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REVIEW

From Physicochemical Constraints to Clinical Prospects of Celastrol: Challenges and Nano Delivery Strategies

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Abstract: Celastrol (CeT) is the first pentacyclic triterpenoid compound isolated from the root bark of *Tripterygium wilfordii*. It has a broad spectrum of pharmacological activities, including anti-fibrosis, anti-tumor, anti-inflammation, immunomodulation, antioxidation, and neuroprotective effects. Despite the considerable therapeutic potential, the clinical application of CeT has been severely hindered by several inherent limitations, including poor aqueous solubility and permeability, low oral bioavailability, short plasma half-life, cytotoxicity, organ toxicity and so on. In recent years, the rapid development of nanotechnology has provided innovative strategies to address these challenges. The targeted drug delivery system based on nanomaterials can improve the administration defects of CeT and enhance its therapeutic efficacy. This review systematically summarizes the challenges faced by CeT in the drug delivery process, and discusses the latest progress of nanodelivery strategies in overcoming these challenges from both active and passive targeting aspects, including the application of nanosystems such as polymer micelles, liposomes, nanoparticles and nanogels, and other nanosystems, providing references for the further development and clinical application of CeT.

Keywords: celastrol, structural defects, traditional chinese medicine, drug delivery systems, targeted delivery, nanomedicine

Introduction

Celastrol (CeT), also known as tripterine, is a natural pentacyclic triterpenoid compound extracted from the roots of *Tripterygium wilfordii*, a traditional Chinese medicinal herb. Over the past decades, CeT has garnered considerable attention due to its diverse pharmacological activities, including anti-inflammatory, anti-tumor, antioxidant, immunoregulatory, anti-fibrotic, and neuroprotective effects. Mechanistically, CeT modulates a broad spectrum of molecular targets—such as hypoxia-inducible factor-1α (HIF-1α), AMP-activated protein kinase (AMPK), signal transducer and activator of transcription 3 (STAT3), proteasomes, heat shock proteins (HSPs), and matrix metalloproteinases (MMPs)—to regulate key biological processes including metabolism, oxidative stress, immune response, and tumor progression.[1–4]

Despite its promising therapeutic potential, the clinical translation of CeT has been severely hindered by several physicochemical and pharmacokinetic limitations. CeT is practically insoluble in water, exhibits poor oral bioavailability, and has a narrow therapeutic window with potential dose-dependent toxicity. These drawbacks are mainly attributed to its rigid structure and hydrophobic surface chemistry, particularly the presence of functional groups such as C-20 carboxyl, C-3 hydroxyl, and C-29 hydroxyl (Figure 1). Consequently, CeT displays suboptimal absorption and systemic exposure following oral administration.

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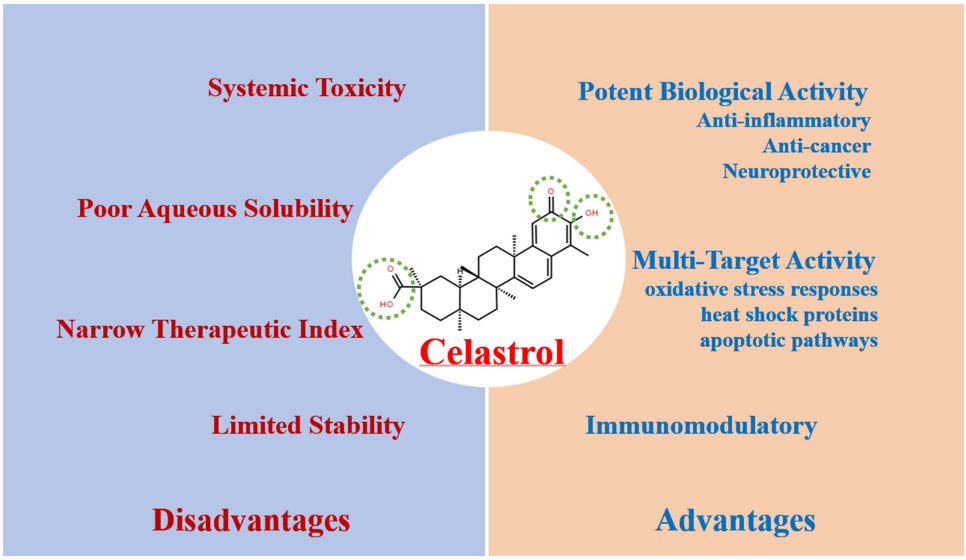

Figure 1 The structure of celastrol and its advantages and disadvantages (Written in Microsoft PowerPoint).

Pharmacokinetic studies across animal models underscore these challenges. In rats, orally administered CeT exhibits a peak plasma concentration (C_{max}) of 66.93 ± 10.28 μg/L, a time to peak (T_{max}) of 6.05 ± 1.12 h, and a clearance rate (CL) of 1.29 ± 0.15 L/h/kg.[5] In comparison, Beagle dogs show lower systemic exposure (Cmax = 35.64 ± 9.54 μg/L) and faster absorption (T_{max} = 2.62 ± 0.69 h).[6] Rabbits display yet another pharmacokinetic profile, with a C_{max} of 149.24 ± 31.21 ng/mL and a T_{max} of only 1.00 ± 0.07 h.[7] These interspecies differences reflect the complexity of CeT metabolism and highlight the necessity for careful formulation and dosing strategies prior to clinical development (Table 1).

To overcome these limitations, researchers have pursued two main strategies. First, chemical modification of CeT—such as introducing hydrophilic moieties like piperazine or polyethylene glycol (PEG)—has improved water solubility, metabolic stability, and safety. Second, nanotechnology-enabled drug delivery systems (NDDSs), including polymeric micelles, liposomes, nanoparticles, and stimuli-responsive carriers, have been developed to enhance CeT's pharmacokinetic behavior and therapeutic index. These nanoformulations enable passive or active tumor targeting, prolonged circulation, and on-demand release in response to tumor-specific stimuli such as low pH, high glutathione (GSH) levels, or elevated temperature.

Our research group has contributed significantly to this field, exploring innovative delivery platforms and biological applications of CeT.[28–30] We have reported glutathione-activated fluorescence probes for CeT-based diagnosis, and engineered CeT nanocarriers capable of inducing lipoautophagy, modulating lipid metabolism, and inhibiting intimal hyperplasia.[31,32] CeT has also shown promise in regulating signaling pathways such as Wnt5a/PKC/mTOR,[33] LXRα/ABCA1,[34] and Wnt/β-catenin[35] in various disease contexts including cardiovascular and renal disorders.

This review aims to systematically summarize (i) the intrinsic structural and physicochemical barriers limiting CeT's druggability, (ii) structure–activity relationship studies and chemical modifications to improve its pharmacological profile, and (iii) the design and optimization of nanocarriers for CeT delivery. Finally, we discuss the translational prospects and remaining challenges for clinical application of CeT-based therapeutics. Beyond nanodelivery, other strategies such as prodrug design and structural modification have also been explored to enhance CeT's efficacy and safety; however, this review will specifically focus on nanocarrier-based systems due to their growing importance and therapeutic promise.

Although CeT has shown good efficacy in preclinical studies, its obvious administration defects represent a critical obstacle to its translation into clinical practice. Consequently, it is an urgent requirement to explore and implement innovative strategies to enhance the performance of CeT.

Table 1 Therapeutic Potential and Mechanism of CeT Based on Animal Models of Various Diseases in vivo Preclinical Studies of CeT: Disease Therapeutic Potential and Pharmacological Mechanisms

Disease	Model	Dosage	Route of Administration	Mechanisms	Ref
Obesity	Diet-induced obesity (DIO) mice	100 μg/kg	Intraperitoneal	CeT improved obesity by activating the hypothalamic leptin receptor-STAT3 pathway to enhance leptin sensitivity and alleviate endoplasmic reticulum stress	[8]
Type 2 diabetes	db/db mice	1.0 mg/kg	Intraperitoneal	CeT suppressed the ChREBP-TXNIP axis, which inhibited gluconogenesis and mitigated, promoted insulin secretion and improved glucose homeostasis	[9]
Colorectal cancer	Nude mice	2 mg/ kg	Inhalation	CeT covalently inhibited peroxidase 1, causing an increase in ROS and leading to cell cycle arrest and apoptosis in colorectal cancer	[10]
Multiple myeloma	Nude mice	0.25 mg/kg	Inhalation	CeT retarded cell cycle arrest at G_1 phase, activated the caspase 3 and NF-kappa B pathway, inhibiting the proliferation and migration of multiple myeloma cell and promoting apoptosis	[11]
Rheumatoid arthritis	C57BL/6 mice	1 mg/kg	Intraperitoneal	CeT covalently bound and dissociated the copper metabolizing MURR1 domain (COMMD) protein 3/8 complex, thereby inhibiting humoral immune and autoimmune responses	[12]
Systemic sclerosis	C57BL6J mice	2 mg/kg	Intraperitoneal	CeT blocked the expression of TGF-β1 protein and the nuclear localization of YAP, antagonized YAP pathway, thus reducing the sustained fibrosis of skin fibroblasts	[13]
Psoriasis	BALB/c mice	20 mg/kg	Per os	CeT inhibited the activation of NF-κB pathway, simultaneously suppressed STIm1-Orai1-mediated calcium influx into keratinocytes and immune cells to improve psoriasis	[14]
Arterial/venous thrombosis	C57BL/6 mice	2 mg/kg	Intraperitoneal	CeT reduced collagen-associated peptide (CRP) or thrombine-induced platelet aggregation, thereby prolongating bleeding time and inhibiting arterial/ venous thrombosis formation	[15]
Acute liver injury	Ppara $^{-/-}$ mice	10 mg/kg	Intraperitoneal	CeT activated PPARα signaling and suppressed the expression of proinflammatory cytokines TNF- α and Egr 1 and oxidative stress response to protect against acute liver injury	[16]
Acute kidney injury	C57BL/6 mice	1 mg/kg	Intraperitoneal	CeT activated the Nrf2/GPX4 pathway to inhibit ferroptosis and reduce LDH release, thereby mitigating renal tubular cell death, inflammation, and oxidative stress	[17]
Alzheimer's disease	P301S Tau transgenic mice 3xTg mice	2 mg/kg	Per os	CeT promoted the degradation of phosphorylated Tau aggregates and significantly improved memory deficit by activating autophagy mediated by the transcription factor EB	[18]
Parkinson's disease	Nrf2-KO mice NLRP3-KO mice Caspase1-KO mice	10 μg/ kg	Intraperitoneal	CeT inhibited NLRP3 inflammasome activation through the Nrf 2-NLRP 3-caspase-1 pathway, and prevented the loss of dopaminergic neurons, reduced neuroinflammation, thereby alleviating movement disorders	[19]
Spinal injury	Wistar rat	1 mg/kg	Intraperitoneal	CeT reduced the production of lipid ROS by upregulating the Nrf 2-xCT-GPX 4 axis, protected the survival of oligodendrocytes and inhibited ferroptosis to repair spinal cord injury	[20]
Secondary brain injury	C57BL/6J mice	2 mg/kg	Intraperitoneal	CeT counteracted the interaction between cAAP activated exchange protein-1 (EPAC-1) and voltage dependent anion selective channel protein 1 (VDAC-1) by downregulating its activity, thereby improving neuronal mitochondrial dysfunction	[21]
Aspergillus fumigatus keratitis	C57BL/6 mice	1 μg/μL	Subconjuncti-val injection	CeT decreased the production of pro-inflammatory mediators IL-1β, TNF- α and MIP-2, and downregulated the expression of lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1) to alleviate aspergillus fumigatus keratitis	[22]

(*Continued*)

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Table 1 (Continued).

Disease	Model	Dosage	Route of Administration	Mechanisms	Ref
Osteoarthritis	SD rat	1 mg/kg	Intra-articular injection	CeT suppressed TLR 2 / NF- κB signaling, reduced the production of inflammatory factors such as COX 2, IL-6, PEG 2; leading to the reduction of osteophyte formation and bone resorption, thereby relieving cartilage damage	[23]
Uveitis	Lewis rat	1 mg/kg	Intraperitonea	CeT reduced the retinal infiltration of Th17 cells via blocking the STAT3-IL17 pathway; and repressed the migration of inflammatory cells as well as the pathological glial response of the retina, thereby mitigating uveitis	[24]
Rosacea	BALB/c mice	2 mg/kg	Intraperitonea	CeT attenuated Th17 immune response to inhibit skin angiogenesis, simultaneously suppressed Ca^{2+} / CaMKII- mTOR-NF- κB pathway to alleviate skin inflammation	[25]
Hepatic fibrosis	C57BL/6 mice	1.0 mg/kg	Intraperitoneal	CeT modulated the antioxidant activity of peroxidase, and up-regulated the expression of heme oxygenase-1 in activated hematopoietic stem cells, increased cellular ROS levels, and induced ferroptosis of hepatic stellate cells, thereby mitigating liver fibrosis	[26]
Subconjuncti-val fibrosis	New Zealand white rabbit	0.125 μg/mL	Subconjuncti-val injection	CeT inhibited TGF-β1- induced activation of HPFs reduced collagen deposition, and prevented subconjunctival fibrosis by blocking TGF-β1/Smad2/ 3-YAP/TAZ signaling pathway	[27]

Defects and Analysis of Celastrol Administration

Poor Aqueous Solubility of CeT

At 37 °C, the aqueous solubility of CeT is only 13.25 ± 0.83 μg/mL, demonstrating strong hydrophobicity and resulting in low intestinal absorption efficiency. The poor water solubility of CeT is mainly attributed to its rigid pentacyclic triterpenoid structure, which contains a large number of nonpolar carbon atoms and a limited number of hydrophilic functional groups. Although CeT possesses polar moieties such as the C-3 and C-29 hydroxyl groups and a C-20 carboxyl group, they are insufficient to offset the overall hydrophobicity of the molecular backbone. Furthermore, the intramolecular hydrogen bonding and planar conjugated system contribute to poor interaction with aqueous environments, further reducing solubility.

