor water solubility, chemical instability, rapid first-pass metabolism, and limited biofilm penetration, all of which significantly compromise their oral bioavailability.[17] These pharmacokinetic limitations present major challenges for clinical translation of TCM therapies.

Recent advances in nanomedicine have demonstrated that nanocarriers can effectively overcome these delivery challenges. Engineered nanocarriers enhance the solubility, stability, and absorption efficiency of TCM active ingredients while simultaneously reducing their potential toxicity. Compared to free TCM compounds, nano-TCM co-delivery systems show significantly improved bioavailability and enhanced therapeutic effects, including superior anti-inflammatory and antioxidant activities.[93–96] Notably, certain nanocarriers such as nanoemulsions and dendrimers exhibit exceptional biofilm penetration capabilities through fusion or permeation mechanisms.[97,98] Biomimetic nanocarriers, characterized by their low immunogenicity and high biocompatibility, show particular promise for overcoming biological barriers and avoiding immune system clearance.[99] Furthermore, these nano-TCM delivery platforms offer flexible administration routes, including intravenous, oral, transdermal, and various mucosal (ocular, nasal) delivery options.[100,101]

Enhance Drug Delivery Targeting Inflammation

Extensive research has confirmed that nanocarriers can significantly alter drug biodistribution patterns.[102,103] A key advantage of nanocarriers is their preferential accumulation in inflamed tissues. For example, cationic liposomes demonstrate significantly higher accumulation in lung tissues of inflamed animal models compared to healthy

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controls.[104] This enhanced permeability and retention (EPR) effect, mediated by pathophysiological vascular leakage, represents the passive targeting mechanism of nanocarriers.[105] Beyond passive targeting, nanocarriers can be engineered for active targeting of specific molecules or cellular phenotypes within inflammatory microenvironments. Liposomes, for instance, can be designed to target specific macrophage phenotypes, thereby modulating phagocytic activity and cytokine secretion profiles.[106] Macrophage-derived extracellular vesicles show particular promise for neuroinflammation therapy due to their enhanced blood-brain barrier (BBB) penetration capabilities.[107] Surface modification strategies further expand nanocarrier targeting potential. Functionalization with surfactants, antibodies, polymers (synthetic or natural), silicon dioxide, metals, or other materials can precisely enhance targeting specificity.[108] Galactose and folic acid-modified resveratrol, which shows improved intestinal absorption and transcellular transport, enhancing its anti-inflammatory efficacy both in vitro and in vivo.[109,110] Lactoferrin-conjugated resveratrol, demonstrating enhanced BBB penetration and neuroprotective effects.[111] Mannose-modified albumin, which effectively targets mannose receptors overexpressed on inflammatory cells.[112]

Control Drug Release

Many TCM active ingredients suffer from poor water solubility, short half-lives, and rapid first-pass elimination. Patients frequently require high-dose regimens to attain therapeutic efficacy, decreasing medication adherence while increasing adverse event risks.[17,113,114] Nanocarrier-based delivery systems have emerged as a promising solution to overcome these limitations. Recent studies demonstrate that engineered nanocarriers can significantly prolong drug release profiles. For example, Silica nanoparticles enable sustained release of silymarin for up to 72 hours.[115] Liposome-encapsulated cryptotanidone administered every 48 hours shows comparable efficacy to daily pirfenidone dosing.[116] Advanced nanocarrier systems can be designed with stimulus-responsive properties for site-specific drug release. Conventional liposomes maintain stability under physiological conditions but release payloads upon encountering specific internal/external triggers. Functionalized liposomes incorporating thermosensitive or pH-sensitive polymers enable precise control of drug release in response to local microenvironment changes.[117] Magnetic nanoparticles have also been investigated for controlled drug release under external magnetic field influence.[108] These controlled-release strategies provide multiple therapeutic advantages, including minimization of direct drug-mucosa contact, prevention of mucosal irritation caused by local drug accumulation, maintenance of optimal therapeutic drug concentrations, reduction in dosing frequency.[17,118]

As Carriers to Co-Deliver Active Ingredients or Therapeutic Agents to Enhance Efficacy

Nanocarrier-mediated co-delivery systems leverage the principle of pharmacological synergy to simultaneously transport multiple TCM active ingredients or therapeutic agents. This strategy enables concurrent modulation of diverse molecular pathways while minimizing toxicity and adverse effects through reduced dosage requirements. Curcumin serves as an exemplary combination partner due to its dual capacity to inhibit drug resistance-associated transcription factor activation and downregulate drug transporter activity.[119] For instance, Curcumin-quercetin nanoemulsions showing superior anti-viral efficacy with reduced doses and improved targeting specificity compared to monotherapies.[120] Macrophage membrane-coated curcumin-platycodin systems achieving significant anti-inflammatory effects in ALI murine models (Figure 2).[121]

Classification of Nanocarriers

Exogenous Nanocarriers

Lipid Nanocarriers

Liposomes

Liposomes are stable spherical vesicles with a bilayer structure formed by phospholipids and cholesterol. Their unique amphiphilic nature, combined with high biocompatibility, structural stability, and ease of surface modification, makes them particularly valuable for overcoming the delivery challenges of TCM compounds.[17] Numerous studies have

