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REVIEW

Bridging Pharmacology and Nanotechnology: Mechanistic Insights into Traditional Chinese Medicine-Based Nanodelivery Systems for Rheumatoid Arthritis

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Objective: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation and joint destruction. Importantly, this review emphasizes the mechanistic linkage among TCM active compounds, nanocarrier design, and rheumatoid arthritis (RA) signaling pathways. By integrating carrier-mediated targeting, microenvironment-responsive release, and pathway-specific modulation (e.g. NF-κB, JAK/STAT, MAPK, Nrf2, and NLRP3), TCM-based nanodelivery systems are shown to remodel the synovial immune microenvironment, enhance intracellular drug accumulation in macrophages and fibroblast-like synoviocytes, and amplify multi-level anti-inflammatory and immunomodulatory effects. This mechanistic integration provides a framework for rational design of next-generation nanomedicines for RA therapy.

Methods: Recent studies were systematically analyzed to categorize lipid-based, polymeric, inorganic, biomimetic, and stimuli-responsive nanocarriers, with emphasis on formulation strategies, pharmacokinetic/pharmacodynamic enhancement, and mechanistic modulation of inflammatory and immune pathways.

Results: Nanodelivery systems not only improve drug solubility, stability, and lesion accumulation, but also reshape the interaction between TCM compounds and RA-associated signaling networks. Distinct classes of phytochemicals exhibit characteristic mechanistic profiles: triterpenoids (e.g. celastrol, triptolide) primarily suppress NF-κB, proteasome activity, and osteoclastogenesis, whereas flavonoids (e.g. baicalin, icariin, curcumin) preferentially regulate NLRP3 inflammasome activation, Th17/Treg balance, and anti-oxidant pathways. Nanocarrier-mediated delivery further amplifies these effects through targeted release, immune cell modulation, and microenvironment-responsive activation.

Conclusion: The integration of nanotechnology with TCM pharmacology provides mechanistic synergy by coupling material-based targeting with pathway-specific regulation. This dual modulation represents a key advantage over conventional therapies and supports the rational design of mechanism-guided TCM-based nanomedicines for RA.

Keywords: rheumatoid arthritis, traditional chinese medicine, nanodelivery system, targeted therapy

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic synovitis, progressive cartilage and bone destruction, and potential involvement of extra-articular organs. Its pathogenesis is highly complex, involving genetic susceptibility, environmental triggers, and dysregulated immune activation. Imbalances among immune cells such as T cells, B cells, and macrophages, together with the excessive expression of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, contribute to abnormal synovial proliferation, angiogenesis, and osteoclast activation, ultimately leading to irreversible joint damage. Although disease-modifying antirheumatic drugs (DMARDs), biologics, and Janus

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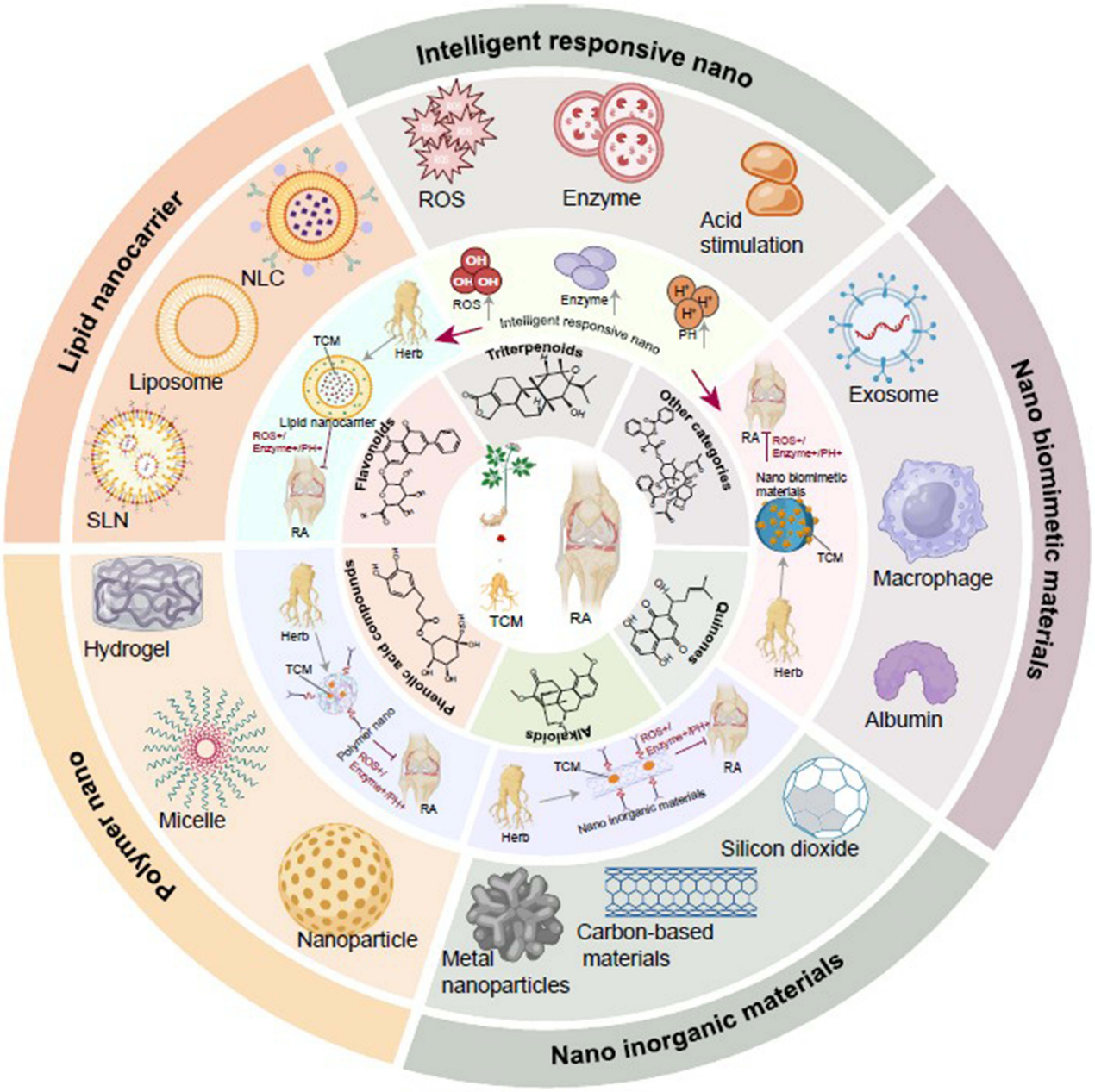
Graphical Abstract



kinase (JAK) inhibitors have significantly improved disease management, limitations such as immune suppression, adverse effects, and drug resistance remain major clinical challenges.[1–3]

Active ingredients derived from traditional Chinese medicine (TCM), such as triptolide, curcumin, resveratrol, and icariin, have attracted increasing attention due to their multi-target activities, low toxicity, and immunomodulatory potential. These natural compounds can modulate key signaling pathways—including NF-κB, MAPK, and JAK/STAT—to suppress inflammatory responses, alleviate oxidative stress, and prevent bone destruction. However, their clinical application is hindered by poor solubility, instability, and low bioavailability.[4–7]

In recent years, the rapid development of nanodelivery systems has provided novel strategies for improving the therapeutic efficacy and targeted delivery of TCM active compounds. Various nanocarrier platforms—including polymeric nanoparticles, liposomes, hydrogels, microneedles, inorganic materials, and biomimetic systems—have demonstrated the ability to enhance drug stability, bioavailability, and lesion accumulation. In particular, stimuli-responsive nanoplatforms that react to pathological signals such as pH, reactive oxygen species (ROS), or enzymatic activity can achieve controlled and site-specific release within the inflammatory microenvironment, further enhancing efficacy and safety.