Due to this low solubility, CeT shows minimal cytotoxicity toward human umbilical vein endothelial cells (HUVECs) at nanomolar concentrations (200 nmol/L or below) in vitro. However, it begins to suppress HUVEC proliferation at concentrations exceeding 600 nM and induces overt cytotoxicity above 1 μM.[36] In vivo studies have further confirmed that excessive doses of CeT (7.5 mg/kg or above) can cause toxic reactions such as thymocyte necrosis, hepatocellular infiltration, and bile duct hyperplasia in rats.[37]

Structural modifications to improve aqueous solubility have been explored. For example, the introduction of hydrophilic moieties, such as piperazine or polyethylene glycol (PEG), at the C-3, C-20,[38] or C-29[39] positions has been shown to increase hydrophilicity and improve solubility, offering a promising strategy to enhance the bioavailability and reduce the toxicity of CeT.

Low Oral Bioavailability of CeT

At present, researches on oral bioavailability of CeT mainly use dog and mouse models.[40] The C_{max} value for a single oral CeT ranges from 0.031 to 0.497 μM. Pharmacokinetic analysis showed that the Cmax value of intravenous injection of CeT was 1701.3 ± 170.7 ng/mL, while that of single oral administration of CeT was only 35.1 ± 7.9 ng/mL, which is about 1/50 of that of intravenous injection, indicating low oral absorption efficiency of CET.[41] Notably, the oral absolute bioavailability of CeT in the rat model is only 17.06 %, and there is a significant gender difference: the absorption efficiency of female rats is significantly better than that of male rats,[42] which may be related to the differences in the

expression and activity of CYP450 enzymes (CYP3A and CYP2C) between the sexes.[43] However, in the beagle model, there was no obvious difference in pharmacokinetic parameters between the two groups.[6]

Generally, the low oral bioavailability of CeT is mainly attributed to the first-pass elimination effect, in which part of the drug is metabolized or broken down when passing through the gastrointestinal tract and liver, thus limiting its absorption efficiency in the gastrointestinal tract, which results in the distribution of its metabolites almost exclusively in the urine. The underlying mechanism of this phenomenon is that the body metabolizes CeT into highly polar II binding products through methylation reactions to reduce its potential toxicity,[44] resulting in a decrease in the amount of drugs entering the bloodstream, and thus weakening the therapeutic effect of CeT.

Short Plasma Half-Life of CeT

The short plasma half-life of CeT means that it is drug rapidly eliminated in the body. The elimination half-life of 1 mg/kg CeT orally in rats is 7.82 ± 1.31 h.[45] In the Beagle model, the elimination half-life of CeT suspension at an oral dose of 1.5 mg/kg is only 1.60 ± 0.13 h;[46] the elimination half-life of oral CeT tablets (1 tablet/kg) is 2.93 ± 0.29 h.[6] The short plasma half-life of CeT may be related to its low membrane affinity[47] and its ability to block the efflux transport mechanism mediated by the intestinal membrane efflux transporter P-glycoprotein (P-gp), an energy dependent efflux pump that can recognize and bind to a variety of substrates with different structures and functions, including drugs, toxins, hormones, etc. It utilizes the energy generated by ATP hydrolysis to transport these substrates from inside the cell to outside, thereby reducing the concentration of substrates inside the cell. Studies have demonstrated that CeT is a substrate for P-gp. After CeT is absorbed by intestinal epithelial cells, P-gp expressed in the gut will pump it out of the cells, hindering the absorption of CeT in the intestine.[48] Additionally, the low water solubility of CeT itself not only limits its absorption by the intestinal mucosa, but also restricts its dissolution and distribution in the body, further shortening the plasma half-life.

Organ Toxicity of CeT

CeT has potent toxic effects, which can abrogate cell proliferation, and induce cell cycle arrest and cell apoptosis. The mechanism of toxicity is that the hydroxyl group of CeT C-3 can excessively activate Caspase-3 protein, promote non-selectively inhibition of normal cell proliferation by Caspase-3, and trigger cell apoptosis.[49] Meanwhile, the C-2, C-3 and C-6 sites are also closely related to the cytotoxicity of CeT, and different structural modifications of these sites can significantly affect their anti-proliferation activity. For example, acetylation of C-2 and C-3 sites of CeT shows stronger cytotoxicity than propionation; the sulfonation and vulcanization modifications of C-6 can enhance the cytotoxicity, while the carbonization modification can dramatically reduce the toxicity.[38] The existing research results have confirmed that CeT has cardiotoxicity, hematopoietic toxicity, reproductive toxicity, hepatotoxicity, and nephrotoxicity.

Cardiotoxicity

CeT has shown cardiotoxic effects in different animal models (such as mice, zebrafish, rats, etc). In a mouse model, after two weeks of CeT administration at a medium dose (2 mg/kg/day) and a high dose (4 mg/kg every 2 days), a decrease in heart weight and systolic function was observed, and CeT induced myocardial damage and cardiac dysfunction exhibited significantly dose-dependent effects.[50] In zebrafish embryo development experiments, treatment with 0.5 μM or higher concentration of CeT can lead to abnormal embryo development, and embryos treated with 1.5 μM CeT showed severe pericardial edema 72 hours after fertilization, indicating that CeT may interfere with normal heart development.[51] After continuous intraperitoneal injection of CeT in rats for 7 days, different dose treatment groups showed varying degrees of cardiac damage: the low-dose group (0.5 mg/kg/d) showed inflammatory cell infiltration in the cardiac pathological section. In the medium dose group (1 mg/kg/d), vacuolar degeneration and acidophilic degeneration of myocardial cells were observed. The high-dose group (2 mg/kg/d) showed the most serious lesions, exhibiting various pathological features such as myocardial vacuolar degeneration, eosinophilic degeneration, interstitial congestion, and lymphocyte infiltration.[52] This cardiac toxicity may be related to the long-term retention of CeT in the potassium ion channel pore region of the human ether associated gene (hERG), which elicits a strong inhibitory effect on it, and thus interferes with the generation of cardiac action potentials.[53]

Hematopoietic Toxicity

CeT at a certain concentration has an inhibitory effect on bone marrow hematopoietic function. To evaluate the hematopoietic toxicity of CeT, mice were intraperitoneously injected with varying doses (0.01, 0.1, 1, or 5 mg/kg/d) of CeT for four consecutive days. The high-dose group (5 mg/kg/d) of CeT displayed characteristic toxic symptoms, including hunched posture and wrinkled hair. Both B cells and T cells originate from hematopoietic stem cells and play an important role in maintaining the homeostasis of the hematopoietic system. Further investigations have found that CeT treatment significantly reduces specific cell populations in the hematopoietic system, including the number of immature B cells, B-1 cells, and ordinary myeloid progenitor cells, indicating that CeT has a noticeable damaging effect on the hematopoietic system.[54] Moreover, it was found that CeT at a dose of 5.0 mg/kg can decrease the number of activated B cells in mice and promote T cell apoptosis.[55] So far, the toxic mechanism of CeT on the hematopoietic system has been reasonably explained from the following two aspects: On the one hand, CeT directly binds to IL-2, modulates its mediated STAT5 phosphorylation, thus blocking IL-2 dependent T cell proliferation and signaling transduction, resulting in impaired T cell function;[56] On the other hand, NF-κB plays a crucial anti-apoptotic role in B cells, and CeT induces B cell apoptosis by inhibiting the NF-κB pathway.[57] The dual mechanisms mentioned above collectively contribute to the hematopoietic toxicity of CeT administration.

Reproductive Toxicity of CeT

CeT exerts a significant inhibitory effect on the reproductive system at a certain dose. In the male reproductive system, 5 μg/mL CeT can suppress sperm function in guinea pigs in a concentration-dependent manner;[58] CeT (0.5 μg/mL and above) can severely block the acrosomal reaction of mouse sperm.[59] In terms of the female reproductive system, after two consecutive weeks of intraperitoneal injection of CeT (1 and 4 mg/kg), female mice showed obvious reproductive toxicity: reduced ovarian weight, decreased number of follicles at all levels, and increased follicular degeneration rate, The high-dose group (4 mg/kg) had a stronger regulatory effect on ovarian weight. CeT treatment also led to a decrease in serum levels of estradiol and progesterone, which further promoted premature ovarian failure and granulosa cell apoptosis.[60] Ca^{2+}, as an intracellular second messenger, plays a key role in the regulation of reproductive functions such as sperm-oocyte interactions. CeT interferes with Ca^{2+}-mediated signaling and function in germ cells by irreversibly blocking T-type calcium channels and antagonizing Ca^{2+} influx. This may partially represent the pivotal mechanism for the reproductive toxicity of CeT.[59]

Hepatotoxicity of CeT

CeT has a dose-dependent toxic effect on primary rat hepatocytes, with minimal toxicity observed at concentrations of 1 μM and below. However, as the concentration of CeT increased from 1μM to 30μM, hepatocyte vitality showed a remarkable downward trend, accompanied by elevated production of reactive oxygen species and decreased mitochondrial membrane potential, leading to severe hepatocyte injury.[61] Through the detection of liver injury markers in the plasma of rats, it was found that the levels of aspartate aminotransferase (AST) were significantly increased in the CeT treatment group, but there was no significant change in the levels of alanine aminotransferase (ALT). In addition, rats treated with high dose (1.8 mg/kg) CeT showed obvious liver pathological changes, including characteristic lesions such as hepatocyte vacuolation, mild cytoplasmic swelling, infiltration of hepatosinusitis cells, and some hepatocyte degeneration, further validating the hepatotoxicity of CeT.[62]

What is interesting in the toxic analysis of CeT is the potential ameliorative effect of CeT on hepatotoxicity induced by acetaminophen (APAP) at 100 nM and above.[63] Whether used alone or in combination with bright blue G (BBG), CeT can effectively attenuate APAP-induced hepatocyte damage and death.[64] It is worth noting that although the promotion of hepatocyte proliferation by CeT alone is weak, it can significantly enhance the nuclear expression of proliferating cell nuclear antigen (PCNA) when combined with BBG, indicating that CeT synergistically accelerates hepatocyte regeneration. These studies reveal that CeT exerts dual effects on the liver, so precise dose optimization or reasonable drug combinations can transform its hepatotoxicity into hepatoprotective effects. The hepatotoxicity caused by CeT may be closely related to its inhibition of liver CYP450 metabolic enzyme activity, leading to its accumulation in liver cells.[61] Nevertheless, CeT mitigates APAP-induced inflammatory cell infiltration by inhibiting the NF-κB pathway.

Simultaneously, the activities of glutathione peroxidase (GPX), glutathione reductase, superoxide dismutase, and catalase increased, showing antioxidant effects, thereby reducing APAP-induced lipid peroxidation and protein carbonization, increasing the content of glutathione (GSH) in the hepatocyte, and enhancing its antioxidant capacity.[63] The interplay of these mechanisms may represent an effective strategy for converting the hepatotoxicity of CeT into hepatoprotective effects.

