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Research progress of natural product-based nanomaterials for the treatment of inflammation-related diseases

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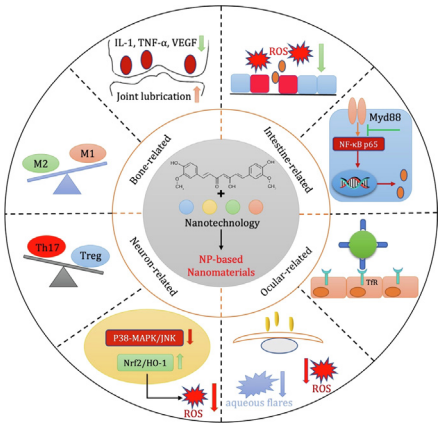
HIGHLIGHTS

- Natural product-based nanomedicine is characterized by diverse classification and abundant function.
- Natural product-based nanomedicine showed exceptional therapeutic efficacy in bone-, intestine-, neuron- and ocular-related inflammatory diseases.
- Challenges in the wide clinical application of natural product-based nanomedicine remain, and further exploration is urgently needed.

GRAPHICAL ABSTRACT

Natural product-based nanomedicine resulting from the combination of natural products with nanotechnology has been extensively investigated to improve the therapeutic index and safety profile of NPs in massive inflammatory diseases, including bone-, intestine-, neuron-, and ocular-related diseases.



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ABSTRACT

Inflammatory diseases present with dysregulated inflammatory reactions and oxidative stress, resulting in heavy health-associated economic burden to society. Current mainstream therapies, including traditional therapies such as steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressants, as well as novel biological strategies such as cytokine and intracellular signal inhibitors, cannot cure inflammatory diseases and always cause a series of unexpected adverse effects. Natural products (NPs), which are complex chemical molecules with abundant biological activities derived from microorganisms and plants, have demonstrated great potential for treating inflammatory diseases with several unresolved drawbacks. Increasing studies have indicated that NP-based nanomedicine resulting from the combination of NPs and nanotechnology may open a brand-new vista for the therapy of inflammatory diseases. In the present review, we summarize the classification of NP-based nanomedicine and its potential therapeutic effects in various inflammatory diseases, as well as further elucidate the challenges in the

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wide clinical application of NP-based nanomedicine to promote a comprehensive understanding and development of inflammatory disease therapy by NP-based nanomedicine.

1. Introduction

Natural products (NPs), also known as natural compounds, which are derived from microorganisms and plants and are complex chemical molecules with abundant biological or pharmacological activities [1]. It has been reported that NPs have been used for treatments since ancient times, and until now, they remained the foundation of half of new drugs, serving as either parent form or optimized derivatives [2]. Among the developed NPs, approximately 61% and 49% have been approved for the treatment of cancer and infection by the US Food and Drug Administration (FDA) and other regulatory agencies [3]. Over the last few decades, accumulating evidence has revealed that the therapeutic impacts of NPs in diverse diseases, including cancer [4], bacterial infections [5], metabolism [6], and autoimmune disorders [7], may be meditated by their anti-inflammatory, antioxidant, antiapoptotic, and immunoregulatory capabilities. Compared with conventional therapies, NPs have several advantages, including various mechanisms of action, multiple chemical structures and natural renewability [7]. However, the major issue in disease treatments by NPs is poor bioavailability, which is attributed to their characteristics of low solubility in aqueous solvents, low absorption, high metabolism, and large biodistribution [1,7]. As a result, a larger dose is needed to obtain the expected therapeutic effects and therefore may lead to increased adverse toxicity and decreased patient compliance. Fortunately, the incorporation of nanotechnology seems to be a promising method for removing barriers to disease treatments by NPs.

Nanotechnology is a scientific method that involves the manipulation and control of matter at the nanoscale and has been extensively applied in diverse fields, such as industry and biomedicine [8]. It has been extensively reported that nanotechnology-based materials exhibit prominent antibacterial effects through multiple mechanisms, such as ROS generation and membrane disruption [9–13]. Moreover, novel nanomaterials have also been explored for improving biocompatibility [14], enabling targeted cell capture [15], anti-inflammation [16], antitumor [17–19], tissue repair and wound healing [20,21], *etc*. NP-based nanomedicine, essentially the combination of nanotechnology with NPs, has demonstrated immense success because the incorporation of nanotechnology could improve the bioavailability, targeting and controlled release profiles of NPs [1]. An increasing number of studies have investigated the therapeutic effects of NP-based nanomedicine in multiple diseases, such as cancer [22], arthritis [23], stroke [24], and wound healing [25]. Most of these diseases are characterized by chronic inflammation due to overexpressed inflammatory mediators such as prostaglandins, nitric oxide (NO), interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, as well as excessive oxidative stress. Therefore, NP-based nanomedicine appears to open a brand-new vista for the therapy of inflammatory diseases.

In the present review, we briefly summarize the classification of NP-based nanomedicine and its potential therapeutic effects in various inflammatory diseases (Fig. 1), as well as further elucidate the challenges in the wide clinical application of NP-based nanomedicine.

2. The classification of natural product-based nanomedicine

Nanotechnology has emerged as an attractive method with tremendous potential to improve the effectiveness of disease treatment by NPs. Compared with the administration of NPs alone, NP-based nanomedicine has demonstrated three major benefits: a significant increase in bioavailability, promising ability to target specific sites and controlled release of drugs [1]. Moreover, compared with other nanomaterials, three strengths of NP-based nanomedicine are also prominent: renewability of NP due to its natural source, abundant chemical structures of NP, and action on multiple mechanisms of NP rather than only one single pathway [7]. Generally, the purpose of applying nanotechnology to NPs is to improve the therapeutic index and safety profile [8]. The nanostructured systems used in NP-based nanomedicine can be categorized as follows.

2.1. Lipid-based nanostructured systems

Lipids are amphipathic or hydrophobic molecules that have been used for the formation of lipid-based nanostructured systems to deliver active ingredients for decades [26]. Lipid-based nanostructured systems are characterized by a lipidic dispersion stabilized by surfactants and have a wide range of representations, including phospholipids, lipid nanoparticles and nanoemulsions [27].

2.1.1. Phospholipids

Phospholipids include micelles and liposomes, which are made of phospholipid unilayers and bilayers, respectively (Fig. 2**a**). Hydrophilic heads face the outside for both micelles and liposomes and therefore can lead to the formation of a core in a hydrophilic environment, such as blood. Regarding micelles, lipophilic tails face the inside to generate the lipophilic core as a drug-containing compartment, while for liposomes, hydrophilic heads face the inside to make the drug-containing compartment hydrophilic. As a result, lipophilic and hydrophilic NPs are supposed to be better suited for combination with micelles and liposomes, respectively. An attractive merit of phospholipids is their great biological safety with no toxic effects on normal cells [1].

2.1.2. Lipid nanoparticles

According to different components, lipid nanoparticles mainly contain two different forms, namely, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) [26]. Lipids applied to these nanoparticles have great biocompatibility and tolerance with the body, such as triglycerides, steroids, and fatty acids. The major parameters determining the characterization of lipid nanoparticles include size, zeta potential, degree of crystallinity, efficiency of entrapment, drug loading and drug release. [28]. SLNs, first-generation lipid nanoparticles composed of a solid lipophilic core stabilized by emulsifiers and surrounded by phospholipids, have demonstrated higher stability than phospholipids and lower toxicity than polymeric nanoparticles [28,29]. Two models for drug incorporation of SLNs have been reported, including the solid solution model and core-shell model (Fig. 2**b**). The drug molecularly disperses in the lipid matrix in the solid solution model but con-

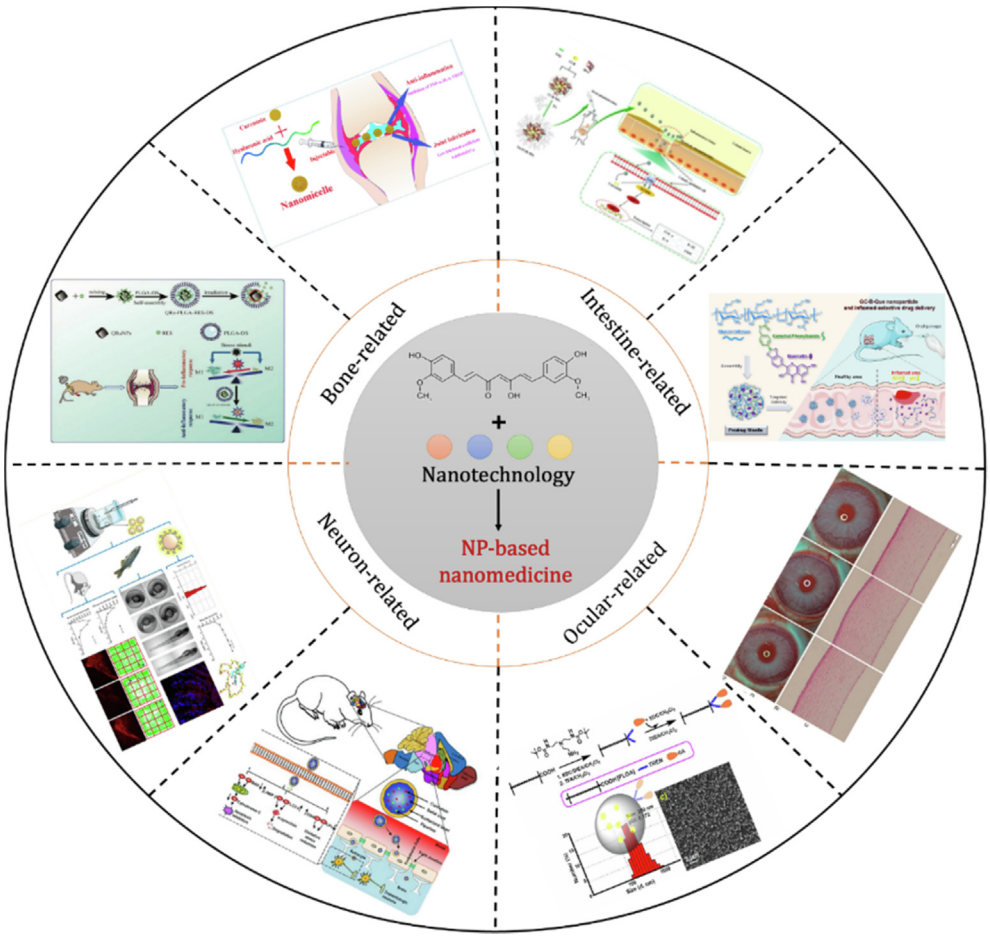


Fig. 1. Schematic illustration of the present review. NP-based nanomedicine resulting from the combination of NPs with nanotechnology has been extensively investigated to improve the therapeutic index and safety profile of NPs in massive inflammatory diseases, including bone-, intestine-, neuron-, and ocular-related diseases. **Abbreviations:** NPs, natural products.

centrates in the outer shell or inner core in the core-shell model [30]. However, the perfect crystalline structure of SLNs results in several inevitable limitations, such as low drug load, drug expulsion during the storage period and burst release [28]. To overcome these disadvantages of SLNs, second-generation lipid nanoparticles, i.e., NLCs, were designed by a mixture of liquid and solid lipids. Due to their imperfect crystalline structure, unstructured nature, and existence of liquid lipids, NLCs present several notable advantages, including higher drug loading capacity, less drug expulsion, elevated drug solubility, and more controllable release profiles than SLNs. Moreover, NLCs appear to be less susceptible than SLNs in gelation during the stages of preparation and storage [30]. Three types of NLCs have been developed: imperfect type, amorphous type, and multiple type (Fig. 2**c**). Specifically, the imperfect type provides imperfections in the crystal order by mixing spatially different lipids to achieve a higher drug payload. The amorphous type presents a special structure of the lipid matrix by combining solid lipids with special lipids, such as hydroxyoctacosanylhydroxystearate, to inhibit crystallization and drug expulsion during the storage period. The multiple type adds liquid regions, i.e., oily nanocompartments to the solid matrix, therefore obtaining higher solubility for lipophilic drugs and lower drug expulsion [30]. The popularity of lipid nanoparticles may be attributed to their remarkable merits, including ease of large-scale production, low toxicity potential, properties of biocompatibility and biodegradability, enhanced drug solubility, possible controlled drug release, *etc.* [28].

2.1.3. Nanoemulsions

Nanoemulsions are thermodynamically unstable oil-in-water (O/W) or water-in-oil (W/O) colloidal dispersions with droplet diameters on the order of 100 nm. In addition to oil and water, an emulsifier responsible for decreasing the interfacial tension between the oil and water phases is also necessary for the formation of nanodroplets [31]. Nanoemulsions are usually achieved through two steps, where macroemulsions are made in a first step, and conversion from macroemulsions to nanoemulsions is implemented in a second step. Methods accomplishing nanoemulsions can generally be classified into two primary types, namely, high-energy and low-energy methods. Specifically, high-energy methods such as high-pressure homogenizers and ultrasonication provide strong external force to disrupt and intermingle the oil and water phases, generating droplets with nanoscale and high kinetic energy (Fig. 3**a**). Low-energy methods such as phase inversion temperature (PIT) and emulsion inversion point (EIP) use the intrinsic physicochemical capabilities of systemic components with little external energy to produce droplets [8,31] (Fig. 3**b**). As a result, low-energy methods appear to be energetically efficient and relatively easy to implement due to the lack of requirements for sophisticated and high-cost equipment [32]. It has been reported that nanoemulsions can transport high loads of lipophilic substances and protect them against oxidation and enzymatic degradation [33]. Studies have demonstrated unique advantages of nanoemulsions, including nanodroplet diameter, prominent stability, transparent appearance, and tunable rheology [31].

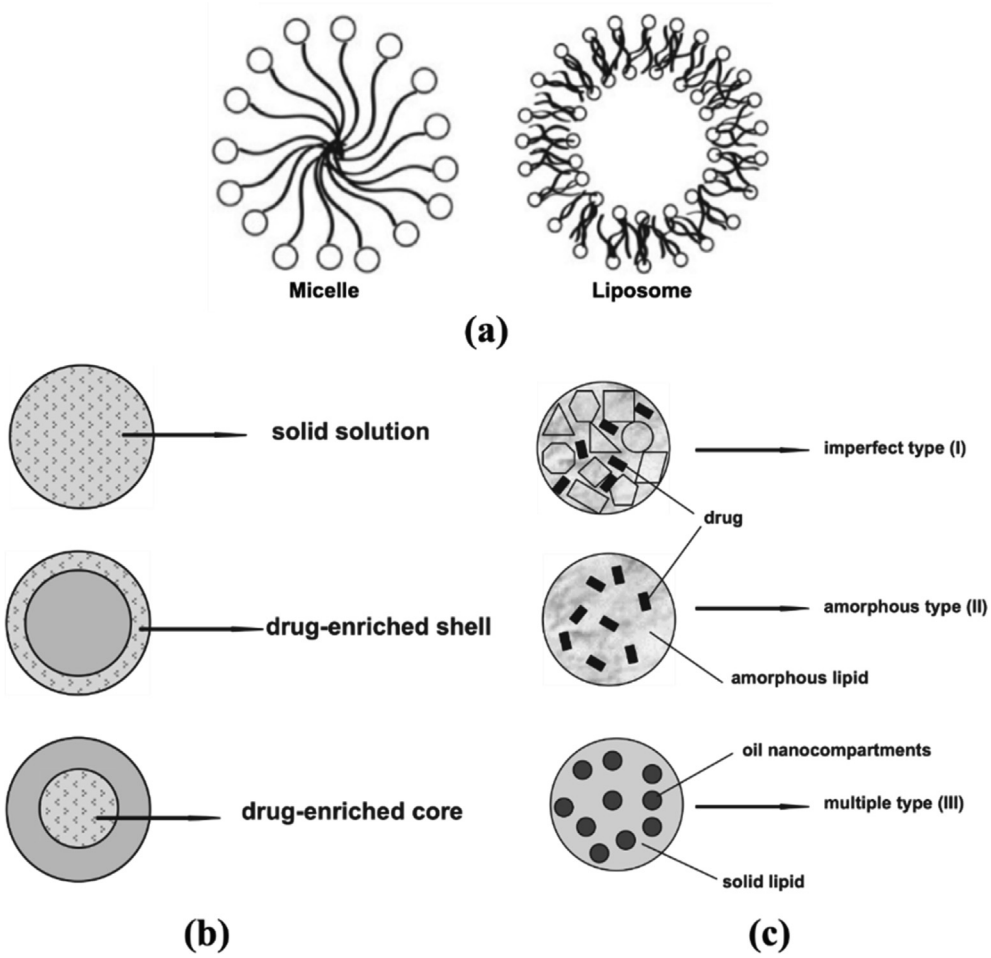


Fig. 2. Schematic representations of lipid-based nanostructured systems used for natural product-based nanomedicine. (a) Micelles and liposomes are made of phospholipid unilayers and bilayers, respectively [1]. (b) Models of drug incorporation of SLNs, including the solid solution model and core-shell model [30]. (c) Types of NLCs, including imperfect type, amorphous type, and multiple type NLCs [30]. Adapted with permission from ref. [1], Copyright from 2015, Dove Medical Press Limited; adapted with permission from ref. [30], Copyright from 2007, Dove Medical Press Limited; adapted with permission from ref. [30], Copyright from 2007, Dove Medical Press Limited.
Abbreviations: SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers

2.2. Protein-based nanostructured systems

Proteins are regarded as ideal natural molecules for nanoparticle formation due to their amphiphilicity, which endows them with the property of interacting with both solvent and loaded agents. It has been reported that protein nanoparticles have been successfully synthesized using multiple proteins, including water-soluble and insoluble proteins, among which albumin, gelatin, elastin, zein, milk proteins, whey proteins, *etc.* [34]. Different protein materials have their respective advantages. For instance, albumin is strongly stable over a wide pH range and preferentially absorbed by inflamed tissues, and milk proteins can interact with macromolecules or micromolecules and have a great surface for self-assembly. The synthesis of protein nanoparticles implicates cross-linkages between native protein molecules and functional groups or derivative groups [35]. Moreover, it is thought that upregulating protein unfolding and downregulating intramolecular hydrophobic interactions are critical for the formation of protein nanoparticles. The most commonly utilized strategies are coacervation/desolvation and emulsion-based methods [34]. Several striking merits of protein nanoparticles have been indicated, including biodegradable and metabolizable properties, as well as surfaces that easily attach therapeutic agents and ligands [36].