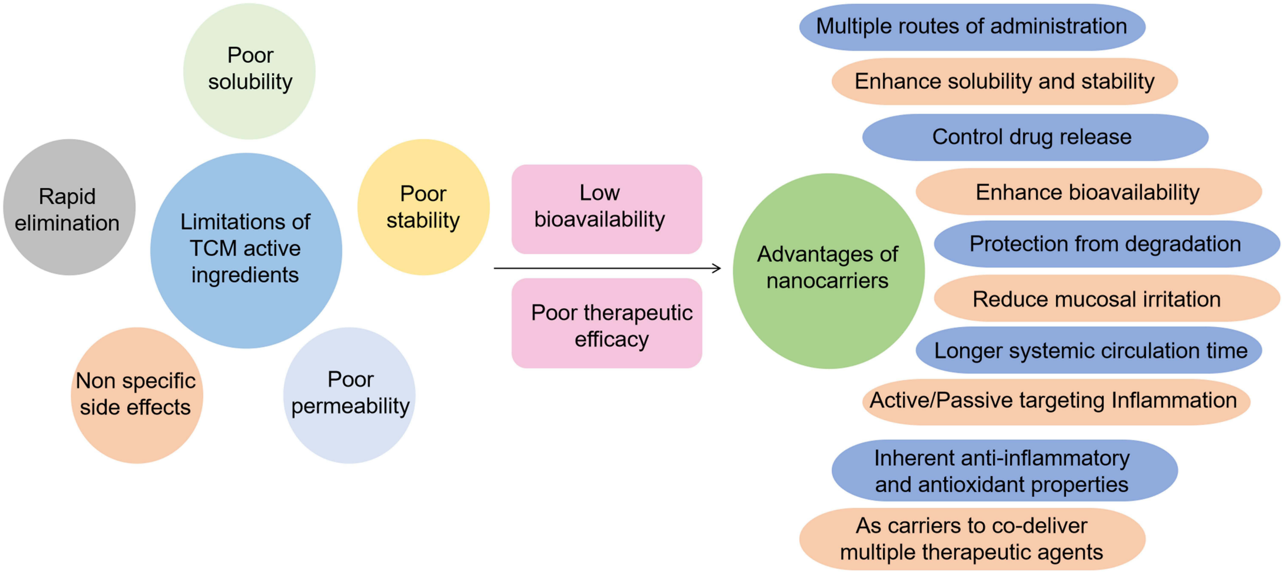

Figure 2 Nanocarrier systems offer significant advantages for delivering TCM active ingredients. The clinical translation of TCM active ingredients is often hindered by inherent limitations, including poor solubility, low stability, rapid clearance, unfavorable pharmacokinetics, and nonspecific side effects—all contributing to low bioavailability. Functional benefits of nanocarriers, such as intrinsic anti-inflammatory/antioxidant properties, enhanced solubility, controlled release, targeted delivery, and co-delivery of therapeutic agents, position them as powerful platforms for TCM delivery.

demonstrated the effectiveness of liposomes for encapsulating and delivering TCM bioactive components including quercetin, resveratrol, and curcumin.[122–124]

Solid Lipid Nanoparticles (SLNs)

SLNs represent another important class of nanocarriers, featuring a solid lipid core that maintains crystalline structure at room temperature. These nanoparticles offer several advantages over liposomes, including greater physical stability and lower production costs.[125] A distinctive characteristic of SLNs is their tendency to adsorb drugs primarily on the particle surface rather than encapsulating them within the core.[126] This property, along with their ability to load both hydrophilic and lipophilic drugs, provide targeted delivery, protect payloads from degradation, and enable controlled release, makes SLNs attractive for TCM applications.[17] However, a significant limitation arises during preparation - the formation of highly crystalline structures in the lipid matrix can lead to drug expulsion and consequently reduced drug loading capacity.[127]

Nanostructured Lipid Carriers (NLCs)

To address these limitations of SLNs, researchers developed NLCs by incorporating liquid lipids (oils) into the solid matrix. This modification disrupts the perfect crystalline structure of SLNs, resulting in improved nanoparticle stability and minimized drug leakage.[125] NLCs have shown particular promise for delivering various TCM compounds such as bergenin,[128] quercetin,[129] and ginsenosides.[130]

Nanoemulsions

Nanoemulsions, consisting of two immiscible liquid phases stabilized by surfactants and co-surfactants, offer another promising delivery platform. These systems are thermodynamically stable and can maintain their stability for extended periods (up to 3 months) at room temperature.[105] The large interfacial surface area of nanoemulsions facilitates efficient drug release and absorption. Furthermore, their versatility allows administration through multiple routes including oral, topical, and parenteral delivery.[100]

Polymeric Nanocarriers

Polymeric Micelles

Polymeric micelles represent an important class of nanocarriers characterized by their core-shell architecture, formed through the self-assembly of amphiphilic block copolymers.[131] The hydrophobic core serves as an effective compartment for encapsulating hydrophobic drugs through either covalent conjugation or physical entrapment, providing protection against degradation while significantly improving drug solubility. Meanwhile, the hydrophilic shell contributes several advantageous features, including excellent biocompatibility, prolonged blood circulation time,[18] enhanced permeability, active targeting capability, and stimuli-responsive properties to temperature and pH changes.[17,28] With their relatively small size range (10–200 nm), superior solubilization capacity, and straightforward preparation and sterilization processes, polymeric micelles offer distinct advantages over other nanocarrier systems. However, their clinical translation faces challenges due to stability limitations that require further optimization.[131]

Polymeric Nanoparticles

Polymeric nanoparticles are submicron-sized colloidal particles fabricated from either natural or synthetic polymers such as Poly(lactic-co-glycolic acid) (PLGA), Polylactide (PLA), silk fibroin (SF), chitosan, inulin, and gelatin. These nanoparticles share many beneficial properties with polymeric micelles, including both active and passive targeting mechanisms, as well as temperature- and pH-responsive behaviors.[132] Among these materials, PLGA has emerged as one of the most versatile and widely investigated polymers in nanomedicine applications.