Nephrotoxicity of CeT

CeT has shown obvious nephrotoxicity in animal experiments at certain doses. In a mouse model of sepsis induced by lipopolysaccharide (LPS), the CeT treatment group (1.5 mg/kg) exhibited more severe renal injury characteristics than the control group: manifested as aggravated destruction of renal tubule structure, accompanied by increased oxidative stress and inflammatory response, suggesting that CeT may exacerbate LPS-induced acute kidney injury (AKI).[65]

Similar to its dual effects on the liver, CeT (1 mg/kg) also displayed renal protective properties. However, there is a clear difference in the dosage required for CeT to exert its protective effect in the liver and kidneys, which may be related to its metabolic profile. As the main organ for CeT metabolism, the liver requires a higher dose to achieve an effective protective concentration in order to overcome its rapid metabolism and clearance effects. In contrast, the kidneys have a powerful ability to uptake and accumulate CeT, and lower doses can also achieve effective therapeutic concentrations. Mechanistically, CeT suppresses the activation of the SMAD family member 3 (Smad3) signaling pathway, and upregulates the expression of cannabinoid receptor 2 (CB2R), thereby effectively alleviating renal fibrosis caused by unilateral ureteral obstruction in mice, improving renal function injury.[66] Furthermore, cisplatin aggravates tubular cell damage by impeding Nrf2 expression, leading to increased oxidative stress and ferroptosis. CeT can inhibit ROS accumulation and ferroptosis process by up-regulating NrF2-mediated GPX4, restore renal function, and have a mighty therapeutic effect on cisplatin induced AKI.[17]

From the perspective of the structure-activity relationship, the C-29 carboxyl group has been identified as the critical active site responsible for the renal protection of CeT. Through coupling modification of the C-29 carboxyl group, CeT not only significantly promotes the functional recovery after renal ischemic injury and maintains its renal protective effect, but also markedly reduces toxicity compared to the parent compound. Collectively, these modified products have dramatically lowered toxicity to the blood system, reproductive system, liver and kidney, and have better safety characteristics.[62]

Improvement Strategies for the Toxicity of CeT

The obvious drug administration defects of CeT limit its further development and utilization. Among the current solutions to improve the delivery defects of CeT, the research and design of a targeted drug delivery system (TDDS) based on nanomaterial is one of the most feasible strategies. As an important type of novel drug delivery system, nanosystems, including polymer micelles, liposomes, microemulsions and nanogels (particle size distribution 50~300 nm) play an important role in targeted drug delivery,[67] which can effectively improve the targeted delivery capability of CeT, improve bioavailability, and prolong systemic circulation time. Therefore, promoting the distribution and cellular uptake of CeT in focal tissues can achieve synergistic sensitization and attenuation of toxicity. At present, nanomedicine is harnessing the power of nanotechnology to demonstrate excellent performance, such as the ability to carry drugs with different solubilities and improve pharmacokinetic and pharmacodynamic properties without any chemical modifications to therapeutic drugs.[68,69] Given the drawbacks of CeT, some of the above issues can be overcome by improving the dosage form or changing the administration method. This strategy provides new ideas and solutions for breaking through the drug delivery barriers of CeT, and lays a solid foundation for further expanding its clinical application scope.

Passive Targeted Drug Delivery System for CeT

CeT Delivery Based on Polymer Micelle

Polymer micelles (PMs) are nanoscale structures that self-assemble in solution when an amphiphilic block or graft copolymers reach a critical concentration, known as the critical micelle concentration (CMC).[70] These micelles have a distinctive core-shell structure, with hydrophobic polymer chains forming the core and hydrophilic chains shaping the

protective outer shell. This unique structure makes PMs particularly suitable for encapsulating hydrophobic drugs, offering protection from enzymatic degradation and increasing their solubility in aqueous environments.[71] The advantages of PMs, including reduced drug toxicity, prolonged circulation time, and selective tumor accumulation, make it a key focus in anticancer drug delivery research field. Generally, the diameter of PM is less than 100 nm. PMs with a dense polyethylene glycol (PEG) shell have been shown to evade detection by the reticuloendothelial system (RES) and preferentially accumulate in solid tumors through enhanced permeability and retention (EPR) effect.[72] The EPR effect refers to the selective accumulation of macromolecules or nanoparticles in tumor tissues following intravenous injection, with minimal distribution to healthy tissues.[73] This phenomenon arises from the leaky vasculature and impaired lymphatic drainage typical of solid tumors, which enable nanoparticles such as polymeric micelles (PMs) to extravasate and remain within the tumor microenvironment. In addition, physicochemical parameters—such as particle size, shape, and surface properties—critically influence the extent of tumor accumulation.[74] Several studies have shown that encapsulating CeT in PMs significantly enhances its antitumor efficacy relative to the free drug, while also improving pharmacokinetic profiles, reducing systemic toxicity, and increasing therapeutic index.[75–77]

However, it is important to note that the EPR effect alone may not be universally effective across all tumor types. Significant inter- and intra-tumoral heterogeneity in vascular permeability, blood flow, and stromal composition can lead to variable and sometimes insufficient nanoparticle accumulation. These factors limit the consistency and predictability of passive targeting based solely on the EPR effect. Therefore, combining EPR-based accumulation with additional strategies—such as active targeting ligands or stimuli-responsive release mechanisms—may be necessary to achieve optimal delivery efficiency in heterogeneous tumor environments.

PEG is one of the most widely used materials in PMs, which can be combined with other polymers such as poly (ε-caprolactone) (PCL) and has both hydrophilicity and biodegradability. The incorporation of PEG into PMs also exhibits stealth properties, reducing protein adsorption and immune recognition, thereby prolonging circulation time in the blood. Zhao et al,[78] incorporated CeT into PEG-PCL nanoparticles and demonstrated anti-inflammatory and anti-obesity effects by suppressing M1 macrophage polarization while preserving M2 macrophage phenotype. Similarly, Li et al[79] encapsulated CeT in PEG-PCL nanoparticles, and further demonstrated its ability to inhibit macrophage infiltration in rat corneas using CNPs (encapsulated CeT in PEG-PCL nanoparticles),[80] PEG-PCL nanoparticles improve the solubility and stability of CeT in biological systems, allowing for more effective and uniform distribution in tissues compared to free CeT. The encapsulation of PEG-PCL nanoparticles minimizes the possibility of direct exposure of CeT to non-target tissues, reduces the likelihood of side effects, and downregulation of the expressions of vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9), and effectively prevent suture-induced corneal neovascularization (CNV).[81,82] These studies indicate the versatility of CeT-loaded PMs not only in cancer treatment but also in managing inflammatory response and promoting tissue regeneration.

In the human retinoblastoma xenograft model of NOD-SCID mice, CNPs exhibited significant inhibitory effects on retinoblastoma. This highlights the potential of CeT-loaded PMs in the prevention of ocular tumors, where targeted drug delivery is important for treating sensitive tissues with minimal toxicity. Meanwhile, Allen et al[83] found that the encapsulation of CeT in poly (ethylene glycol)-b-poly (propylene sulfide) (PEG-b-PPS) micelles dramatically reduced the cytotoxicity and the number of neutrophils and inflammatory monocytes in atherosclerotic plaques in $LDLR^{-/-}$ mice compared to unencapsulated CeT. The application of PEG-b-PPS micelles for CeT delivery extends the therapeutic scope of CeT beyond cancer therapy, demonstrating its potential in preventing cardiovascular diseases.

PEG and its derivatives are widely utilized in drug delivery systems due to their diverse physicochemical properties, making them highly versatile drug carriers. A research team led by Zhang et al[84] used PEG, PEG-conjugated octadecylamine (PEG-C18), and triethylene glycol (TEG) as nanocarriers for encapsulating CeT. Their findings further revealed that PEG-C_{18}/CeT and PEG/CeT exhibited superior encapsulation abilities for CeT. Based on the release profiles, PEG/CeT had the slowest release rate, while TEG/CeT released CeT at a relatively faster rate. These data suggest that the rate of CeT release from PMs can be fine-tuned by modifying the PEG derivatives, enabling the customization of controlled drug release profiles according to specific therapeutic requirements. Based on their release

rates, PEG-C18/CeT and TEG/CeT exhibited a higher level of cytotoxicity, indicating the importance of optimizing the encapsulation efficiency and release kinetics in CeT-based formulations.

In addition to modulating drug release kinetics, PEG can also be used for material functionalization, broadening its potential for advanced applications. Song et al[85] developed a novel drug delivery system using PEGylated reduced graphene oxide (rGO)-PEG/CeT, which avoids recognition by the reticuloendothelial system through PEGylation, and achieves effective synergistic chemo/photothermal therapy. Compared with single chemotherapy or photothermal therapy, rGO-PEG/CeT exhibited enhanced tumor-killing ability and significantly inhibited tumor metastasis. PEGylation not only increased the water solubility of CeT, but also elevated its systemic circulation and tumor-targeting capabilities through the EPR effects. A PEG derivative (DC1000) is self-assembled into nanoparticles in water, producing various beneficial effects.[39] These nanoparticles showed better drug loading capacity and stability, surpassing traditional polymer micelles in terms of drug encapsulation and structural stability. With these features, PEGylated nanoparticles enable more efficient delivery and sustained release of CeT, providing significant advantages for anti-tumor therapy. By incorporating near-infrared dyes, Xie et al[86] developed a nanomedicine. This is a self-assembled nanoparticles (NPs) encapsulating CeT through the integration of disulfide bonds and intermolecular π-π interactions. Upon administration, this nanomedicine accumulated in the tumor area of mice with non-small cell lung cancer (NSCLC), releasing drugs to suppress tumor growth while facilitating fluorescence and photoacoustic imaging, thereby elevating the multifunctionality of the delivery system.

Although polymeric micelles (PMs) have demonstrated significant potential in enhancing the therapeutic efficacy of CeT—notably by improving its aqueous solubility, reducing systemic toxicity, and passively targeting tumors via the enhanced permeability and retention (EPR) effect—several limitations still hinder their clinical translation. Most notably, conventional PMs often suffer from low drug-loading capacity and structural instability under physiological conditions, leading to premature drug release and reduced bioavailability. To address these issues, recent studies have explored strategies such as introducing π–π stacking or hydrogen bonding interactions between CeT and core-forming polymers, thereby enhancing micelle stability and loading efficiency. Additionally, core-crosslinking using disulfide bonds or pH-sensitive linkages has been shown to stabilize micelle architecture during circulation while enabling triggered release in the reductive or acidic tumor microenvironment. Compared to other nanocarriers, PMs offer advantages such as ease of self-assembly and scalability; however, they typically lack active targeting capability and are more prone to dilution-induced disassembly in vivo. Future research should focus on developing hybrid micelle systems with improved structural integrity, responsive release profiles, and potential for ligand-mediated active targeting, thereby expanding the applicability of PMs as a robust platform for CeT delivery (Figure 2).

CeT Delivery Based on Liposomes

Liposome-based CeT delivery is regarded as one of the most advanced nanocarrier systems, typically utilizing particle sizes ranging from 50 to 200 nm.[87] Owing to its unique lipid bilayer structure, water-soluble drugs are encapsulated in the aqueous core, whereas lipophilic drugs are entrapped within the bilayers.[88] The amphiphilicity, biocompatibility, and biodegradability of liposomes confer several advantages for delivering traditional Chinese medicine (TCM) components, including enhanced efficacy, improved safety, increased bioavailability, sustained release, and targeted drug delivery. In our research group, we innovatively used the Hep1-6 cell membrane and hyaluronic acid to wrap CeT and successfully prepared liposome HMCLPS. This delivery platform offers multiple advantages, including controlled drug release, enhanced targeting, and excellent immunocompatibility, providing a new strategy for targeted therapy of liver cancer. Through this technology, the delivery efficiency and therapeutic effectiveness of CeT have been significantly improved, while reducing potential toxic side effects.[89]

Liposomes are usually composed of phospholipids and cholesterol. Common preparation methods include thin-film dispersion, reverse-phase evaporation, chemical gradient, double emulsion, and solvent injection techniques. Zhang et al[90] developed CeT-loaded liposomal nanoparticles (CeT-LN) by dispersing a mixture of CeT, lecithin, sodium oleate, and soybean oil ethanol into water. In simulated physiological fluids, the release rate of CeT remains below 0.2 %, which helps to increase oral bioavailability. The sustained-release properties not only improve the pharmacokinetics of CeT, but may also reduce systemic toxicity, which is a key consideration for its broader therapeutic applications. In addition, the