From a drug delivery perspective, the inflamed synovial microenvironment in RA exhibits enhanced vascular permeability, acidic pH, elevated reactive oxygen species (ROS), and overexpression of matrix metalloproteinases (MMPs), which together provide a pathological basis for nanomedicine-based targeting strategies.[8,9] Nanoparticles can exploit the enhanced permeability and retention (EPR)-like effect in inflamed joints and enable site-specific drug accumulation, thereby increasing local drug concentration while reducing systemic exposure.[10,11] In addition, surface-functionalized nanocarriers (eg., folate-, hyaluronic acid-, or peptide-modified systems) allow for active targeting of synovial macrophages, fibroblast-like synoviocytes (FLS), and activated endothelial cells, further enhancing therapeutic precision.[12]

Unlike prior reviews that primarily categorize nanocarrier types or summarize therapeutic outcomes, this manuscript provides a mechanistic integration across three interconnected dimensions: (i) rational nanocarrier design and functionalization strategies, (ii) pathway-specific modulation by traditional Chinese medicine (TCM) active compounds, and (iii) remodeling of the synovial immune and inflammatory microenvironment. By systematically linking carrier physicochemical properties with intracellular trafficking, immune cell targeting, and signaling pathway regulation (eg., NF-κB, MAPK, JAK/STAT, PI3K/Akt, and Nrf2 pathways), this review moves beyond descriptive classification and offers a mechanistically driven framework for understanding how TCM-based nanomedicines achieve enhanced therapeutic efficacy in rheumatoid arthritis (RA). This integrated perspective represents a conceptual advancement over existing nanomedicine and TCM-focused reviews, which typically emphasize carrier taxonomy or therapeutic efficacy without mechanistically connecting carrier design to immune microenvironment remodeling and pathway-level regulation.

Pathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by chronic synovial inflammation, cartilage degeneration, and bone erosion, which severely impair patients' quality of life and cause extensive systemic damage. The pathogenesis of RA involves the interplay among genetic susceptibility (eg., *HLA-DRB1*), environmental factors (such as smoking and microbial dysbiosis), and the breakdown of immune tolerance.[13] The pathological process is driven by abnormal activation of helper T cells, B cells, and macrophages within the synovium, leading to the overproduction of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6) and matrix metalloproteinases (MMPs). These mediators promote synovial hyperplasia, inflammatory cell infiltration, degradation of the cartilage matrix, and bone destruction.[14]

In addition, oxidative stress is frequently observed in RA synovial tissues. The excessive accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) disrupts cellular structures and activates signaling pathways such as NF-κB, further amplifying the inflammatory cascade. Recent studies have also revealed that novel cell death modalities, including ferroptosis, play critical roles in RA pathogenesis, providing new therapeutic targets for future intervention.[15]

Current RA treatments primarily rely on nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and both conventional and biological DMARDs. However, these approaches are limited by suboptimal efficacy, adverse effects, and the inability to achieve complete remission. Consequently, developing precise drug delivery systems that target inflamed joints while minimizing systemic toxicity has become a major research focus, laying the foundation for integrating TCM active compounds with nanomaterial-based delivery strategies.

Recent advances in rheumatoid arthritis (RA) pathogenesis emphasize a tightly interconnected cascade linking immune dysregulation, oxidative stress, and progressive joint destruction. Aberrant activation of innate and adaptive immune cells, including macrophages, T helper cells (particularly Th1 and Th17 subsets), and B cells, leads to sustained production of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17. These cytokines not only perpetuate synovial inflammation but also promote excessive reactive oxygen species (ROS) generation, resulting in redox imbalance within the synovial microenvironment.[16]

Oxidative stress further amplifies inflammatory signaling through redox-sensitive pathways, particularly NF-κB and MAPK, and contributes to activation of the NLRP3 inflammasome, thereby promoting IL-1β maturation and pyroptosis. This inflammatory–oxidative axis drives fibroblast-like synoviocyte (FLS) activation, enhances matrix metalloproteinase (MMP) secretion, and accelerates cartilage degradation. In parallel, oxidative stress and inflammatory mediators stimulate osteoclast differentiation and bone resorption, leading to progressive bone erosion. Collectively, these interlinked immune–oxidative–destructive processes establish a self-perpetuating vicious cycle that underlies synovial hyperplasia, cartilage destruction, and bone loss in RA, thereby providing multiple mechanistic intervention points for traditional Chinese medicine (TCM) compounds and nanodelivery-based therapeutic strategies.

To provide a systematic overview of the molecular and cellular mechanisms underlying rheumatoid arthritis (RA), Figure 1 schematically summarizes the key pathogenic pathways involved in disease initiation and progression. The diagram integrates immune dysregulation, inflammatory cytokine cascades, oxidative stress, and joint-destructive processes, highlighting major signaling pathways such as NF-κB, MAPK, JAK/STAT, and NLRP3 inflammasome activation. Importantly, this schematic also illustrates the primary therapeutic intervention points targeted by traditional Chinese medicine (TCM) active compounds and TCM-based nanodelivery systems.

Physiological Characteristics of Rheumatoid Arthritis

RA leads to joint deformity, restricted mobility, and loss of function. Moreover, RA is often accompanied by systemic pathological and physiological alterations such as anemia, atherosclerosis, interstitial lung disease, and osteoporosis, indicating that the disease extends beyond articular involvement. Inflamed synovial tissue secretes multiple matrix