2.3. Carbohydrate-based nanostructured systems

Carbohydrates, a huge group of molecules that extensively exist in nature, including simple sugars up to large polysaccharides, have high stability, nontoxicity and biodegradability in the human body [37]. Polysaccharides are carbohydrates with modifiable functional groups and multiple size ranges and have been predominantly used for the formation of nanomaterials for drug delivery. Among them, cyclodextrins and chitosan are two commonly used forms [35]. Cyclodextrins are water-soluble macromolecules produced by enzymatic degradation of starch. They have hydrophilic outer surfaces and lipophilic inner cavities, with the shape of truncated cones. The hydrophilic surfaces allow hydrogen bonding cohesive interactions, and the lipophilic cavities provide guest molecules with a suitable environment for interaction [38]. Chitosan, a linear polysaccharide with a positive charge, derives from the deacetylation of chitin that extensively exists in the exoskeleton of crustaceans. In addition to its biocompatibility and mucoadhesive properties, similar to other polysaccharides, chitosan is also suitable for modifications such as ionic crosslinking and covalent binding to form a variety of nanomaterials, such as nanoparticles and films [37]. The physical properties and biological functions of polysaccharides play critical roles in developing nanoparticles. For instance, chitosan is positively charged; therefore, low molec-

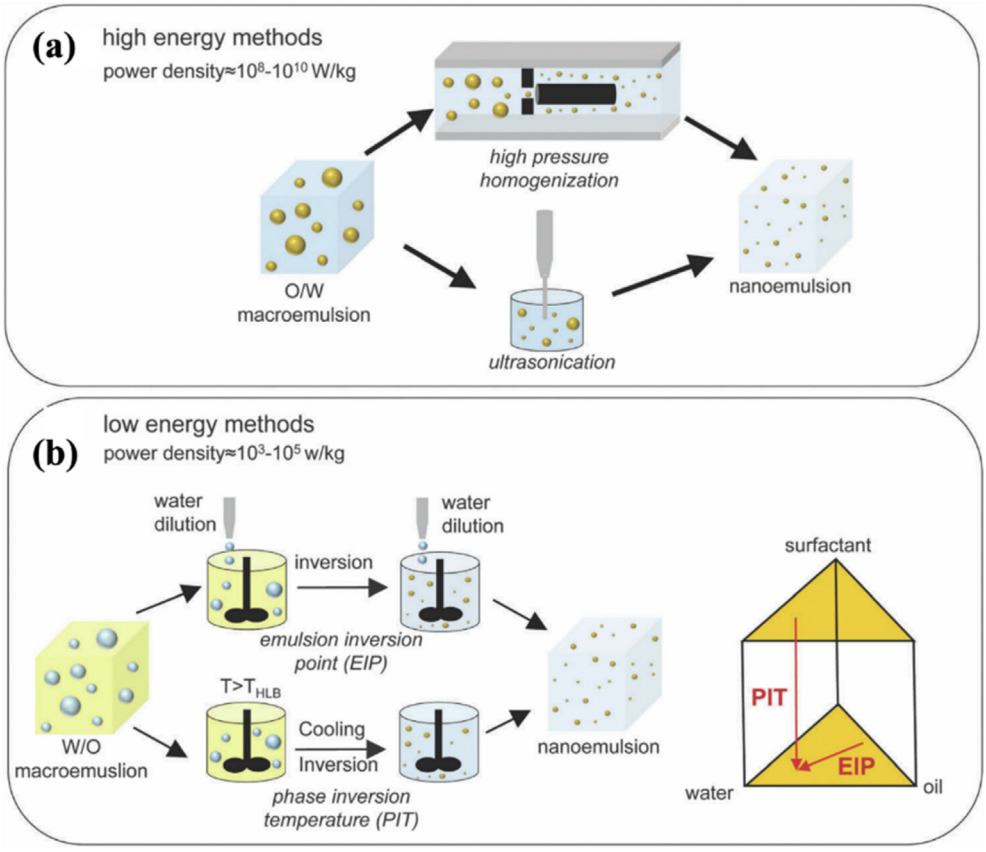


Fig. 3. Schematic representations of high-energy and low-energy methods for preparing nanoemulsions. (a) High-energy methods such as high-pressure homogenizers and ultrasonication provide strong external force to disrupt and intermingle the oil and water phases, generating droplets with nanoscale and high kinetic energy [31]; (b) Low-energy methods such as PIT and EIP use intrinsic physicochemical capabilities of systemic components with little external energy to produce droplets. The PIT method induces a phase inversion upon cooling of the mixture, whereas the EIP approach induces a phase inversion by water dilution [31]. Adapted with permission from ref. [31], Copyright from 2016, The Royal Society of Chemistry. **Abbreviations:** PIT, phase inversion temperature; EIP, emulsion inversion point.

ular weight polyanions could serve as ionic crosslinkers, whereas other types of polysaccharides are negatively charged. Studies have demonstrated several advantages of polysaccharide-based nanomedicines, including cost effectiveness, low toxicity, great biodegradability, physiological stability, prolonged residence time in the body and increased specific site accumulation due to decreased uptake by the mononuclear phagocyte system [37].

2.4. Polymeric nanoparticles

As one of the most extensively researched nanostructured systems in combination with NPs, polymeric nanoparticles are nanocarriers composed of polymers, including two different structural organizations, namely, nanospheres and nanocapsules [1,39]. The nanospheres are made of a porous polymeric matrix, while the nanocapsules contain a central core surrounded by a polymeric membrane (Fig. 4**a**). As a result, NPs can be uniformly dispersed among the matrix in nanospheres but can usually be placed at the cores in nanocapsules [29,40]. The polymers used for the production of polymeric nanoparticles are generally classified into synthetic and natural polymers (Fig. 4**b**). The most commonly utilized synthetic polymers are aliphatic polyesters, including polylactic-co-glycolic acid (PLGA), polyglycolic acid (PGA), polylactic acid (PLA), polyethylene glycol (PEG), and polyvinyl alcohol (PVA), due to their biocompatibility and biodegradability [8,41]. Natural polymers, such as chitosan, a sort of polysaccharide, have been gradually applied due to their biodegradability and low toxicity [42,43]. However, compared with synthetic polymers, natural polymers may have limitations in designing degradation rates and physical characteristics [8]. Studies have demonstrated several advantages of polymeric nanoparticles, including easy production, protecting drugs against hydrolytic enzymes, elevating drug permeability, improving safety profile, targeting delivery, *etc.* [44].

2.5. Metallic nanostructured systems

2.5.1. Magnetic nanoparticles

The typical design of magnetic nanoparticles for applications in biomedical fields comprises magnetic cores, protective coatings, organic linkers, and active biomolecules [45]. Various bottom-up and top-down synthetic strategies have been applied to synthesize magnetic nanoparticles, including coprecipitation, ultrasonication, thermal decomposition, mechanical milling, *etc.* [46]. The magnetic property of the core enables these nanoparticles to be manipulated by an external magnetic field to achieve the goal of targeted transportation. Iron oxide-based materials such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are extensively used for the core of magnetic nanoparticles due to their biosafety to the body [45]. The coating could not only protect the magnetic core against corrosion but also prevent the possible leakage of some toxic components. Many natural and synthetic polymers, such as carbohydrates, proteins, PEG and gold, are suitable materials for the formation of coatings. Organic linkers are essentially a sort of surface modification that strengthens the binding of biomolecules with the surface of nanoparticles and controls the release process. Organic linkers that create electrostatic interactions are the most commonly used

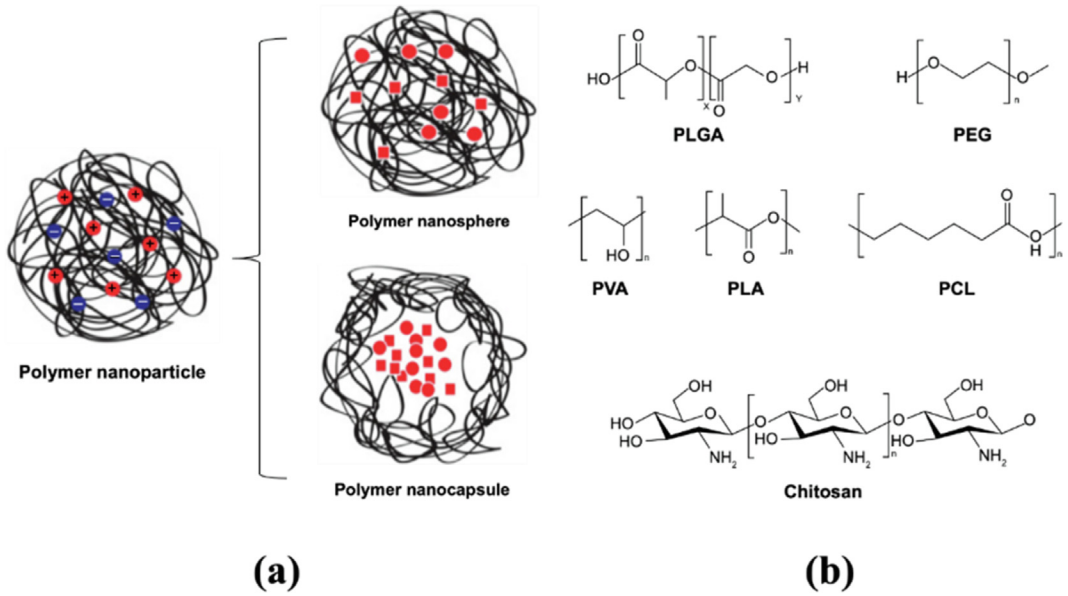


Fig. 4. Schematic representations of polymeric nanoparticles used for natural product-based nanomedicine. (a) The nanospheres are made of a porous polymeric matrix, while the nanocapsules contain a central core surrounded by a polymeric membrane [1]. (b) The polymers used for the production of polymeric nanoparticles are generally classified into synthetic and natural [1]. Adapted with permission from ref. [1], Copyright from 2015, Dove Medical Press Limited. **Abbreviations:** PLGA, polylactic-co-glycolic acid; PEG, polyethylene glycol; PVA, polyvinyl alcohol; PLA, poly-l-lactic acid; PCL, polycaprolactone

because this binding force is relatively easy to manipulate [45]. Several advantages of magnetic nanoparticles, including biocompatibility, flexible surface modification and high magnetic moments, have emerged, leading to them being favorable for biomedical applications [46].

2.5.2. Coordination polymer-based nanoparticles

Coordination polymer-based nanoparticles (CPNs), also known as nanoscale metal-organic frameworks (NMOFs), are hybrid materials formed by the self-assembly between metal ions or clusters and polydentate bridging ligands [47]. Generally, four synthetic methods have been reported for the synthesis of CPNs, including solvothermal, nanoprecipitation, reverse microemulsion and surfactant-templated solvothermal reactions, among which the former two synthetic strategies are surfactant-free, while the latter two synthetic strategies require surfactants [48]. The incorporation of biomedical agents into CPNs can be achieved by two approaches, namely, direct incorporation during CPN synthesis and postsynthesis loading via covalent attachment or noncovalent interaction. Interestingly, the combination of these two approaches also leads to the formation of multimodal nanoparticles incorporating different biomedical agents. To enhance the stability of CPNs and prevent inappropriately premature release of incorporated agents, silica encapsulation and coating with organic polymers are developed as two major strategies to modify the surfaces of CPNs [48]. Compared with traditional nanomaterials, CPNs manifest many advantages, including superior structure, component tunability, great capability of chemical modification, inherent biocompatibility, exceptional biodegradability, *etc*., making them attractive tools for loading therapeutic agents [47,49].

3. Therapeutic effects of natural product-based nanomedicine in inflammatory diseases

Inflammation is a positive biological defense response of the body to baneful stimuli, including injury and antigens, with the purpose of eliminating stimuli and repairing injured tissues, ultimately leading to recovery to homeostasis. However, prolonged and uncontrolled inflammatory reactions have been identified as the major causes of various diseases, including cardiovascular dysfunctions, metabolic disturbances, autoimmune disorders, and cancer, resulting in a high health-associated economic burden on society [50]. Moreover, the interplay between inflammation and oxidative stress also plays important roles in the pathogenesis and progression of these diseases. For instance, reactive oxygen species (ROS) released from inflammatory cells result in oxidative stress and enhance cellular signaling pathways linked to elevated proinflammatory gene expression [51]. Steroids, non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressants are the three main traditional medications used to treat inflammatory crises; nevertheless, they always cause a series of unexpected adverse effects, such as osteoporosis, angioedema, hemolytic anemia, and immunodeficiency-associated problems [50,52]. Compared with conventional drugs, NPs have demonstrated anti-inflammatory, antioxidant, and immunoregulatory properties to achieve pharmacological effects with fewer adverse effects. NP-based nanomedicine, resulting from the incorporation of nanotechnology into NPs, has been extensively investigated to improve the therapeutic index and safety profile of NPs in massive inflammatory diseases (Table 1) [51].

3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammation-related disorder that primarily involves the joints, resulting in cartilage and bone damage, body disability, and several extra-articular manifestations, especially comorbidities implicating vasculature and metabolism [53]. Therapeutic strategies for RA have been explored, including conventional therapies such as disease modifying anti-rheumatic drugs (DMARDs), NSAIDs and glucocorticoids, as well as novel therapies such as cytokine inhibitors, intracellular signal inhibitors and stem cell transfer. However, several limitations remain unresolved, including long- and short-term adverse effects involving the gastrointestinal system and central nervous system and high cost. [53,54]. Over the last few decades, NP-based nanomedicine has been extensively investigated in experi-

Table 1
The therapeutic effects of NPs-based nanomedicine in *in vivo* and *in vitro* models of inflammatory diseases.

Diseases	NPs	Subjects	Nano formulations	Therapeutic effects	Ref
RA	CUR	CFA-induced arthritis rats	CUR-NEs	Decreased the expression of IL-1β and TNF-α in both synovial fluid and blood serum	[43]
	CUR	CFA-induced arthritis rats	CUR-NEG	Mitigated body weight loss, decreased tibiotarsus joint thickness and paw edema volume, downregulated expressions of IL-1β and TNF-α in both joint tissue homogenate and serum	[44]
	CUR	CFA-induced arthritis rats	CUR-NEG	Ameliorated arthritic score and paw swelling, relieved serum biochemical parameters, decreased pro-inflammatory cytokines in both synovial tissues and serum, as well as improved radiological and histological manifestations	[45]
	CUR	CFA-induced arthritis rats	CUR-Lipo	Suppressed progression of arthritis and decreased levels of immune cells and pro-inflammatory cytokines	[46]
	DimCUR	CIA rats	DimCUR-Lipo	Attenuated paw swelling and arthritis progression through decreasing lymphocytes numbers, improving cell cycle dysfunction, and suppressing DPPI and MMP-2/9 expression	[47]
	CUR	CFA-induced arthritis rats	CUR SLNs	Mitigated many symptoms, ameliorated biochemical markers, and preserved joints radiological changes through relieving oxidant-inflammatory and immunomodulatory cascades	[10]
	CUR	CIA rats	CUR-NM	Relieved joint swelling and paw edema, improved histological manifestations, and decreased levels of serum IL-1, TNF-α and VEGF	[48]
	RES	CIA mice/ LPS-induced RAW 264.7 Mø	QRu-PLGA-RES-DS nanoparticles	Mitigated clinical score and prevented cartilage erosion Decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines through promoting the transformation of macrophages from M1 to M2 type	[50]
	RES	CFA-induced arthritis rats	PLA-RES-NMMs	Attenuated the knee swelling, cartilage lesions and synovial inflammation, and decreased plasma levels of TNF-α	[51]
	RES/ CUR	CFA-induced arthritis rats	RES-CUR-LNCs	Decreased paw edema and ameliorated histopathological manifestations with potential safety and biocompatibility	[52]
	QUE	CFA-induced arthritis rats	QUE-TGA-CdTe QDs	Reduced paw edema volume and soft tissue swelling, promoted cartilage regeneration, normalized hematological inflammatory parameters, and decreased lipid peroxidation and increased antioxidants in paw tissues	[54]
	QUE	CFA-induced arthritis rats	QUE-NEG	Decreased paw volume, arthritic index and joint stiffness scores, and reduced levels of hematological CRP and RF	[55]
	BER	CFA-induced arthritis rats/ AA-FLS	BER-Lipo-PEG	Improved the physical parameters, inhibited the development of arthritis and decreased the expressions of pro-inflammatory cytokines through suppressing Wnt1/β-catenin signaling pathway	[58]
	CA	CFA-induced arthritis rats/ synovial Mø/ BMSCs	CA-MLipo	Ameliorated ankle joints inflammation and restored body weight loss Decreased pro-inflammatory cytokines and restricted macrophages differentiation into osteoclasts through enhancing OPG production	[60]
	WA	CFA-induced arthritis rats/ synovial Mø	WA-MLipo	Prevented weight loss, attenuated joint swelling, suppressed ankle joint inflammation, inhibited osteoclast genesis, and switched the macrophages from pro-inflammatory M1 to anti-inflammatory M2 phenotype	[62]
	MOR	CFA-induced arthritis rats/ spleen and synovial Mø	MOR-MLipo	Ameliorated paw edema, body weight loss, joint space narrowing, pannus formation and cellular infiltration Increased production of OPG, and decreased production of VEGF, NF-κβ-p65, and pro-inflammatory meditators	[64]
	SIN	CFA-induced arthritis rats	SIN-TS Lipo	Reduced paw thickness and arthritic score, attenuated histological pathologic characterizations, and decreased pro-inflammatory cytokines	[65]
	TRI	CIA rats	TRI-LHP	Attenuated joint swelling and decreased production of Flk-1, Flt-4 and HIF-1α in synovium, as well as IL-6 in serum	[67]
	SIT	CFA-induced arthritis rats	SIT-SLNs	Mitigated paw edema, arthritic score and body weight loss, increased levels of antioxidants and anti-inflammatory cytokines, and decreased levels of pro-inflammatory cytokines	[69]
	PIP	CFA-induced arthritis rats	PIP-SLNs	Reduced paw volume, relieved bone erosion and destruction, and decreased inflammatory cell infiltration, connective tissue proliferation and TNF-α in the synovial fluid	[71]
	EMB	CFA-induced arthritis rats	EMB-CNPs	Relieved arthritic score and paw swelling, decreased inflammatory markers, downregulated oxidant levels whereas upregulated antioxidant levels	[73]
	HES	CFA-induced arthritis rats	HES GA-Ag nanoparticles	Reduced arthritic score, paw swelling, inflammatory cells infiltration and granulomatous inflammation in ankle joints tissues, and downregulated levels of TLRs 2 and 4 in spleen tissues	[75]
IBD	CUR	DSS-induced colitis mice/ Caco-2 cells	CUR-TA/Gnp/HSA nanoparticles	Reduced DAI, suppressed body weight loss and colon length shortening, attenuated histological symptoms and signs of colonic inflammation, along with great biocompatibility and low toxicity	[80]
	CUR	DSS-induced colitis mice/ LPS-induced mouse RAW 264.7 Mø and BMDMs	CUR-CHI polymer	Elevated survival rate, improved clinical symptoms, reduced DAI, mitigated colonic shortening, and decreased expression of pro-inflammatory mediators	[81]
	CUR	DSS-induced colitis mice/ Caco-2 cells	CUR-PEG polymer	Ameliorated weight loss, recovered shortened colon length, decreased DAI scores, improved histopathological characterizations, and exerted antioxidant and anti-inflammatory effects	[82]

(*continued on next page*)

Table 1 (*continued*)

Diseases	NPs	Subjects	Nano formulations	Therapeutic effects	Ref
	CUR	DSS-induced colitis mice/ Caco-2 cells/LPS-induced J774 Mø	CUR-PLGA/PM nanoparticles	Relieved clinical activity score, preserved intact colonic architecture, and decreased MPO activity and TNF-α expression in colon Increased CUR permeation across the Caco-2 cell monolayers and decreased TNF-α secretion in LPS-induced J774 macrophages	[83]
	CUR	DSS-induced colitis mice/CT-26 cells/LPS-induced RAW 264.7 Mø	CUR-PF127/PLGA nanoparticles	Attenuated body weight loss and MPO activity, recovered colon length, and downregulated pro-inflammatory cytokines and upregulated anti-inflammatory cytokines in blood Prevented the production of pro-inflammatory cytokines in LPS-induced RAW 264.7 macrophages	[84]
	CUR	AA-induced colitis rats/Vero and HCT 116 cell lines	CUR-PAAm-g-XG nanoparticles	Mitigated weight loss and colon length shortening, decreased MPO activity and tissue nitrite levels, and improved histopathological features with no extra cytotoxicity	[85]
	CUR	DSS-induced colitis guinea pigs	CUR-SBLNs	Reduced colon weight/length increment and leucocyte infiltration, decreased oxidative stress and TNF-α production, and maintain relatively normal colonic structure	[86]
	CUR	DSS-induced colitis mice	CUR-CH/AG/CAP nanoparticles	Recovered colon length, decreased DAI and spleen weight, improved histological manifestation, and downregulated MPO activity and IL-6 and TNF-α levels	[87]
	CUR/PIP	DSS-induced colitis mice	CUR-PIP-SMEDDS	Improved body weight loss, intestinal bleeding and diarrhea, recovered colon length, relieved histopathological manifestations, and exerted antioxidant and anti-inflammatory effects	[88]
	CUR	DSS-induced colitis mice/ Caco-2 cells/LPS-induced J774 murine Mø	CUR-SNEDDS CUR-NLC CUR-NC	CUR-NLC reduced neutrophil infiltration and TNF-α expression in DSS-induced colitis mice CUR-NC conferred the highest CUR permeability across Caco-2 cells CUR-SNEDDS and CUR-NLC decreased TNF-α production in LPS-induced J774 murine macrophages	[89]
	CUR	DSS-induced colitis mice/ LPS-induced RAW 264.7 Mø	CUR/CAT-PF127-PLGA nanoparticles	Attenuated body weights loss and colon shortening, decreased spleen weight and colonic MPO activity, downregulated pro-inflammatory cytokines and upregulated anti-inflammatory cytokines, and relieved histopathological inflammatory characterizations	[90]
	RES	TNBS-induced colitis mice/ Caco-2 cells	RES-FA-PLGA nanoparticles	Attenuated macroscopic damage and histopathological manifestations, decreased expression levels of IL-6 and TNF-α, and reduced SOD and MPO activities in colon tissues	[91]
	RES	TNBS-induced colitis rats/ LPS-induced RAW 264.7 Mø	RES-SF nanoparticles	Decreased damage score and weight/length ratio, improved intestinal epithelium barrier function, upregulated antioxidant content and downregulated inflammatory mediators Reduced production of nitrite in LPS-incubated RAW 264.7 macrophages	[92]
	RES	Winnie mice	RES-BLG nanosphere	Increased body weight, decreased DAI, improved histopathological features and upregulated expression of anti-inflammatory cytokine IL-10	[93]
	QUE	DSS-induced colitis mice	QUE-B-GC micelles	Decreased spleen index, attenuated body weight loss and DAI, recovered colon length and appearance, relieved histopathological manifestations, and downregulated expression levels of IL-6, TNFα, and iNOS	[94]
	QUE	TNBS-induced colitis rats	QUE-CHI/NUT nanovesicles	Ameliorated mucosal and tissue damage, decreased clinical activity score and colon/body weight ratio, and relieved MPO activity	[95]
	QUE	DSS-induced colitis mice	QUE-SF nanoparticles	Decreased DAI, relieved histopathological manifestations, and suppressed colonic expression of massive inflammation-related mediators	[96]
	EMB	AA-induced colitis rats	EMB-LNs	Reduced clinical activity and macroscopic scores, improved spleen weight and wet colon weight/length ratio, decreased expression levels of MPO, LPO and LDH while increased expression level of GSH	[97]
	EMB	DNBS-induced colitis rats	EMB-GG MPs	Reduced macroscopic activity scores, enhanced GSH colonic activity, and suppressed MPO and LPO colonic activity	[98]
	EMB	AA-induced colitis rats	EMB-ENT MSs	Reduced ulcer activity scores, increased GSH concentration, and decreased MPO and LPO concentration	[99]
	GIN	DSS-induced colitis mice/colon-26 cells/RAW 264.7 Mø	GDNPs 2	Decreased production of pro-inflammatory cytokines whereas increased production of anti-inflammatory cytokines, elevated IECs proliferation and enhanced E-cadherin expression	[100]
	SIL	AA-induced colitis rats	SIL nanoparticles	Improved macroscopic and histopathological scores, reduced MPO activity and IL-6 and TNF-α expression	[101]
	GRA	DSS-induced colitis mice	GELNs	Mitigated severity and progression of colitis, and restored the decreased villus height through promoting proliferation of intestinal stem cells	[102]
	CAPE/ PIC	DSS-induced colitis mice	CAPE/PIC-ALB nanoparticles	Ameliorated weight loss and DAI, improved colon morphology, decreased MPO activity and pro-inflammatory cytokines expression	[103]
AD	CUR	Tg2576 transgenic mice	CUR-PEG-PLA nanoparticles	Improved working and cue memory	[107]
	CUR	5XFAD transgenic mice	CUR/Se PLGA nanospheres	Reduced Aβ loading and alleviated associated memory deficits	[108]
	CUR	Wistar rats/NSCs	CUR-PLGA nanoparticles	Induced the NSCs proliferation and neuronal differentiation, and reversed Aβ-induced learning and memory impairments	[109]
	CUR	APP/PS1dE9 mice	CRT-bound S1/	Improved the spatial memory and recognition ability, decreased	[106]