Dendrimers

Dendrimers constitute a unique class of highly branched, monodisperse macromolecules with well-defined core-shell nanostructures. Their distinctive architecture features discrete dendritic branches that radiate outward in concentric layers from a central core, creating abundant surface functional groups for drug conjugation or chemical modification, along with internal cavities for drug encapsulation.[133] The precise control over dendrimer synthesis allows for tailored adjustment of molecular weight, surface functionality, and hydrophilicity, enabling optimization of drug-loading capacity, biocompatibility, and pharmacokinetic profiles.[134] Furthermore, dendrimers offer administration route flexibility,[101] making them particularly attractive for delivering both small molecule drugs and larger biomolecules. Nevertheless, potential cytotoxicity associated with cationic surface charges remains an important consideration that requires careful evaluation during dendrimer design.[133]

Inorganic Nanoparticles

Inorganic nanoparticles are nanoparticles prepared from inorganic materials such as metals, oxides, semiconductors and carbon-based structures. Owing to their excellent physical stability, large surface area, and sensitivity to light, magnetic fields, and ultrasonic signals, inorganic nanoparticles facilitate drug delivery through light/heat and magnetic field therapy.[135] At present, widely used inorganic nanoparticles include gold nanoparticles, silica nanoparticles, magnetic nanoparticles, and nanotubes.[17,136]

Nanocrystals

Drug nanocrystals represent a unique class of nanocarriers consisting of pure drug particles with diameters below 1 μm, typically stabilized in nanosuspension formulations. These nanocrystals can be prepared through two principal methodologies: top-down approaches involving mechanical size reduction techniques such as high-pressure homogenization or milling, and bottom-up approaches utilizing antisolvent crystallization processes. In the latter method, carefully selected antisolvents (including various surfactants and polymers) are employed to induce controlled solute supersaturation and subsequent crystallization. The exceptionally high surface area-to-volume ratio of nanocrystals constitutes their most distinctive physicochemical characteristic, which directly contributes to enhanced dissolution rates and improved bioavailability. However, due to their prolonged persistence in biological environments, factors such as nanotoxicity and dose must be considered during their interaction with biological tissues.[137]

Heparin Based Nanocarriers

Heparin, a naturally occurring glycosaminoglycan, exhibits remarkable biocompatibility and contains abundant chemically modifiable functional groups along its backbone.[138] The low-molecular-weight derivatives of heparin (LMWHs) demonstrate enhanced multifunctionality, including anticoagulant activity, anti-inflammatory effects, angiogenesis inhibition, and antitumor properties.[139] These unique characteristics have positioned heparin-based nanomaterials as promising drug delivery platforms. For instance, LMWH-conjugated polymeric micelles have shown significant potential in reducing atherogenesis in murine models by simultaneously addressing vascular inflammation and dyslipidemia.[140] Additionally, heparin's specific binding affinity for heparanase enables effective regulation of the PI3K/AKT/mTOR signaling pathway,[141] a critical cascade involved in mediating inflammatory processes.[142]

Bionic Nanocarriers

Protein-Based Nanoparticles

Serum proteins represent a class of naturally occurring biomacromolecules that possess several advantageous characteristics for drug delivery applications, including exceptional biocompatibility, inherent biodegradability, intrinsic targeting capabilities, minimal toxicity, and low immunogenicity. These proteins contain abundant surface-exposed functional residues such as amino and carboxyl groups, which facilitate chemical conjugation with therapeutic agents and imaging probes. Among the most extensively studied serum protein-based nanocarriers are albumin, ferritin/apoferritin, transferrin, low-density lipoprotein, high-density lipoprotein, and hemoglobin, each demonstrating unique advantages for targeted drug delivery.[143,144]

Red Blood Cell (RBC)-Based Nanocarriers

As the most abundant circulatory cells, RBCs are easily accessible and exhibit several advantageous biological characteristics, including prolonged circulation time, low immunogenicity, and high deformability.[145] Their natural ability to freely traverse vascularized tissues makes them ideal candidates for drug delivery applications. Recent studies have shown that functional modification of RBC membranes can significantly enhance their targeting specificity and controlled drug release capabilities.[146] Currently, three main approaches are employed for drug loading onto RBCs: drug internalization through hypotonic preswelling techniques;[147] drug anchoring on RBC membrane surfaces via covalent or non-covalent coupling methods;[145] and drug encapsulation within membrane-derived vesicles.[148] Notably, research has demonstrated that selective placement of intravascular catheters combined with intravenous injection of RBC-drug co-delivery systems can significantly enhance drug uptake in downstream target organs.[149] However, this delivery system has limitations - RBCs cannot actively deliver drugs to extravascular targets.[150] And the loaded drugs may disrupt normal RBC function, potentially leading to hemolysis and cellular aggregation.[151,152]