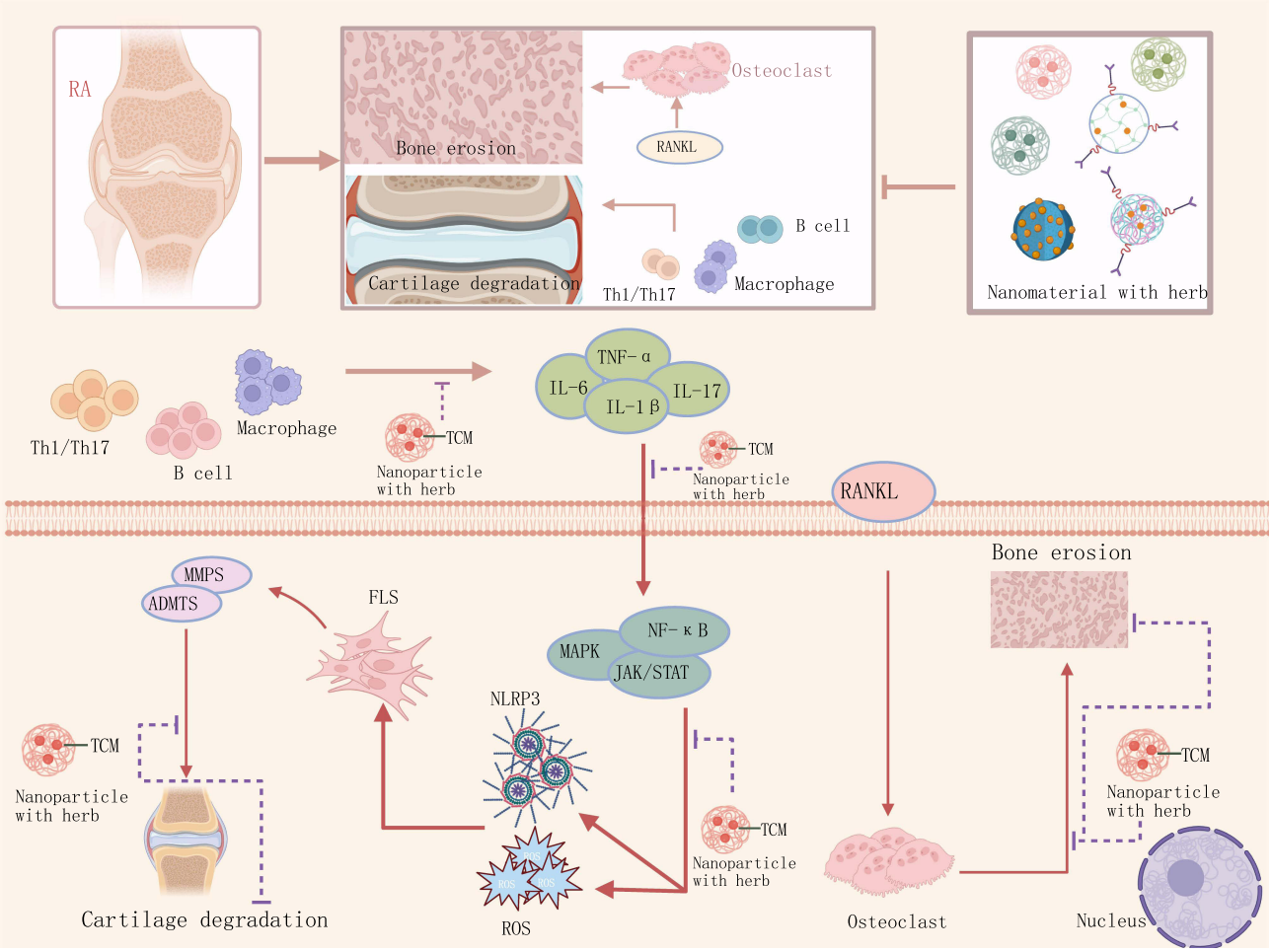


Figure 1 Schematic illustration of the pathogenic mechanisms of rheumatoid arthritis and major therapeutic intervention points.

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metalloproteinases (MMPs), which exacerbate cartilage matrix degradation. Simultaneously, imbalanced macrophage polarization (increased M1-type and decreased M2-type), enhanced oxidative stress, and abnormal energy metabolism contribute to the onset and progression of RA.[17]

The pathological evolution of RA is a persistent process centered on the synovium, underpinned by immune dysregulation, and characterized by systemic inflammation and tissue destruction. These pathological features not only highlight the chronic and multifactorial nature of RA but also provide a theoretical basis for the development of targeted therapeutic strategies.

Application of Active Compounds from Traditional Chinese Medicine in RA Therapy

In recent years, bioactive compounds derived from traditional Chinese medicine (TCM) have shown great potential in the treatment of RA due to their multi-target actions, low toxicity, and strong immunomodulatory properties. Material. Increasing experimental evidence has demonstrated that individual TCM monomers can effectively alleviate RA symptoms through diverse mechanisms, including modulation of immune responses, inhibition of pro-inflammatory cytokines, regulation of oxidative stress, and induction of apoptosis.

These findings suggest that TCM-derived active ingredients may serve as promising therapeutic candidates for RA management, especially when combined with advanced nanodelivery platforms to overcome pharmacokinetic limitations and enhance site-specific efficacy. The major categories of nanocarrier-based delivery systems for RA-related phytochemicals are summarized in Table 1.

Table 1 Representative TCM Active Ingredients with Pharmacological Mechanisms in Rheumatoid Arthritis

Category	Active Compound	Source Herb	Main Pharmacological Effects	Mechanism/ Target	Experimental Mode	Ref.
Terpenoids	Triptolide	*Tripterygium wilfordii*	Anti-inflammatory, immunosuppressive	Inhibits NF-κB, MAPK, JAK/STAT pathways	CIA mice, synovial cells	[4]
	Celastrol	*Tripterygium wilfordii*	Anti-inflammatory, antioxidant; reduces bone erosion and synovitis	Inhibits NF-κB and proteasome activity; regulates heat shock proteins	CIA model, osteoclast differentiation, synovial cells	[18]
	Triptolide lactone	*Tripterygium wilfordii*	Potent immunosuppressive and anti-inflammatory	Suppresses NF-κB activation and multiple inflammatory transcription programs	CIA mice, RA-FLS, T cells	[19]
	Oleanolic acid	*Gynostemma pentaphyllum, Ligustrum lucidum*	Anti-inflammatory, anti-rheumatic	Inhibits PI3K/Akt pathway	CIA rats	[20]
	Ginsenosides	*Panax ginseng*	Anti-inflammatory, immunomodulatory	Downregulates TNF-α, IL-1β, IL-6	FLS or T cell assays, CIA mice	[21]
	Aescin	*Aesculus hippocastanum*	Anti-inflammatory, antioxidant, immunoregulatory	Suppresses TNF-α and IL-6 expression and release	CIA mouse model	[22]
Flavonoids	Curcumin	*Curcuma longa*	Antioxidant, anti-inflammatory	Inhibits JAK/STAT and MAPK; promotes M2 polarization	RA-FLS, CIA mice	[5]
	Icariin	*Epimedium brevicornum*	Immunomodulatory, anti-inflammatory	Modulates Th17/Treg balance; inhibits STAT3	CIA rats, T cell model	[7]
	Baicalin	*Scutellaria baicalensis*	Anti-inflammatory, antioxidant	Inhibits NLRP3 inflammasome and IL-1β	RA-FLS, animal model	[23]
	Rutin	*Sophora japonica, Ruta graveolens*	Antioxidant, anti-inflammatory	Inhibits MMP-9 activity; regulates NO and GSH	FCA-induced RA rats	[24]
	Astragalin	*Astragalus membranaceus, Trifolium pratense*	Anti-inflammatory, antioxidant	Inhibits TNF-α and IL-6 expression	CIA model, synovial cells	[25]

(*Continued*)

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Table 1 (Continued).