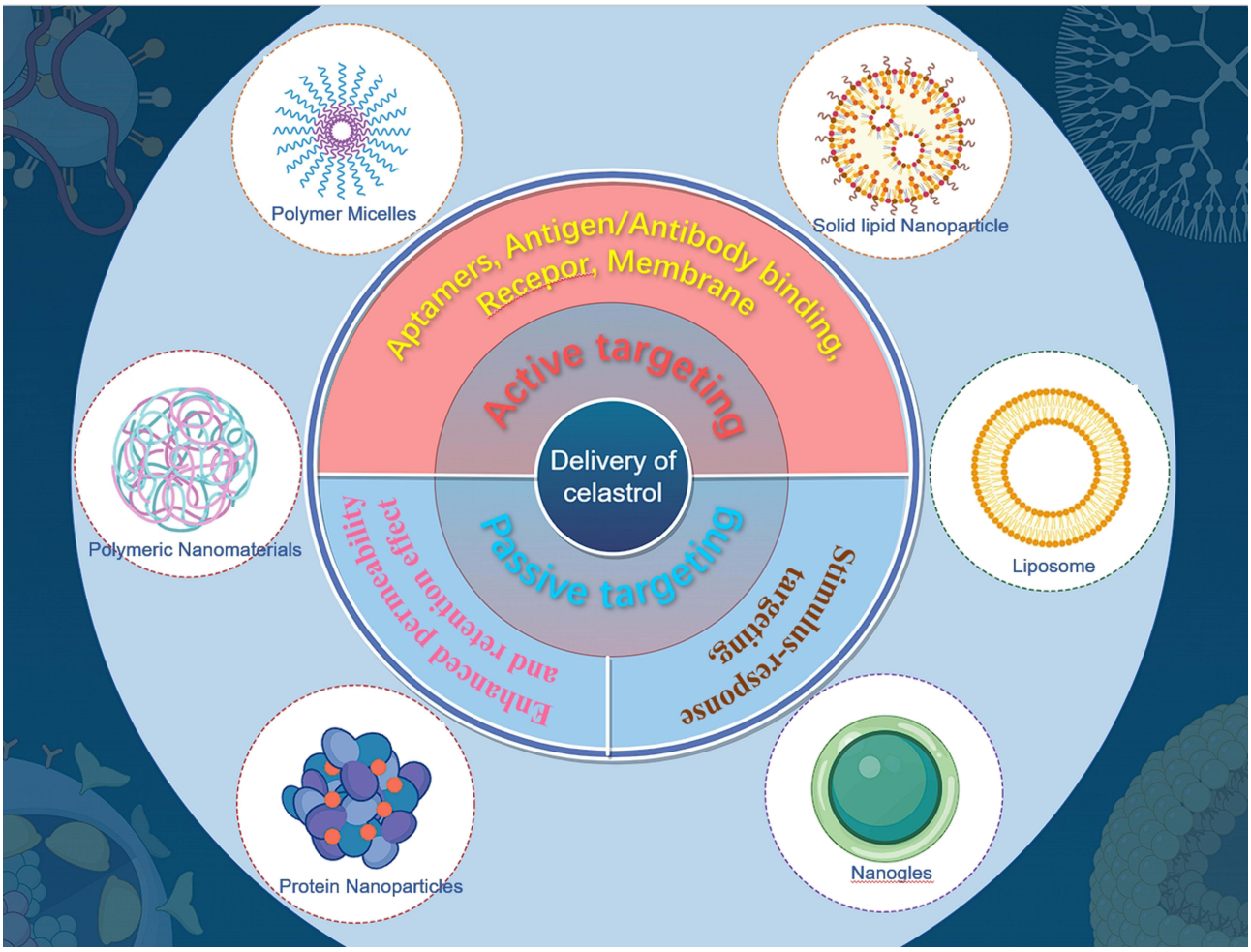

Figure 2 Schematic diagram of CeT targeted preparation classification. The active and passive targeting strategies used to deliver celastrol through different nanocarrier systems. The internal red ring highlights active targeting strategies that utilize specific interactions, such as aptamers, antigen/antibody binding, receptor-mediated uptake, and membrane targeting. The nanocarriers that support active targeting for celastrol include polymer Micelles, solid lipid nanoparticles, liposomes. The blue section represents passive targeting strategies that utilizes EPR effect and tumor microenvironment-specific features. Nanocarriers facilitating the passive targeting of celastrol include polymeric nanomaterials, protein nanoparticles, and nanogels. The combination of active and passive targeting in these nanocarriers improves therapeutic efficacy and minimizes off-target effects of celastrol, demonstrating the versatile approach of nanomedicine in treating complex diseases such as cancers (Written in Microsoft PowerPoint).

surface charge of liposomes plays a crucial role in drug delivery, affecting the skin penetration and therapeutic efficacy of CeT. The negatively charged nanostructured lipid carriers (NLCs) loaded with cationic CeT exhibit enhanced transdermal permeability and anti-melanoma efficacy, with notable advantages compared to free CeT. These findings indicate the importance of optimizing physical and chemical properties, such as particle charge, to improve drug bioavailability and efficacy.[91]

Altering the composition of liposome allows for functional modification. For instance, Chen et al[92] have developed galactosylated liposomes modified with 1,2-dipalmitoyl-sn-glycero-3- phosphoethanolamine-polyethylene glycol (C-GPL) to enhance the water solubility of CeT, achieving high encapsulation efficiency, serum stability, and drug controlled release. This modification can also improve circulation time and reduce the clearance rate of the reticuloendothelial system (RES). In addition, peptide-conjugated phospholipid nanoparticles (PC-PLNs) were designed to target CeT to damaged endothelial cells and podocytes in the glomerulus.[93] By increasing endothelial nitric oxide synthase (eNOS) to augment nitric oxide (NO) levels and suppressing vascular cell adhesion molecule-1 (VCAM-1) expression, this system exerts anti-inflammatory effects to alleviate endothelial damage.[94,95]

Taken together, liposomes are widely regarded as one of the most promising nanocarriers in drug delivery due to their excellent biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and hydrophobic drugs. In the

context of celastrol (CeT), liposomal formulations have demonstrated improved aqueous dispersibility, prolonged circulation time via PEGylation, and enhanced accumulation at tumor sites through the EPR effect. Moreover, stimuli-responsive liposomes—engineered to respond to pH, redox potential, or enzymatic activity—have shown great potential in achieving site-specific and controlled drug release, thereby improving therapeutic index while minimizing off-target toxicity. However, one of the major challenges remains the limited encapsulation efficiency of CeT, primarily due to its poor aqueous solubility and rigid planar structure. This issue is often exacerbated by the choice of preparation method (eg, thin-film hydration vs ethanol injection) and lipid composition. To address this, recent advances have included the use of cholesterol to modulate membrane fluidity, incorporation of charged lipids (eg, DOTAP or DSPE-PEG) to enhance drug-lipid interactions, and co-loading with phospholipid-compatible synergistic agents from traditional Chinese medicine (TCM). Compared with polymeric micelles, liposomes offer superior biocompatibility and lower systemic toxicity, but generally exhibit less structural stability in circulation and may suffer from premature leakage. Therefore, further optimization—such as lipid composition refinement, hybrid membrane coating, or microfluidic preparation techniques—may be essential for translating liposomal CeT formulations into clinical applications.

CeT Delivery Based on Polymer Nanoparticles

Polymer nanoparticles (PNPs) act as drug delivery vehicles synthesized from biocompatible and biodegradable polymers, typically ranging in size from 10 to 1000 nm. PNPs exhibit considerable potential for targeted drug delivery due to their straightforward manufacturing process, thereby improving safety and therapeutic efficacy while minimizing adverse reactions.[96,97] Currently, a wide array of polymers is employed as excipients in nanoparticle fabrication, including poly (lactic-co-glycolic acid) (PLGA), chitosan, phosphatidylcholine, polycaprolactone, and sodium carboxymethyl cellulose.[98,99]

Chitosan (CS) has attracted widespread attention in the development of nanocarriers due to its excellent biocompatibility and biodegradability, both of which have been approved for clinical application by the FDA. Chitosan and its derivatives are well-established as outstanding polymer nanocarriers, frequently used for delivering drugs such as CeT. Zeng et al[100] developed CeT-CS conjugates through amide bond formation, and their water solubility was significantly enhanced compared to natural CeT. At equivalent dosages, CeT-CS conjugate exhibits anticancer efficacy comparable to CeT, but with substantially reduced toxicity. This improved toxicity profile enhances the clinical appeal of CeT-CS conjugates, particularly in long-term cancer treatments.

Conjugating CeT with glycyrrhetinic acid-modified carboxymethyl chitosan-thioketal-rhein (GCTR) forms CeT/GCTR polymeric micelles (PMs), which exhibit prolonged release in blood circulation, particularly rapid release in the tumor microenvironment.[101] This type of system highlights the potential for stimuli-responsive delivery, where environmental triggers such as tumor-specific pH values or redox gradients can facilitate targeted drug release. Additionally, the functionalization of chitosan-based polymers further enhances drug-targeting abilities. For example, co-loading luteolin (LU) and CeT into low molecular weight chitosan forms CeT@LU-CA-CS nanomicelles, which can be internalized into renal tubules through megalin receptors, providing targeted therapeutic effects for renal diseases.[7,102,103]

Dendritic polymers present another promising approach for targeted drug delivery. These highly branched macromolecular structures allow for precise control of drug retention and release properties.[104,105] Boridy et al,[106] encapsulated CeT within fourth-generation polyamidoamine (G4) dendritic polymers with amino (CeT/G4-NH_2) and hydroxyl (CeT/G4-OH) terminal groups, resulting in improvements in water solubility of CeT by 7- and 12-fold, respectively. Low molecular weight polyethylene glycol (PEG) dendrimers, including G2, have also been used in drug delivery due to their unique dendritic structure and superior properties. Ding et al[107] synthesized an amphiphilic hybrid compound, G2-C18, which exhibited excellent stability and favorable release patterns. Compared with free CeT, CeT-loaded nanoparticles significantly enhanced the inhibition of cancer cell proliferation, indicating that the lipophilic chain-linked dendritic hybrid nanocarrier improves the anticancer activity of CeT, providing valuable insights for carrier design.

In addition to liposomes and micelles, polymer-based nanoparticles represent a versatile platform for the delivery of celastrol (CeT), especially in overcoming its intrinsic drawbacks such as poor aqueous solubility, rapid systemic clearance, and limited bioavailability. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA),[108] poly

(N,N-diethylacrylamide) (PDEAA), poly(2-(diisopropylamino)ethyl methacrylate) (PDPA),[109] poly(ε-caprolactone),[110] and glycosylated poly(amidoamine) dendrimers[111] have been employed to fabricate nanocarriers with tailored physicochemical properties. These systems offer several advantages, including enhanced drug stability through encapsulation in a hydrophobic polymeric matrix, prolonged systemic circulation via PEGylation or surface modification, and tunable release profiles triggered by internal stimuli such as pH or redox conditions. Notably, CeT-loaded polymer nanoparticles have also been designed for co-delivery with other chemotherapeutics or imaging agents, thereby enabling combination therapy or theranostic applications. Compared with liposomes, polymeric nanoparticles generally exhibit greater structural integrity and sustained release capabilities, which can further reduce dosing frequency and systemic toxicity. However, their translation into clinical use faces obstacles, including complex synthesis routes, batch-to-batch reproducibility issues, and stringent requirements for scalable manufacturing under GMP conditions. Future efforts should focus on optimizing polymer composition and crosslinking strategies to enhance encapsulation efficiency, while employing advanced fabrication methods such as nanoprecipitation, microfluidics, or 3D printing to ensure quality control and reproducibility.

CeT Delivery Based on Nanogel

Hydrogels (HG) are three-dimensional polymeric networks formed by the crosslinking of hydrophilic polymers. Because of its excellent biocompatibility and potential for controlled drug delivery, hydrogels are frequently injected directly into lesion sites for therapeutic applications. In addition to preventing drug diffusion into surrounding healthy tissues to reduce side effects, hydrogels can also control the drug release and maintain therapeutic levels at the target site for extended periods.[112,113] This controlled release provides sustained therapeutic effects, which is crucial for managing chronic diseases and localized treatment strategies.

On the basis of previously mentioned benefits, the combination of hydrogels and nanoparticles introduces an advanced drug delivery approach. By combining the properties of hydrogels and nanoparticles, nanoparticles are integrated into the hydrogel matrix to further extend the drug release. This approach represents a key application of hydrogels in nanomedicine and shows their potential in innovative drug delivery systems. In particular, the combination of the drug retention properties of hydrogels and the powerful anti-inflammatory activity of CeT makes it an ideal platform for transdermal drug delivery, especially for the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA). Injectable hydrogels can be prepared using dynamic cross-linking mechanisms, which allow for injection and retention within tissues due to their shear-thinning and self-healing properties. These characteristics facilitate localized, sustained release of encapsulated therapeutics directly at the area of inflammation. Furthermore, hydrogels used to treat RA have the potential to alleviate local inflammation, while minimizing systemic exposure, thereby reducing adverse effects associated with conventional treatments. Interestingly, Soni et al[114] developed a novel injectable hydrogel system consisting of adamantane-modified hyaluronic acid (Ad-HA) cross-linked with macrophage-targeting nanoparticles (cyclodextrin nanoparticles, CDNP). This system provides continuous release of CeT, effectively inhibiting pro-inflammatory signaling transduction for up to two weeks, significantly prolonging its circulation time and therapeutic action. Such extended drug release profiles are particularly beneficial for chronic diseases, reducing the requirement for frequent dosing and improving patient compliance. Despite the numerous advantages of nanoscale hydrogels, such as continuous drug release, excellent biocompatibility and biodegradability, the studies on CeT-loaded nanohydrogels remain relatively insufficient.