Macrophage-Based Nanocarriers

Macrophages, as natural immune cells, possess inherent anti-inflammatory properties through their phagocytic activity and innate inflammatory homing capabilities, making them promising cellular carriers for anti-inflammatory therapy. Current research has identified two primary approaches for drug loading into macrophages. The first approach relies on macrophage-mediated phagocytosis to internalize therapeutic agents.[153] However, this method faces challenges due to potential drug cytotoxicity to macrophages and drug degradation by lysosomal enzymes. To overcome these limitations, researchers have developed strategies where drugs are first encapsulated within protective nanocarriers such as liposomes or polymeric nanoparticles before being loaded into macrophages.[154,155] The alternative approach involves surface conjugation of drugs or drug-loaded nanoparticles to macrophages through covalent or non-covalent interactions.[153] While this method avoids lysosomal degradation, it may interfere with critical cellular functions including signaling pathways and adhesion mechanisms.[156]

Exosomes

Exosomes are nanoscale extracellular vesicles (40–160 nm in diameter) secreted by nearly all cell types. These natural vesicles contain a diverse cargo of biologically active components, including proteins, nucleic acids, lipids, cytokines, enzymes, signal transduction proteins, and adhesion molecules.[157] Their endogenous composition confers several advantageous properties for drug delivery, such as low toxicity, high biocompatibility, intrinsic targeting ability, and the capacity to cross biological barriers while avoiding immune clearance. However, significant challenges remain in the clinical translation of exosome-based therapies, primarily due to the inefficient isolation from biological fluids and cell culture media, as well as their inherent heterogeneity and complex composition.[99] Interestingly, recent studies have

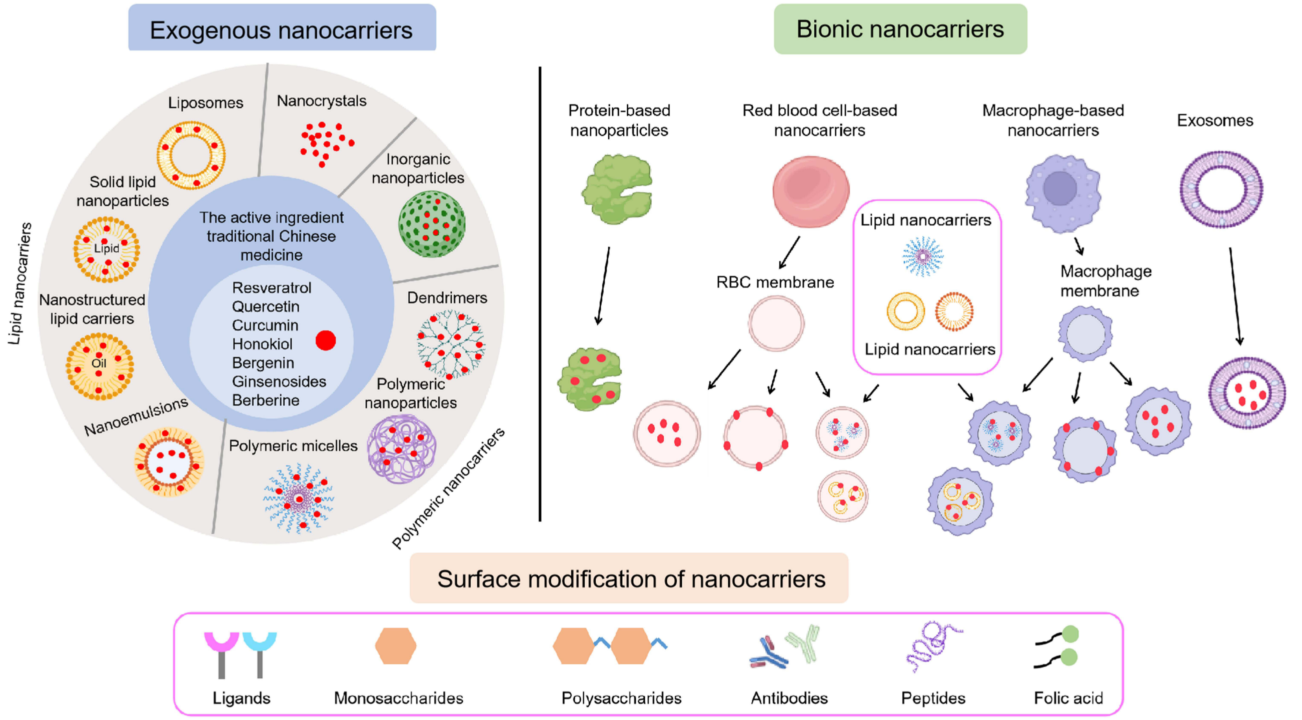

Figure 3 Classification of nanocarriers and possible drug loading methods. This figure summarizes two major categories of nanocarriers (exogenous and bionic systems) for delivering TCM active ingredients, along with surface modification strategies (antibodies, peptides, monosaccharides, polysaccharides, folic acid, and ligands) to enhance targeting capability in co-delivery systems.

identified milk as a promising alternative source of exosomes, as these vesicles demonstrate cross-species tolerance and minimal immunogenicity or inflammatory responses (Figure 3).[158]

Nano-TCM Active Ingredient Co-Delivery Systems in Inflammation-Mediated Diseases

Neuroinflammatory Diseases

The BBB presents a significant challenge for drug delivery to the central nervous system, particularly for TCM active ingredients.[159] To overcome this limitation, various nano-TCM delivery systems have been developed to enhance neuroprotective efficacy.