Category	Active Compound	Source Herb	Main Pharmacological Effects	Mechanism/ Target	Experimental Mode	Ref.
Phenolic acids	Resveratrol	*Polygonum cuspidatum, grape skin*	Antioxidant, immunomodulatory	Activates SIRT1/Nrf2; inhibits ROS generation	RA rat synovium	[6]
	Paeonol	*Paeonia suffruticosa*	Antioxidant, anti-inflammatory	Inhibits p38 MAPK and COX-2 expression	RA rat synovium	[26]
	Cichoric acid	*Cichorium intybus*	Anti-inflammatory	Inhibits TNF-α, IL-1β, COX-2	Inflammatory cell model	[27]
	Chlorogenic acid	*Lonicera japonica Thunb*	Anti-inflammatory, antioxidant, immunomodulatory	Inhibits IL-1β, IL-6, TNF-α release	CIA mice	[28]
	Thymol	*Thymus vulgaris*	Anti-inflammatory, antioxidant, immunomodulatory	Inhibits IL-1β, IL-6, TNF-α release	CIA mice	[29]
Alkaloids	Sinomenine	*Sinomenium acutum*	Anti-inflammatory, analgesic, immunoregulatory	Inhibits NF-κB; modulates ROS	RA rat synovial cells	[30]
	Berberine	*Coptis chinensis*	Anti-inflammatory; inhibits FLS proliferation	Suppresses MAPK/NF-κB; induces apoptosis	RA-FLS model	[31]
	Piperine	*Piper nigrum*	Anti-inflammatory, analgesic, immunomodulatory	Inhibits NF-κB; downregulates IL-1β, TNF-α; reduces FLS inflammation	RA-FLS, FCA/CIA animal model	[32]
Quinones	Tanshinone IIA	*Salvia miltiorrhiza*	Anti-inflammatory, immunomodulatory	Inhibits TLR4/NF-κB and JAK/STAT pathways	CIA mice	[33]
	Shikonin	*Lithospermum erythrorhizon*	Anti-inflammatory; inhibits synovial proliferation	Activates AMPK/UCP2; promotes M2 macrophage polarization	CIA mice, macrophages	[34]
Others	Glycyrrhizic acid	*Glycyrrhiza uralensis*	Anti-inflammatory, antioxidant	Inhibits HMGB1-TLR4/NF-κB pathway	CIA rats	[35]
	Sesbania sesban extract	*Sesbania sesban (Fabaceae)*	Anti-inflammatory; sustained release; reduces joint inflammation	Suppresses NO production and cytokines	Cell inflammation model	[36]
	Melittin	*Bee venom*	Strong anti-inflammatory, analgesic, immunoregulatory	Inhibits NF-κB and COX-2 expression	RA-FLS, macrophages, CIA model	[37]

Challenges in Rheumatoid Arthritis Drug Delivery and Rationale for Nanotechnology

The clinical management of rheumatoid arthritis (RA) faces multiple pharmacokinetic and pharmacodynamic challenges that limit therapeutic efficacy. Conventional small-molecule anti-rheumatic drugs often exhibit rapid systemic clearance, poor accumulation in inflamed synovial tissues, and limited penetration into the dense inflammatory pannus, resulting in suboptimal joint-specific drug exposure and dose-limiting systemic toxicity.[38]

In addition, many disease-modifying anti-rheumatic drugs (DMARDs) suffer from poor aqueous solubility and unfavorable biodistribution, which further restrict their therapeutic index.[39] Biologic agents, while highly effective in selected patient populations, are associated with high production costs, immunogenicity, increased risk of infection, and the requirement for parenteral administration, which collectively limit long-term accessibility and patient compliance.

These limitations have driven extensive research into nanotechnology-based drug delivery systems aimed at enhancing joint targeting, prolonging systemic circulation, improving intracellular delivery to synovial macrophages and fibroblast-like synoviocytes, and enabling microenvironment-responsive drug release. By addressing key barriers in RA pharmacotherapy, nanomedicine provides a rational platform for improving both therapeutic efficacy and safety while potentially reducing systemic adverse effects.[40]

Integration of Nanodelivery Systems and Active Compounds of Traditional Chinese Medicine in RA Therapy

Lipid-Based Nanodelivery Systems Containing TCM Active Compounds

Lipid-based nanocarriers have been extensively applied in TCM research due to their excellent biocompatibility, biodegradability, and high encapsulation efficiency for lipophilic compounds. This category primarily includes liposomes, solid lipid

nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), which can effectively improve drug stability and bioavailability while enhancing targeting and controlled-release performance.

Liposomes

Liposomes are vesicular structures composed of phospholipid bilayers, resembling cellular membranes, and are capable of encapsulating both hydrophilic and hydrophobic drugs.[41] Surface modification can further improve their stability and targeting ability. For example, Li and Han[42] developed folic acid-modified liposomes loaded with ginsenosides (particle size 249.13 ± 1.40 nm, encapsulation efficiency 93.33 ± 0.05%). In adjuvant-induced arthritis (AIA) rats, this system significantly reduced joint swelling and suppressed TNF-α and IL-1β expression, with histological analysis confirming marked alleviation of synovial hyperplasia. Feng et al[43] further designed a novel liposomal formulation using ginsenosides as membrane stabilizers instead of cholesterol, thereby improving structural stability and conferring joint-targeting ability. Adin et al[44] co-encapsulated methotrexate and mangiferin in trans-liposomes formulated as a topical gel (mean diameter 148.6 nm, encapsulation efficiency 74.2%). After transdermal administration, the *Cmax* of mangiferin increased to 6.94 ± 0.51 μg/mL (oral route: 3.74 ± 1.91 μg/mL), and $AUC_{0-24}h$ rose to 43.92 ± 7.90 μg·h/mL. This formulation significantly reduced ankle swelling in CFA-induced arthritis rats, showing superior efficacy compared with commercial diclofenac gel. Wang and Shen[45] developed long-circulating liposomes for celastrol delivery (average diameter ~72 nm, encapsulation efficiency 78.8%), which extended the elimination half-life ($t_{1/2}$) to 11.71 h and mean residence time (MRT) to 7.98 h, markedly improving pharmacokinetics. Zhang and Chen et al[46] encapsulated melittin into liposomes combined with a dissolving microneedle platform, achieving efficient transdermal delivery, reduced systemic toxicity, and enhanced local anti-inflammatory effects.

Beyond classical liposomes, other vesicular nanocarriers—including niosomes, cubosomes, bilosomes, and ethosomes—have demonstrated significant potential for anti-rheumatic drug delivery. These systems differ in membrane composition, internal nanostructure, and physicochemical stability, which can profoundly influence drug loading capacity, release kinetics, and biological performance.[47]

Niosomes, composed of non-ionic surfactants, exhibit improved chemical stability and cost-effectiveness compared with phospholipid-based liposomes. Cubosomes, characterized by a bicontinuous cubic liquid crystalline structure, enable high drug-loading capacity and sustained drug release. Bilosomes, incorporating bile salts, enhance membrane flexibility and permeability, which has been associated with improved transdermal and oral delivery of anti-inflammatory agents. Collectively, these vesicular systems expand the design space for optimizing drug delivery and therapeutic outcomes in RA.