CeT Delivery Based on Stimulus-Responsive Nanoparticles

Stimulus-responsive drug release and targeted delivery represent two highly promising approaches in the cancer research field, with enormous potential in intelligent and personalized therapy. Intelligent drug delivery systems are usually designed to respond to physical or chemical stimuli (such as temperature, light, magnetic fields, hypoxia, glucose, pH, ultrasound, enzymes, and redox potential) or pathological microenvironments and external interventions.[115,116] Nanocarriers made from stimulus-responsive materials can transport drugs to target area or cells, releasing them upon encountering specific stimuli. The cancer microenvironments differ markedly from normal tissues, such as the elevated

reactive oxygen species (ROS) caused by chronic inflammation and increased glutathione (GSH) levels for cellular self-protection.[117,118]

It is known that the disruptions in molecular redox balance are closely associated with disease progression. Incorporating the redox-responsive moieties into the polymer matrices enables the targeting of key molecules such as ROS, GSH, and hydrogen sulfide (H_2S), allowing redox-responsive materials to undergo structural changes, thus triggering the release of encapsulated therapeutics.[118] For example, An et al[119] developed CeT-loaded polymer micells (C-PEPS) based on the diblock copolymer poly (ethylene glycol)-block-poly (propylene sulfide) (PEG-b-PPS). The hydrophilic PEG blocks have low toxicity and prolonged circulation, while the hydrophobic PPS block renders the micelles ROS-responsive.[120] Similarly, bilirubin-loaded CeT-conjugated polyethylene glycol nanoparticles (BRNPs) are also sensitive to ROS, effectively scavenging intracellular ROS and downregulating nitric oxide levels.[121]

Generally, there is a pH difference between pathological tissues (such as cancer, infections, and inflammation) and normal physiological pH (7.4), which enables selective drug release at the lesion site. Thus, pH-responsive drug delivery systems are highly favored in clinical drug delivery.[122–124] Jin et al[125] encapsulated CeT in mesoporous silica nanoparticles (HMSNs) capped with chitosan to create pH-responsive nanomedicine (CeT@HMSNs-Cs), which has strong solubility and is suitable for intra-articular injection in osteoarthritis therapy. CeT@HMSNs-Cs remains stable in alkaline conditions (pH 7.7) due to the chitosan coating, while showing enhanced solubility in acidic environments (pH 6.0). Based on the tumor microenvironments with H_2O_2-overexpression, Zheng et al[126] designed a smart nano factory (AUC-GOx/CeT) using a dual H_2O_2 amplification strategy named "external supply, internal promotion". Au-doped Ag_2S serves as a carrier for glucose oxidase (GOx) and CeT, while CuS exhibits responsive degradative behavior, releasing copper ions (Cu^{2+}) ions and activating second near-infrared (NIR-II) fluorescence and Fenton-like activity. The exposed GOx catalyzes the conversion of intratumoral glucose into gluconic acid and hydrogen peroxide (H_2O_2). This process effectively consumes glucose within the tumor, cutting off its main energy source and inducing tumor starvation. The production of H_2O_2 as a byproduct also contributes to oxidative stress in the tumor environment, thereby improving the therapeutic effect.

In addition, temperature and light can also serve as triggers for stimulus-responsive drug delivery systems.

A CeT-loaded thermosensitive liposome complex based on ferritin protein has been developed to improve tumor-specific accumulation and penetration.[127] This thermosensitive system can specifically release CeT in response to local heating, typically applied through external heating devices or thermal therapy. By increasing the temperature in the tumor area, liposomes become unstable and release CeT directly to the tumor region. This targeted release minimizes systemic exposure, reduces side effects, as well as improves drug efficacy. Light, especially near-infrared (NIR) light, can also be used to trigger drug release in CeT-loaded systems. NIR light can penetrate into tissues deeply, making it effective for activating drug release at deeper tumor areas. However, despite these advantages, NIR-based systems still face several challenges. One concern is the potential risk of phototoxicity to healthy tissues, especially with repeated or prolonged exposure. Moreover, while NIR light penetrates more deeply than visible light, its effective penetration is still limited (typically up to 1–2 cm), which may reduce efficacy in treating deep-seated tumors or large tumor masses. These limitations should be carefully considered when designing and applying NIR-triggered drug delivery systems for clinical use. Based on this case, liposome complexes can be designed to respond to NIR light, release CeT upon exposure, and enhancing penetration into tumor tissues. Moreover, the photosensitizer dihydroxyphenyl e6 (Ce6) commonly used in photodynamic therapy (PDT) can self-assemble with CeT to form stable complexes (CeCe, a nanoparticle formed by CeT and photosensitizer Ce6) due to intermolecular interactions, without the requirement for carriers. Upon light exposure, CeCe generates ROS within tumor cells, exacerbating oxidative stress and initiating autophagy.[128] Despite the multi-functionality and intelligence provided by stimulus-responsive drug delivery systems, current technologies face challenges in terms of scalability and clinical application (Figure 3).

CeT Delivery Based on Protein Particles

Proteins and enzymes are widely applied as versatile biomaterials in medicine due to their inherent specificity, biodegradability, low toxicity, and superior biocompatibility with cell receptors and substrates. Protein nanoparticles are generated by the self-assembly of natural or modified proteins into nanoscale structures. The synthesis and

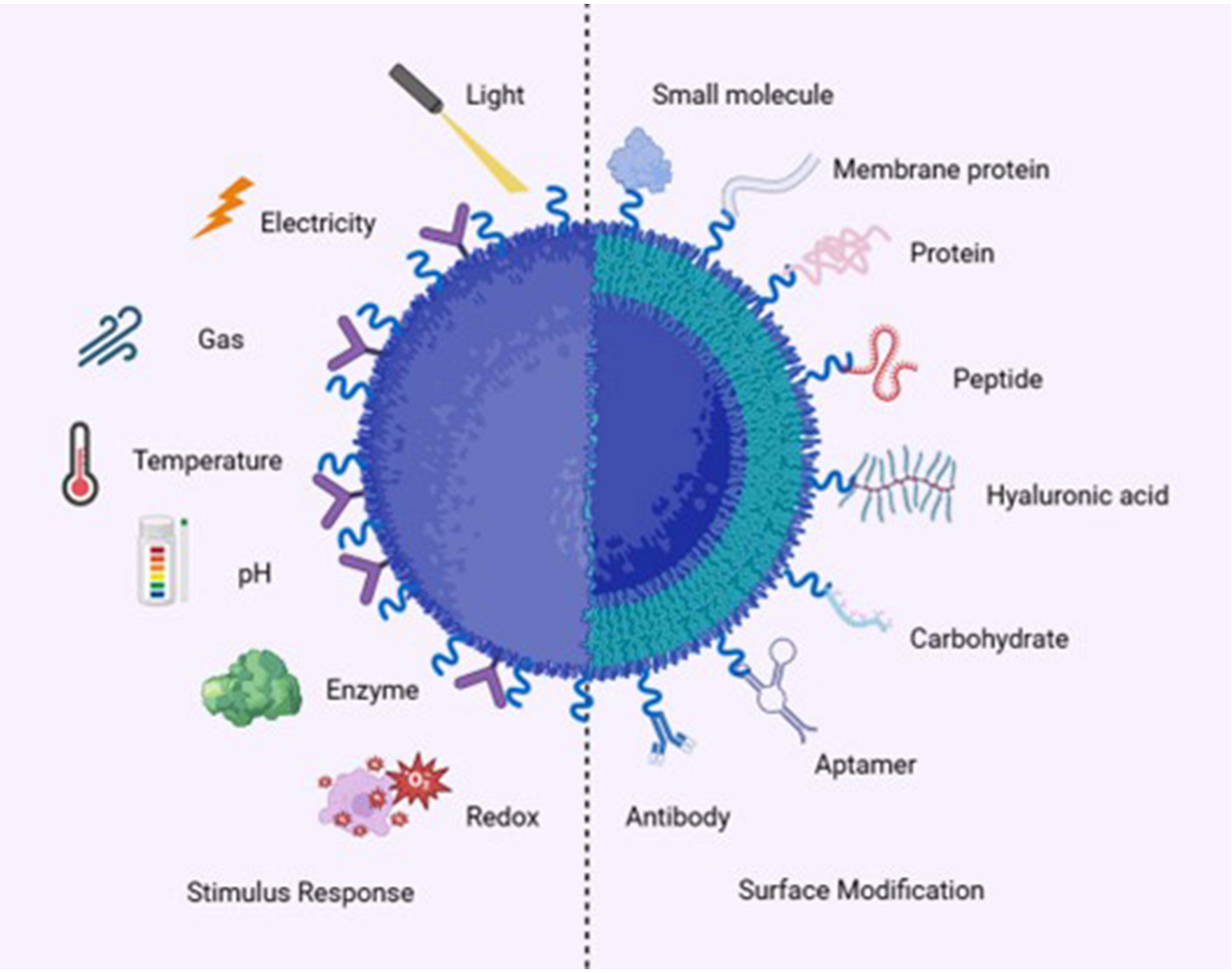

Figure 3 Surface modification of nanoparticle and types of stimulus-response. There are two main methods for modifying nanomaterials. One approach involves designing stimuli-responsive materials that undergo specific changes due to factors such as temperature, pH, laser irradiation, enzymatic stimulation within biological systems, or other environmental stimuli. Through this method, drugs are released at the stimulated site to achieve targeted effects. Another method involves attaching ligands, small molecules, proteins, membrane proteins, antibodies, etc, to the surface of materials. These ligands then bind to the surface of target cells, allowing for subsequent drug release (Written in Microsoft PowerPoint).

encapsulation of these protein nanoparticles are typically carried out under mild conditions, without the need for harmful chemicals or organic solvents, making them ideal candidates for drug delivery systems where safety and compatibility are crucial. Proteins such as silk fibroin, albumin, gelatin, soy protein, 30Kc19, lipoprotein, and ferritin have been used to synthesize these nanoparticles through the emulsion, electrospray, desolvation and other technologies.[129]

Silk fibroin (SF) is a naturally derived protein with unique properties including flexibility, moisture permeability, and controlled drug release, making it an ideal drug carrier. CeT-loaded silk fibroin nanoparticles (CeT-SFNPs) were prepared using an improved desolvation method.[130] These SFNPs exhibit sustained pH-responsive drug release and excellent biocompatibility. Compared to free CeT, CeT-SFNPs displayed enhanced anticancer activity, including greater inhibition of colony formation and increased apoptosis of pancreatic cancer cells. The ability of SFNPs to selectively release drugs in response to pH alterations demonstrates its potential for targeted cancer therapy, particularly in acidic tumor microenvironments.

Human serum albumin (HSA) is the most abundant plasma protein and presents multiple advantages for nanoparticle formulations, including enhanced pharmacokinetics, prolonged circulation time, improved drug efficacy, and reduced toxicity.[131,132] Fan et al[133] encapsulated CeT in lactosylated bovine serum albumin (Lac-BSA) through high-pressure homogenization to form CeT-Lac-BSA nanoparticles. Compared with free CeT, CeT-BSA nanoparticles exhibited

significantly improved cellular uptake, enhanced intestinal absorption, and greater hepatic accumulation.[134,135] These findings suggest the potential of albumin-based nanoparticles for treating metabolic and liver diseases, as well as their application in cancer therapy.

Lactoferrin (LF) is recognized for its strong tumor-targeting abilities due to its high affinity for overexpressed receptors in cancer cells, such as low-density lipoprotein (LDL) and transferrin (Tf) receptors.[136] Conjugating CeT with LF enables dual-targeting, utilizing the anticancer activity of drugs and the tumor-targeting efficiency of LF, leading to superior therapeutic outcomes.

Protein-based nanoparticles offer an inherently biocompatible and biodegradable platform for celastrol (CeT) delivery, with materials such as albumin, gelatin, and silk fibroin frequently used due to their ability to bind hydrophobic drugs and facilitate passive targeting via the enhanced permeability and retention (EPR) effect. These systems can improve CeT's solubility and stability through hydrophobic interactions and hydrogen bonding within the protein matrix. However, achieving precise control over drug release kinetics remains a key limitation, as protein degradation and drug diffusion rates may vary under physiological conditions, potentially leading to premature or delayed drug release and suboptimal therapeutic efficacy. To overcome these challenges, strategies such as crosslinking, enzymatic modification, or conjugation with targeting ligands have been investigated to enhance structural integrity and enable site-specific release. Compared to polymeric or lipid-based carriers, protein nanoparticles exhibit superior biocompatibility and natural degradability but generally suffer from lower mechanical stability and more variable release profiles. Therefore, further refinement in formulation design and process standardization is essential to fully harness their potential for clinical translation in CeT delivery.

Active Targeted Drug Delivery System for CeT

Passive targeting utilizes the EPR effects, particularly in tumor tissues exhibiting heightened vascular permeability and impaired lymphatic drainage. This leads to the preferential accumulation of nanoparticles within the tumors. In contrast, active targeting involves the conjugation of specific ligands to the surface of nanocarriers, allowing them to bind to receptors overexpressed on target cells. This ligand-receptor interaction triggers receptor-mediated endocytosis, enabling selective accumulation of nanoparticles within target cells. This interaction triggers receptor-mediated endocytosis, facilitating selective accumulation within target cells.[137,138] The active targeting strategies have a dual advantage: concentrating drug delivery at the tumor sites while minimizing accumulation in non-target organs, thereby reducing systemic toxicity and improving therapeutic efficacy. Furthermore, when combined with stimuli-responsive systems, active targeting ensures precise nanoparticle accumulation at tumor sites, achieving controlled drug release, enhancing therapeutic outcomes, and minimizing adverse reactions.[139]

Folate receptors (FR) are frequently overexpressed in several cancer types, including breast cancer, ovarian cancer, and lung cancer. This makes folate an ideal ligand for selective drug delivery. By conjugating folate with nanoparticles, selective uptake by cancer cells is facilitated, while sparing normal cells from drug exposure.[140–142] Niu et al[143] designed $PLGA_{5000}$-TK-PEG_{2000}-FA nanoparticles for CeT encapsulation, constructing a ROS-sensitive, tumor-targeted nanocarrier. The folate moiety on the surface of nanoparticle facilitates the active targeting of tumor cells. Upon exposure to elevated ROS levels in the tumor microenvironment, the thioether ketone (TK) bond is cleaved, releasing CeT and amplifying ROS production, which triggers apoptosis and contributes to the treatment of ovarian cancer.