Research demonstrates that resveratrol-loaded PLGA and Polyethylene glycol (PEG) nanoparticles effectively cross the BBB, attenuating neuroinflammation and oxidative stress while providing neuroprotection.[111,160] Similarly, exosome-encapsulated resveratrol exhibits potent anti-inflammatory effects in both central and peripheral nervous systems.[107] These therapeutic benefits appear mediated through modulation of critical signaling pathways including STAT3, NF-κB, MAPK, and AKT.[161,162]

In Alzheimer's disease (AD) pathology, characterized by extracellular amyloid-β (Aβ) aggregation.[163] Nanocarrier systems have shown particular promise. Polymeric and silica nanoparticles significantly improve quercetin bioavailability, reducing neuronal apoptosis and Aβ plaque formation in AD models.[164,165] Plasma exosome-delivered quercetin similarly ameliorates cognitive deficits in AD mice.[166]

Curcumin nanoformulations demonstrate multimodal neuroprotection by inhibiting M1 microglial activation, suppressing pro-inflammatory cytokines (TNF-α, IL-1β), and preserving BBB integrity during cerebral ischemia-reperfusion injury.[167]

Honokiol delivery systems exhibit excellent oral bioavailability and potent anti-AD effects, including reduced neuroinflammation (TNF-α, IL-6, IL-1β), suppressed glial activation, and decreased Aβ deposition.[168] Intravenous honokiol nanocapsules additionally show efficacy in autoimmune encephalomyelitis models.[169]

While ginsenosides possess inherent neuroprotective properties, their poor BBB penetration limits clinical application.[170] Innovative solutions include transferrin receptor-targeted nanoparticles for sustained Rg1 release in diabetic cerebral infarction,[171] and macrophage membrane-coated G-Rg3 delivery systems that enhance brain targeting in ischemic injury (Table 1).[172,173]

Inflammatory Lung Disease

The lipid core nanocapsule-resveratrol co-delivery system demonstrates remarkable stability, enhanced oral bioavailability, and preferential lung accumulation. This formulation effectively mitigates ALI in murine models by suppressing ERK and PI3K/AKT pathway activation, thereby reducing both inflammatory responses and oxidative stress.[174] Further enhancing targeting precision, folate-modified exosomes have been engineered to specifically deliver resveratrol and celastrol to M1 macrophages. This approach significantly inhibits M1 polarization in pulmonary macrophages, attenuates cytokine storm severity, and improves survival rates in septic mice.[175]

Macrophages' innate capacity for inflammation-directed phagocytosis enables their effective accumulation in inflamed tissues. When employed as quercetin carriers, macrophages demonstrate significant efficacy in alleviating acute pneumonia in murine models.[176] An alternative strategy utilizing nanoemulsions co-encapsulating quercetin and curcumin achieves a 99% viral inhibition rate following intranasal administration.[120]

Advanced targeting has been achieved through receptor-binding peptide (RBP)-modified exosomes, which selectively deliver curcumin to inflamed lung tissues.[177] In ovalbumin (OVA)-induced asthma models, curcumin-loaded nanomicelles exhibit 9.24-fold greater oral bioavailability than free curcumin, accompanied by significantly enhanced anti-inflammatory effects.[178]

The bovine serum albumin-bergenin co-delivery system displays exceptional stability while effectively ameliorating ALI through multiple mechanisms: reducing pulmonary inflammatory cell infiltration, suppressing TNF-α production, and enhancing myeloperoxidase activity.[179]

For COVID-19-related pathologies, the PEG-albumin-ginsenoside system improves survival in animal models by concurrently inhibiting thrombosis, vasculitis, and cytokine storms via modulation of NF-κB and SREBP2 signaling pathways.[180]

Innovative cell membrane-based approaches have utilized MLE-12 pulmonary epithelial cells, selected for their ROS-responsive properties. MLE-12 membrane-coated berberine nanomicelles achieve targeted pulmonary delivery, demonstrating superior therapeutic outcomes compared to free berberine. This system significantly downregulates inflammatory mediators and ameliorates LPS-induced lung injury in mice (Table 2).[181]

Inflammatory Bowel Disease (IBD)

Galactose- or folate-modified nanocarriers significantly improve colitis treatment by enhancing resveratrol's intestinal absorption and transcellular transport.[109,110] Similarly, milk-derived exosomes effectively protect resveratrol from degradation in the harsh gastrointestinal environment while maintaining its bioactivity, leading to notable colitis alleviation in rat models.[182] The SF nanoparticle-resveratrol system demonstrates therapeutic efficacy against colitis comparable to dexamethasone.[183]

ROS-mediated oxidative stress plays a pivotal role in IBD pathogenesis, making ROS targeting a promising therapeutic strategy. The pH/ROS dual-responsive PEG-chitosan nanomicellar system encapsulating quercetin shows minimal drug release under physiological conditions but achieves nearly complete quercetin release in inflamed intestinal regions of IBD mice. This targeted release profile results in significant suppression of pro-inflammatory mediators including TNF-α, IL-6, and iNOS.[184]