Table 1 (*continued*)

Diseases	NPs	Subjects	Nano formulations	Therapeutic effects	Ref
			CUR-loaded PLGA nanoparticles	levels of Aβ, ROS, TNF-α and IL-6 while increased SOD activity and synapses number in the brain	
	CUR	APP/PS1 mice	CUR/B6-PLGA-PEG nanoparticles	Improved spatial and memory abilities, and reduced cognitive impairment, hippocampal Aβ formation and tau protein hyperphosphorylation	[110]
	CUR	$A\beta_{1-42}$ and D-gal-treated SD rats/BCECs	CUR/Lf mNLCs	Demonstrated efficient BBB penetration and preferential accumulation, reduced oxidative stress-associated damage, and ameliorated the histopathological characters in the brain	[111]
	ANT	$A\beta_{1-42}$-injected C57BL/6N mice	ANT-PEG/Au nanoparticles	Mitigated the memory impairment and protected the pre- and postsynaptic proteins from $A\beta_{1-42}$-induced synaptic dysfunction	[112]
	ANT	SH-SY5Y cell lines	ANT-PLGA/PEG nanoparticles	Increased cell viability against $A\beta_{1-42}$, relieved various AD-related proteins, neuroinflammatory markers and apoptosis markers	[113]
PD	CUR	Transgenic drosophila	ALG-CUR nanocomposite	Delayed the loss of climbing ability, and suppressed the oxidative stress and apoptosis in the brain	[118]
	CUR/PIP	Balb/c mice Rotenone-induced C57BL/6 mice PC12 cells	CUR/PIP GMO nanoparticles	Prevented αS protein aggregation into oligomers and fibrils, suppressed rotenone-induced cytotoxicity, oxidative stress, and apoptosis, activated ALP, as well as alleviated rotenone-induced motor coordination deficits and inhibited dopaminergic neuronal degeneration	[119]
	PUE	MPTP-induced mice/ zebrafish embryos/SH-SY5Y cells	PUE-NCs	Improved behavioral impairments and mobility, mitigated neurotoxicity and loss of TH^+ neurons, increased levels of dopamine and its metabolites, as well as exerted potent antioxidative capacity in the brain with nontoxicity Protected SH-SY5Y cells against MPP^+-induced cellular damage	[120]
HD	CUR	3-NP-induced rats	CUR-SLNs	Improved neuromotor coordination and increased mitochondrial complexes activity and cytochrome levels, decreased mitochondrial swelling, lipid peroxidation, protein carbonyls and ROS, as well as recovered GSH level and SOD activity	[122]
MS	CUR	RRMS patients	Nano CUR	Downregulated the Th17 cells-associated parameters	[125]
	CUR	RRMS patients	Nano CUR	Upregulated the Treg cells-associated parameters	[126]
	CUR	RRMS patients	Nano CUR	Modulated the expression of various miRNAs in the peripheral blood	[124]
Cornea inflammatory diseases	QUE/ EGCG	HCE cells	QUE-loaded PLGA nanoparticles with EGCG	Demonstrated additive effects on the antioxidant activity and increased intracellular ROS inhibition capabilities	[129]
Uveitis	CUR	Canine lens protein-induced uveitis dogs	CUR-PLGA-GA_2	Caused remarkable levels of CUR in aqueous humor, and relieved several ocular inflammatory parameters	[131]
Ocular inflammation	CUR	SAS-induced ocular inflammation in rabbits	CUR-PVCL-PVA-PEG nanomicelles	Increased the antioxidant activity and attenuated the ocular inflammation with high biocompatibility and bioavailability	[134]
Ocular inflammation	MYR	SAS-induced ocular inflammation in rabbits	MYR-PVCL-PVA-PEG nanomicelles	Increased the antioxidant activity and attenuated the ocular inflammation with high biocompatibility and bioavailability	[135]

Abbreviations:

NPs: natural products;

RA, rheumatoid arthritis; IBD: inflammatory bowel disease; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; MS, multiple sclerosis;

CUR: curcumin; DimCUR, dimethyl curcumin; RES, resveratrol; QUE, quercetin; BER, berberine; CA, p-coumaric acid; WA, aithaferin A; MOR, morin; SIN, sinomenine hydrochloride; TRI, triptolide; SIT, β-sitosterol; PIP, piperine; EMB, embelin; HES, hesperidin; GIN, ginger; SIL, silybin; GRA, grape; CAPE, caffeic acid phenethyl ester; PIC, piceatannol; ANT, anthocyanin; PUE, puerarin; EGCG, epigallocatechin gallate; MYR, myricetin;

CFA, complete Freund's adjuvant; CIA, collagen-induced arthritis; LPS, lipopolysaccharide; Mø, macrophage; AA-FLS, adjuvant-induced arthritic fibroblast-like synoviocytes; BMSCs, bone marrow stromal cells; DSS, dextran sulfate sodium; BMDMs, bone marrow-derived macrophage; AA-induced colitis, acetic acid-induced colitis; TNBS, 2,4,6-trinitrobenzenesulfonic acid; DNBS, dinitrobenzenesulfonic acid; NSCs, neural stem cells; SD, Sprague–Dawley; BCECs, brain capillary endothelial cells; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 3-NP, 3-nitropropionic acid; RRMS, relapsing-remitting multiple sclerosis; HCE, human corneal epithelial; SAS, sodium arachidonate solution;

CUR-NEs, curcumin-loaded nanoemulsions; CUR-NEG, curcumin-loaded nanoemulsions gel; CUR-Lipo, curcumin-loaded liposomes; DimCUR-Lipo, dimethyl curcumin-loaded liposomes; CUR-SLNs, curcumin-loaded solid lipid nanoparticles; CUR-NM, curcumin-loaded nanomicelle; QRu-PLGA-RES-DS, quadrilateral ruthenium-poly lactic-co-glycolic acid-resveratrol-dextran sulfate; PLA-RES-NMMs, poly-lactic acid-resveratrol-nano mixed micelles; LNCs, lipid-core nanocapsules; QUE-TGA-CdTe QDs, quercetin-loaded thio glycolic acid-capped cadmium telluride quantum dots; QUE-NEG, quercetin-loaded nanoemulsions gel; BER-Lipo-PEG, PEGylated liposomal berberine; CA-MLipo, p-coumaric acid-loaded mannnosylated liposomes; WA-MLipo, aithaferin A encapsulated mannosylated liposomes; MOR-MLipo, mannose decorated liposomal morin; SIN-TS Lipo, sinomenine hydrochloride-loaded thermosensitive liposome; TRI-LHP, triptolide-loaded liposome hydrogel patch; SIT-SLNs, β-sitosterol-loaded solid lipid nanoparticles; PIP-SLNs, piperine-loaded solid lipid nanoparticles; EMB-CNPs, embelin-loaded chitosan nanoparticles; HES GA-Ag nanoparticles, hesperidin-loaded in gum acacia stabilized green silver nanoparticles; CUR-TA/Gnp/HSA nanoparticles, curcumin-encapsulated tannic acid-coated, Genipin-crosslinked human serum albumin nanoparticles; CUR-CHI polymer, curcumin-chitosan polymer; CUR-PEG polymer, curcumin-ss-polyethylene glycol polymer; CUR-PLGA/PM nanoparticles, curcumin-poly lactic-co-glycolic acid/polymethacrylate nanoparticle; CUR-PF127/PLGA nanoparticles, curcumin-loaded pluronic F127-functionalized porous poly lactic-co-glycolic acid nanoparticles; CUR-PAAm-g-XG nanoparticles, curcumin-loaded pH-sensitive hydrolyzed polyacrylamide-grafted-xanthan gum copolymeric nanoparticles; CUR-SBLNs, curcumin-loaded solid binary lipid nanoparticles; CUR-CH/AG/CAP nanoparticles, curcumin-chitosan/sodium alginate/cellulose acetate phthalate nanoparticles; CUR-PIP-SMEDDS, curcumin and piperine-loaded self-microemulsifying drug delivery system; CUR-SNEDDS, curcumin-loaded self-nanoemulsifying drug delivery systems; CUR-NLC, curcumin-loaded nanostructured lipid carriers; CUR-NC, curcumin-loaded lipid core-shell protamine nanocapsules; CUR/CAT-PF127-PLGA nanoparticles, curcumin/catalase coencapsulated, pluronic F127 functionalized, poly lactic-co-glycolic acid-based nanoparticles; RES-FA-PLGA nanoparticles, resveratrol-loaded folate-conjugated-poly lactic-co-glycolic acid nanoparticles;

RES-SF nanoparticles, resveratrol-loaded silk fibroin nanoparticles; RES-BLG nanosphere, resveratrol-encapsulated β-lactoglobulin nanosphere; QUE-B-GC micelles, quercetin covalently linked to glycol chitosan by aryl boronic ester micelles; QUE-CHI/NUT nanovesicles, quercetin-loaded chitosan/nutriose-coated nanovesicles; QUE-SF nanoparticles, quercetin-loaded silk fibroin nanoparticles; EMB-LNs, embelin-loaded lipid nanospheres; EMB-GG MPs, embelin-loaded guar gum microparticles; EMB-ENT MSs, embelin-loaded enteric-coated microspheres; GDNPs, ginger-derived nanoparticles 2; SIL nanoparticles, silybin nanoparticles; GELNs, grape exosome-like nanoparticles; CAPE/PIC-ALB nanoparticles, caffeic acid phenethyl ester/piceatannol-loaded albumin nanoparticles; CUR-PEG-PLA nanoparticles, curcumin-polyethylene glycol-polylactic acid nanoparticles; CUR/Se PLGA nanospheres, curcumin/selenium poly lactic-co-glycolic acid nanospheres; CUR-PLGA nanoparticles, curcumin-poly lactic-co-glycolic acid nanoparticles; CRT-bound S1/CUR-loaded PLGA nanoparticles, cyclic CRTIGPSVC peptide-bound S1/curcumin-loaded poly lactic-co-glycolic acid nanoparticles; CUR/B6-PLGA-PEG nanoparticles, curcumin/B6 peptide poly lactic-co-glycolic acid- polyethylene glycol nanoparticles; CUR/Lf mNLCs, curcumin/lactoferrin low-density lipoprotein-mimetic nanostructured lipid carriers; ANT-PEG/Au nanoparticles, anthocyanin-loaded polyethylene glycol gold nanoparticles; ANT-PLGA/PEG nanoparticles, anthocyanin-

mental models of RA and has demonstrated exceptional therapeutic effects.

Curcumin (CUR) is a hydrophobic polyphenolic compound derived from the roots of the plant Curcuma longa [55]. CUR ameliorated changes in paw volume and histopathological manifestations, such as inflammatory cell infiltration, and decreased weight indices of the thymus and spleen in complete Freund's adjuvant (CFA)-induced arthritis rats. Zheng et al. then incorporated CUR into oil-water nanoemulsions (NEs), leading to the formation of CUR-loaded NEs (CUR-NEs), through a high-pressure homogenization technique and found that CUR-NEs significantly decreased IL-1β and TNF-α expression in both synovial fluid and blood serum of CFA-induced arthritis rats. Importantly, the expression levels of IL-1β and TNF-α in rats orally administered CUR-NEs were similar to those in rats injected with CUR solution, suggesting the feasibility of oral administration of CUR-Nes [56]. A study prepared nanoemulsion gels loaded with CUR (CUR-NEG) by the spontaneous emulsification method and demonstrated that the topical application of CUR-NEG could mitigate body weight loss and decrease tibiotarsal joint thickness and paw edema volume in CFA-induced arthritis rats. Further examination revealed significantly downregulated expression of TNF-α and IL-1β in both joint tissue homogenates and serum of CUR-NEG-treated arthritis rats [57]. Another study also evaluated the therapeutic effects of topical delivery of CUR-NEG in CFA-induced arthritis rats and showed similar results, as illustrated by the ameliorated arthritic score and paw swelling, relieved serum biochemical parameters such as alanine aminotransferase (ALT) and aspartate aminotransferases (AST), decreased pro-inflammatory meditators in both synovial tissues and serum, and improved radiological and histological manifestations in CUR-NEG-treated arthritis rats [58]. Moreover, liposomes were also used in combination with CUR. A study using different CUR formulations in CFA-induced arthritis rats indicated that liposomal CUR (CUR-Lipo), which was made by microencapsulating CUR in liposomes, efficiently suppressed the progression of arthritis with noticeably decreased levels of immune cells and proinflammatory meditators, including leukocytes, neutrophils, IL-1, IL-6 and TNFα, whereas other CUR formulations showed less or even no therapeutic effects on arthritis [59]. Sun et al. synthesized liposomes encapsulating dimethyl CUR (DimCUR-Lipo) through a thin-film method based on soybean phosphatidylcholine (SPC)/cholesterol (CHOL)/dimethyl CUR and further revealed that DimCUR-Lipo significantly attenuated paw swelling and arthritis progression by decreasing lymphocyte numbers, improving cell cycle dysfunction, and suppressing dipeptidyl-peptidase I (DPPI) and matrix metalloprotein (MMP)-2/9 expression in collagen-induced arthritis (CIA) rats [60]. In addition, another study investigating the therapeutic effects of CUR-loaded solid lipid nanoparticles (CUR SLNs) on CFA-induced arthritis rats found that CUR SLNs could remarkably and dose-dependently mitigate many symptoms, ameliorate biochemical markers, and preserve joint radiological changes by relieving oxidant-inflammatory and immunomodulatory cascades [23]. Additionally, Fan et al. synthesized a type of nanomicelle composed of hyaluronic acid and CUR (CUR-NM) and demonstrated that CUR-NM relieved joint swelling and paw edema and improved histological manifestations, including no remarkable inflammation in synovial tissue and smooth cartilage surface in CIA rats. Further experiments verified the anti-inflammatory effects of CUR-NM, as illustrated by the decreased production of serum IL-1, TNF-α and vascular endothelial growth factor (VEGF). Interestingly, the hyaluronic acid that existed in CUR-NM could exert the function of joint lubrication by significantly decreasing friction between the cartilage surfaces around joints, therefore protecting the cartilage against RA-induced damage, suggesting more potential benefits of the combination of NPs with nanotechnology rather than NPs themselves [61] (Fig. 5).

Resveratrol (RES), a naturally occurring polyphenol phytoalexin that exists in various plants, such as grapes, soy and nuts, has exhibited abundant biological functions in the treatment of inflammatory diseases [62]. Chen et al. used quadrilateral ruthenium (QRu) nanoparticles with photothermal effects as the core and the thermosensitive molecular PLGA as the shell, encapsulated RES into it via hydrophobic interactions and employed surface-modified dextran sulfate (DS), finally leading to the formation of QRu-PLGA-RES-DS nanoparticles. *In vitro* studies in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages indicated that the QRu-PLGA-RES-DS nanoparticles with photothermal effects remarkably suppressed the inflammatory responses, as evidenced by the decreased levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as increased levels of anti-inflammatory cytokines such as IL-4, IL-10, and transforming growth factor (TGF)-β, through promoting the differentiation of macrophages from the M1 type toward the M2 type. Further *in vivo* experiments in CIA mice showed that the treatment of QRu-PLGA-RES-DS nanoparticles with photothermal responses significantly mitigated the clinical score and prevented cartilage erosion and degradation by regulating the inflammatory microenvironment by inducing M2 macrophage polarization and suppressing the recruitment and infiltration ability of M1 macrophages [63] (Fig. 6). Another study synthesized PLA-coated RES-loaded nano mixed micelles (PLA-RES-NMMs) by thin film hydration and found that the intraarticular injection of PLA-RES-NMMs significantly attenuated knee swelling, cartilage lesions and synovial inflammation in CFA-induced arthritis rats. Further examination demonstrated markedly decreased plasma levels of the proinflammatory cytokine TNF-α in PLA-RES-NMM-treated arthritic rats [64]. Interestingly, another study coencapsulated RES and CUR into lipid-core nanocapsules (RES-CUR-LNCs) and found that RES-CUR-LNCs noticeably decreased paw edema and ameliorated histopathological manifestations such as synovial tissue fibrosis and cartilage damage in CFA-induced arthritis rats. Moreover, the application of RES-CUR-LNCs showed potential safety and biocompatibility, as illustrated by the normal levels of

loaded poly lactic-co-glycolic acid/polyethylene glycol nanoparticles; ALG-CUR nanocomposite, alginate-curcumin nanocomposite; CUR/PIP GMO nanoparticles, curcumin/piperine coloaded glycerol monooleate nanoparticles; PUE-NCs, puerarin nanocrystals; CUR-SLNs, curcumin-encapsulated solid lipid nanoparticles; Nano CUR, nanocurcumin; QUE-loaded PLGA nanoparticles with EGCG, quercetin-loaded poly lactic-co-glycolic acid nanoparticles with epigallocatechin gallate; CUR-PLGA-GA_2, curcumin-encapsulated double-headed polyester nanoparticles using gambogic acid-coupled poly lactic-co-glycolic acid; CUR-PVCL-PVA-PEG nanomicelles, curcumin-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer nanomicelles; MYR-PVCL-PVA-PEG nanomicelles, myricetin-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer nanomicelles;

IL, interleukin; TNF, tumor necrosis factor; DPPI, dipeptidyl-peptidase I; MMP, matrix metalloprotein; VEGF, vascular endothelial growth factor; CRP, C-reactive protein; RF, rheumatoid factor; OPG, osteoprotegerin; NF-κβ, nuclear factor kappa β; Flk, fetal liver kinase; Flt, fetal liver tyrosine kinase; HIF, hypoxia-inducible factor; TLRs, toll-like receptors; DAI, disease activity index; MPO, myeloperoxidase; SOD, superoxide dismutases; iNOS, inducible nitric oxide synthase; LPO, lipid peroxides; LDH, lactate dehydrogenase; GSH, glutathione; IECs, intestinal epithelial cells; Aβ, amyloid β; ROS, reactive oxygen species; BBB, blood–brain barrier; αS, α-synuclein; ALP, autophagy–lysosome pathway; MPP^+, 1-methyl-4-phenylpyridinium ion; Th17, T helper 17; Treg, regulatory T.