Hyaluronic acid (HA) is a natural polysaccharide, and is widely used to modify nanoparticle surfaces due to its specific interaction with CD44 receptors.[144] CD44 receptors have been found overexpressed in various cancers, including breast, colon, and pancreatic cancers.[145] HA-modified nanoparticles selectively bind to CD44 receptors on these cancer cells, enhancing their uptake.[146] This interaction forms the foundation for cell membrane-modified nanoparticles, which is an innovative approach for increasing drug delivery specificity and targeting efficiency.[147] Similarly, nanoparticles derived from red, white blood cells or other cell types offer enhanced biocompatibility, reduced off-target distribution, and minimized systemic toxicity. Furthermore, they prolong the circulating half-life of drugs, thereby improving retention and bioavailability.[148]

Neutrophils, as essential components of the immune system, exhibit high motility and facilitate the distribution of nanoparticles throughout the body. Given that their membranes are derived from immune cells, neutrophil membranes

have low immunogenicity, allowing them to evade clearance by the immune system.[149,150] Cao et al,[151] developed neutrophil membrane-coated poly (ethylene glycol)-poly (lactic-co- glycolic acid) (PEG-PLGA) nanoparticles (NNPs). These NNPs demonstrated the ability to cross the blood-pancreas barrier, promoting targeted drug delivery to the pancreas in vivo. In orthotopic and ectopic tumor models, NNPs loaded with CeT showed significantly enhanced tumor suppression. Moreover, Zhou et al[152] observed that NNPs/CeT effectively reduced serum amylase and pancreatic malondialdehyde levels in rat models of acute pancreatitis, surpassing CeT solution and standard nanoparticles.

Furthermore, blood cell membrane coatings, such as those used in neutrophil membrane-coated PEG-PLGA nanoparticles (NNPs), have shown promise in enhancing targeted drug delivery due to their natural affinity for inflammation areas and tumor tissues. Inspired by these biomimetic strategies, researchers have explored other modifications to improve targeting abilities, particularly targeting immune cells and macrophages. For example, dextran sulfate (DS) can be used to target macrophages expressing scavenger receptor-A (SR-A), forming nanomicelles through self-assembly of DS-PVGLIG-CeT and Abps-TK-Cur,[153] DS-modified nano micelles are a powerful platform for delivering drugs to macrophage related diseases and tumor microenvironments, improving the efficacy of encapsulated drugs while reducing systemic side effects. Similarly, Zhu et al,[154] developed a peptide-modified, biomimetic blood-brain barrier (BBB)-penetrating albumin nanosystem specifically designed for targeted delivery to the brain. This nanosystem co-delivers TGF-β receptor I (TGFβRI) inhibitors, providing dual functionality for targeting and therapy. Peptide modification enhances the permeability of BBB, enabling the nanosystem to specifically deliver therapeutic agents to brain tissues, which is particularly advantageous for treating neurological disorders and brain cancers. This example highlights the multifunctionality of biomimetic and modified nanocarriers in overcoming biological barriers for precision drug delivery, indicating their potential in treating complex diseases such as cancers and neurodegenerative diseases.[155,156]

To refine active targeting systems for CeT, researchers are exploring a wider range of ligands beyond traditional folate and hyaluronic acid. Emerging ligands, such as peptides, antibodies, and aptamers, can specifically bind to receptors overexpressed on tumor cells, enhancing receptor-mediated uptake. For example, peptides can target integrins in invasive tumors, while aptamers allow the targeting of specific biomarkers with minimal immunogenicity. Dual-ligand targeting, which combines two ligands onto a single nanocarrier, further increases selectivity by addressing the receptor variability of tumors. For CeT, this may involve pairing folate and transferrin to target typical cancer receptors, thus enhancing selective uptake, reducing off-target effects, and improving its therapeutic index (Table 2). Moreover, combining active

Table 2 Overview of Different Delivery Systems for Celastrol

Types of Nanocarriers	Characterization	Targeted Method	Type of Treatment	References
Polymeric Micelles	Size:45~165 nm Zeta:-12.03~ -21.3 mV DL:5.1~36.8 %	Passive targeting	Retinoblastoma, Liver cancer, Pancreatic cancer	[80,81,101,157]
	Size:119~154 nm Zeta:-15.3~-34.8 mV DL:5.4~ 9.1 %	Active targeting	Lung cancer, Breast cancer, Melanoma, Pancreatitis	[39,150,152,158]
	Size:68.6~135 nm Zeta:-7.3~10.6 mV DL:4.7~ 6.6 %	Stimuli-responsive	Liver cancer, Arthritis, Rheumatoid Arthritis	[111,119,121]
	Size:305 nm	Stimuli-responsive	Liver cancer and Breast cancer	[71]
	Size:16.3 nm DL:22 %	Passive targeting	Atherosclerosis	[83]
	Size:189.9 nm Zeta:-11.91 mV DL:3.46 %	Active targeting	Rheumatoid arthritis	[155]
	Size:50–70 nm Zeta:0 mV DL:7.36~28.57 %	Passive targeting	Obesity, Corneal neovascularization	[78,79]

(*Continued*)

Table 2 (Continued).

Types of Nanocarriers	Characterization	Targeted Method	Type of Treatment	References
Liposomes	Size:174 nm Zeta:-8.5 mV DL: 28.5 %	Passive targeting	Breast cancer	[140]
	Size:115.3~139.4 nm Zeta:-8.5~-47.8 mV EE: 73.4~90.5 %	Active targeting	Liver cancer, Cervical cancer	[92,127]
	Size:126 nm Zeta:-25 mV EE: 98.5 %	Passive targeting	Rheumatoid arthritis	[159]
	Size:75 nm Zeta:20 mV EE: 86.9 % DL: 14.8 %	Active targeting	Acute kidney injury	[102]
	Size:90.2±9.7 nm Zeta:26.4±4.2 mV EE: 69.3±5.1 %	Active targeting	Melanoma	[91]
	Size:245.61±1.03 nm Zeta:−11.15±1.49 mV	Active targeting	Liver injury	[94]
	Size:114±1.85 nm Zeta:11.5±1.03 mV EE:94.83±0.87 % DL:2.83±0.02 %	Active targeting	Kidney injury	[93]
Polymeric Nanoparticles	Size:43.7~ 175.5nm Zeta:-36.6~49.6 mV DL:2.83~82.4 %	Passive targeting	Melanoma, Breast cancer, Liver cancer, Pleural Mesothelioma, Prostate cancer, Pancreatic carcinoma	[82,103,107,108,110,151,160–162]
	Size:43.7~204 nm Zeta:-49.97~3.5 mV DL:4.45~42 %	Active targeting	Melanoma, Rheumatoid arthritis, Liver cancer, Breast cancer	[109,120,153,163–165]
	Size:75.4~210 nm Zeta:-49.97~-8 mV DL:7.5~64 %	Stimuli-responsive	Lung cancer, Pancreatic cancer, Prostatic cancer, Liver cancer	[86,100,166,167]
	Size:121 nm Zeta:-49.97~-8 mV DL:11.2 % EE:56 %	Stimuli-responsive	Ovarian cancer	[143]
	Size:99±1 nm Zeta:−30±0.8 mV DL:2.6±0.03 % EE:94.4±1.1 %	Passive targeting	Rheumatoid arthritis	[156]
	Size:120 nm DL:98.5 % EE:10 %	Passive targeting	Acute kidney injury	[168]
	Size:162.2±6.6 nm Zeta:−5.3±0.4 mV EE:90 %	Stimuli-responsive	Rheumatoid arthritis	[169]
	Size: 51.25 ±2.086 nm Zeta: −3.12 ±0.49 mV	Active targeting	Rheumatoid arthritis	[149]
Nanogels	Size: 82.22 ±1.09 nm	Passive targeting	Rheumatoid arthritis	[114]
Protein Nanoparticles	Size: 126.8 nm Zeta:-12 mV EE:75%	Passive targeting	Glioma	[154]
	Size: 157.8~313.1 nm Zeta:-34.2~19 mV EE:87 % DL:5.98~63.5 %	Active targeting	Pancreatic cancer, Breast cancer	[130,136,144]
	Size: 78.5±2.7 nm Zeta: −1.45 ±1.19 mV DL:2.4±0.07% EE:94.6±1.7%	Passive targeting	Rheumatoid arthritis	[170]

(*Continued*)

https://doi.org/10.2147/IJN.S539586

Table 2 (Continued).

Types of Nanocarriers	Characterization	Targeted Method	Type of Treatment	References
	Size:125.6~158.6 nm Zeta:-25.7~-26.02 mV DL:13.62~13.88 % EE:75–79 %	Passive targeting	Non-alcoholic fatty liver, Obesity	[133,134]
	Size:122.5±0.9 nm Zeta:-29.2 mV EE:75 %	Passive targeting	Rheumatoid arthritis	[135]
	Size:95±0.22 nm Zeta:-23.2±0.2 mV EE:94.95±0.34 % DL:2.35±0.17 %	Active targeting	Glomerulonephritis	[171]
Inorganic Material	Size:105~300 nm Zeta:1~50mV DL:19~26 %	Passive targeting	Neuroblastoma, Squamous cell carcinoma, Breast cancer, Cervical cancer and lung cancer	[172–175]
	Size:21.5~243 nm Zeta:-14.7~-17.5 mV DL:50 %	Active targeting	Breast cancer, Ovarian cancer, Glioblastoma	[85,141,176,177]
	Size:260.76 nm Zeta:19.9±0.7 mV DL:28.2 %	Stimuli-responsive	Rheumatoid arthritis	[125]

targeting with stimuli-responsive release mechanisms such as pH or ROS-sensitive adapters can enable specific release of CeT in the acidic or oxidative environment of tumors, thereby optimizing efficacy and minimizing side effects (Fig 3).

Conclusion and Future Perspectives

Celastrol (CeT), a potent pentacyclic triterpenoid derived from traditional Chinese medicine, exhibits a wide spectrum of pharmacological effects, including anti-inflammatory, immunomodulatory, and anticancer activities. However, its clinical translation remains significantly hindered by multiple physicochemical and pharmacokinetic challenges. Its extremely low aqueous solubility (<0.01 mg/mL) severely restricts dissolution and absorption in the gastrointestinal tract, while its rapid systemic clearance and short half-life make it difficult to maintain therapeutic plasma levels. Moreover, CeT has a narrow therapeutic index and induces dose-dependent hepatotoxicity, nephrotoxicity, and gastrointestinal irritation, limiting safe dose escalation and long-term use. These issues collectively hinder its systemic application and highlight the need for advanced delivery strategies.

Nanotechnology-based drug delivery systems (NDDS) offer a multifaceted solution to these problems. Encapsulation of CeT into polymeric nanoparticles, liposomes, or micelles has significantly improved its water dispersibility, protected it from premature degradation, and prolonged its circulation time. Passive targeting through the enhanced permeability and retention (EPR) effect enhances CeT accumulation in tumor tissues, while active targeting via ligand modifications (eg, folic acid, peptides, antibodies) enables more precise delivery to overexpressed receptors on tumor cells. Notably, stimulus-responsive NDDS—such as pH-sensitive, GSH-responsive, or enzyme-cleavable systems—have demonstrated site-specific drug release, reducing off-target exposure and improving therapeutic index.

In preclinical studies, CeT-loaded NDDS have achieved improved tumor growth inhibition, reduced systemic toxicity, and enhanced survival compared to free CeT. Some systems also enable co-delivery with chemotherapeutics, immunomodulators, or antioxidants, producing synergistic effects and partially overcoming CeT monotherapy limitations. Beyond cancer, NDDS have shown potential in autoimmune diseases, where targeted delivery of CeT to inflamed tissues may suppress aberrant immune responses with reduced toxicity. In neurodegenerative diseases, engineered nanocarriers may facilitate CeT delivery across the blood–brain barrier, opening new therapeutic possibilities.

Despite these advances, several challenges remain. Many CeT-based NDDS are still in early developmental stages, and their long-term safety, biodegradation behavior, and pharmacokinetics in humans are not well understood. Moreover, batch-to-batch reproducibility, large-scale manufacturing, and regulatory hurdles remain significant barriers to clinical

translation. In addition, the tumor microenvironment is heterogeneous across cancer types and stages, requiring individualized delivery strategies.

Future efforts should focus on optimizing delivery system composition, tuning drug release kinetics, and integrating multifunctional components (eg, imaging probes, stimuli-responsive motifs) for theranostic applications. Robust in vivo pharmacokinetic and biodistribution studies, along with toxicity evaluation in relevant disease models, are essential. Furthermore, bridging the gap between preclinical success and clinical translation requires early integration of good manufacturing practices (GMP), scalable synthesis methods, and regulatory alignment.

In conclusion, NDDS offer a comprehensive platform to address the major limitations of CeT and unlock its full therapeutic potential. Through rational design, disease-specific customization, and rigorous evaluation, CeT-based nanomedicines hold promise not only in oncology but also in treating complex inflammatory and neurodegenerative diseases.