Mechanistically, vesicular nanocarriers enhance anti-rheumatic efficacy by promoting endocytosis-mediated intracellular delivery and facilitating lysosomal escape, thereby increasing cytosolic drug availability in synovial macrophages and fibroblast-like synoviocytes. In addition, surface-modified vesicles enable receptor-mediated uptake, which further improves synovial targeting and amplifies inhibition of NF-κB and MAPK signaling within inflamed joints.

Solid Lipid Nanoparticles (SLNs)

SLNs, developed in the early 1990s, are composed of solid lipid matrices stabilized by surfactants, combining the advantages of emulsions and polymeric nanoparticles. They offer high drug-loading capacity and sustained-release properties[48.] Studies have shown[49] that piperine-loaded SLNs significantly alleviated inflammation and joint swelling in RA rat models, with therapeutic efficacy comparable to or exceeding that of diclofenac sodium, demonstrating strong therapeutic potential.

Nanostructured Lipid Carriers (NLCs)

NLCs represent the second generation of lipid nanocarriers, overcoming the limitations of SLNs such as low drug-loading capacity and instability. For instance, berberine-loaded NLCs[50] markedly reduced arthritis scores and ankle swelling in CIA rats, improving gait and pain behaviors.Tang and Gu et al[51] developed triptolide lactone-loaded NLCs (mean diameter 139.6 nm, encapsulation efficiency 97.2%), exhibiting good skin permeability and sustained-release properties. In vivo microdialysis showed higher skin drug concentrations than plasma, significantly reducing arthritis

scores, paw edema, and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6).Pal et al[52] reported that thymohydroquinone-loaded NLCs displayed superior transdermal permeability and anti-inflammatory activity compared with free drugs.

Importantly, the physicochemical properties and in vivo performance of solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are highly dependent on the lipid matrix composition. Different solid lipids, such as glyceryl monostearate, stearic acid, and Compritol ® 888 ATO, as well as liquid lipids, including medium-chain triglycerides and oleic acid, can significantly affect particle crystallinity, drug-loading capacity, release behavior, and long-term stability. Therefore, formulation composition should be considered a critical determinant of therapeutic performance rather than a purely technical parameter.

From a mechanistic perspective, SLNs and NLCs prolong systemic circulation and enable sustained drug release, leading to prolonged inhibition of inflammatory signaling pathways in synovial tissues. The lipid matrix further facilitates membrane interaction and intracellular trafficking, thereby enhancing intracellular drug accumulation in macrophages and reducing rapid drug efflux, which collectively contributes to enhanced and sustained suppression of pro-inflammatory cytokine production.

Polymeric Nanodelivery Systems Containing TCM Active Compounds

Polymer-based nanocarriers utilize natural or synthetic polymers with controllable particle sizes, excellent biocompatibility, and biodegradability to enhance the stability and delivery efficiency of TCM compounds. Through surface functionalization and stimuli-responsive design, these systems can achieve sustained release, targeted delivery, and barrier penetration, becoming a key direction in RA nanotherapy research.[53]

Polymeric Hydrogels

Polymeric hydrogels possess excellent biocompatibility and injectability, making them suitable for sustained intra-articular delivery.[54] Researchers[55] designed a supramolecular hydrogel composed of hyaluronic acid, cyclodextrin, and polyethylene glycol for efficient loading and controlled release of cichoric acid. In CIA rats, the hydrogel significantly downregulated IL-1β, IL-6, and TNF-α levels, exhibiting potent anti-inflammatory activity. Another study[36] developed a silk fibroin-based in situ hydrogel carrying *Sesbania sesban* extract, which possesses notable anti-inflammatory effects. The injectable formulation rapidly gelled within the joint cavity and sustained drug release for over 20 days, effectively relieving arthritis symptoms.Chen et al[56] constructed an RGD-modified hyaluronic acid–gold nanoparticle hydrogel for targeted delivery of triptolide lactone, enabling photothermal therapy and imaging-guided treatment. Under near-infrared irradiation, the system achieved localized release and thermal effects, significantly improving inflammation in CIA mice.

Polymeric Micelles

Polymeric micelles, self-assembled from amphiphilic copolymers, possess a core–shell structure with high water solubility and stability. Their hydrophobic core efficiently encapsulates poorly soluble drugs, while the hydrophilic shell enhances circulation time[57].Fan and Xu et al[58] designed reactive oxygen species (ROS)-responsive micelles to deliver curcumin, incorporating folic acid for active targeting of inflammatory macrophages. In CIA rats, this system selectively released curcumin under high ROS conditions, significantly reduced IL-1β and IL-6 expression, and ameliorated cartilage damage.

Polymeric Nanoparticles

Polymeric nanoparticles, constructed from natural or synthetic polymers, are solid colloidal carriers with excellent degradability, protective capacity, and controlled-release properties.[59] In one study, a copolymer-based nanoparticle system co-delivering chlorogenic acid (CGA) and methotrexate (MTX)[60] enhanced tissue targeting and anti-inflammatory efficacy, significantly reducing cartilage erosion and inflammatory cytokine expression in CIA rats. Guo et al[61] developed MMP/ROS dual-responsive nanoparticles loaded with celastrol, achieving RA-specific targeting and enhanced accumulation in inflamed joints.Additionally, chitosan-based nanoparticles were employed to deliver rutin[62] and aescin,[63] which effectively downregulated TNF-α and IL-6 levels, improved synovial pathology, and demonstrated good safety profiles in animal models.

Overall, polymeric nanocarriers—with their diverse structural designs and functional modifications—greatly enhance the therapeutic efficacy of TCM active ingredients in RA treatment.

Inorganic Nanodelivery Systems Containing TCM Active Compounds

Inorganic nanocarriers have attracted increasing attention in RA therapy due to their structural stability, tunable surface functionality, and controllable drug release behavior. Common inorganic systems include mesoporous silica, metal oxides, and carbon-based nanomaterials[64.]These carriers can significantly enhance drug loading capacity, lesion accumulation, and stimuli-responsive release.

Mesoporous silica nanoparticles (MSNs) are particularly advantageous due to their high surface area and tunable pore structure. Wu and Chen et al[65] developed triptolide-loaded MSNs coated with polydopamine and modified with glucosamine to achieve pH-responsive and joint-targeted delivery. The system provided sustained release under inflammatory conditions, effectively alleviated synovitis and joint damage, prolonged lesion retention, and reduced systemic toxicity.