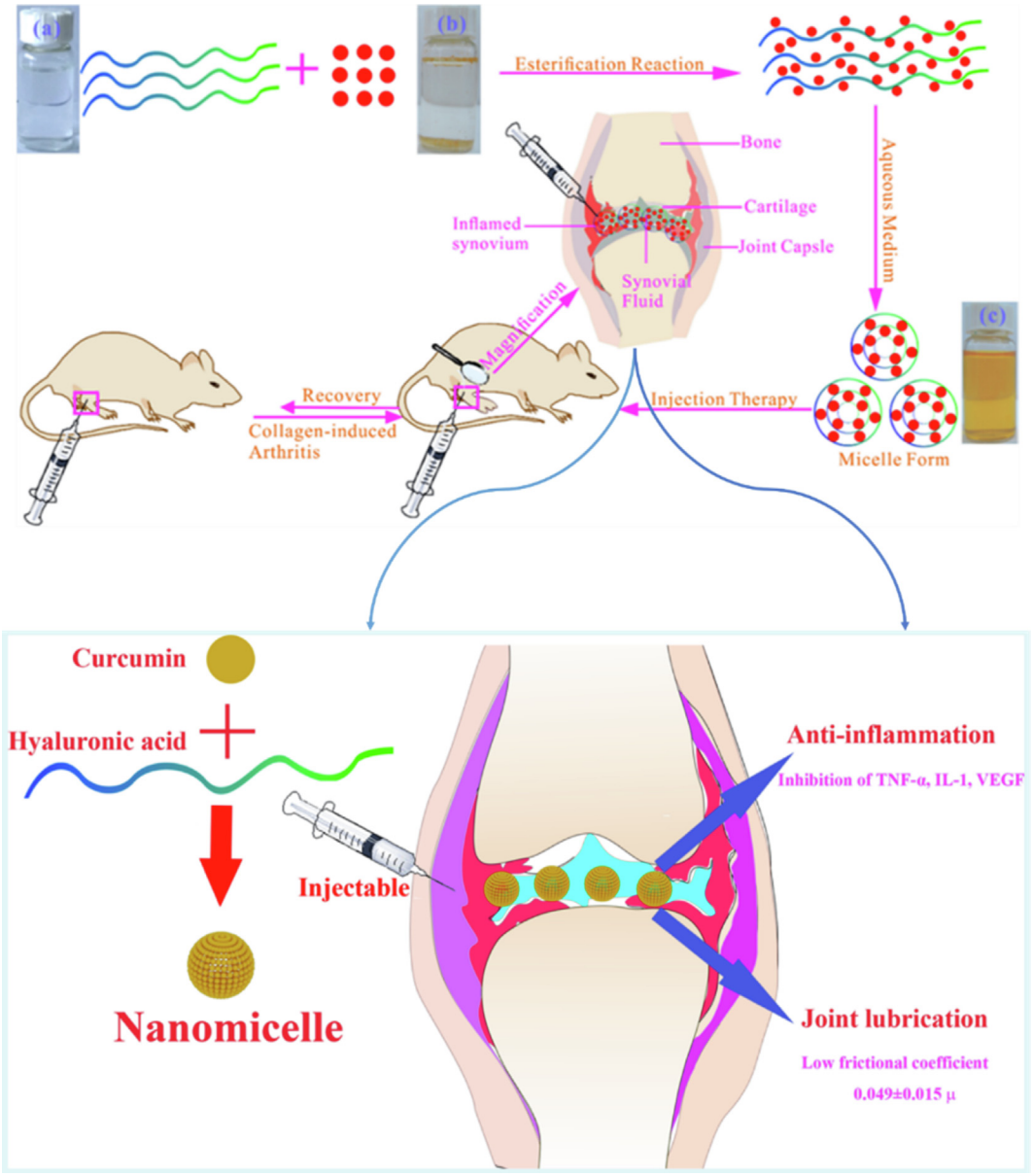


Fig. 5. The topical application of the CUR-HA nanomicelle to CIA rats not only exerted anti-inflammatory effects by decreasing the expression levels of IL-1, TNF-α and VEGF but also promoted joint lubrication by decreasing friction between the cartilage surfaces around joints [61]. Adapted with permission from ref. [61], Copyright from 2018, American Chemical Society. **Abbreviations:** CUR, curcumin; HA, hyaluronic acid; CIA, collagen-induced arthritis; IL, interleukin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

serum hepatic biochemical markers, including AST, ALT and alkaline phosphatase (ALP) [65].

Quercetin (QUE) is a major representative flavonoid and is widely found in dietary vegetables and fruits such as onions, asparagus, apples, cherries, *etc.* [66]. Jeyadevi et al. prepared QUE-loaded thioglycolic acid-capped cadmium telluride quantum dots (QUE-TGA-CdTe QDs) and found that the oral administration of QUE-TGA-CdTe QDs significantly reduced paw edema volume, mitigated joint space narrowing and soft tissue swelling, promoted complete cartilage regeneration, and normalized hematological inflammatory parameters in CFA-induced arthritis rats. Further investigation revealed remarkably decreased levels of lipid peroxidation and increased levels of enzymatic antioxidants, including superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT), and nonenzymatic antioxidants, such as glutathione (GSH), in paw tissues. The potential mechanism of QUE-TGA-CdTe QDs of the abovementioned therapeutic effects might be attributed to the neutralization of massive free radicals generated at the inflammation sites and inhibition of cyclooxygenase (COX)-2 enzyme production [67]. Another study synthesized QUE-loaded NEG (QUE-NEG) by the spontaneous emulsification method and indicated its therapeutic effects via topical application in CFA-induced arthritis rats, as evidenced by the significantly decreased paw volume, arthritic index and joint stiffness scores, as well as suppressed production of hematological C-reactive protein (CRP) and rheumatoid factor (RF) [68].

Berberine (BER), a bisbenzylisoquinoline alkaloid derived from various medicinal plants, such as *Cortex phellodendri*, *Rhizoma coptidis* and *Hydrastis canadensis*, has demonstrated antiarthritic, anti-inflammatory and antiangiogenic impacts on CFA-induced

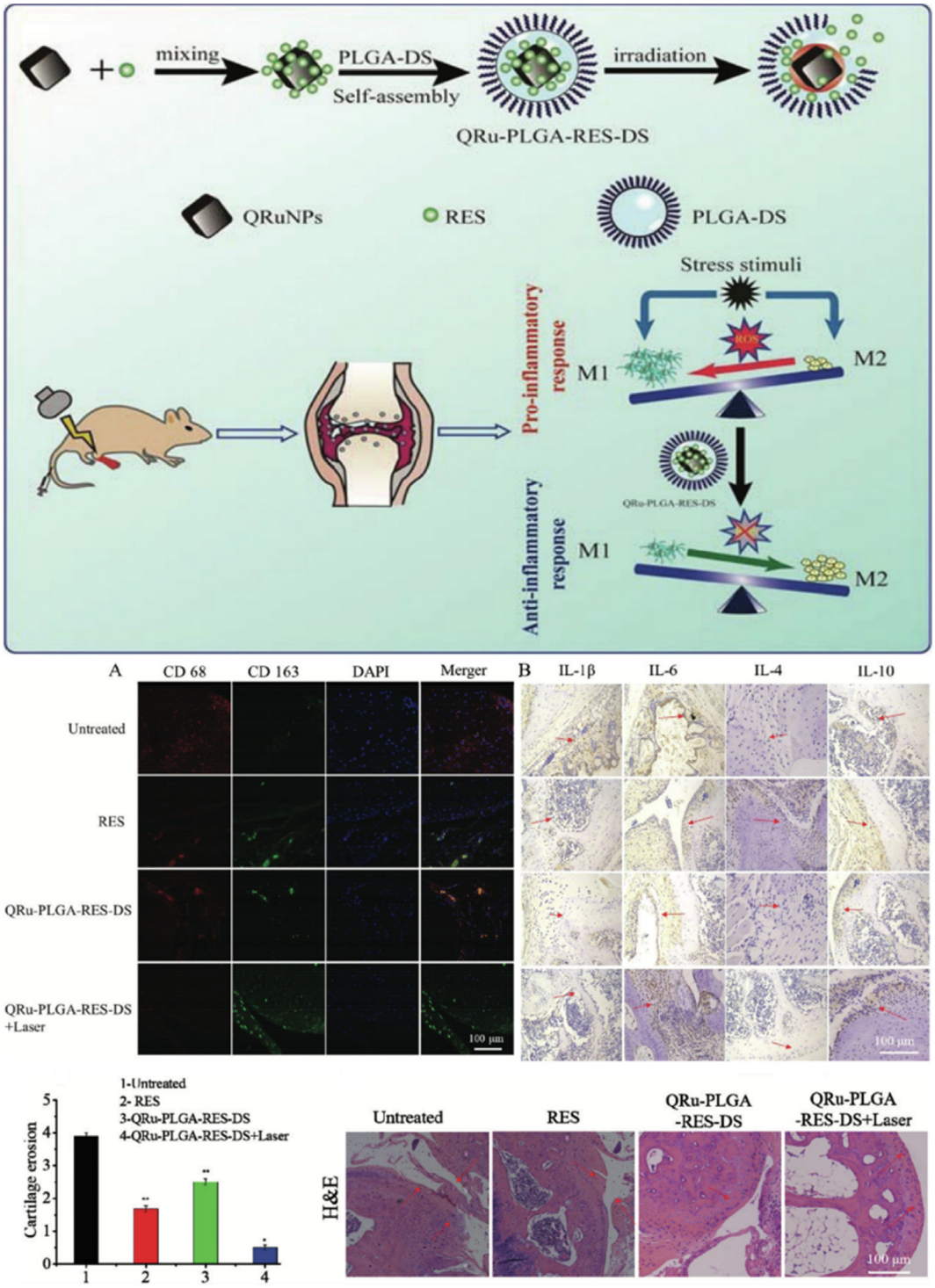


Fig. 6. Treatment of the QRu-PLGA-RES-DS nanoparticles with photothermal responses in CIA mice significantly mitigated the clinical score and prevented cartilage erosion and degradation by regulating the inflammatory microenvironment by inducing M2 macrophage polarization and suppressing the recruitment and infiltration ability of M1 macrophages [63]. Adapted with permission from ref. [63], Copyright from 2019, The Royal Society of Chemistry. **Abbreviations:** QRu-PLGA-RES-DS, quadrilateral ruthenium-polylactic-co-glycolic acid-resveratrol-dextran sulfate; CIA, collagen-induced arthritis; IL, interleukin.

arthritis and bovine type II collagen-induced arthritis [69,70]. Sujitha et al. synthesized PEGylated liposomal BER (BER-Lipo-PEG) using the thin-film hydration technique with several modifications based on 1,2-distearoyl-Sn-glycero-3-phosphocholine (DSPC)/CHOL/PEG/BER and further explored its therapeutic effects in both CFA-induced arthritis rats and adjuvant-induced arthritic fibroblast-like synoviocytes (AA-FLSs). The results demonstrated that BER-Lipo-PEG significantly improved physical parameters such as paw edema and body weight, inhibited the development of arthritis, as evidenced by preserved joint space, mitigated pannus formation, ameliorated cellular infiltration, and decreased expression of proinflammatory cytokines such as IL-1β, IL-6, IL-23 and TNF-α. They further revealed that the therapeutic effects of BER-Lipo-PEG may be mediated by the suppressed Wnt1/β-catenin signaling pathway through microRNA (miR)-23a activation [71].

p-Coumaric acid (CA), a dietary phenolic acid that widely exists in vegetables, fruits and beverages, has shown promising antiarthritic effects in CFA-induced arthritis [72]. A study incorporated CA into a mannose-fabricated liposomal delivery system by the thin film hydration method, resulting in the formation of CA-loaded mannosylated liposomes (CA-MLipo), and found that CA-MLipo could ameliorate ankle joint inflammation and restore body weight loss in CFA-induced arthritis rats. Further experiments in synovial macrophages primarily isolated from arthritis rats revealed that treatment with CA-MLipo decreased the expression of proinflammatory cytokines, including IL-1β, IL-6, IL-23 and TNF-α, and restricted macrophage differentiation into osteoclasts accompanied by suppressed tartrate-resistant acid phosphatase (TRAP) and MMP-9 expression and impaired NFATc1 activation. TRAP and MMP-9 are proteolytic enzymes secreted by preosteoclasts or osteoclasts, and NFATc1 is the major transcription factor potentially driving the differentiation of osteoclasts. Additionally, *in vitro* studies also indicated that CA-MLipo could enhance osteoprotegerin (OPG) production in bone marrow stromal cells to suppress polarization from macrophages to preosteoclasts [73].

Withaferin A (WA) is a steroidal lactone derived from the roots of the medicinal herb *Withania somnifera* [74]. WA-encapsulated mannosylated liposomes (WA-MLipos), which were made by the thin film hydration method based on WA/mannose/DSPC/CHOL, have demonstrated preferential and potential targeted internalization into synovial macrophages in CFA-induced arthritic rats [75]. Treatment with WA-MLipos significantly prevented weight loss, attenuated joint swelling, and suppressed ankle joint inflammation, as evidenced by the relief of the joint space, pannus formation, cartilage damage and cellular infiltration. Further evaluation of synovial tissues revealed that WA-MLipos treatment conferred negative osteoclastogenesis by increasing the production of OPG and decreasing the production of receptor activator of nuclear factor-κβ ligand (RANKL). Moreover, experiments in isolated synovial macrophages treated with WA-MLipos showed downregulated M1 macrophage-mediated pro-inflammatory mediators (IL-1β, IL-6, TNF-α, MCP-1, and VEGF) but upregulated anti-inflammatory cytokines (IL-10), along with decreased expression levels of the M1 surface marker CD86 but increased expression levels of the M2 surface marker CD163, suggesting that WA-MLipos treatment could positively switch macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype [75].

Morin (MOR), a sort of dietary bioflavonoid commonly found in guava leaves, apples, onions and the Moraceae family, has demonstrated effective impacts on mitigating the progression of CFA-induced arthritis with the combination of indomethacin [76]. Sultana et al. synthesized mannose-decorated liposomal morin (MOR-MLipos) through a thin film hydration technique and further found that MOR-MLipos markedly ameliorated both paw edema and body weight loss in CFA-induced arthritis rats. Histopathological analyses evaluated the established characteristics of arthritis, including joint space narrowing, pannus formation and cellular infiltration, and further found that MOR-MLipos treatment significantly relieved these features. Experiments in spleen and synovial macrophages primarily derived from CFA-induced arthritis rats demonstrated that MOR-MLipos were more preferentially taken up. Moreover, MOR-MLipos noticeably increased the production of OPG and decreased the production of VEGF, the transcription factor nuclear factor kappa β (NF-κβ)-p65, and proinflammatory meditators, including inducible nitric oxide synthase (iNOS), IL-1β, IL-6, IL-17 and TNF-α [77].

Sinomenine hydrochloride (SIN) is a naturally occurring alkaloid originating from *Caulis sinomenii* with notable anti-inflammatory and immunoregulatory capabilities. Shen et al. developed a novel thermosensitive liposome (TS Lipo) based on dipalmitoyl phosphatidylcholine (DPPC)/hydrogenated SPC/CHOL and then synthesized SIN-loaded TS Lipo (SIN-TS Lipo) using a pH gradient technique. Interestingly, the SIN-TS Lipo showed thermosensitive drug release behavior, i.e., the rate of drug release at 43 °C was much faster than that at 37 °C. *In vitro* studies demonstrated that SIN-TS Lipo could be efficiently taken up by LPS-treated human umbilical vein endothelial cells (HUVECs) with good biocompatibility. They further indicated that the therapeutic method of SIN-TS Lipo combined with microwaves in CFA-induced arthritis rats drastically reduced paw thickness and arthritic score, attenuated histological pathologic characterizations such as pannus formation and synovial inflammation, and decreased secretion of proinflammatory cytokines such as IL-6 and TNF-α. The superior therapeutic effects of SIN-TS Lipo combined with microwaves may be attributed to its passive lesion-targeting capability and fast temperature-sensitive drug release ability [78].

Triptolide (TRI) is a diterpene triepoxide with massive pharmacological activities that serves as the main active component of extracts originating from the medicinal herb *Tripterygium wilfordii Hook F* [79]. A study developed a novel TRI-loaded transdermal delivery system, namely, a triptolide-loaded liposome hydrogel patch (TRI-LHP), and further delivered TRI-LHP into a CIA rat model using a microneedle array. The results eliminated hepatic first-pass metabolism and digestive toxicity of TRI, suggesting potential exceptional bioavailability and safety. They also indicated that TRI-LHP attenuated joint swelling and decreased the production of fetal liver kinase (Flk)-1, fetal liver tyrosine kinase (Flt)-4 and hypoxia-inducible factor (HIF)-1α in the synovium, as well as IL-6 in serum. Notably, given that Flk-1 and Flt-4 are two receptors of VEGF with high affinity and HIF-1α could induce the expression of VEGF, the results also suggested that the therapeutic effects of TRI-LHP may be attributed to the suppressed production and biological activity of VEGF [80].

β-Sitosterol (SIT) is a phytosterol abundantly present in various plant species with massive health benefits [81]. Zhang et al. prepared SIT-loaded SLNs (SIT-SLNs) using the double emulsion solvent displacement method and indicated that the SIT-SLNs noticeably mitigated paw edema and arthritic scores and increased body weight in CFA-induced arthritis rats. Molecular experiments demonstrated increased levels of SOD, GSH, CAT and IL-10, as well as decreased levels of malonaldehyde (MDA), IL-1β, IL-6, IL-17, TNF-α, COX-2 and prostaglandin E2 (PGE2), in SIT-SLN-treated arthritis rats, suggesting the antioxidant and anti-inflammatory capabilities of SIT-SLNs. Further investigation revealed that these therapeutic effects may be associated with suppressed NF-κβ and activated heme oxygenase-1 (HO-1)/nuclear factor erythroid 2-related factor 2 (Nrf-2) signaling pathways [82].

Piperine (PIP), an alkaloid present in the fruits and roots of Piper nigrum, Piper longum and other Piper species belonging to the Piperacea family, has demonstrated anti-inflammatory and anti-arthritic therapeutic effects in both human IL-1β-stimulated FLSs and arthritic rat models [83]. A study indicated that oral and topical administration of PIP-encapsulated SLNs (PIP-SLNs), which were synthesized by the melt emulsification sonication technique based on PIP and glyceryl monosterate, significantly reduced paw volume, relieved bone erosion and destruction, and decreased inflammatory cell infiltration and connective tissue proliferation in CFA-induced arthritis rats. Further investigation revealed a noticeable reduction in TNF-α in the synovial fluid of PIP-SLN-treated rats, indicating a potential mechanism of the disease modifying the anti-rheumatic activity of PIP-SLNs [84].

Embelin (EMB), a naturally occurring alkyl-substituted hydroxyl benzoquinone serving as the major component of *Embelia ribes*, showed exceptional biological activities for the treatment of chronic diseases [85]. Cui et al. synthesized EMB-loaded chitosan nanoparticles (EMB-CNPs) using the ionotropic gelation method

with several modifications and further found therapeutic effects of EMB-CNPs in CFA-treated rats, as evidenced by dose-dependent relief of the arthritic score and paw swelling. They further revealed that these protective effects against arthritis were mediated by antioxidant and anti-inflammatory capabilities, since EMB-CNPs downregulated MDA and NO levels, upregulated antioxidant levels, and reduced the expression of inflammatory markers, including IL-1β, IL-6, TNF-α and NF-κβ [86].

Hesperidin (HES) is also a natural flavonoid derived from citrus fruits and vegetables and has demonstrated experimental therapeutic effects in an arthritis rat model [87]. Rao et al. constructed HES-loaded gum acacia-stabilized green silver nanoparticles (HES GA-Ag nanoparticles) and found that oral delivery of HES GA-Ag nanoparticles significantly reduced the arthritic score, mitigated paw swelling, and diminished inflammatory cell infiltration and granulomatous inflammation in ankle joint tissues of CFA-induced arthritis rats. Furthermore, they demonstrated significantly decreased levels of Toll-like receptors (TLRs) 2 and 4 in spleen tissues of arthritic rats, suggesting a possible mechanism of therapeutic effects by HES GA-Ag nanoparticles [88].

3.2. Inflammatory bowel disease

Inflammatory bowel disease (IBD) comprises two main forms, namely, Crohn's disease (CD) and ulcerative colitis (UC), characterized by chronic relapsing inflammation in the gastrointestinal tract, leading to clinically intermittent abdominal pain and diarrhea occurring over an extensive spectrum of severity [89]. Although currently available therapeutics for IBD are abundant, including traditional drugs such as aminosalicylates and steroids, biological therapies such as TNF-α monoclonal antibody, and several novel therapeutics such as fecal microbiota transplantation and stem cells, it is still difficult for some patients to obtain the expected therapeutic effects or even noticeable adverse effects [90]. Various NP-based nanomedicines have been experimentally applied to IBD models and have shown prominent therapeutic effects, which may provide potential strategies for further clinical therapy.