The CXCL12-CXCR4 axis represents another important target for IBD therapy, as CXCL12 is markedly upregulated in inflamed tissues. Researchers have developed CXCR4-rich cell membrane vesicles that naturally home to inflammatory intestinal regions. These biomimetic vesicles not only facilitate targeted delivery of curcumin but also help evade immune clearance and prolong circulation time due to their native membrane composition (Table 3).[185]

In both dextran sulfate sodium (DSS)-induced ulcerative colitis and LPS-stimulated macrophage inflammation models, berberine-loaded PLGA nanoparticles (BPL-NPs) exhibit superior water solubility and bioactivity compared

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Table 1 Nano-TCM Active Ingredient Co-Delivery Systems for Neuroinflammatory Diseases

TCM Active Ingredient	Nanocarrier Classification	Composition	Animal Model	Main Effects	Ref
Resveratrol	Polymeric nanoparticles	PLGA nanoparticles conjugated with lactoferrin	MPTP-induced PD mice	Increased BBB permeability; enhanced neuroprotective effects; attenuated ROS generation.	[111]
	Polymeric micelles	PEG-Acetal-PCL-PEG; cRGD; triphenylphosphine	Ischemia-reperfusion injury tMCAO mice	Increased BBB permeability; alleviated oxidative stress and inflammation; regulated M1/M2 polarization of microglia.	[160]
	Exosomes	Exosomes derived from macrophages	Multiple sclerosis mice	Inhibited inflammation in the central nervous system and peripheral nervous system.	[107]
Quercetin	Polymeric nanocarriers	PLGA nanoparticles; phosphatidic acid; sialic acid; 5-hydroxytryptamine-moduline	AD rats	Increased BBB permeability; prevented Aβ accumulation, lipid peroxidation, and neuronal apoptosis.	[164]
	Inorganic nanocarriers	Silica nanocarriers; Superparamagnetic nanoparticles; PEG-3000	Hippocampal neuronal cultures were obtained from postnatal mice (<2 day old)	Increased bioavailability; interfered with Aβ aggregation; minimized Aβ-induced ROS generation.	[165]
	Exosomes	Plasma exosomes	Okadaic acid-induced AD mice	Improved brain targeting; enhanced bioavailability; inhibited p-tau; reduced formation of insoluble neurofibrillary tangles.	[166]
Curcumin	Polymeric micelles	Block copolymer mPEG$_{5K}$-b-PLA$_{8K}$	Cerebral ischemia-reperfusion injury in mice	Increased BBB permeability; reduced oxidative stress and inflammation by protecting the BBB and inhibiting M1-microglial activation.	[167]
Honokiol	Nanoemulsions	Kolliphor® HS-15 (surfactant); PEG-400 (co-surfactant); MCT (oil)	TgCRND8 mice of AD	Improved oral bioavailability; inhibited Aβ deposition, tau hyperphosphorylation, and neuroinflammation by suppressing the JNK/CDK5/GSK-3β signaling pathway; modulated gut microbiota.	[168]
	Nanoemulsions	Soybean phosphatidylcholine; cholesterol	Autoimmune encephalomyelitis mice	Suppressed the infiltration of activated microglia and Th1 cells into the spinal cord; reduced demyelination and inflammation in the spinal cord.	[169]
G-Rg1	Polymeric micelles	γ-PGA (hydrophilic group); L-PAE (hydrophobic side chain)	Diabetes rats complicated with diabetic cerebral infarction	Sustained release drug; penetrated the BBB with high concentration; reduced the cerebral infarction volume; promoted neuronal recovery.	[171]
G-Rg3	Liposomes; Macrophage-based nanocarriers	Macrophage membrane; liposomes	Middle cerebral artery occlusion rats	Enhanced brain targeting; prolonged drug half-life; improved the inflammatory environment of the brain; reduced the infarct size.	[172]
	Liposomes; Macrophage-based nanocarriers	Macrophage membrane; liposomes	Middle cerebral artery occlusion rats	Alleviated inflammation and apoptosis; improved therapeutic effects.	[173]

Table 2 Nano-TCM Active Ingredient Co-Delivery Systems for Inflammatory Lung Disease