Other inorganic systems, such as metal nanoparticles and oxide-based carriers, also exhibit therapeutic potential. For instance, iron-based nanoparticles can exert anti-inflammatory effects by regulating ROS levels[66.] A gold nanorod–copper sulfide core–shell nanostructure (Au NR@CuS) has been reported to integrate photothermal therapy (PTT), photodynamic therapy (PDT), and chemotherapy (CT) in a single system.[67] Electromagnetic coupling between the Au nanorod core and the CuS shell enhances near-infrared light absorption and photothermal conversion efficiency. In addition, the Au NR@CuS structure suppresses charge carrier recombination and promotes Fenton-like reactions, facilitating reactive oxygen species generation for improved PDT efficacy. The octahedral CuS shell allows high drug loading, while surface modification with vasoactive intestinal peptide and hyaluronic acid enables targeted delivery to RA synovial cells. In collagen-induced arthritis models, this multifunctional nanoplatform alleviated synovial proliferation and joint edema, highlighting its potential for RA treatment, while carbon-based nanomaterials show promise due to their superior biocompatibility and drug-loading capacity.[68,69]

Mechanistically, Inorganic Nanodelivery Systems enhance therapeutic efficacy by enabling controlled and sustained intracellular drug release following endocytosis, thereby maintaining prolonged intracellular drug concentrations in synovial macrophages and fibroblast-like synoviocytes. In addition, surface-modified polymeric systems can regulate cellular uptake pathways and intracellular trafficking, leading to enhanced modulation of NF-κB, JAK/STAT, and MAPK signaling cascades in inflammatory cells.

Overall, inorganic nanocarriers offer new strategies for efficient delivery of TCM compounds and represent promising platforms for targeted RA therapy.

Biomimetic Nanodelivery Systems Containing TCM Active Compounds

Biomimetic nanocarriers mimic the natural structures of cell membranes, proteins, or exosomes, offering excellent immune evasion, biocompatibility, and specific targeting properties[70.] These systems can enhance accumulation of TCM compounds at inflamed sites, prolong circulation time, and reduce systemic toxicity.

Albumin Nanoparticles

Bovine serum albumin (BSA) serves as an effective drug carrier due to its natural affinity for inflamed tissues. Syed et al[71] developed BSA nanoparticles co-loaded with methotrexate and curcumin, exhibiting high encapsulation efficiency and sustained-release performance. The system enhanced joint accumulation, reduced systemic toxicity, and demonstrated the feasibility of biomimetic nanodelivery platforms for RA therapy.

Cell Membrane Vesicles

Cell-mimicking vesicles with phospholipid bilayer structures possess favorable skin permeability. In one study[72] mangiferin-loaded vesicles significantly improved drug solubility and skin penetration, effectively alleviating arthritis symptoms in vivo and demonstrating good dermal safety—highlighting their potential for transdermal RA therapy.

Exosome-Based Delivery

Exosomes are nanosized (30–100 nm) extracellular vesicles capable of transferring proteins and genetic materials, thereby modulating intercellular communication[73]. Yan and Liu et al [74] developed adipose-derived stem cell exosomes (ADSCs-EXO) loaded with icariin (ICA). The system inhibited M1 macrophages and promoted M2 polarization in vitro, while in CIA rats it significantly reduced synovial inflammation, suppressed cytokine expression, and preserved cartilage integrity, demonstrating strong therapeutic potential.

Macrophage-Mimetic Delivery

Proinflammatory M1 macrophages play a key role in RA pathogenesis through sustained cytokine secretion and synovial damage.[75] Li and Liu et al[76] constructed apoptotic macrophage-derived vesicles loaded with shikonin (SHK) to specifically target inflamed M1 macrophages. The formulation promoted M2 polarization, alleviated synovial hyperplasia, and reduced cartilage and bone erosion in CIA mice, showcasing excellent immunoregulatory and therapeutic effects.

Peptide-Modified Delivery Systems

Peptide-modified nanocarriers exhibit superior targeting and tissue-penetration capabilities. Common modifications include receptor-binding peptides, cell-penetrating peptides, and anti-inflammatory peptides. Surface functionalization with specific peptide sequences can markedly enhance drug accumulation within inflamed joints[77]. For instance, one study[78] developed an Fmoc–Phe–Phe peptide–hyaluronic acid conjugate capable of efficiently loading and sustainably releasing curcumin, displaying strong anti-inflammatory efficacy both in vitro and in vivo.

Mechanistically, biomimetic nanocarriers, such as cell membrane–coated nanoparticles and exosome-mimetic vesicles, exploit homologous targeting and immune evasion to enhance accumulation within inflamed synovial tissues. These systems facilitate preferential uptake by activated macrophages and synovial fibroblasts while reducing clearance by the mononuclear phagocyte system, thereby increasing local drug exposure and strengthening suppression of inflammatory and immune signaling pathways.

Stimuli-Responsive Nanodelivery Systems

In this section, stimuli-responsive modules (eg., pH-, ROS-, and enzyme-responsive components) are discussed as functionalization strategies that can be integrated into polymeric, lipid-based, and biomimetic nanocarriers, rather than as an isolated carrier category.

Beyond conventional lipid, polymeric, inorganic, and biomimetic platforms, various stimuli-responsive nanocarriers have been developed to exploit RA's pathological microenvironment—characterized by acidity, elevated ROS levels, and overexpressed enzymes. These systems release drugs specifically at inflamed sites, thereby improving therapeutic precision and minimizing systemic toxicity.[79] Wang and Cao et al[80] constructed a smart Fe (III)-coordinated nanodrug assembly (GF-TF) integrating tofacitinib, gallic acid, and folic acid, achieving precise joint targeting and image-guided release. Addition of deferoxamine (DFO) triggered Fe (III) chelation, structural disassembly, and controlled drug release, enhancing treatment accuracy. Another study[81] designed a ROS-responsive microneedle system composed of fucoidan, luteolin, and sinomenine linked via thioacetal bonds. The platform achieved local sustained release, suppressed M1 macrophages, and promoted M2 polarization, thereby reducing synovial inflammation and facilitating cartilage repair. Furthermore, fucoidan enhanced mechanical strength and stability of the microneedles, demonstrating the synergistic advantages of integrating TCM with nanotechnology. A near-infrared (NIR)-responsive thermosensitive hydrogel incorporating black phosphorus nanosheets (BPNs) and platelet-rich plasma (PRP) has been developed for rheumatoid arthritis (RA) therapy.[82] Under NIR irradiation, BPNs induce localized photothermal effects and reactive oxygen species generation to eliminate hyperplastic synovial tissue, while their degradable products support osteogenesis; meanwhile, the chitosan-based hydrogel enables sustained drug release, reduces joint friction, and protects cartilage. In arthritis animal models, this stimuli-responsive nanoplatform alleviated joint edema, indicating its potential for integrated RA treatment.

Mechanistically, stimuli-responsive nanocarriers enable site-specific drug activation within the inflamed synovial microenvironment. pH- and ROS-responsive systems preferentially release their payload under acidic and oxidative conditions, leading to selective amplification of anti-inflammatory signaling in inflamed joints while minimizing off-target drug release and systemic toxicity.

Collectively, stimuli-responsive systems exhibit superior specificity and controllability, offering innovative strategies for the precise delivery of TCM-derived compounds in RA therapy. Representative studies on different nanocarrier materials for herbal medicine delivery in RA are listed in Table 2.