CUR has demonstrated exceptional therapeutic effects in an experimental IBD model [91]; nevertheless, several challenges are still unresolved, such as poor bioavailability and low stability [92]. Its nanoformulations have been extensively explored and seem to open a new door for improving the therapeutic efficacy of CUR in IBD. Luo et al. synthesized CUR-encapsulated tannic acid (TA)-coated genipin (Gnp)-crosslinked human serum albumin (HSA) nanoparticles (CUR-TA/Gnp/HSA nanoparticles) using a modified oil-in-water (O/W) single emulsion-solvent evaporation technique. The formulated nanoscale system efficiently improved CUR release in the simulated gastric fluid and enhanced its colon adhesion and cell uptake ability. Oral administration of the CUR-TA/Gnp/HSA nanoparticles into dextran sulfate sodium (DSS)-induced colitis mice noticeably reduced the disease activity index (DAI), suppressed body weight loss and colon length shortening, and attenuated histological symptoms and signs of colonic inflammation, along with great biocompatibility and low toxicity. Further exploration revealed remarkable suppression of inflammation in the intestinal mucosa, as evidenced by decreased myeloperoxidase (MPO) activity and reduced production of inflammatory markers, including IL-1β, IL-6, TNF-α, and iNOS, which may be related to the inhibition of the TLR4-linked NF-κB signaling pathway [93] (Fig. 7). Han et al. synthesized stable CUR-chitosan polymer (CUR-CHI polymer) through self-assembly of CUR-chitosan conjugates, which were formed by incorporating CUR into a chitosan scaffold by self-hydrolyzable ester linkages, and indicated that oral delivery of the CUR-CHI polymer efficiently accumulated in inflamed gut sites, elevated the survival rate, improved clinical symptoms, reduced DAI, and mitigated colonic shortening in DSS-induced colitis mice. Further investigation also revealed significantly decreased production of proinflammatory mediators such as IL-6, TNF-α, interferon (IFN)-β, and iNOS. in the colonic tissues of colitis mice. Moreover, *in vitro* studies in the LPS-activated mouse macrophage cell line Raw264.7 and primary mouse bone marrow-derived macrophages (BMDMs) also demonstrated that the CUR-CHI polymer suppressed the expression of these proinflammatory mediators in a dose-dependent manner [94] (Fig. 8). Not only natural chitosan but also synthetic polymers were used to formulate nanoparticles with CUR. A study prepared PEG-ss-CUR polymer (CUR-PEG polymer), a sort of nanomedicine made of PEG and CUR joined by disulfide bonds, and found that CUR-PEG could substantially accumulate in the inflamed tissues of the intestine in DSS-induced colitis mice with lower cytotoxicity and higher membrane permeability. Oral administration of CUR-PEG significantly ameliorated weight loss, recovered shortened colon length, decreased DAI scores, and improved histopathological characterizations in DSS-induced colitis mice. Further examination revealed the antioxidant and anti-inflammatory effects of CUR-PEG, as evidenced by the markedly decreased MPO activity, malondialdehyde (MDA) content, and IL-6 and TNF-α expression in the colonic tissue of CUR-PEG-treated colitis mice [95]. Another study synthesized CUR-loaded polymeric pH-sensitive PLGA/polymethacrylate (PM) nanoparticles (CUR-PLGA/PM nanoparticles) through the modified spontaneous emulsification solvent diffusion technique and demonstrated their exceptional therapeutic impacts in DSS-induced colitis mice, as evidenced by the efficient accumulation in inflammatory colon tissues, relieved clinical activity score, preserved intact colonic architecture, and decreased MPO activity and TNF-α expression in the colon. *In vitro* studies indicated that CUR-PLGA/PM nanoparticles could increase CUR permeation across Caco-2 cell monolayers and decrease TNF-α secretion in LPS-treated J774 macrophages [96]. Moreover, CUR-loaded pluronic F127 (PF127)-functionalized porous PLGA nanoparticles (CUR-PF127/PLGA nanoparticles) were also formed and demonstrated great biocompatibility and a higher cellular uptake rate of CUR. *In vitro* studies in LPS-stimulated RAW 264.7 macrophages indicated that the CUR-PF127/PLGA nanoparticles had a higher capability to significantly prevent the expression of proinflammatory cytokines such as IL-6, IL-12 and TNF-α than other CUR formulations. Moreover, the oral administration of CUR-PF127/PLGA nanoparticles significantly attenuated body weight loss, decreased MPO activity and spleen weight, recovered colon length, downregulated the expression of proinflammatory cytokines (IL-6, IL-12 and TNF-α) and upregulated the expression of anti-inflammatory cytokines (IL-10) in blood [97]. Notably, synthetic and natural polymers were also applied in the formation of CUR nanoparticles. Mutalik et al. prepared novel CUR-loaded pH-sensitive hydrolyzed polyacrylamide-grafted-xanthan gum (PAAm-g-XG) copolymeric nanoparticles (CUR-PAAm-g-XG nanoparticles) and demonstrated their capabilities of controlled and targeted release of CUR as well as higher systematic absorption than free CUR. *In vitro* studies in Vero and HCT116 cell lines showed no extra cytotoxicity of the grafted copolymeric nanoparticles. Oral delivery of the CUR-PAAm-g-XG nanoparticles significantly attenuated weight loss and colon length shortening, decreased MPO activity and tissue nitrite levels, and improved histopathological features such as necrosis, ulceration, congestion, and edema in acetic acid (AA)-induced colitis rats [98]. Lipid nanoparticles were also utilized for the formation of CUR nanoformulations. Sharma et al. prepared CUR-loaded solid binary lipid nanoparticles (CUR-SBLNs) using the emulsion solvent evaporation method and found a higher concentration of CUR in inflamed intestinal tissues in CUR-SBLN-treated DSS-induced colitis guinea pigs. Moreover, the oral delivery of CUR-SBLNs significantly ameliorated colon weight/length incre-

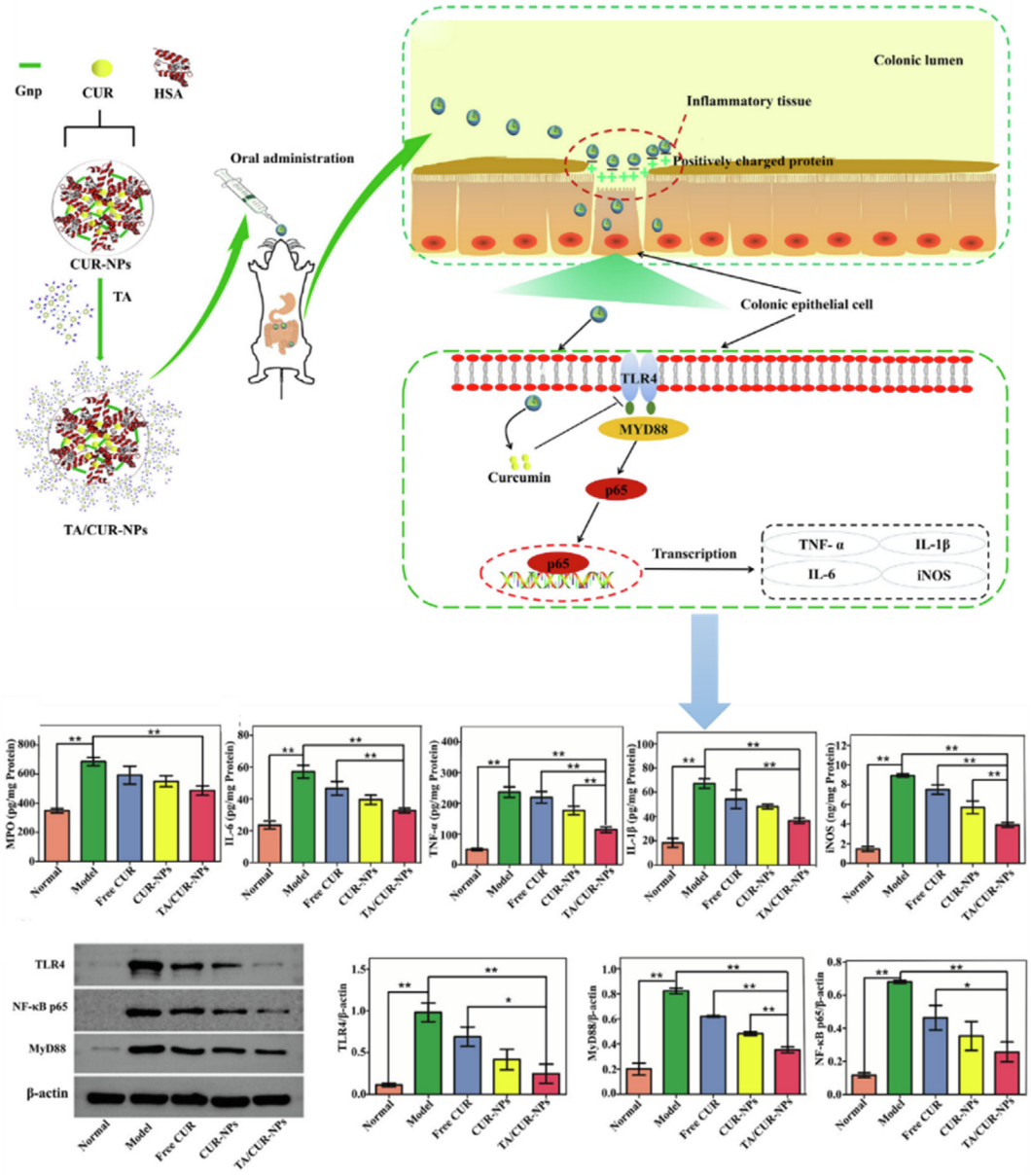


Fig. 7. Oral administration of the CUR-TA/Gnp/HSA nanoparticles into DSS-induced colitis mice significantly mitigated disease progression by suppressing inflammation in the intestinal mucosa, as evidenced by decreased MPO activity and reduced expression of inflammatory mediators, including IL-1β, IL-6, TNF-α, and iNOS, which may be associated with the inhibition of the TLR4-linked NF-κB signaling pathway [93]. Adapted with permission from ref. [93], Copyright from 2020, Elsevier. **Abbreviations:** CUR-TA/Gnp/HSA, curcumin-encapsulated tannic acid-coated, genipin-crosslinked human serum albumin; DSS, dextran sulfate sodium; MPO, myeloperoxidase; IL, interleukin; TNF, tumor necrosis factor; iNOS, inducible nitric oxide synthase; TLR, Toll-like receptor; NF-κB, nuclear factor kappa β.

ments, reduced leucocyte infiltration, decreased the production of oxidative stress, downregulated the secretion of the pro-inflammatory cytokine TNF-α, and maintained a relatively normal colonic structure, similar to healthy animal groups [99]. Another study developed novel core-shell nanoparticles composed of CUR nanocrystals in the core and chitosan (CH), sodium alginate (AG) and cellulose acetate phthalate (CAP) polyelectrolyte multilayers in the shell (CUR-CH/AG/CAP nanoparticles) and demonstrated preferential accumulation of CUR-CH/AG/CAP nanoparticles in the colon, especially in inflamed colonic tissue. Oral administration of the CUR-CH/AG/CAP nanoparticles remarkably recovered colon length, decreased DAI and spleen weight, and improved histological manifestations, such as edema and neutrophil and macrophage infiltration, in DSS-induced colitis mice. Further examination revealed significantly lower MPO activity and IL-6 and TNF-α expression in the colon samples of CUR-CH/AG/CAP nanoparticle-treated colitis mice [100]. Notably, CUR was coloaded with several other substances in nanostructured systems to exert therapeutic effects in experimental colitis models. A study formulated the CUR and piperine (PIP)-loaded self-microemulsifying drug delivery system (CUR-PIP-SMEDDS) and indicated that utilizing SMEDDS as delivery media and coencapsulating with CUR and PIP could improve the stability by protecting them against metabolism by the colon enzyme system. Retention enema administration of CUR-PIP-SMEDDS to DSS-induced colitis mice significantly improved the clinical manifestations, including body weight loss, intestinal bleeding and diarrhea, recovered the colon length, and reduced the histopathological manifestations, such as inflammatory cell infiltration and mucosal damage. Further experiments suggested the antioxidant and anti-inflammatory capabilities of

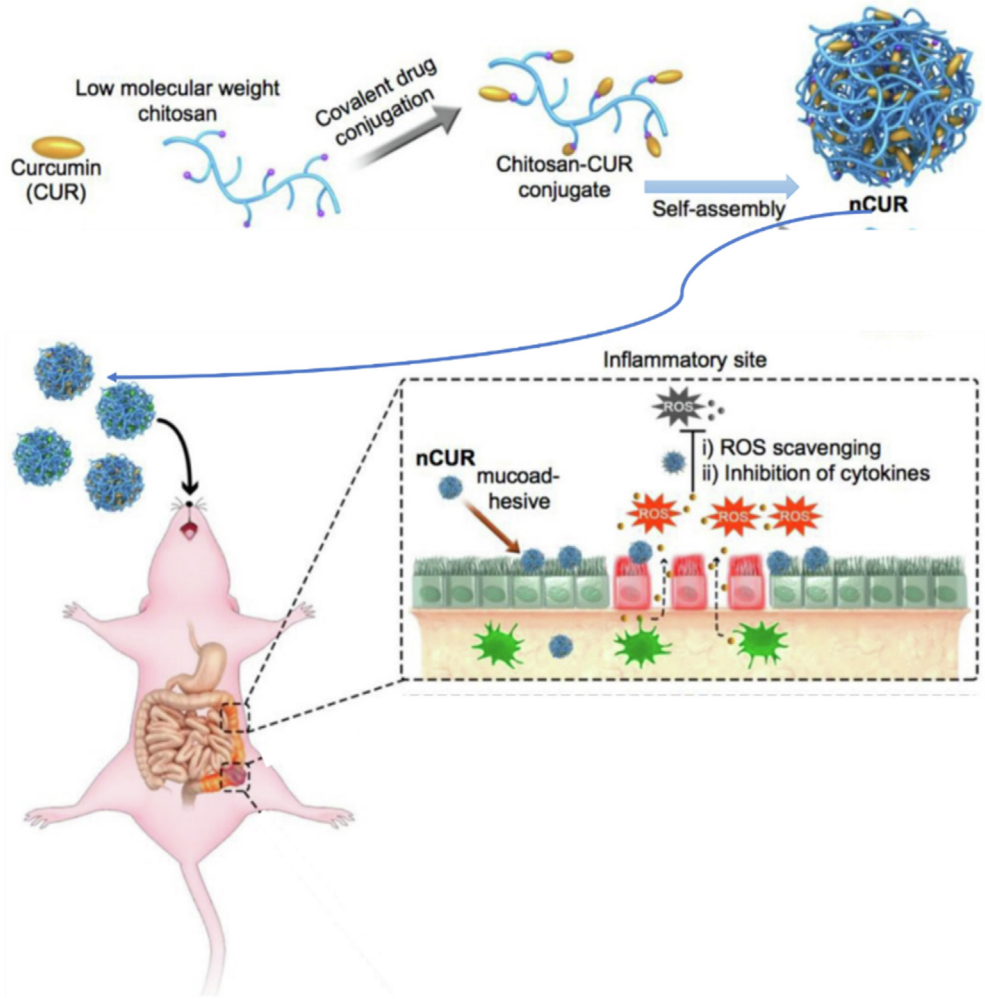


Fig. 8. Oral delivery of the CUR-CHI polymer in DSS-induced colitis mice efficiently accumulated in inflamed gut sites, scavenged ROS and decreased the expression of proinflammatory mediators such as IL-6, TNF-α, and IFN-β. in colotis tissues [94]. Adapted with permission from ref. [94], Copyright from 2019, Ivyspring International Publisher. **Abbreviations:** CUR-CHI polymer, curcumin-chitosan polymer; DSS, dextran sulfate sodium; ROS, reactive oxygen species; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

the CUR-PIP-SMEDDS, as evidenced by the decreased MPO activity, MDA content, and IL-6 and TNF-α expression in colonic tissues [101]. An interesting study explored and compared the *in vitro* and *in vivo* therapeutic efficacy of three CUR-loaded lipid-based nanocarriers, including CUR-loaded self-nanoemulsifying drug delivery systems (CUR-SNEDDSs), CUR-loaded nanostructured lipid carriers (CUR-NLC) and CUR-loaded lipid core-shell protamine nanocapsules (CUR-NC), in experimental colitis. CUR-NC conferred the highest CUR permeability across Caco-2 cell monolayers; however, it failed to decrease the production of TNF-α in LPS-induced J774 murine macrophages, whereas CUR-SNEDDS and CUR-NLC did. Moreover, only CUR-NLCs significantly reduced neutrophil infiltration and TNF-α expression in *in vivo* models of DSS-induced colitis mice [102] (Fig. 9). The study suggests that the essentially increased drug retention at the intestinal inflammatory site rather than increased drug permeability is correlated with higher therapeutic efficacy in colitis treatments.Additionally, Huang et al. synthesized CUR/catalase (CAT)-coencapsulated, pluronic F127 (PF127)-functionalized, PLGA-based nanoparticles (CUR/CAT-PF127-PLGA nanoparticles) by a double-emulsion solvent evaporation method and demonstrated the prominent ROS-responsive drug release capacity and exceptional biocompatibility of CUR/CAT-PF127-PLGA nanoparticles. *In vitro* studies in RAW 264.7 macrophages suggested that PF127 could facilitate the cellular uptake of nanoparticles and that CAT could suppress the degradation of CUR by ROS, collectively leading to the high cellular uptake percentage of the CUR/CAT-PF127-PLGA nanoparticles. Moreover, the CUR/CAT-PF127-PLGA nanoparticles presented excellent antioxidant and anti-inflammatory effects in LPS-stimulated RAW 264.7 macrophages, as evidenced by the decreased levels of ROS, IL-6, IL-12 and TNF-α and the increased level of IL-10. Further *in vivo* studies in DSS-induced colitis mice indicated that the oral administration of CUR/CAT-PF127-PLGA nanoparticles significantly attenuated body weight loss and colon shortening, decreased spleen weight and colonic MPO activity, downregulated serum proinflammatory cytokines, upregulated anti-inflammatory cytokines, and relieved histopathological inflammatory characterizations, suggesting their great therapeutic effects [103].

RES-based nanomedicine has also been explored in the treatment of experimental colitis models. A study formulated RES-loaded folate (FA)-conjugated PLGA nanoparticles (RES-FA-PLGA nanoparticles) and indicated that the RES-FA-PLGA nanoparticles conferred the highest percentage and rate of RES transport through the Caco-2 cell monolayer. Oral administration of the RES-FA-PLGA nanoparticles in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis mice demonstrated no macroscopic damage in colon tissues that were comparable to the colons of

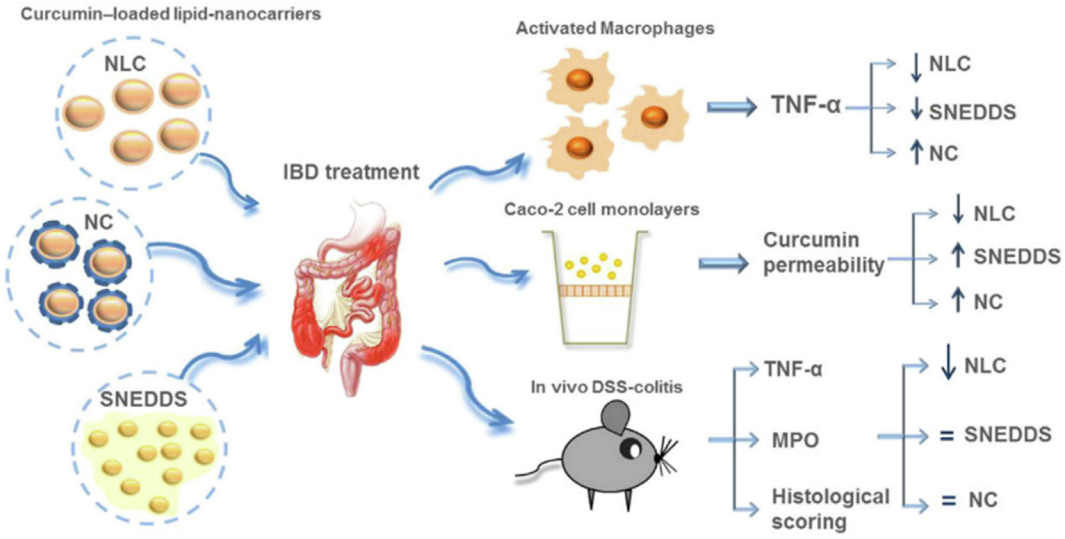


Fig. 9. Exploration and comparison of the *in vitro* and *in vivo* therapeutic efficacy of three CUR-loaded lipid-based nanocarriers (CUR-SNEDDS, CUR-NLC and CUR-NC) in experimental colitis [102]. Adapted with permission from ref. [102], Copyright from 2016, Elsevier. **Abbreviations:** CUR, curcumin; CUR-SNEDDS, curcumin-loaded self-nanoemulsifying drug delivery system; CUR-NLC, curcumin-loaded nanostructured lipid carrier; CUR-NC, curcumin-loaded lipid core-shell protamine nanocapsule.

healthy controls. Moreover, histopathological examination also demonstrated that RES-FA-PLGA nanoparticle-treated colitis mice showed no aggregation of inflammatory cells, and their villi, submucosal and lamina propria layers were identical to the intestines of healthy rats. Further investigation in colon tissues revealed that treatment with RES-FA-PLGA nanoparticles significantly decreased the expression levels of IL-6 and TNF-α and reduced superoxide dismutase (SOD) and MPO activities [104]. Another study formulated RES-loaded silk fibroin nanoparticles (RES-SF nanoparticles) through an incubation method and indicated their great biocompatibility. The application of RES-SF nanoparticles to LPS-treated mouse RAW 264.7 macrophages significantly decreased the production of nitrite. Further experiments in TNBS-induced colitis rats showed that the intracolon administration of RES-SF nanoparticles markedly decreased the damage scores and weight/length ratio. Biochemical analyses revealed upregulated GSH content and downregulated inflammatory mediators, including proinflammatory cytokines such as IL-1β, IL-6, IL-12 and TNF-α, chemokines such as cytokine-induced neutrophil chemoattractant (CINC)-1 and monocyte chemoattractant protein (MCP)-1, and adhesion molecules such as intercellular adhesion molecule (ICAM)-1, in the colonic tissues of RES-SF nanoparticle-treated colitis rats, suggesting the prominent antioxidant and anti-inflammatory effects of the RES-SF nanoparticles. Interestingly, the RES-SF nanoparticles also noticeably improved intestinal epithelium barrier function, since they increased the production of primary components of the colonic mucus layer, including mucins MUC-2 and MUC-3, as well as bioactive peptides implicated in epithelial repair, including trefoil factor (TFF)-3 and villin [105]. Given that colitis induced by DSS or TNBS is acute colitis, Pujara et al. synthesized RES-encapsulated β-lactoglobulin nanospheres (RES-BLG nanospheres) and explored their therapeutic effects in Winnie mice with spontaneous UC, which closely represents the clinical manifestations of IBD. Oral delivery of RES-BLG nanospheres to Winnie mice significantly increased body weight, decreased DAI, and improved histopathological features, including recovery of colonic epithelium, an increase in goblet cell number and a decrease in neutrophil infiltration. Further examination in colon tissues revealed remarkably increased production of the anti-inflammatory cytokine IL-10 [106].