TCM Active Ingredient	Nanocarrier Classification	Composition	Animal Model	Main Effects	Ref
Resveratrol	Polymeric micelles	Poly (ε-caprolactone); capric/caprylic triglyceride; sorbitan monostearate; polysorbate 80	LPS-induced ALI mice	Reduced lung inflammation; inhibited MDA level and SOD activity; inhibited ERK and PI3K/AKT pathways.	[174]
	Polymeric micelles	Poly (ε-caprolactone); capric/caprylic triglyceride; sorbitan monostearate; polysorbate 80	LPS-induced ALI mice	Increased drug bioavailability; enhanced therapeutic effects.	[123]
	Exosomes	Folic acid-functionalized exosomes	LPS-induced ALI mice	Specifically targeted inflammatory macrophages; inhibited the proinflammatory M1 macrophages; enhanced and prolonged therapeutic effects.	[175]
Quercetin	Nanoemulsions	The oily phase with castor oil, egg lecithin and the natural compounds; the aqueous phase composed by the surfactant PEG 660-stearate	Murine β-COV-induced porcine nasal mucosa	Prevented viral adsorption; decreased local inflammatory responses.	[120]
Quercetin; Curcumin	Liposomes; Macrophage-based nanocarriers	Lecithin; cholesterol; macrophages	LPS-induced acute pneumonia mice	Enhanced storage stability; targeted inflammatory tissues; enhanced therapeutic efficacy.	[176]
Curcumin	Nanoemulsions	PEG-60 hydrogenated castor oil; pluronic F127	OVA-induced asthma mice	Enhanced bioavailability; enhanced anti-inflammatory effect.	[178]
	Exosomes	RAGE-binding peptide (RBP)-linked exosomes	LPS-induced ALI mice	Increased anti-inflammatory effects; increased drug intracellular delivery efficiency.	[177]
Bergenin	Protein-based nanoparticles	Bovine serum albumin nanoparticles	LPS-induced ALI mice	Enhanced oral bioavailability; enhanced anti-inflammatory effect.	[179]
G-Rgx365; G-Rg6	Polymeric nanoparticles; Protein-based nanocarriers	PEGylated nanoparticle; albumin	Plasma from SARS-CoV-2-infected patients; septic mice	Suppressed blood clot formation and vascular inflammation; alleviated tissue damage and cytokine storms; reduced histone H4 and NETosis-related factors.	[180]
Berberine	Polymeric nanoparticles; Cell-based nanocarriers	PLGA; PEG; MLE-12 cell membrane	LPS-induced ALI mice	Targeted pulmonary inflammation; ROS-response characteristics; improved the bioavailability of berberine.	[181]

Table 3 Nano-TCM Active Ingredient Co-Delivery Systems for IBD

TCM Active Ingredient	Nanocarrier Classification	Composition	Animal Model	Main Effects	Ref
Resveratrol	Polymeric nanoparticles	PLGA; Tween 80; N-oleoyl-d-galactosamine	Sprague-Dawley (SD) rats	Enhanced oral bioavailability; promoted the intestinal drug absorption; improved anti-inflammatory effect.	[110]
	Polymeric nanoparticles	Folic acid-conjugated PLGA	TNBS-induced rats	Protect drug from rapid degradation; enhanced intestinal drug permeation; improved anti-inflammatory effect.	[109]
	Polymeric nanoparticles	SF nanoparticles	TNBS-induced rats	Controlled drug release; immunomodulatory properties; enhanced intestinal anti-inflammatory effects.	[183]
	Exosomes	Milk-derived exosomes	Acetic acid-induced colitis rats	Protection under acidic conditions; enhanced drug intestinal permeation; relieved the colitis.	[182]
Quercetin	Polymeric micelles	PEG-chitosan nanomicellar	DSS-induced mice	Controlled drug release; enhanced inflammatory-targeting ability; improved intestinal anti-inflammatory effects.	[184]
Curcumin	Cell membrane vesicles	CXCR4-enriched MC-3T3 cells membrane	DSS-induced mice	Targeted delivery; evaded immune clearance; prolonged circulation time.	[185]
Berberine	Polymeric nanoparticles	PLGA	DSS-induced mice	Enhanced water solubility and bioactivity; ameliorated intestinal epithelial cell apoptosis and improved gut barrier function by targeting the IL-6/IL-6R axis	[186]

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to free berberine. The BPL-NPs effectively reduce intestinal epithelial cell apoptosis and restore gut barrier function through selective modulation of the IL-6/IL-6R signaling axis.[186]

Rheumatoid Arthritis (RA) and Osteoarthritis (OA)

The nano-resveratrol co-delivery system demonstrates excellent transdermal penetration capability, efficiently delivering resveratrol into joint cavities to alleviate RA symptoms.[187] When administered via intra-articular injection, this system significantly reduces TNF-α levels in knee joints, providing therapeutic benefits in rat OA models.[188]

Cadmium telluride semiconductor nanoparticles have been developed to enhance quercetin delivery, showing remarkable efficacy in promoting cartilage regeneration in OA rats through dual mechanisms of augmenting antioxidant enzyme activity and suppressing inflammatory mediator expression.[189]

Another promising approach involves the exosome-curcumin system, which targets the regulatory gene hsa-miR-126-3p in chondrocyte metabolism. In IL-1β-induced OA mice, this system effectively reduces chondrocyte catabolism and inflammation by upregulating hsa-miR-126-3p expression and subsequently inhibiting ERK1/2, PI3K/AKT, and p38 phosphorylation.[190] Combination therapy using PLGA nanoparticles co-loaded with curcumin and meloxicam demonstrates superior anti-inflammatory effects compared to single-drug treatments in joint inflammation models.[191]

The xanthan gum-silver nanoparticle-bergenin system represents an innovative low-dose therapeutic approach, exhibiting enhanced immunomodulatory and antioxidant properties compared to free bergenin.[64] This formulation significantly ameliorates OA symptoms in rats through multi-target inhibition of ROS, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), and Toll-like receptors (TLR-2, TLR-4).

Similarly, the nanocarrier-CK system effectively mitigates cartilage defects in OA mice by modulating gene expression patterns - downregulating cartilage degradation, inflammation, and lipogenesis markers while upregulating PPAR expression (Table 4).[192]

Conclusion and Future Prospects

This review systematically summarizes the anti-inflammatory mechanisms of key TCM active ingredients (resveratrol, quercetin, curcumin, bergenin, honokiol, ginsenosides, and berberine), which primarily involve modulation of SIRT1/SIRT3-mediated regulation of NF-κB, MAPK, PI3K/AKT, STAT3, and NRF2/HO-1 signaling pathways. We further elucidate the critical relationship between mitochondrial oxidative stress and inflammatory responses. While these compounds show significant therapeutic potential, their clinical translation has been limited by poor bioavailability, necessitating the development of nano-TCM delivery systems to enhance their pharmacokinetic profiles and therapeutic efficacy.