Table 2 Summary of Nanodelivery Systems for TCM Active Ingredients in RA Therapy

Nanocarrier Type	Active Compound	Particle Size (nm)	EE/DL (%)	Administration Route	Main Pharmacodynamic Outcomes	Ref
Liposome	*Ginsenosides*	249.1 ± 1.4	93.3 ± 0.05	PO/IV	Reduced paw swelling in AIA rats; inhibited TNF-α and IL-1β expression	[36]
	Celastrol	~72	78.8	IV	Extended $t_1/_2$ to 11.71 h, increased MRT to 7.98 h; improved pharmacokinetics	[37]
	Mangiferin	148.6	74.2	TD	Increased Cmax to 6.94 μg/mL (vs. 3.74); AUC_{0-24}h 43.92 μg·h/mL; reduced inflammation	[22]
SLNs	*Piperine*	100–200	NR	PO/IV	Significantly reduced joint swelling in RA rats; efficacy comparable to diclofenac	[40]
NLCs	Triptolide lactone	139.6	97.2%	TD	Higher skin vs. plasma concentration; reduced inflammation and cytokine levels	[42]
	Thymohydroquinone	~150	NR	TD	Improved permeability and anti-inflammatory activity compared to free drug	[43]
Hydrogel	*Cichoric acid*	Micron-scale	76.2%	IA	Sustained release >20 days; downregulated IL-1β, IL-6, TNF-α	[46]
	Sesbania sesban extract	Micron-scale	NR	IA	Rapid gelation post-injection; sustained release >20 days; reduced inflammation	[47]
	Triptolide lactone	Micron-scale	NR	IA	Localized release and thermoresponsive behavior; improved inflammation in CIA mice	[48]
Micelle	Curcumin	~100	NR	IV	Targeted inflammatory macrophages; reduced cytokines; alleviated cartilage damage	[50]
Nanoparticle	*Chlorogenic acid*	~120	NR	IV	Reduced cartilage erosion and cytokine expression in CIA model	[51]
	Celastrol	~100	NR	IV	Increased joint accumulation; suppressed cytokines; attenuated cartilage degradation	[53]
	Rutin/Aescin	~200	NR	PO/IV	Downregulated TNF-α and IL-6; improved synovial pathology; no significant toxicity	[54,55]
MSNs	*Triptolide*	~120	NR	IV	pH-responsive release; prolonged retention at lesions; reduced systemic toxicity	[56]
Albumin NPs	*Curcumin*	163	68.2/75.7	IV	Significantly reduced arthritis index and cytokines; superior to free MTX	[61]
Exosome NPs	*Icariin*	~100	92.4	IV	Reduced arthritis index and paw thickness; decreased TNF-α, IL-1β, IL-6; increased IL-10	[64]
Cell membrane vesicles	*Mangiferin*	148.6 nm	74.23	TD	Improved skin permeation (C_{max} = 6.94 ± 0.51 μg/mL; AUC_{0-24}h = 43.92 ± 7.90 μg·h/mL) vs oral; in vivo anti-arthritic efficacy exceeded diclofenac gel.	[62]
	Shikonin	100-200	NR	IV	Promoted M2 polarization; reduced inflammation; alleviated synovial hyperplasia	[66]
Peptide modification	*Curcumin*	Micron-scale	NR	IV	Vesicles self-assembled via Fmoc-FF peptide + HA; Cur embedded through π–π interactions; demonstrated inflammation	[68]
Smart Response	Gallic acid/Folic acid	Micron-scale	NR	TD	A metal-polyphenol nanostructure with dual therapeutic-imaging functionality is assembled from TF, GA, FA, and Fe(III). It can accumulate at arthritis lesions and enable self-monitoring; controlled release and high-precision treatment are achieved by triggering structural disassembly through the addition of deferoxamine to chelate Fe(III).	[70]
	Sinomenine	Micron-scale	NR	TD	Fucose-luteolin amphiphilic polymers containing sulfone bonds self-assemble into nanoparticles encapsulating SIN, which are then loaded onto soluble microneedles to achieve ROS-responsive release. This approach suppresses M1 macrophage inflammation, promotes M2 polarization, alleviates synovitis, and repairs cartilage tissue.	[71]

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Repurposed Drugs and Nanoformulation Strategies for RA Therapy

Drug repurposing has emerged as a cost-effective and time-efficient strategy for rheumatoid arthritis (RA) therapy, as it leverages existing pharmacokinetic, safety, and manufacturing data to accelerate clinical translation. Several small-molecule drugs originally approved for non-rheumatic indications, including anti-malarial agents (eg., hydroxychloroquine), immunomodulatory drugs, statins, and anti-diabetic agents (eg., metformin), have demonstrated anti-inflammatory and immunoregulatory effects relevant to RA pathogenesis.[83]

However, the clinical application of many repurposed drugs in RA is limited by suboptimal biodistribution, dose-limiting systemic toxicity, and insufficient accumulation in inflamed synovial tissues. Nanoformulation strategies provide an effective approach to overcome these limitations by enhancing synovial targeting, improving intracellular delivery to synovial macrophages and fibroblast-like synoviocytes, and reducing off-target exposure.[84]

Recent studies have demonstrated that nano-enabled delivery of repurposed drugs, such as methotrexate, dexamethasone, statins, and other immunomodulatory small molecules, significantly enhances therapeutic efficacy and safety in experimental RA models. These nanoformulations promote preferential accumulation in inflamed joints, prolong drug retention, and enable sustained suppression of inflammatory signaling pathways, including NF-κB and JAK/STAT, while minimizing systemic adverse effects.[85]

Collectively, the integration of drug repurposing with nanotechnology-based delivery represents a promising translational strategy to improve the therapeutic index of existing drugs and expand the repertoire of effective treatment options for RA.

Integrated Mechanistic Insights Across Different Classes of TCM Compounds

To provide an integrated mechanistic perspective, the major classes of TCM-derived compounds reviewed in this manuscript exhibit both shared and distinct regulatory effects on key pathogenic pathways in rheumatoid arthritis.[86]

Triterpenoids (eg., celastrol, triptolide, asiatic acid) represent a class of highly potent anti-inflammatory and immunosuppressive agents. These compounds predominantly target central inflammatory hubs, including NF-κB, MAPK, and JAK/STAT signaling, resulting in robust suppression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[87–89] In addition, triterpenoids uniquely regulate protein homeostasis and stress-response pathways, including HSP90 inhibition and modulation of PI3K/AKT/mTOR signaling, thereby promoting apoptosis and autophagy in activated synovial fibroblasts and immune cells.[88,89] This profile suggests that triterpenoids primarily function as strong upstream inhibitors of inflammatory signal amplification in RA.

Flavonoids (eg., baicalin, quercetin, lute to olin, amentoflavone) exhibit a broader immunomodulatory and antioxidant mechanism. In addition to moderate inhibition of NF-κB and MAPK signaling, flavonoids prominently activate cytoprotective pathways such as Nrf2/HO-1, leading to attenuation of oxidative stress and redox-sensitive inflammatory signaling.[90,91] Furthermore, flavonoids have been reported to regulate adaptive immune balance, including modulation of Th17/Treg differentiation and suppression of aberrant macrophage polarization. These findings indicate that flavonoids act as multi-level modulators that integrate anti-inflammatory, antioxidant, and immune-regulatory effects rather than acting as strong single-pathway inhibitors.