QUE has also been incorporated into nanotechnology and has demonstrated great experimental therapeutic effects in IBD models. Shen et al. synthesized functional prodrug micelles comprising QUE covalently linked to glycol chitosan (GC) by aryl boronic ester as a responsive linker (QUE-B-GC micelles) and demonstrated their pH/ROS dual-responsive capability and sustained release behavior. *In vivo* biodistribution experiments indicated the preferential accumulation of GC-B-Que micelles in intestinal inflammation sites. Oral delivery of the QUE-B-GC micelles in DSS-induced colitis mice tremendously decreased the spleen index, mitigated body weight loss and DAI, recovered colon length and appearance, and relieved histopathological manifestations, including restoration of colon structure and goblet cells, improvement of mucosal structures, and mitigation of inflammatory cell infiltration. Moreover, the production of major proinflammatory meditators, including IL-6, TNFα, and iNOS, was remarkably downregulated in colitis mice treated with QUE-B-GC micelles [107] (Fig. 10). Castangia et al. formulated QUE-loaded chitosan/nutriose-coated nanovesicles (QUE-CHI/NUT nanovesicles), which have demonstrated great resistance to the gastrointestinal environment and the ability to efficiently increase the accumulation of QUE in the colon. Oral application of the QUE-CHI/NUT nanovesicles macroscopically ameliorated mucosal and tissue damage, decreased the clinical activity score (CAS) and colon/body weight ratio, and relieved MPO activity in TNBS-induced colitis rats [108]. Another study explored the potential therapeutic effects of QUE-loaded silk fibroin nanoparticles (QUE-SF nanoparticles) formed by a simple incubation method in DSS-induced colitis mice. Oral delivery of the QUE-SF nanoparticles remarkably decreased the DAI of colitis mice. Histopathological examination further verified the therapeutic effects of the QUE-SF nanoparticles, as illustrated by the relieved damage in the mucosal barrier, increased goblet cells with mucin content and decreased inflammatory cell infiltration. Moreover, the application of QUE-SF nanoparticles efficiently suppressed the colonic expression of massive inflammation-related mediators, including IL-1β, IL-6, TNF-α, MCP-1, ICAM-1 and iNOS [109].

The therapeutic effects of EMB-based nanomedicine in experimental IBD were also prominent. A study synthesized EMB-loaded lipid nanospheres (EMB-LNs) through homogenization followed by an ultrasonication method based on soybean oil/virgin coconut oil as a liquid lipid carrier and soya/egg lecithin as a stabi-

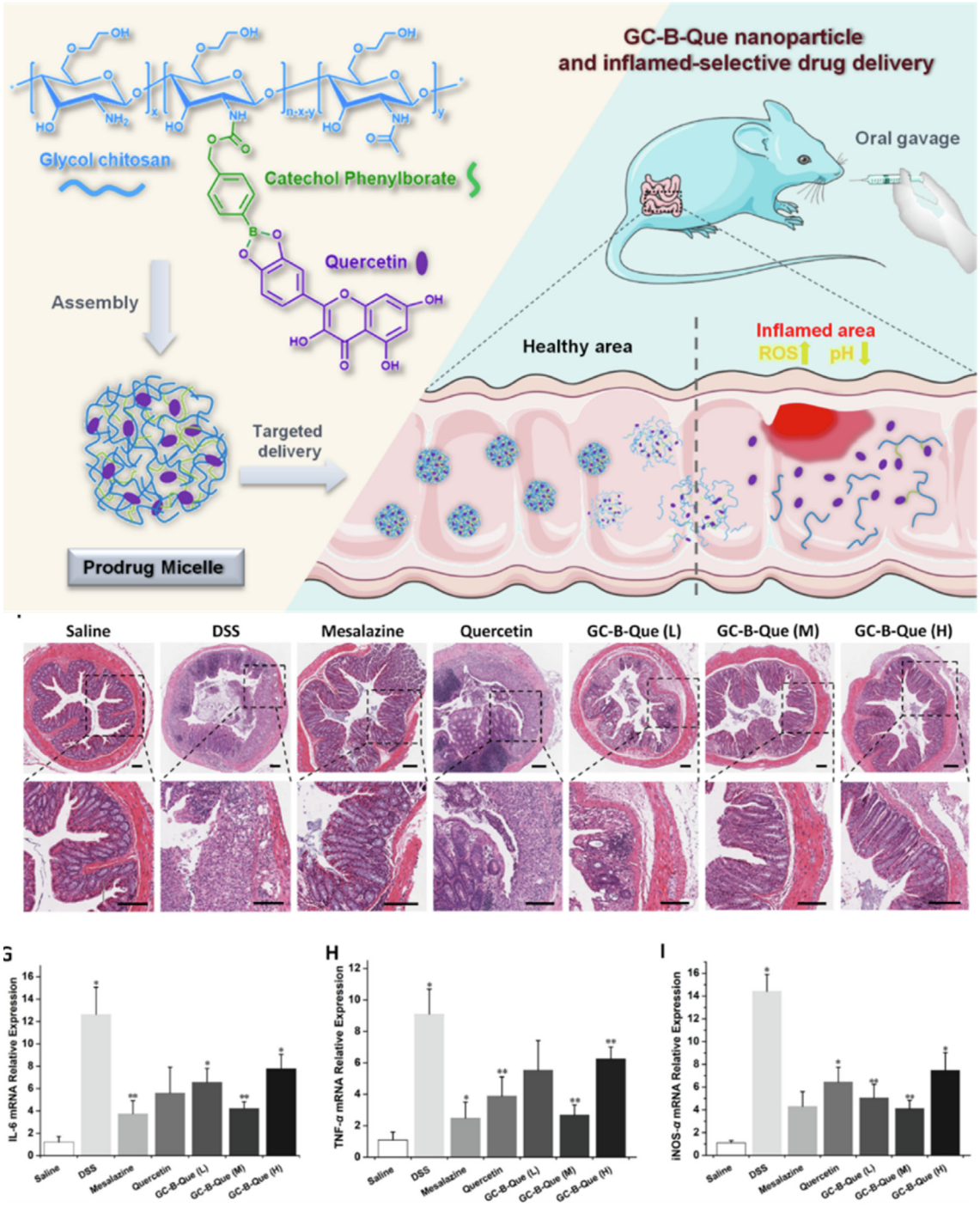


Fig. 10. Oral delivery of QUE-B-GC micelles with pH/ROS dual-responsive properties and sustained release behavior in DSS-induced colitis mice resulted in preferential accumulation in intestinal inflammation sites, mitigated clinical symptoms, relieved histopathological manifestations, and downregulated expression levels of proinflammatory meditators, including IL-6, TNFα, and iNOS [107]. Adapted with permission from ref. [107], Copyright from 2021, American Chemical Society. **Abbreviations:** QUE-B-GC, quercetin covalently linked to glycol chitosan by aryl boronic ester; ROS, reactive oxygen species; DSS, dextran sulfate sodium; IL, interleukin; TNF, tumor necrosis factor; iNOS, inducible nitric oxide synthase.

lizer. Oral administration of EMB-LNs in AA-induced colitis rats remarkably decreased clinical activity and macroscopic scores, improved spleen weight and wet colon weight/length ratio, and histologically recovered colonic mucosa from edema, necrotic destruction and inflammatory cell infiltration. Moreover, treatment with EMB-LNs significantly downregulated the production of MPO, lipid peroxides (LPO) and lactate dehydrogenase (LDH) and upregulated the expression level of GSH, suggesting the antioxidant and anti-inflammatory capabilities of the EMB-LNs [110]. Sharma et al. synthesized EMB-loaded guar gum microparticles (EMB-GG MPs) by the emulsification method. Oral administration of EMB-GG MPs in dinitrobenzenesulfonic acid (DNBS)-induced colitis rats significantly reduced the macroscopic activity scores and almost completely recovered the colonic mucosa from DNBS-induced colonic damage. Further examinations suggested the antioxidant and anti-inflammatory effects of EMB-GG MPs, as

evidenced by the remarkably enhanced GSH colonic activity and suppressed MPO and LPO colonic activity. Moreover, treatment with EMB-GG MPs showed comparatively fewer adverse effects than another traditional dosage form [111]. Another study prepared EMB-loaded enteric-coated microspheres (EMB-ENT MSs) with the remarkable sustained release of EMB. Treatment with EMB-ENT MSs in AA-induced colitis rats remarkably reduced the ulcer activity scores and protected the colonic mucosa from AA-induced colitis damage. Further experiments demonstrated increased GSH concentrations and decreased MPO and LPO concentrations in colitis rats treated with EMB-ENT MSs [112].

Ginger (GIN) is the rhizome of Zingiber officinale with abundant bio*active* constituents, including 6-gingerol and 6-shogaol. Ginger-derived nanoparticle 2 (GDNP 2), a specific type of nanoparticle derived from ginger juice by the sucrose gradient ultracentrifugation technique, comprises high levels of lipids, few proteins, 125 distinct microRNAs (miRNAs), and large amounts of 6-gingerol and 6-shogaol. Zhang et al. found that oral application of GDNPs 2 to DSS-induced colitis mice dramatically prevented intestinal inflammation, as evidenced by decreased lipocalin-2 (Lcn-2) expression, MPO activity, and local lymphocytic infiltration. Further analyses revealed that GDNP 2 significantly downregulated the production of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α but upregulated the production of anti-inflammatory cytokines such as IL-10 and IL-22. Interestingly, GDNP 2-treated mice showed elevated levels of survival and proliferation of intestinal epithelial cells (IECs) and increased expression of E-cadherin, which plays a critical role in epithelial cell adhesion and normal intestinal barrier function and homeostasis. Together, these results suggested the dual efficacies of GDNPs on DSS-induced colitis, including mitigating damaging factors and promoting healing factors. *In vitro* experiments further demonstrated that GDNPs 2 could be efficiently absorbed by colon-26 epithelial-like cells and RAW 264.7 Mø-like cells have great biocompatibility and no toxicity [113].

Silymarin, a major component derived from the fruits and seeds of milk thistle extract, is a mixture of several flavanins, among which silybin (SIL) is the main and most active biological constituent of silymarin. Varshosaz et al. found that SIL nanoparticles, which were synthesized by Eudragit RL PO nanoparticles loaded with SIL using the emulsification solvent evaporation method, could improve macroscopic and histopathological scores in AA-induced colitis rats. They further indicated that SIL nanoparticles conferred anti-inflammatory effects against AA-induced colitis by decreasing MPO activity and the expression of proinflammatory cytokines, such as IL-6 and TNF-α [114].

Grape (GRA) exosome-like nanoparticles (GELNs), derived from the juice of edible plant grapes containing many lipids, proteins and miRNAs, can penetrate the mouse intestinal mucus barrier and be taken up by intestinal stem cells, which play a vital role in intestinal epithelial differentiation and tissue homeostasis. A study indicated that oral delivery of GELNs to DSS-induced colitis mice mitigated the severity and progression of colitis and histologically restored the decreased villus height by promoting intestinal stem cell proliferation via the Wnt/β-catenin signaling pathway [115].

Caffeic acid phenethyl ester (CAPE) is a phenolic compound isolated from honeybee propolis, and piceatannol (PIC) is a natural agent found in the seeds of Euphorbia lagascae. CAPE/PIC-loaded albumin nanoparticles (CAPE/PIC-ALB nanoparticles), which were made of albumin nanoparticles loaded with CAPE/PIC and fabricated using a modified desolvation technique, exhibited remarkable therapeutic effects on DSS-induced colitis. CAPE/PIC-ALB nanoparticles noticeably ameliorated weight loss and DAI, improved colon morphology, and decreased MPO activity and proinflammatory cytokine expression in DSS-induced colitis mice. Further analyses revealed a significant decrease in the expression of hypoxia-inducible factor (HIF) and nuclear factor kappa β (NF-κβ) transcription proteins, namely, HIF-1α and p65, induced by CAPE/PIC-ALB nanoparticles [116].

3.3. Neuron-associated inflammatory diseases

Alzheimer's disease (AD) is a neurodegenerative disease resulting in progressive memory loss and dementia, with significant pathological characteristics, including amyloid β (Aβ) accumulation, neurofibrillary tangles, and neuronal loss. Increasing evidence has demonstrated the involvement of inflammation in the development of AD [117,118]. Given the low solubility, poor bioavailability and insufficient capability to cross the blood–brain barrier (BBB) of traditional drugs and treatment strategies, there has been no effective treatment for AD until now. In addition, it is worth noting that AD is essentially a complex, multifactorial disorder, and traditional single-target therapeutic strategies may have little effect on the prevention of AD [119]. NP-based nanomedicine has also been investigated for the treatment of AD. It has been reported that nanoparticle technology can effectively improve the bioavailability of CUR. Cheng et al. synthesized novel and stable CUR nanoparticles by encapsulating PEG-PLA di-block polymer micelles with CUR (CUR-PEG-PLA nanoparticles) utilizing a multi-inlet vortex mixer (MIVM) and flash nanoprecipitation. The synthesized CUR-PEG-PLA nanoparticles could remain constant in particle size during the storage period for more than one year. An increase in scores on the radial arm maze (RAM) and contextual fear conditioning reflex (CFC) tests was clearly observed in AD model Tg2576 mice after 3 months of treatment, suggesting that the CUR-PEG-PLA nanoparticles have an enhancing effect on memory function in mice. Measurements of amyloid plaque density, pharmacokinetics, and Madin-Darby canine renal cell monolayer penetration demonstrated excellent penetration across the BBB, great mean brain residence time and plaque stabilization. Moreover, the administration of CUR-PEG-PLA nanoparticles produced significantly higher concentrations of CUR in plasma, up to six times that of regular CUR [120]. Huo et al. synthesized PLGA nanospheres with CUR-loaded selenium (Se) nanoparticles (CUR/Se PLGA nanospheres) as an effective target delivery system and performed a systematic analysis of the morphological structure, size distribution, and chemical interactions between the polymer and the nanosphere formulation (Fig. 11**a**). They confirmed that the CUR/Se PLGA nanosphere drug delivery system was effective in reducing Aβ loading and alleviating associated memory deficits in AD model transgenic mouse (5XFAD) brain samples. Considering the high safety profile of CUR compounds in human clinical trials and the ability to bind Aβ and iron in plaques via intermolecular hydrogen bonds, CUR/Se PLGA nanospheres may serve as great candidates for localizing amyloid plaques in AD brains. Furthermore, fluorescence microscopy also verified the specific binding properties of the CUR/Se PLGA nanospheres to Aβ plaques [121]. The mechanisms of CUR-coated PLGA nanoparticles (CUR-PLGA nanoparticles) in enhancing brain function were further investigated by Tiwari et al. They reported that these novel nanoparticles could affect the self-regenerative capacity of the brain by targeting endogenous neural stem cells (NSCs) to induce neurogenesis and therefore may serve as a novel therapeutic approach for neurodegenerative diseases such as AD. Specifically, the CUR-PLGA nanoparticles effectively induced NSC proliferation and neuronal differentiation *in vitro* and in the hippocampus and subventricular zone *in vivo*. Moreover, the application of CUR-PLGA nanoparticles reversed Aβ-induced learning and memory impairments in a rat model of the AD-like phenotype. Further exploration revealed that these synthesized nanoparticles participated in the regulation of neurogenesis by activating the Wnt/β-catenin signaling pathway through interac-

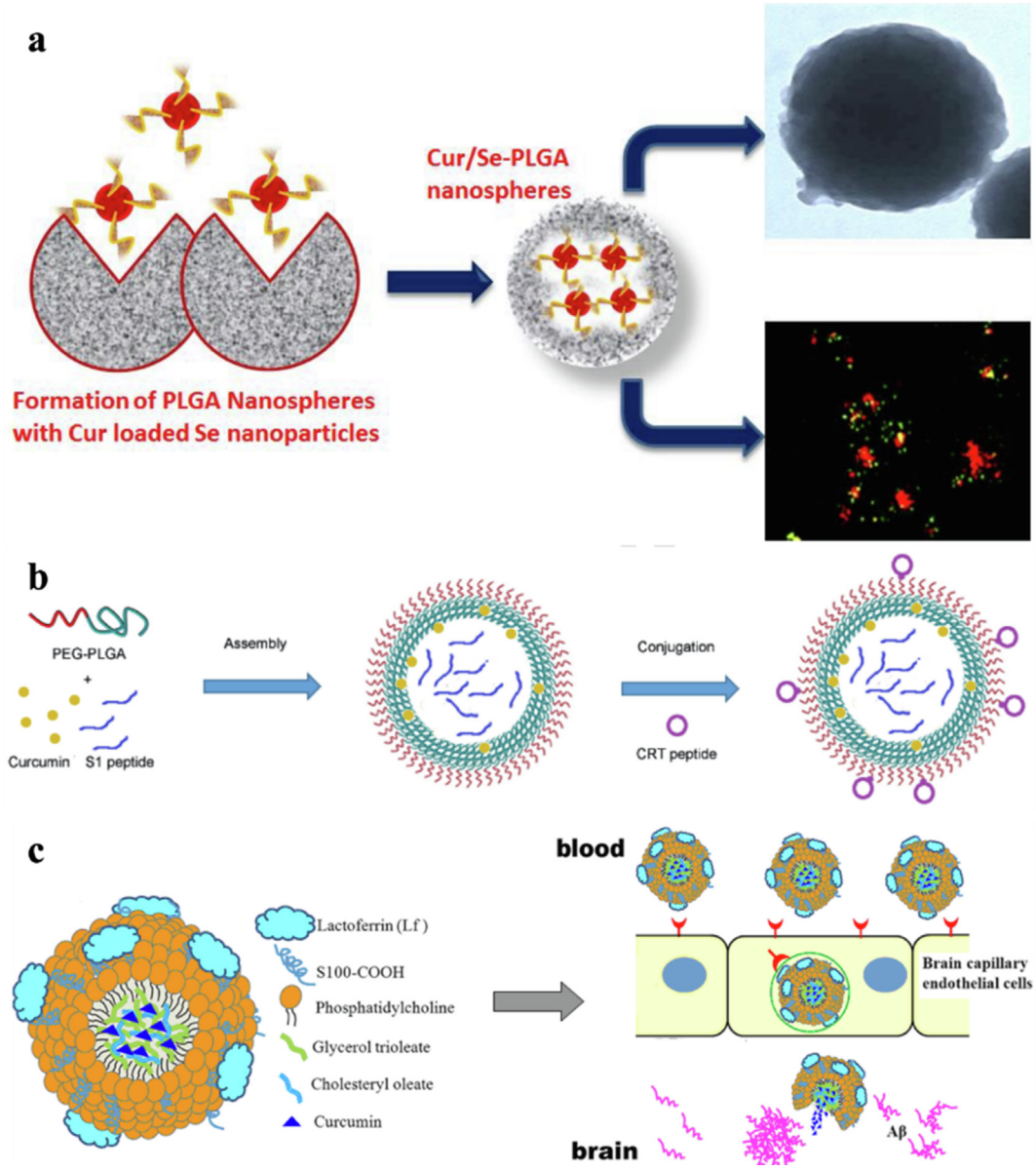


Fig. 11. (**a**) Schematic illustration of the CUR/Se PLGA nanospheres [121]. (**b**) Schematic illustration of the CRT-bound S1/CUR-loaded PLGA nanoparticles[119]. (**c**) Schematic illustration of the CUR/Lf mNLCs. CUR/Lf mNLCs mediate their cellular uptake in BCECs via the Lf receptor [124]. Adapted with permission from ref. [121], Copyright from 2018, Elsevier; Adapted with permission from ref. [119], Copyright from 2017, Oncotarget; adapted with permission from ref. [124], Copyright from 2015, Elsevier. **Abbreviations:** CUR/Se PLGA nanospheres, curcumin/selenium polylactic-co-glycolic acid nanospheres; CRT-bound S1/CUR-loaded PLGA nanoparticles, cyclic CRTIGPSVC peptide-bound Aβ production inhibitor S1/curcumin-loaded polylactic-co-glycolic acid nanoparticles; CUR/Lf mNLCs, curcumin/lactoferrin low-density lipoprotein-mimetic nanostructured lipid carriers; BCECs, brain capillary endothelial cells.