Data Sharing Statement

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

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest

References

1. Yao S-S, Han L, Tian Z-B, et al. Celastrol inhibits growth and metastasis of human gastric cancer cell mkn45 by down-regulating microrna-21. *Phytother Res*. 2019;33(6):1706–1716. doi:10.1002/ptr.6359
2. Liu X, Zhao P, Wang X, et al. Celastrol mediates autophagy and apoptosis via the ros/jnk and akt/mtor signaling pathways in glioma cells. *J Exp Clin Cancer Res*. 2019;38(1):184. doi:10.1186/s13046-019-1173-4
3. Zhang C-J, Zhu N, Long J, et al. Celastrol induces lipophagy via the lxrα/abca1 pathway in clear cell renal cell carcinoma. *Acta Pharmacol Sin*. 2021;42(9):1472–1485. doi:10.1038/s41401-020-00572-6
4. Chen P, Wang B, Li M, et al. Celastrol inhibits the proliferation and migration of mcf-7 cells through the leptin-triggered pi3k/akt pathway. *Comput Struct Biotechnol J*. 2022;20:3173–3181. doi:10.1016/j.csbj.2022.06.042
5. Zengfu W, Dali C, Zhongwei W. Effects of diclofenac on the pharmacokinetics of celastrol in rats and its transport. *Pharm Biol*. 2018;56:269–74. doi:10.1080/13880209.2018.1459740
6. Jun Z, Shijia L, Jie-Hui H, et al. LC-MS/MS method for determination of tripterine in plasma: pharmacokinetic study in beagles. *China J Chin Mat Medica*. 2016;41:2727–31. doi:10.4268/cjcmm20161426

7. May S, Wedad M, Ossama Y. Laminated chitosan-based composite sponges for transmucosal delivery of novel protamine-decorated tripterine phytosomes: ex-vivo mucopenetration and in-vivo pharmacokinetic assessments. *Carbohydr Polym*. 2018;188:108–20. doi:10.1016/j.carbpol.2018.01.095
8. Junli L, Jaemin L, Mario Andrés Salazar H, et al. Treatment of obesity with celastrol. *Cell*. 2015;161:999–1011. doi:10.1016/j.cell.2015.05.011
9. Duanfang Z, Xiaoli L, Xiaoqiu X, et al. Celastrol targets the chrebp-txnip axis to ameliorates type 2 diabetes mellitus. *phytomedicine*. 2023;110:154634. doi:10.1016/j.phymed.2022.154634
10. Xu H, Huabin Z, Chunyong D, et al. Celastrol suppresses colorectal cancer via covalent targeting peroxiredoxin 1. *Signal Transd Targeted Ther*. 2023;8. doi:10.1038/s41392-022-01231-4
11. Muthu K, Kwang Seok A, Jong H, et al. Celastrol attenuates the invasion and migration and augments the anticancer effects of bortezomib in a xenograft mouse model of multiple myeloma. *Front Pharmacol*. 2018;9:365. doi:10.3389/fphar.2018.00365
12. Taiichiro S, Akira N, Emiko A, et al. Celastrol suppresses humoral immune responses and autoimmunity by targeting the COMMD3/8 complex. *Sci Immunol*. 2023;8:eadc9324. doi:10.1126/sciimmunol.adc9324
13. Pratyusha C, Shiwen X, Bahja Ahmed A, et al. Tripterygium wilfordiiderivative celastrol, a yap inhibitor, has antifibrotic effects in systemic sclerosis. *Ann Rheumatic Dis*. 2023;82:1191–204. doi:10.1136/ard-2023-223859
14. Xiaoman Y, Bin T, Yilan C, et al. Celastrol inhibits store operated calcium entry and suppresses psoriasis. *Front Pharmacol*. 2023;14:1111798. doi:10.3389/fphar.2023.1111798
15. Li X, Jie Z, Yingying L, et al. Celastrol inhibits platelet function and thrombus formation. *Biochem Biophys Res Commun*. 2024;693:149366. doi:10.1016/j.bbrc.2023.149366
16. Qi Z, Ping T, Ting Z, et al. Celastrol ameliorates acute liver injury through modulation of PPARA. *Biochem Pharmacol*. 2020;178:114058. doi:10.1016/j.bcp.2020.114058
17. Minling P, Zhen W, Yiyi W, et al. Celastrol alleviated acute kidney injury by inhibition of ferroptosis through Nrf2/GPX4 pathway. *Biomed Pharmacother*. 2023;166:115333. doi:10.1016/j.biopha.2023.115333
18. Chonglin Y, Cheng-fu S, Ashok I, et al. Celastrol enhances transcription factor EB (TFEB)-mediated autophagy and mitigates tau pathology: implications for Alzheimer's disease therapy. *Acta Pharmaceutica Sinica B*. 2022;12:1707–22. doi:10.1016/j.apsb.2022.01.017
19. Chenyu Z, Miao Z, Bingwei W, et al. The Nrf2-NLRP3-caspase-1 axis mediates the neuroprotective effects of celastrol in Parkinson's disease. *Redox Biol*. 2021;47:102134. doi:10.1016/j.redox.2021.102134
20. Wenyuan S, Chuanhao L, Quan L, et al. Celastrol inhibits oligodendrocyte and neuron ferroptosis to promote spinal cord injury recovery. *Phytomedicine*. 2024;128:155380. doi:10.1016/j.phymed.2024.155380
21. Xiang L, Wenwen L, Guannan J, et al. Correction to "celastrol ameliorates neuronal mitochondrial dysfunction induced by intracerebral hemorrhage via targeting cAMP-activated exchange protein-1". *Adv Sci*. 2024;11:2406154. doi:10.1002/advs.202406154
22. Qing-yuan S, Cui L, Jing L, et al. Celastrol ameliorates aspergillus fumigatus keratitis via inhibiting lox-1. *Int Immunopharmacol*. 2019;70:101–9. doi:10.1016/j.intimp.2019.02.017
23. Guangxia Y, Kai W, Hua S, et al. Celastrol ameliorates osteoarthritis via regulating tlr2/nf-κb signaling pathway. *Front Pharmacol*. 2022;13:963506. doi:10.3389/fphar.2022.963506
24. Shengjin X, Jinrun C, Mengyun D, et al. Celastrol ameliorates experimental autoimmune uveitis through STAT3 targeting and gut microenvironment reprofiling. *Int Immunopharmacol*. 2024;25:111339. doi:10.1016/j.intimp.2023.111339
25. Qingyu Z, Jian Y, Guorong Y, et al. Celastrol inhibits ll37-induced rosacea by inhibiting ca2+/caMKII-mTOR-NF-κB activation. *Biomed Pharmacother*. 2022;153:113292. doi:10.1016/j.biopha.2022.113292
26. Piao L, Dandan L, Qian Z, et al. Celastrol induces ferroptosis in activated HSCs to ameliorate hepatic fibrosis via targeting peroxiredoxins and Ho-1. *Acta Pharmaceutica Sinica B*. 2022;12:2300–14. doi:10.1016/j.apsb.2021.12.007
27. Yiwei W, Xingchen G, Xue S, et al. Celastrol alleviates subconjunctival fibrosis induced by silicone implants mimicking glaucoma surgery. *Eur J Pharm Biopharm*. 2024;201:114352. doi:10.1016/j.ejpb.2024.114352
28. Hongfang L, Chang-Feng D, Neng Z, et al. An ultrasensitive GSH-specific fluorescent probe unveils celastrol-induced ccRCC ferroptosis. *Bioorg Chem*. 2023;134:106454. doi:10.1016/j.bioorg.2023.106454
29. Shuo Z, Neng Z, Yaning S, et al. Celastrol mediates CAV1 to attenuate pro-tumorigenic effects of senescent cells. *Phytomedicine*. 2024;129:155614. doi:10.1016/j.phymed.2024.155614
30. Chanjuan Z, Qin Y, Chang-Feng D, et al. GSH-specific fluorescent probe for sensing, bioimaging, rapid screening of natural inhibitor celastrol and ccRCC theranostics. *Anal Chim Acta*. 2023;1248:340933. doi:10.1016/j.aca.2023.340933
31. Jun G, Yaning S, Neng Z, et al. Celastrol functions as an emerging manager of lipid metabolism: mechanism and therapeutic potential. *Biomed Pharmacother*. 2023;164:114981. doi:10.1016/j.biopha.2023.114981
32. Jun-lan T, Yi J, Xian-Ya C, et al. Celastrol: the new Dawn in the treatment of vascular remodeling diseases. *Biomed Pharmacother*. 2023;158:114177. doi:10.1016/j.biopha.2022.114177
33. Yaning S, Leping L, Chang-Feng D, et al. Celastrol ameliorates vascular neointimal hyperplasia through wnt5a-involved autophagy. *Int J Bio Sci*. 2021;17:2561. doi:10.7150/ijbs.58715
34. Chan-Juan Z, Neng Z, Jia L, et al. Celastrol induces lipophagy via the lxrα/abca1 pathway in clear cell renal cell carcinoma. *Acta Pharmacol Sin*. 2020;49:1472–85. doi:10.1038/s41401-020-00572-6
35. Chanjuan Z, Neng Z, Yuxiang W, et al. Celastrol attenuates lipid accumulation and stemness of clear cell renal cell carcinoma via cav-1/lox-1 pathway. *Front Pharmacol*. 2021;12:658092. doi:10.3389/fphar.2021.658092
36. Zhang D, Marconi A, Xu L, et al. Tripterine inhibits the expression of adhesion molecules in activated endothelial cells. *J Leukoc Biol*. 2006;80 (2):309–319. doi:10.1189/jlb.1005611
37. Rita C, Tânia C, João G, et al. AB0096 efficacy and safety of oral administration of pure celastrol in AIA rats. *Marine Pollution Bull*. 2017;123:357–364. doi:10.1016/j.marpolbul.2017.09.010
38. Wei H, Bo L, Hongtao X. Celastrol: progresses in structure-modifications, structure-activity relationships, pharmacology and toxicology. *Eur J Med Chem*. 2020;204. doi:10.1016/j.ejmech.2020.112644
39. Wei-Guang S, Han-Guang W, Rui W, et al. Synthesis and anti-tumor activity study of water-soluble peg-celastrol coupling derivatives as self-assembled nanoparticles. *Bioorg Med Chem Lett*. 2019;29:685–7. doi:10.1016/j.bmcl.2019.01.042