Current research on nanocarrier systems demonstrates considerable promise for pharmacological applications. These systems offer several advantages, including established safety profiles, flexible administration routes, and both passive and active targeting capabilities that significantly improve the bioavailability of TCM compounds. Among exogenous nanocarriers, lipid-based systems are particularly valuable for targeted delivery due to their amphiphilic nature, structural stability, biocompatibility, and ease of surface modification. Similarly, polymeric nanoparticles are widely utilized for their high drug encapsulation efficiency. However, potential nanotoxicity associated with certain carriers (eg, inorganic nanoparticles and nanoemulsions) requires careful evaluation. Studies have documented that inorganic nanoparticle accumulation may lead to hepatotoxicity,[193] with slow hepatic metabolism and prolonged retention being major contributing factors.[194] For instance, 28-day oral administration of silver nanoparticles in rats caused dose-dependent chronic liver injury, evidenced by altered alkaline phosphatase and cholesterol levels, along with inflammatory infiltration in hepatic tissues.[195] Comparable findings show that magnetite iron oxide nanoparticles induce chronic pulmonary inflammation and granuloma formation in mice.[196] At the molecular level, mesoporous silica and titanium dioxide nanoparticles activate inflammasome pathways,[197,198] while repeated silver nanoparticle exposure leads to thymic atrophy, splenomegaly, and lymphocyte suppression.[199]

Compared to synthetic nanocarriers, biomimetic nanocarriers utilize endogenous components (eg, erythrocytes, leukocytes, macrophages) through surface functionalization to achieve “self-camouflage”, exhibiting superior properties such as reduced immunogenicity, enhanced biocompatibility, prolonged circulation time, and targeted accumulation at

Table 4 Nano-TCM Active Ingredient Co-Delivery Systems for RA and OA

TCM Active Ingredient	Nanocarrier Classification	Composition	Animal Model	Main Effects	Ref
Resveratrol	Nanocrystals	Nano-resveratrol; hyaluronic acid	Complete freund's adjuvant (CFA)-induced mice	Penetrated the cuticle layer of the skin for effective drug delivery; enhanced therapeutic effects.	[187]
	Polymeric micelles	Poloxamer 188; poloxamer 407; PLA	CFA-induced arthritis rats	Enhanced therapeutic effects.	[188]
Quercetin	Inorganic nanocarriers	Cadmium telluride semiconductor nanoparticles	CFA-induced arthritis rats	Enhanced anti-inflammatory and antioxidant effects; enhanced cartilage regeneration.	[189]
Curcumin	Polymeric nanoparticles	PLGA nanoparticles	CFA-induced arthritis rats	Reduced joint inflammation, and promoted cartilage regeneration.	[191]
Bergenin	Inorganic nanocarriers	Xanthan gum-silver nanoparticles	CFA-induced arthritis rats	Enhanced oral bioavailability; inhibited the expression of ROS, inflammatory cytokines and TLR.	[64]
CK	Polymeric nanoparticles	Polycaprolactone nanofibers	Medial meniscus (DMM) surgery-induced OA mice	Alleviated cartilage defects by inhibiting genes related to cartilage degradation, inflammation, and lipogenesis, and upregulating PPAR expression.	[192]

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disease sites.[19] However, the limited availability of natural source materials poses substantial challenges for large-scale production. Artificial exosomes have emerged as a promising alternative to natural exosomes and warrant further exploration.[200] Current technological constraints continue to impede the translation of nanocarrier systems from preclinical research to industrial-scale manufacturing.[201] There is an urgent need for comprehensive characterization of nanocarrier properties, including physicochemical parameters, enzymatic stability, morphological characteristics, and storage stability. Parallel research efforts should focus on developing nanocarriers with optimal safety profiles, structural stability, biocompatibility, controlled release kinetics, and high drug-loading capacity. To enhance targeting precision, various surface modification strategies have been investigated, employing ligands, macromolecules (monosaccharides, polysaccharides, peptides, folic acid, antibodies), surfactants, synthetic/natural polymers, and metallic components for nanocarrier functionalization.[202]

In inflammation-related diseases, numerous studies have reported nanocarrier systems delivering resveratrol, quercetin, and curcumin. However, research on nanocarriers incorporating honokiol, bergenin, and ginsenosides, and berberine remains limited despite their potent anti-inflammatory and antioxidant properties. Notably, clinical studies evaluating nano-formulated TCM active ingredient delivery systems are still insufficient. Importantly, nanocarriers co-delivering multiple active ingredients and/or therapeutic agents demonstrate superior efficacy compared to single-component formulations. This finding suggests a novel therapeutic strategy: combining nano-formulated TCM systems with conventional medications may achieve enhanced therapeutic outcomes at reduced and safer doses. For functionalized nanocarriers, a key challenge remains the identification of specific receptors and cytokines at lesion sites to enable precise targeting.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Chaoqun Sun, Ju Chen, and Shuyou Bai shared the first authorship.

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Disclosure

The authors declare no conflicts of interest.

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