tion with Wnt inhibitor factor (Wif)-1, Dickkopf (Dkk) and glycogen synthase kinase (GSK)-3β [122]. In addition, CUR-based nanomedicine was also applied in combination with other ingredients, such as peptides, to exert better therapeutic effects. Huang et al. designed a novel PLGA nanoparticle loaded with the Aβ production inhibitor S1 (PQVGHL peptide) and CUR. To improve the permeability of the BBB, novel drug-loaded PLGA nanoparticles were conjugated with an iron-mimetic peptide, namely, the brain-targeting peptide CRT (cyclic CRTIGPSVC peptide), to target the transferrin receptor (TfR), leading to the synthesis of CRT-bound S1/CUR-loaded PLGA nanoparticles (Fig. 11b). The Y-maze and new object recognition tests showed that PLGA nanoparticles effectively elevated the spatial memory and recognition ability of AD mice, with remarkably decreased levels of Aβ, ROS, TNF-α and IL-6 in the brain while increased SOD activity and synapse number, confirming that the novel CRT-bound drug-loaded PLGA nanoparticles have multi-targeted capabilities to simultaneously deliver S1 peptide and CUR, as well as increase their bioavailability in the brain [119]. Fan et al. designed new brain-targeting nanoparticles, namely, PLGA-PEG nanoparticles conjugated with the B6 peptide and loaded with CUR (CUR/B6-PLGA-PEG nanoparticles), in which PLGA-PEG was used to improve bioavailability and the B6 peptide aimed to increase the BBB permeability of CUR. The PLGA-PEG-B6/CUR nanoparticles demonstrated relatively low toxicity with good biocompatibility and could be effectively taken up in HT22 cells. Further *in vivo* and *in vitro* experiments, such as the Morris water maze assay, Bielshovsky silver staining, immunostaining and immunoblotting, showed that the novel nanoparticles significantly enhanced the spatial and memory abilities of AD model APP/PS1 transgenic mice and reduced cognitive impairment, hippocampal

Aβ formation and tau protein hyperphosphorylation [123]. Another study reported novel low-density lipoprotein (LDL)-mimetic NLCs modified with lactoferrin (Lf) and loaded with CUR (CUR/Lf mNLCs) with excellent brain-targeted delivery capabilities (Fig. 11**c**). They investigated the uptake behaviors and potential cytotoxicity of different formulations in brain capillary endothelial cells (BCECs), experimentally confirming that CUR/Lf mNLCs mediated cellular uptake in BCECs via the Lf receptor. Further *in vitro* imaging studies revealed the efficient BBB penetration and preferential accumulation of CUR/Lf mNLCs in the brain. Moreover, CUR/Lf mNLCs have demonstrated their abilities to decrease oxidative stress-associated damage and ameliorate histopathological characteristics in the brains of AD model rats [124]. In addition to CUR, Ali et al. explored the enhanced neuroprotective effects of anthocyanin (ANT)-loaded PEG gold nanoparticles (ANT-PEG/Au nanoparticles) in an $A\beta_{1\text{-}42}$-injected AD mouse model. ANT-PEG/Au nanoparticles mitigated memory impairment in $A\beta_{1\text{-}42}$-injected mice and effectively protected pre- and postsynaptic proteins from $A\beta_{1\text{-}42}$-induced synaptic dysfunction. Regarding the detailed mechanism, they verified that ANT-PEG/Au nanoparticles could inhibit apoptosis and neurodegeneration in $A\beta_{1\text{-}42}$-induced mice by blocking tau protein 413 and 404 serine hyperphosphorylation through the phosphorylated phosphatidylinositol 3-kinase (p-PI3K)/p-pAkt/phosphorylated glycogen synthase kinase-3β (p-GSK3β) pathway [125]. Similarly, Amin et al. also focused on improving the bioavailability of ANTs and used a polymer-based nanoparticle approach to prepare novel biodegradable nanoparticles. They encapsulated ANT in biodegradable nanoparticle formulations based on PLGA and stabilizer PEG-2000. The formulated ANT-PLGA/PEG nanoparticles demonstrated neuroprotective and free radical scavenging properties via the p38-mitogen-activated protein kinase (MAPK)/c-Jun N-terminal kinase (JNK) pathways along with the activation of endogenous nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1) in the $A\beta_{1\text{-}42}$-stimulated SH-SY5Y cell lines (Fig. 12). Notably, the administration of ANT-PLGA/PEG nanoparticles effectively relieved various AD-related proteins, such as beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1), neuroinflammatory markers, such as p-NF-κβ, TNF-α and iNOS, and apoptosis markers, including Bax, Bcl2 and Caspase-3, suggesting great therapeutic potential in mitigating AD pathology [126].

Parkinson's disease (PD) is considered one of the most common neurodegenerative brain disorders and is caused by the selective and progressive loss of dopaminergic neurons in the substantia nigra, leading to subsequent deficiency of dopamine in the basal ganglia [127]. Moreover, proinflammatory immune-mediated mechanisms and oxidative stress play pivotal roles in the pathogenesis and development of PD [128,129]. The ideal drug for the treatment of PD has not yet been identified; fortunately, it has been reported that massive NPs exert anti-PD capabilities through not only antioxidative and anti-inflammatory activities but also regulatory effects on protein misfolding and PD-related pathways [130]. However, several problems, such as poor bioavailability and drug limitations of the BBB, remain unresolved. Although CUR has been reported to cross the BBB to exert neuroprotective effects in neurological diseases, nanoparticles have elevated half-lives, solubility and stability. Siddique et al. synthesized an alginate-CUR nanocomposite (ALG-CUR nanocomposite) with smooth and spherical morphology by a wet-milling method and investigated the effects of this novel nanocomposite on PD using a transgenic Drosophila model. They further observed that oral administration of ALG-CUR nanocomposites could remarkably delay the impairment of the climbing ability of PD model flies and suppress oxidative stress and apoptosis in the brains of PD model flies in a dose-dependent manner, suggesting the potent therapeutic potential of alginate-CUR nanocomposites in relieving PD [131]. Interestingly, Kundu et al. synthesized CUR and PIP coloaded glycerol monooleate (GMO) nanoparticles (CUR/PIP GMO nanoparticles) with multiple surfactant coatings to effectively elevate the bioavailability of drugs and enable both drugs to exert anti-parkinsonism effects across the BBB. Specifically, *in vitro* studies using atomic force microscopy (AFM) analysis and thioflavin T (ThT) binding assays showed the excellent ability of the novel CUR/PIP GMO nanoparticles to prevent α-synuclein (αS) protein aggregation into oligomers and fibrils. Further *in vitro* studies in PC12 cells indicated that the administration of these novel nanoparticles significantly suppressed rotenone-induced cytotoxicity, αS protein accumulation, oxidative stress and apoptosis and activated the autophagy–lysosome pathway (ALP). Moreover, *in vivo* studies revealed that the oral delivery of CUR/PIP GMO nanoparticles showed great plasma bioavailability and brain biodistribution, alleviated rotenone-induced motor coordination deficits and inhibited the degeneration of dopaminergic neurons in PD model mice [132] (Fig. 13). Another study reported novel puerarin (PUE) nanocrystals (PUE-NCs) for the potential treatment of PD. *In vitro* evaluations in MDCK cells indicated that the PUE-NCs caused no noticeable toxicity accompanied by enhanced cellular uptake behaviors and improved permeability. Moreover, the PUE-NCs also protected SH-SY5Y cells against 1-methyl-4-phenylpyridinium ion (MPP^+)-stimulated cellular damage. Toxicity analysis in zebrafish embryos further confirmed their nontoxicity *in vivo*. PUE-NC-treated SD rats showed higher pharmacokinetic levels in both plasma and brain than PUE alone-treated rats. *In vivo* studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD model mice revealed that oral delivery of PUE-NCs remarkably mitigated behavioral impairments and mobility, mitigated MPTP-induced neurotoxicity and loss of TH^+ neurons, and increased the levels of dopamine and its metabolites. Additionally, PUE-NCs decreased the expression of MDA and increased the activity of SOD and GSH in the brains of PD mice, suggesting a potent antioxidative capacity [133] (Fig. 14).

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by chorea, involuntary movements and anxiety, and neuroinflammation and oxidative stress participate in its progression [134,135]. A study explored the therapeutic effects of CUR-encapsulated SLNs (CUR-SLNs) on 3-nitropropionic acid (3-NP)-treated HD rats. CUR-SLN-administered HD rats demonstrated remarkably improved neuromotor coordination and increased mitochondrial complex activity and cytochrome production, accompanied by notably decreased mitochondrial swelling, lipid peroxidation, protein carbonyls and excess ROS. Moreover, the administration of CUR-SLNs recovered the GSH level and SOD activity. Further investigation revealed that the antioxidant properties of CUR-SLNs may be mediated through the activation of the nuclear factor-erythroid 2 (Nrf2) pathway [135].

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disorder of the central nervous system (CNS) characterized by demyelination and distinct degrees of axonal loss, along with a relapsing-remitting (RR) or progressive course. Inflammatory responses, including enhanced cytokine release and promoted antibody production, can further lead to BBB damage, macrophage activation, and the induction of several oxidative stress pathways [136,137]. Excitingly, a clinical trial indicated that treatment with nanocurcumin capsules 80 mg/day for 6 months in relapsing-remitting multiple sclerosis (RRMS) patients effectively downregulated T helper 17 (Th17) cell-associated parameters, including Th17 frequency, IL-17 and retinoic acid-receptor-related orphan nuclear receptor gamma (RORγt) expression, as well as IL-17 secretion by peripheral blood mononuclear cells (PBMCs), suggesting the ability of nanocurcumin to recover the dysregulation of Th17 cells in MS patients [138]. Moreover, this therapeutic strategy

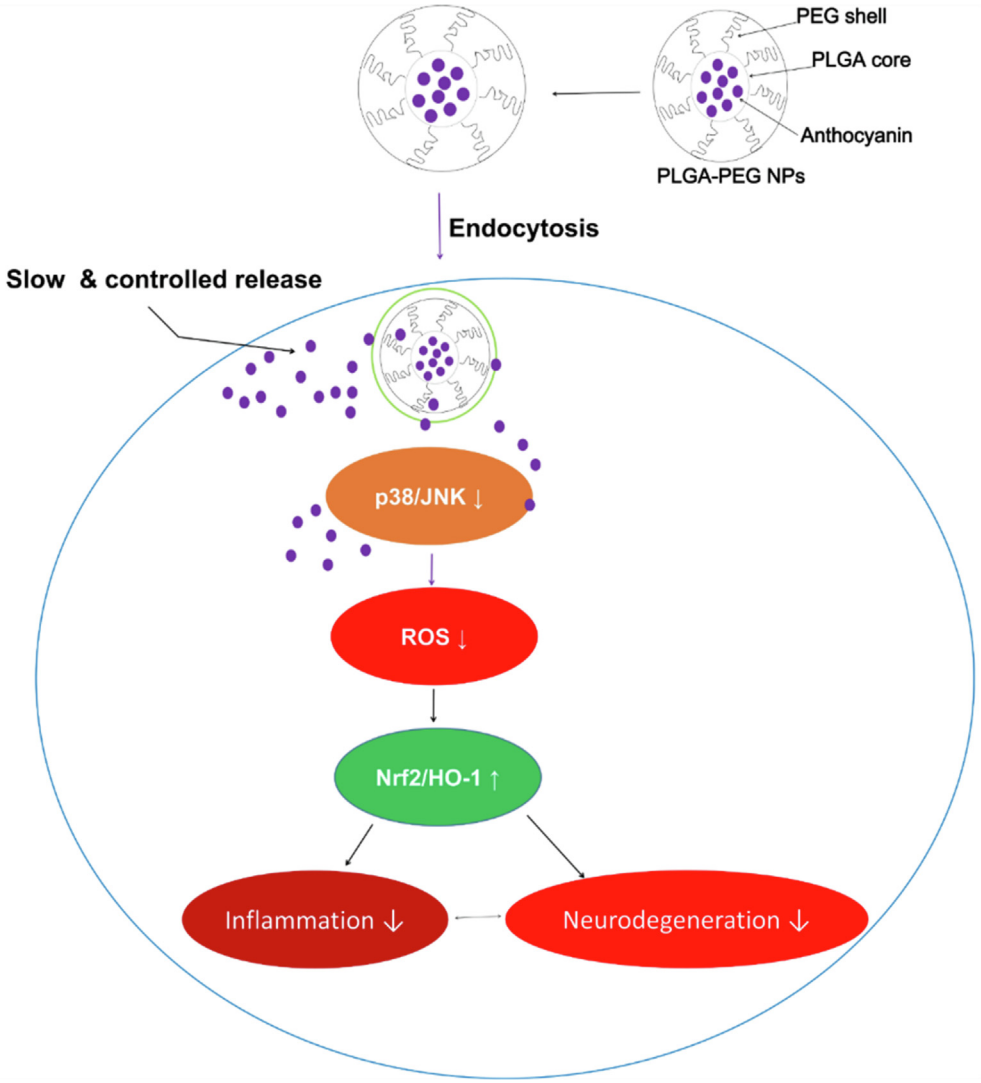


Fig. 12. Schematic representation of the intracellular uptake of the ANT-PLGA/PEG nanoparticles by SH-SY5Y cell lines via endocytosis. In the cellular cytoplasm, the endosome is broken down by lysosomal enzymes, and the drug is released in the cytoplasm and then reverts $A\beta_{1-42}$-induced Aβ pathology by abrogating ROS generation via the P38-MAPK/JNK pathways accompanied by induction of Nrf2 and HO-1 [126]. Adapted with permission from ref. [126], Copyright from 2017, BioMed Central. **Abbreviations:** ANT-PLGA/PEG nanoparticles, anthocyanin-loaded polylactic-co-glycolic acid/polyethylene glycol nanoparticles; Aβ, amyloid β; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1.

upregulated regulatory T (Treg) cell-associated parameters, including the frequency of Treg cells, expression of IL-10, TGF-β and forkhead box P3 (FoxP3), and secretion of IL-10 and TGF-β by PBMCs, suggesting the ability of nanocurcumin to recover the dysregulation of Treg cells in MS patients [139]. Interestingly, nanocurcumin also modulated the expression of various miRNAs in the peripheral blood of RRMS patients [137].

3.4. Ocular-associated inflammatory diseases

The cornea, which contains the outer epithelium, corneal fibroblasts and inner endothelium, covers the front surface of the eye and serves as a protective barrier against injury induced by ultraviolet radiation, ambient pollutants, *etc*. Therefore, the cornea is usually exposed to oxidative stress. Fortunately, the cornea has a self-developed antioxidant defense system composed of nonenzymatic and enzymatic antioxidants to eliminate free radicals and ROS. However, continuous exposure to oxidative stress and aging may impair the antioxidant defense system and promote ROS accumulation, resulting in functional and structural damage to corneal epithelial cells, fibroblasts, and endothelial cells [140–142]. Chittasupho et al. synthesized QUE-loaded PLGA nanoparticles through the solvent displacement method and verified that the encapsulation of QUE into PLGA nanoparticles elevated the solubility, controlled release ability, physical stability, and chemical stability of QUE. The combination of QUE-loaded PLGA nanoparticles with epigallocatechin gallate (EGCG) demonstrated additive effects on antioxidant activity and increased intracellular ROS inhibition capabilities in human corneal epithelial (HCE) cells. Notably, the in situ thermosensitive gel loaded with QUE-loaded PLGA nanoparticles and EGCG presented a suitable gelation temperature and time for the delivery of ocular drugs, suggesting a potential effective drug delivery system for antioxidant activity in HCE cells [142].

Uveitis is a common inflammatory ocular disease resulting in severe sight-threatening symptoms and includes various heterogeneous clinical entities [143]. A study reported the therapeutic efficacy of the oral administration of CUR-encapsulated double-headed polyester nanoparticles using gambogic acid-coupled PLGA (CUR-PLGA-GA_2) in a dog model of canine lens protein-induced

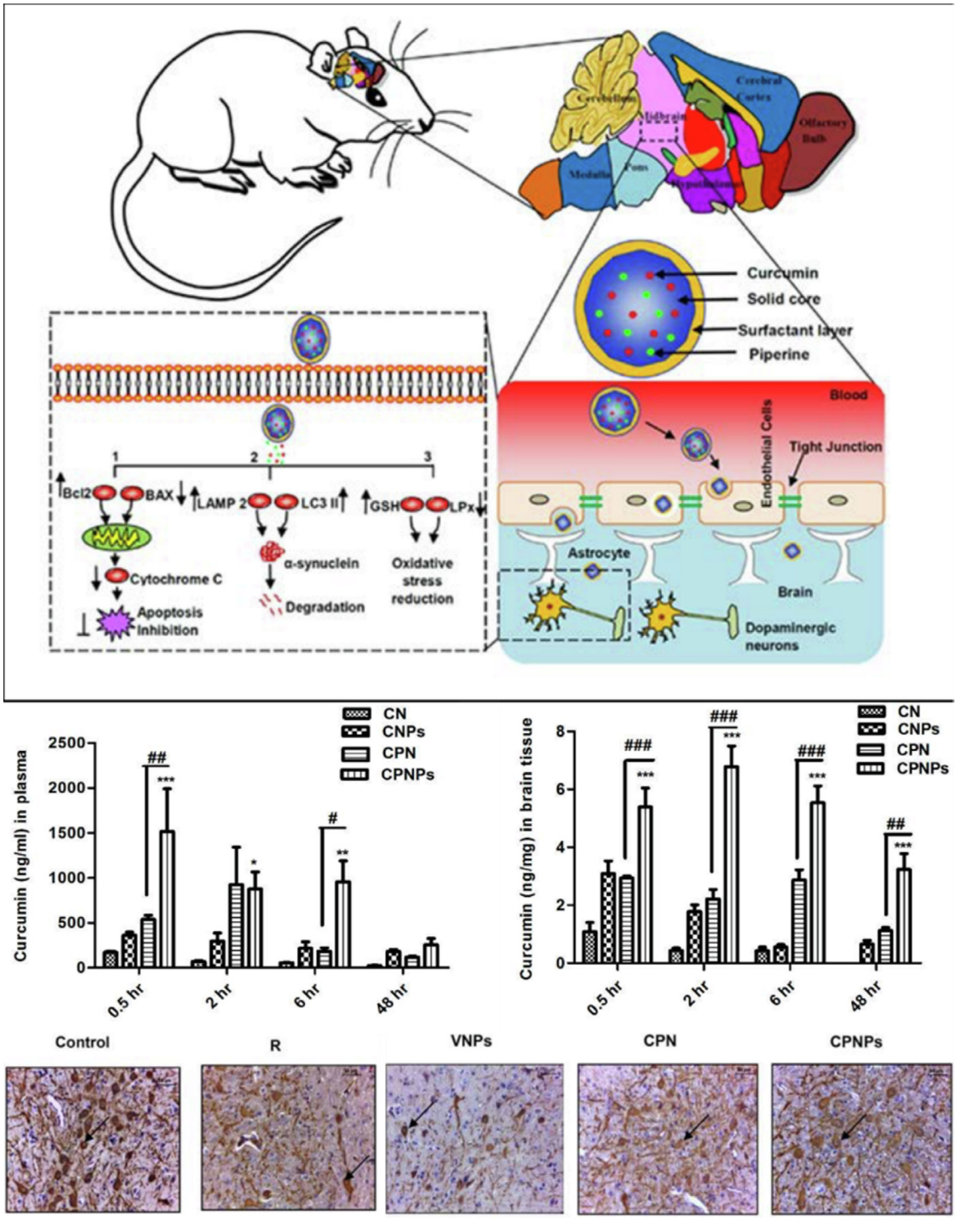
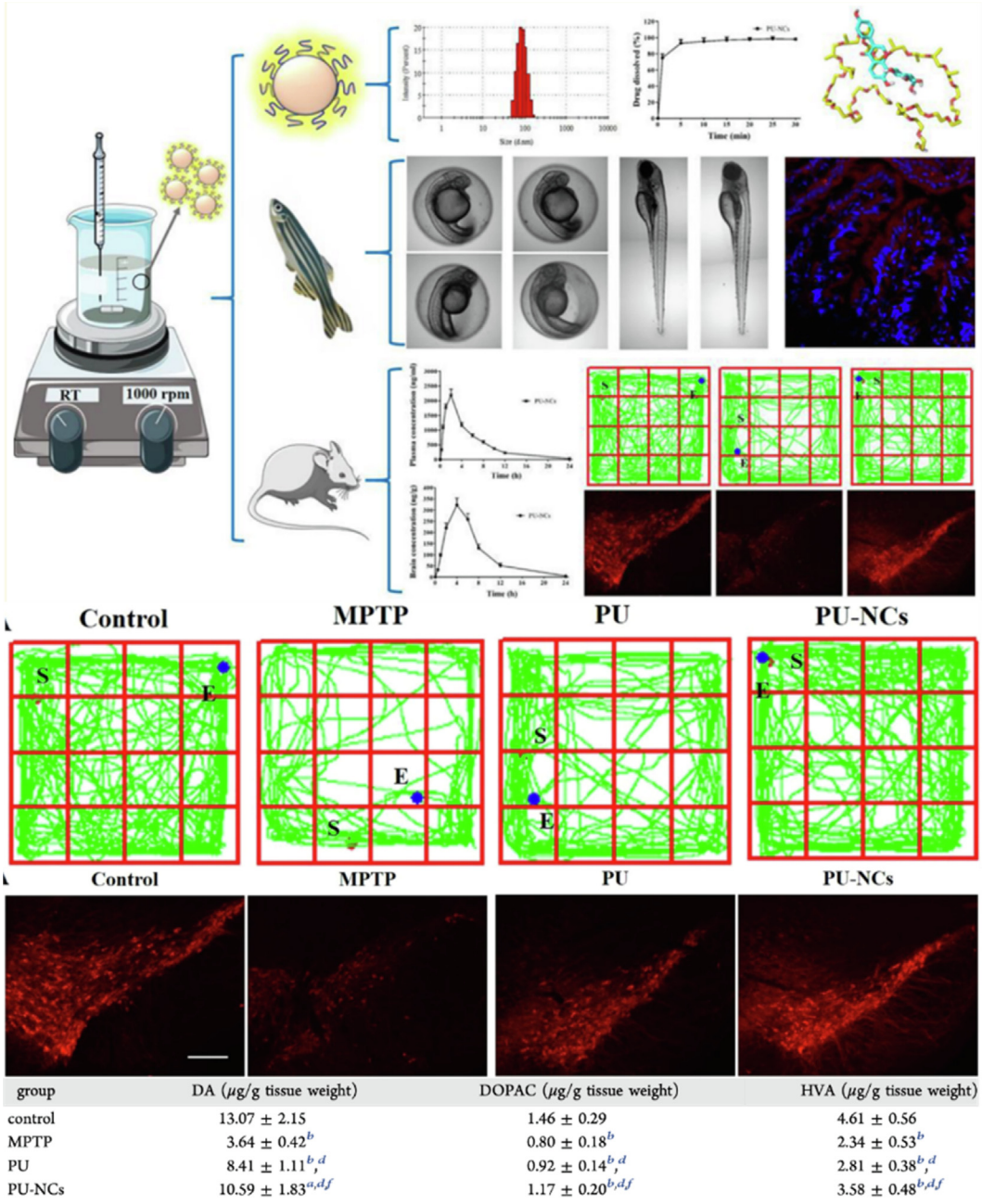