Alkaloids (eg., sinomenine, tetrandrine) primarily exert anti-rheumatic effects through calcium signaling modulation, inhibition of NF-κB activation, and suppression of macrophage and T-cell activation.[87] Alkaloids also influence synovial angiogenesis and fibroblast-like synoviocyte proliferation, suggesting a particular role in regulating synovial hyperplasia and immune cell infiltration.

Polyphenols and phenolic acids (eg., mangiferin, ellagic acid, cinnamic acid derivatives) mainly target oxidative stress–associated inflammatory cascades, including Nrf2, TLR4/NF-κB, and NLRP3 inflammasome pathways.[92] These compounds have been increasingly linked to regulation of pyroptosis and ferroptosis, thereby connecting redox imbalance with inflammatory cell death mechanisms in RA pathogenesis.

Polysaccharides and glycosides (eg., astragaloside IV, glycyrrhizin, chitosan- and hyaluronic acid–associated systems) contribute to immunomodulation through regulation of macrophage polarization, dendritic cell maturation, and cytokine

secretion. In particular, hyaluronic acid–related systems additionally provide CD44-mediated targeting of inflamed synovial tissues, integrating pharmacological and targeting functions.[93]

Collectively, while most classes converge on common inflammatory signaling axes such as NF-κB, MAPK, and JAK/STAT, each class displays characteristic mechanistic signatures. Triterpenoids predominantly act as potent upstream inflammatory signal suppressors, flavonoids function as redox–immune integrators, alkaloids regulate synovial and immune cell activation, and polyphenols and polysaccharides bridge oxidative stress, inflammasome activation, and immune regulation.[92] This mechanistic complementarity provides a strong rationale for the incorporation of diverse TCM compounds into nanodelivery systems to achieve multi-level and synergistic regulation of RA pathogenesis.

Biosafety and Safety Considerations of Nanomaterials in RA Therapy

Although nanodelivery systems offer significant therapeutic advantages for rheumatoid arthritis, biosafety and long-term safety remain critical considerations for successful clinical translation. Potential concerns include nanoparticle-induced cytotoxicity, complement activation, unintended immune stimulation, and long-term tissue accumulation. The physicochemical properties of nanocarriers, including particle size, surface charge, composition, and degradation products, critically influence their biodistribution, clearance, cellular uptake, and immunogenicity.[94]

Biodegradable and biocompatible materials such as poly (lactic-co-glycolic acid) (PLGA), lipid-based carriers, chitosan, and hyaluronic acid generally exhibit favorable safety profiles and have been widely explored in RA nanotherapy. However, systematic evaluation of chronic toxicity, immunogenicity, off-target organ accumulation, and potential nanomaterial-induced immune sensitization remains insufficient in many preclinical studies. This is particularly relevant for chronic inflammatory diseases such as RA, where repeated and long-term administration is required.[95,96]

Moreover, surface functionalization and biomimetic strategies, including cell membrane-coated nanoparticles, may alter immune recognition and circulation behavior, necessitating careful safety assessment. Future studies should incorporate standardized biosafety testing, including long-term in vivo toxicity, immunogenicity profiling, and organ distribution analysis, to facilitate the clinical translation of TCM-based nanomedicines for RA therapy.[97]

Conclusion and Perspectives

Compared with conventional DMARDs and biologics, TCM-based nanomedicines may offer several potential advantages. In addition to multi-target regulation of inflammatory and immune pathways, TCM compounds are generally associated with lower production costs and greater accessibility, which may improve long-term treatment affordability.[98] Furthermore, the polypharmacological nature of TCM-derived compounds, when combined with nanocarrier-mediated targeted delivery, may reduce the likelihood of single-target drug resistance and improve sustained therapeutic response.[99] These features highlight the translational value of integrating TCM pharmacology with nanotechnology beyond conventional single-target strategies. Active ingredients derived from traditional Chinese medicine (TCM) provide a rich pharmacological basis for the treatment of rheumatoid arthritis (RA) due to their multi-target activities, low toxicity, and immunomodulatory properties. However, their clinical translation remains limited by intrinsic pharmacokinetic drawbacks such as poor solubility, instability, and uneven biodistribution. The emergence of nanodelivery systems offers innovative solutions to overcome these barriers. Through the development of diverse nanocarrier platforms—including liposomes, polymeric nanoparticles, hydrogels, inorganic materials, and biomimetic or stimuli-responsive systems—researchers have markedly improved the encapsulation efficiency, bioavailability, and lesion-targeting capability of TCM compounds. Some systems have also achieved inflammation microenvironment–responsive release (eg., triggered by pH, ROS, or enzymes), thereby enhancing therapeutic efficacy while minimizing systemic toxicity. Collectively, these advances highlight the great potential of TCM–nanodelivery hybrids in mitigating inflammation, restoring immune homeostasis, and preventing bone destruction in RA.

Nevertheless, most current studies remain focused on the structural and physicochemical design of carrier systems—such as size control, surface modification, drug-loading optimization, and release kinetics—while systematic investigations into the pharmacodynamic mechanisms of TCM compounds, including molecular targets, signaling pathways, and immunoregulatory networks in RA, are still insufficient. Many studies are confined to in vitro or early-stage animal experiments, lacking dynamic analyses of the interactions between TCM components and the immune microenvironment, as well as integrative analyses of pharmacological target networks and metabolic pathways. This "material-centered but mechanism-deficient" research

paradigm results in a weak connection between nanocarrier functionality and the intrinsic pharmacological properties of TCM compounds, limiting both the depth and breadth of clinical translation.

Future studies should, therefore, build upon the structural optimization of nanocarriers while emphasizing mechanistic elucidation and system-level analysis of immunometabolic regulation induced by TCM–nanocomposite therapies. On one hand, multi-omics technologies (including transcriptomics, metabolomics, and proteomics), coupled with computational tools such as molecular docking and network pharmacology, can help identify key signaling pathways and molecular targets involved in RA modulation. On the other hand, the incorporation of intelligent responsive mechanisms, combination therapy strategies, and multi-target regulation approaches may achieve synergistic optimization of both material functionality and pharmacological efficacy. Moreover, establishing standardized pharmacokinetic and toxicological evaluation frameworks will be essential for verifying biosafety and facilitating clinical translation.

The integration of traditional medicine and nanotechnology represents not only a technological innovation for enhancing drug delivery efficiency but also a scientific pathway toward elucidating the mechanistic basis of natural therapeutics and achieving precision therapy for RA. Only through the dual coupling of material science and pharmacological mechanism studies—grounded in a deep understanding of drug–disease interactions—can mechanism-guided design and clinically translatable TCM-based nanodelivery systems be realized, ultimately providing a more scientific and systematic therapeutic strategy for rheumatoid arthritis.

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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.

Disclosure

The authors report no potential conflicts of interest in this article.

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