Fig. 13. Oral delivery of the CUR/PIP GMO nanoparticles showed great plasma bioavailability and brain biodistribution, alleviated rotenone-induced motor coordination deficits and inhibited the degeneration of dopaminergic neurons in PD model mice [132]. Adapted with permission from ref. [132], Copyright from 2016, American Chemical Society. **Abbreviations:** CUR/PIP GMO nanoparticles, curcumin/piperine coloaded glycerol monooleate nanoparticles; PD, Parkinson's disease.

uveitis, which was similar to intraocular inflammation after cataract surgery. PLGA-GA_2 nanoparticles were used to elevate the bioavailability of CUR for their capability to cross intestinal barriers via transferrin receptors (TfRs) in a noncompetitive manner. Further evaluation revealed that oral administration of CUR-PLGA-GA_2 caused remarkable levels of CUR in the aqueous humor and significantly relieved several ocular inflammatory parameters, such as aqueous flares and myosis, suggesting the great potential of PLGA-GA_2 nanoparticles to systemically deliver drugs across ocular barriers [144] (Fig. 15).

Except for systemic administration, topical instillation is regarded as the most convenient and common route for ocular drug delivery. In fact, the treatments of nearly 90% of ocular disorders involve the topical application of eyedrops, especially for the anterior segment of the eye. However, the low ocular bioavailability (less than 5%), poor ocular drug penetration, and transient res-



group	DA (μg/g tissue weight)	DOPAC (μg/g tissue weight)	HVA (μg/g tissue weight)
control	13.07 ± 2.15	1.46 ± 0.29	4.61 ± 0.56
MPTP	3.64 ± 0.42[b]	0.80 ± 0.18[b]	2.34 ± 0.53[b]
PU	8.41 ± 1.11[b,d]	0.92 ± 0.14[b,d]	2.81 ± 0.38[b,d]
PU-NCs	10.59 ± 1.83[a,d,f]	1.17 ± 0.20[b,d,f]	3.58 ± 0.48[b,d,f]

Fig. 14. Oral administration of the PUE-NCs remarkably restored the behavioral impairments and mobility, mitigated the MPTP-induced neurotoxicity and loss of TH^+ neurons, and increased the levels of dopamine and its metabolites in MPTP-induced PD model mice [133]. Adapted with permission from ref. [133], Copyright from 2019, American Chemical Society. **Abbreviations:** PUE-NCs, puerarin nanocrystals; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease.

idence time on the ocular surface serve as the major unresolved challenges related to topical application. Fortunately, the incorporation of nanotechnology may help drugs cross the static barriers of the ocular surface, i.e., the tight junctions of the conjunctiva, as well as the dynamic barriers consisting of fast tear turnover and conjunctival vasculature [145–147]. Ganugula et al. indicated that the topical installation of CUR-PLGA-GA_2 led to significant mitigation of ocular inflammatory parameters, including aqueous flare, miosis, and chemosis, compared with those in untreated controls within the early phase of canine lens protein-induced ocular inflammation [144]. Another promising option to increase the corneal bioavailability of therapeutic drugs is the polymeric nanogel formulation based on a new amphiphilic polymer polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PVCL-PVA-PEG), which has also demonstrated excellent storage stability and ocular tolerance [147–149]. Li et al. synthesized CUR-loaded PVCL-PVA-PEG nanomicelles (CUR-PVCL-PVA-PEG nanomicelles) by a solvent evaporation/film hydration technique and further confirmed that CUR encapsulated with PVCL-PVA-PEG nanomicelles led to a remarkable increase in solubility, chemical stability, and antioxidant capability. *In vitro* cytotoxicity tests on HCE cells and *in vivo* ocular tolerance tests on rabbit eyes demonstrated the high biocompatibility and good tolerance of the CUR-PVCL-PVA-PEG nanomicelles. Moreover, i*n vitro* HCE cell uptake tests and *in vivo* corneal permeation tests in both mice and rabbits presented enhanced uptake behavior and increased permeation. Importantly, the application of CUR-PVCL-PVA-PEG nanomicelle solution dose-dependently attenuated inflammation

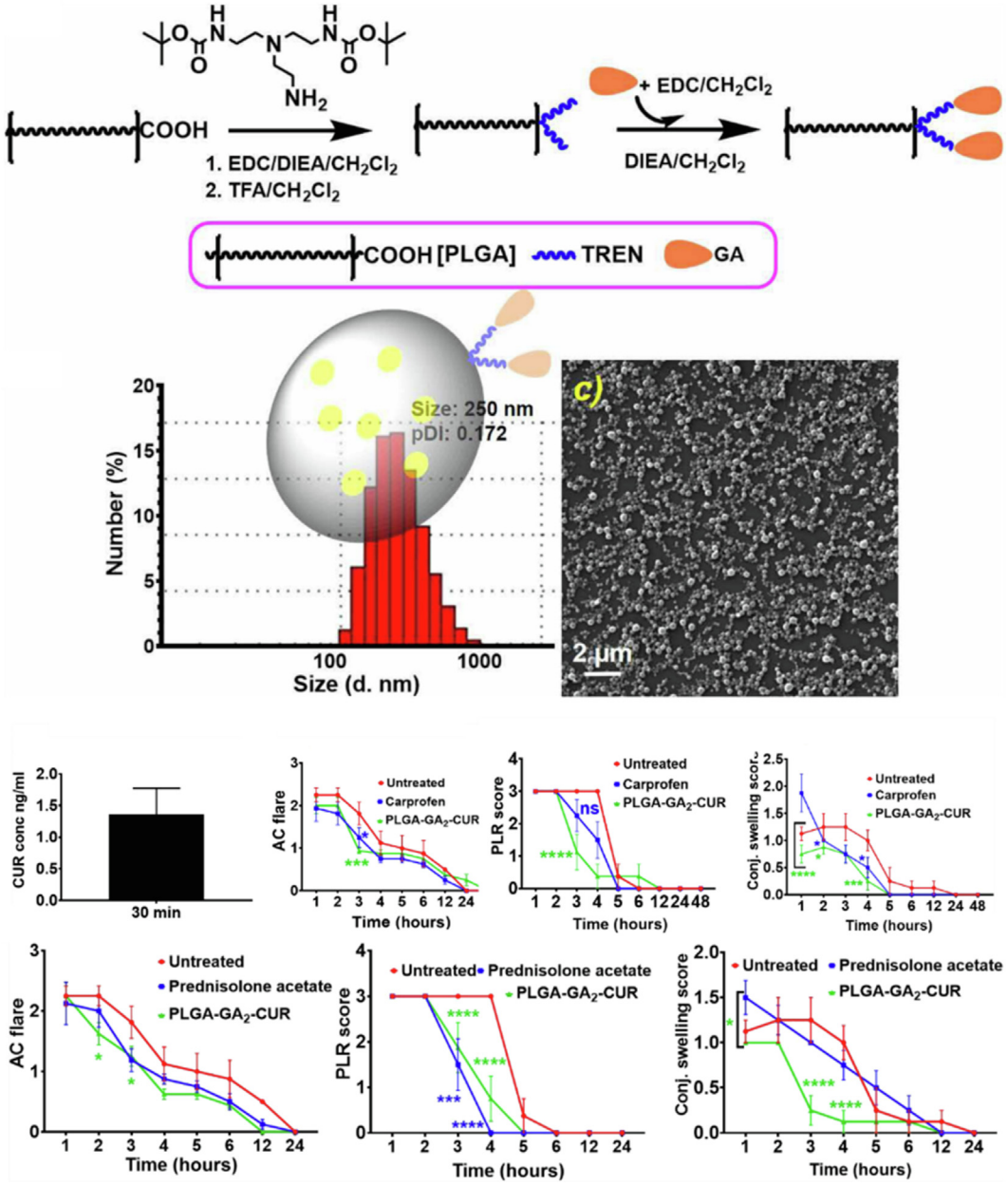


Fig. 15. Oral administration of CUR-PLGA-GA_2 caused remarkable levels of CUR in the aqueous humor and significantly relieved several ocular inflammatory parameters, including aqueous flare, myosis and chemosis [144]. Adapted with permission from ref. [144], Copyright from 2020, American Association for the Advancement of Science. **Abbreviations:** CUR-PLGA-GA_2, curcumin-encapsulated double-headed polyester nanoparticles using gambogic acid-coupled polylactic-co-glycolic acid.

in sodium arachidonate solution (SAS)-induced inflammatory rabbit eyes, suggesting that the novel PVCL-PVA-PEG nanomicelles may serve as potential topical delivery systems for the ocular anti-inflammatory application of CUR [147]. Similarly, another study reported that myricetin (MYR) could be efficiently encapsulated into PVCL-PVA-PEG nanomicelles, presenting enhanced solubility and chemical stability. The MYR-PVCL-PVA-PEG nanomicelles demonstrated great biocompatibility and bioavailability, increased antioxidant activity, and remarkably suppressed SAS-induced ocular inflammation in rabbits [148] (Fig. 16).

4. Challenges in the wide clinical application of NP-based nanomedicine

At present, NP-based nanomedicine resulting from the combination of NPs with nanotechnology has been extensively explored and demonstrated three major prominent advantages, including significantly increased bioavailability, promising ability to target specific sites and controlled release of drugs compared with NPs alone. Compared with inorganic nanomaterials, NP-based nanomedicines demonstrate more abundant chemical structures and adequate preclinical experience, which collectively endow NP-based nanomedicines with great potential for application in clinical practice. Moreover, one certain NP may exert therapeutic effects by acting on various mechanisms rather than only one molecular pathway. This fascinating property confers on NP-based nanomedicine uniqueness that traditional inorganic nanomaterials do not have. Although numerous studies have revealed the efficient experimental therapeutic effects of NP-based nanomedicines in various inflammatory diseases, the wide clinical application of NP-based nanomedicines seems to be difficult. Several challenges remain to be unresolved.

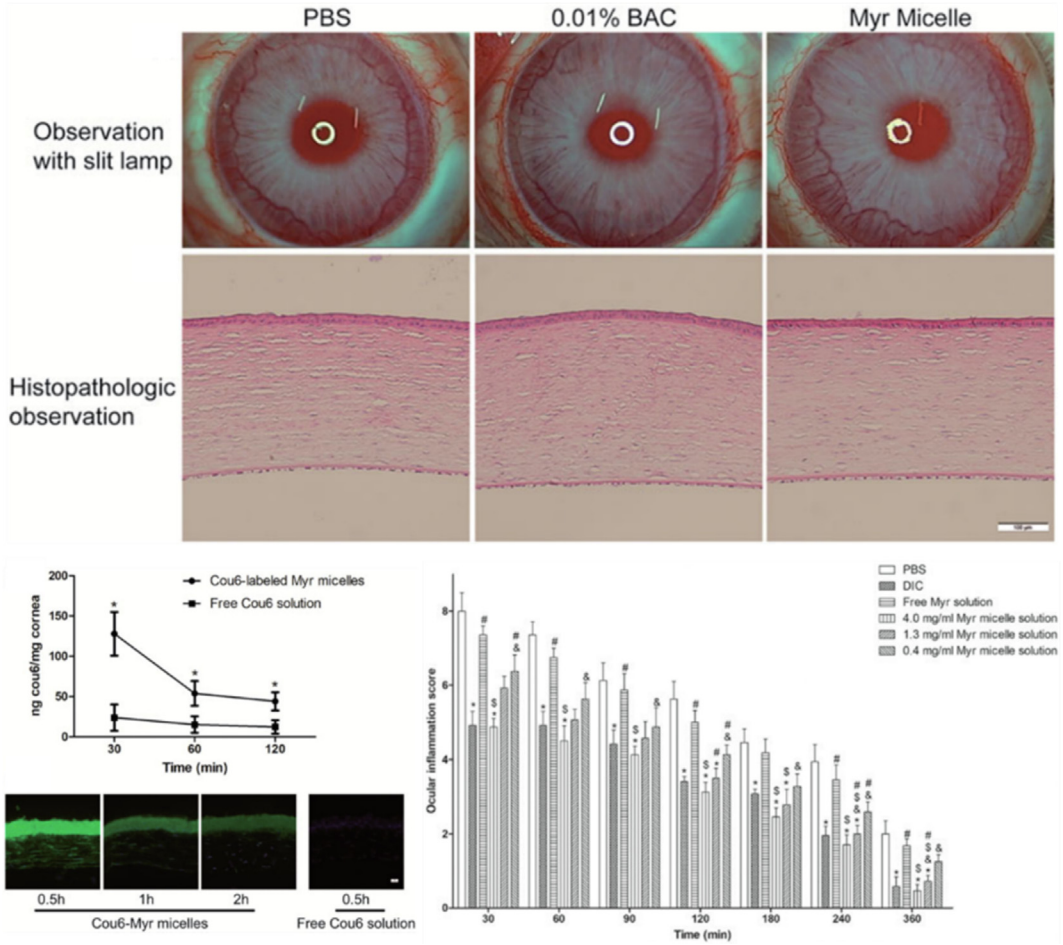


Fig. 16. Topical application of MYR-PVCL-PVA-PEG nanomicelles remarkably improved the corneal permeation capability and suppressed SAS-induced ocular inflammation in rabbits [148]. Adapted with permission from ref. [148], copyright from 2019, Taylor & Francis Group. **Abbreviations:** MYR-PVCL-PVA-PEG nanomicelles, myricetin-polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer nanomicelles; SAS, sodium arachidonate solution.

First, one of the major concerns is the potential toxicity of nanoparticles, particularly for those that could navigate across biological membranes, for instance, the BBB and blood-ocular barriers [124,144]. Although these studies have demonstrated low or no toxicity of the nanoparticles used in *in vitro* or *in vivo* experiments, extensive and comprehensive evaluations are urgently needed. Second, it is known that the ability to target specific sites, resulting in higher therapeutic effects and lower adverse effects, serves as a fascinating merit of nanomedicine. Nevertheless, nanoparticles may undergo changes such as surface shapes, charges and attached ligands when traveling across the body, resulting in impaired bioavailability and targeting capability. Moreover, the immune macrophage system in the spleen and liver could shorten the half-life of nanoparticles; therefore, the nanoparticles may have been degraded before arriving at the target sites. Another advantage of nanomedicine is the controlled release manner of drugs. However, several nanoparticles, such as liposomes, may be difficult to incorporate with releasing drugs in a controlled manner [1,150,151]. Most studies have reported the exceptional experimental therapeutic effects of NP-based nanomedicine; nevertheless, few systemically investigated the possible intrinsic mechanisms responsible for this. Making such a comprehensive exploration is of great necessity and may deepen our understanding of the role of NP-based nanomedicine in disease treatments. Additionally, the observed ideal therapeutic effects of NP-based nanomedicine in animal models cannot represent the actual effects in the human body because of the remarkable genetic and physiological distinctions. There is a tremendous lack of evidence-based clinical data evaluating the actual safety and efficacy of NP-based nanomedicine in patients. It is undeniable that randomized clinical trials (RCTs) are still the gold standard for clinical practice.

Therefore, further exploration should be implemented in these research directions: 1) To comprehensively evaluate the potential toxicity and optimize the treatment protocols, aiming to minimize the toxicity as much as possible; 2) To improve the targeting capability and drug-controlled release manner, aiming to exert the prominent merits of NP-based nanomaterials compared to NP alone; 3) To systematically investigate the possible intrinsic therapeutic mechanisms of these NP-based nanomaterials, aiming to deepen our understanding of the therapeutic effects; 4) To carry out more research, particularly RCTs in human systems, to observe the actual effects of these experimental efficient NP-based nanomaterials, aiming to provide detailed and convincing guidance on clinical practice.

5. Conclusion

The major issue of disease treatments by NPs derived from microorganisms and plants is the poor bioavailability caused by their low solubility and absorption, high metabolism, and large biodistribution. NP-based nanomedicine, essentially the combination of NPs with nanotechnology, seems to open a new door for the application of NPs due to their prominent merits, including a

significant increase in bioavailability, promising ability to target specific sites and controlled release of drugs. The experimental therapeutic effects of NP-based nanomedicines in various inflammatory diseases have been explored extensively and demonstrated ideal results. However, several unresolved challenges, such as potential toxicity, uncertain change in the body, lack of evidence-based clinical data, *etc*., still limite the wide clinical application of NP-based nanomedicine. Undoubtedly, the development of nanotechnology, especially that associated with NP delivery, plus a comprehensive understanding of the intrinsic mechanisms of therapeutic effects of NP-based nanomedicine, as well as abundant evidence-based clinical data, will together improve the therapeutics of inflammatory diseases.

CRediT authorship contribution statement

Fan Cao: Data curation, Formal analysis, Investigation, Methodology, Writing-original draft. **Si-Yu Gui:** Data curation, Formal analysis, Investigation, Methodology, Writing-original draft. **Xiang Gao:** Data curation, Formal analysis, Investigation, Methodology, Writing-original draft. **Wei Zhang:** Software, Visualization. **Zi-Yue Fu:** Software, Visualization. **Li-Ming Tao:** Funding acquisition, Project administration, Supervision. **Zheng-Xuan Jiang:** Funding acquisition, Project administration, Supervision. **Xu-Lin Chen:** Resources, Validation. **Hai-Sheng Qian:** Resources, Validation. **Xian-Wen Wang:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing-review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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