40. Cheng W, Shun-dong D, Xingtao Z, et al. Celastrol as an emerging anticancer agent: current status, challenges and therapeutic strategies. *Biomed Pharmacother*. 2023;163:114882. doi:10.1016/j.biopha.2023.114882
41. Siyan Z, Amy P, Felicia O, et al. Oral bioavailability evaluation of celastrol-encapsulated silk fibroin nanoparticles using an optimized lc-ms/ms method. *Molecules*. 2020;25:3422. doi:10.3390/molecules25153422
42. Hannah Ying L, Pei Shi O, Lingzhi W, et al. Celastrol in cancer therapy: recent developments, challenges and prospects. *Cancer Lett*. 2021;521:252–67. doi:10.1016/j.canlet.2021.08.030
43. Wenjie W, Sydney M. Abstract P267: sex differences in Cyp450 activity and the development of hypertension and renal injury in the Dahl S rat. *Hypertension*. 2016;68:AP267. doi:10.1161/hyp.68.suppl_1.p267
44. Xiaojuan J, Chengqing Y, Rong D, et al. Toxic metabolites and metabolic soft spots of celastrol based on glutathione metabolic capture and high-resolution mass spectrometry. *Expert Opin Drug Metab Toxicol*. 2023;19:1023–32. doi:10.1080/17425255.2023.2294042
45. Wenzheng J, Jun Z. Oral bioavailability and gender-related pharmacokinetics of celastrol following administration of pure celastrol and its related tablets in rats. *J Bioequivalence Bioavailability*. 2015;144:195–200. doi:10.1016/j.jep.2012.09.005
46. Yan C, Liang Y, Lei Z, et al. Effect of cell-penetrating peptide-coated nanostructured lipid carriers on the oral absorption of tripterine. *Int J Nanomed*. 2012;4581. doi:10.2147/ijn.s34991
47. Guangkui Y, Hanhua Z, Wei W, et al. Investigation of the influence of glycyrrhizin on the pharmacokinetics of celastrol in rats using lc-ms and its potential mechanism. *Xenobiotica*. 2016;47:607–13. doi:10.1080/00498254.2016.1211773
48. Hong L, Jie L, Lu L, et al. Elucidation of the intestinal absorption mechanism of celastrol using the Caco-2 cell transwell model. *Planta Med*. 2016;82:1202–7. doi:10.1055/s-0035-1568597
49. Hongjian Z, Guorui Z, Hu-ri P, et al. Synthesis and characterisation of celastrol derivatives as potential anticancer agents. *J Enzyme Inhibition Med Chem*. 2017;33:190–8. doi:10.1080/14756366.2017.1404590
50. Yin Z, Zhao Z. Induction of the ER stress response in NRVMS is linked to cardiotoxicity caused by celastrol. *Acta Biochim Biophys Sin*. 2022;54:1180. doi:10.3724/abbs.2022104
51. Wang S, Liu K, Wang X, et al. Toxic effects of celastrol on embryonic development of zebrafish (danio rerio). *Drug Chem Toxicol*. 2011;34 (1):61–65. doi:10.3109/01480545.2010.494664
52. Chuanxin L, Chenning Z, Wenxin W, et al. Integrated metabolomics and network toxicology to reveal molecular mechanism of celastrol induced cardiotoxicity. *Toxicol Appl Pharmacol*. 2019;383:114785. doi:10.1016/j.taap.2019.114785
53. Wei Z, Liping X, Liya P, et al. Cardiac toxicity of triptergium wilfordii hook f. may correlate with its inhibition to hERG channel. *Heliyon*. 2019;5. doi:10.1016/j.heliyon.2019.e02853
54. Sophie K, Eliver G, Leonore A, et al. Development of B cells and erythrocytes is specifically impaired by the drug celastrol in mice. *PLoS One*. 2012;7:e35733. doi:10.1371/journal.pone.0035733
55. Tianhong X, Huiqiang L, Xin L, et al. Celastrol ameliorates lupus by promoting apoptosis of autoimmune t cells and preventing autoimmune response in mrl/lpr mice. *Res Sq*. 2023;11:1. doi:10.1136/lupus-2023-001057
56. Okki C, Joong-Woon L, Youngjin J, et al. Celastrol, which targets IL-2/CD25 binding inhibition, induces t cell-mediated antitumor activity in melanoma. *Eur J Pharmacol*. 2024;962:176239. doi:10.1016/j.ejphar.2023.176239
57. Steve G, Mathis G, Yukio N, et al. Genetic approaches in mice to understand Rel/Nf-κB and IκB function: transgenics and knockouts. *Oncogene*. 1999;18:6888–95. doi:10.1038/sj.onc.1203236
58. Yirang Y, Zhiping G, Qi S, et al. In vitro inhibition of celastrol on spermatozoa fertilization ability of Guinea pig. *Yao xue xue bao= Acta Pharmaceutica Sinica*. 1995;30:331–5. doi:10.16438/j.0513-4870.1995.05.003
59. Jun-ping B, Yuhan S, Xin F, et al. Effects of demethylzeylasteral and celastrol on spermatogenic cell Ca2+ channels and progesterone-induced sperm acrosome reaction. *Eur J Pharmacol*. 2003;464:9–15. doi:10.1016/s0014-2999(03)01351-7
60. Wen F, Dandan L, Mingming W, et al. Celastrol induces premature ovarian insufficiency by inducing apoptosis in granulosa cells. *Biomed Pharmacother*. 2023;169:115815. doi:10.1016/j.biopha.2023.115815
61. Chunhuan J, Zijun W, Lili W, et al. CYP450s-activity relations of celastrol to interact with triptolide reveal the reasons of hepatotoxicity of tripterygium wilfordii. *Molecules*. 2019;24:2162. doi:10.3390/molecules24112162
62. Xun H, Mengdi J, Yu F, et al. Novel low-toxic derivative of celastrol maintains protective effect against acute renal injury. *ACS Omega*. 2018;3:2652–60. doi:10.1021/acsomega.7b01890
63. Ayşe Tarbin J, Mehtap K, Büket A. Celastrol ameliorates Acetaminophen-induced oxidative stress and cytotoxicity in HepG2 cells. *Hum Exp Toxicol*. 2017;37:742–51. doi:10.1177/0960327117734622
64. Abdel-Aziz H, Mohamed E, Mohamed F, et al. Repression of Acetaminophen-induced hepatotoxicity by a combination of celastrol and brilliant blue g. *Toxicol Lett*. 2017;275:6–18. doi:10.1016/j.toxlet.2017.04.012
65. Mengqiu W, Wei-yi C, Xiaowen Y, et al. Celastrol aggravates LPS-induced inflammation and injuries of liver and kidney in mice. *Am J Transl Res*. 2018;10:2078.
66. Ming T, Xu C, Kun Z, et al. Celastrol alleviates renal fibrosis by upregulating cannabinoid receptor 2 expression. *Cell Death Dis*. 2018;9:601. doi:10.1038/s41419-018-0666-y
67. Algar W, Massey M, Rees K, et al. Photoluminescent nanoparticles for chemical and biological analysis and imaging. *Chem Rev*. 2021;121 (15):9243–9358. doi:10.1021/acs.chemrev.0c01176
68. Cheng L, Wang X, Gong F, et al. 2D nanomaterials for cancer theranostic applications. *Adv Mater*. 2020;32(13):e1902333. doi:10.1002/adma.201902333
69. Stater E, Sonay A, Hart C, et al. The ancillary effects of nanoparticles and their implications for nanomedicine. *Nat Nanotechnol*. 2021;16 (11):1180–1194. doi:10.1038/s41565-021-01017-9
70. Ghezzi M, Pescina S, Padula C, et al. Polymeric micelles in drug delivery: an insight of the techniques for their characterization and assessment in biorelevant conditions. *J Control Release*. 2021;332:312–336. doi:10.1016/j.jconrel.2021.02.031
71. Lee J, Kim K, Kwon I, et al. Intracellular glucose-depriving polymer micelles for antiglycolytic cancer treatment. *Adv Mater*. 2023;35(10): e2207342. doi:10.1002/adma.202207342
72. Feng L, Zhu C, Yuan H, et al. Conjugated polymer nanoparticles: preparation, properties, functionalization and biological applications. *Chem Soc Rev*. 2013;42(16):6620–6633. doi:10.1039/c3cs60036j

73. Gajbhiye K, Salve R, Narwade M, et al. Lipid polymer hybrid nanoparticles: a custom-tailored next-generation approach for cancer therapeutics. *Mol Cancer*. 2023;22(1):160. doi:10.1186/s12943-023-01849-0
74. Shi Y, Van Der Meel R, Chen X, et al. The EPR effect and beyond: strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics*. 2020;10(17):7921–7924. doi:10.7150/thno.49577
75. Gautam S, Singh N, Marwaha D, et al. Celastrol-loaded polymeric mixed micelles shows improved antitumor efficacy in 4 T1 bearing xenograft mouse model through spatial targeting. *Int J Pharm*. 2024;659:124234. doi:10.1016/j.ijpharm.2024.124234
76. Xu X, Lu W, Zhang H, et al. Hepatoma-targeting and ros-responsive polymeric micelle-based chemotherapy combined with photodynamic therapy for hepatoma treatment. *Int J Nanomed*. 2024;19:9613–9635. doi:10.2147/ijn.s475531
77. Nan S, Che Y, Gong T, et al. Renal-targeted drug delivery by chitosan oligosaccharide micelles with hsa-enriched protein Corona for the treatment of ischemia/reperfusion-induced acute kidney injury. *ACS Appl Mater Interfaces*. 2024;16(37):49913–49925. doi:10.1021/acsami.4c09665
78. Zhao J, Luo D, Zhang Z, et al. Celastrol-loaded peg-pcl nanomicelles ameliorate inflammation, lipid accumulation, insulin resistance and gastrointestinal injury in diet-induced obese mice. *J Control Release*. 2019;310:188–197. doi:10.1016/j.jconrel.2019.08.026
79. Li Z, Yao L, Li J, et al. Celastrol nanoparticles inhibit corneal neovascularization induced by suturing in rats. *Int J Nanomed*. 2012;7:1163–1173. doi:10.2147/ijn.s27860
80. Li Z, Guo Z, Chu D, et al. Effectively suppressed angiogenesis-mediated retinoblastoma growth using celastrol nanomicelles. *Drug Deliv*. 2020;27(1):358–366. doi:10.1080/10717544.2020.1730522
81. Li Z, Wu X, Li J, et al. Antitumor activity of celastrol nanoparticles in a xenograft retinoblastoma tumor model. *Int J Nanomed*. 2012;7:2389–2398. doi:10.2147/ijn.s29945
82. Li J, Jia Y, Zhang P, et al. Celastrol self-stabilized nanoparticles for effective treatment of melanoma. *Int J Nanomed*. 2020;15:1205–1214. doi:10.2147/ijn.s232603
83. Allen S, Liu Y-G, Kim T, et al. Celastrol-loaded peg-b-pps nanocarriers as an anti-inflammatory treatment for atherosclerosis. *Biomater Sci*. 2019;7(2):657–668. doi:10.1039/c8bm01224e
84. Zhang Y, Ding L, Wang T, et al. A celastrol drug delivery system based on peg derivatives: the structural effects of nanocarriers. *molecules*. 2023;28(3):1040.
85. SoNg X, Zhu R, Guo D, et al. Celastrol loaded pegylated nanographene oxide for highly efficient synergistic chemo/photothermal therapy. *Anticancer Agents Med Chem*. 2023;23(3):306–316. doi:10.2174/1871520622666220519094936
86. Xie X, Zhan C, Wang J, et al. An activatable nano-prodrug for treating tyrosine-kinase-inhibitor-resistant non-small cell lung cancer and for optoacoustic and fluorescent imaging. *Small*. 2020;16(38):e2003451. doi:10.1002/smll.202003451
87. Cheng X, Gao J, Ding Y, et al. Multi-functional liposome: a powerful theranostic nano-platform enhancing photodynamic therapy. *Adv Sci*. 2021;8(16):e2100876. doi:10.1002/advs.202100876
88. Zhang Y, Sun C, Wang C, et al. Lipids and lipid derivatives for rna delivery. *Chem Rev*. 2021;121(20):12181–12277. doi:10.1021/acs.chemrev.1c00244
89. He P, Zou M, Zhang C, et al. Celastrol-loaded hyaluronic acid/cancer cell membrane lipid nanoparticles for targeted hepatocellular carcinoma prevention. *Cells*. 2024;13(21):1819.
90. Zhang X, Zhang T, Zhou X, et al. Enhancement of oral bioavailability of tripterine through lipid nanospheres: preparation, characterization, and absorption evaluation. *J Pharmaceut Sci*. 2014;103(6):1711–1719. doi:10.1002/jps.23967
91. Chen Y, Zhou L, Yuan L, et al. Formulation, characterization, and evaluation of in vitro skin permeation and in vivo pharmacodynamics of surface-charged tripterine-loaded nanostructured lipid carriers. *Int J Nanomed*. 2012;7:3023–3032. doi:10.2147/ijn.s32476
92. Chen X, Hu X, Hu J, et al. Celastrol-loaded galactosylated liposomes effectively inhibit akt/c-met-triggered rapid hepatocarcinogenesis in mice. *Mol Pharmaceut*. 2020;17(3):738–747. doi:10.1021/acs.molpharmaceut.9b00428
93. Wu Q, Wang J, Wang Y, et al. Targeted delivery of celastrol to glomerular endothelium and podocytes for chronic kidney disease treatment. *Nano Res*. 2022;15(4):3556–3568. doi:10.1007/s12274-021-3894-x
94. Zheng J, Yang N, Wan Y, et al. Celastrol-loaded biomimetic nanodrug ameliorates apap-induced liver injury through modulating macrophage polarization. *J Mol Med*. 2023;101(6):699–716. doi:10.1007/s00109-023-02321-8
95. Li W, Zhang T, Ye Y, et al. Enhanced bioavailability of tripterine through lipid nanoparticles using broccoli-derived lipids as a carrier material. *Int J Pharm*. 2015;495(2):948–955. doi:10.1016/j.ijpharm.2015.10.011
96. Richfield O, Piotrowski-Daspit A, Shin K, et al. Rational nanoparticle design: optimization using insights from experiments and mathematical models. *J Control Release*. 2023;360:772–783. doi:10.1016/j.jconrel.2023.07.018
97. Tehrani S, Bharadwaj P, Leblond Chain J, et al. Purification processes of polymeric nanoparticles: how to improve their clinical translation? *J Control Release*. 2023;360:591–612. doi:10.1016/j.jconrel.2023.06.038
98. Ong S, Zhang C, Dong X, et al. Recent advances in polymeric nanoparticles for enhanced fluorescence and photoacoustic imaging. *Angew Chem*. 2021;60(33):17797–17809. doi:10.1002/anie.202101964
99. Alamdari S, Amini M, Jalilzadeh N, et al. Recent advances in nanoparticle-based photothermal therapy for breast cancer. *J Control Release*. 2022;349:269–303. doi:10.1016/j.jconrel.2022.06.050
100. Zeng X, Zhu X, Tian Q, et al. Celastrol-conjugated chitosan oligosaccharide for the treatment of pancreatic cancer. *Drug Delivery*. 2022;29(1):89–98. doi:10.1080/10717544.2021.2018521
101. Zhang X, Xu X, Wang X, et al. Hepatoma-targeting and reactive oxygen species-responsive chitosan-based polymeric micelles for delivery of celastrol. *Carbohydr Polym*. 2023;303:120439. doi:10.1016/j.carbpol.2022.120439
102. Pang M, Duan S, Zhao M, et al. Co-delivery of celastrol and lutein with ph sensitive nano micelles for treating acute kidney injury. *Toxicol Appl Pharmacol*. 2022;450:116155. doi:10.1016/j.taap.2022.116155
103. Xiao Y, Li X, Mao J, et al. Reverse anti-breast cancer drug resistance effects by a novel two-step assembled nano-celastrol medicine. *Nanoscale*. 2022;14(21):7856–7863. doi:10.1039/d2nr02064e
104. Nooreen R, Nene S, Jain H, et al. Polymer nanotherapeutics: a versatile platform for effective rheumatoid arthritis therapy. *J Control Release*. 2022;348:397–419. doi:10.1016/j.jconrel.2022.05.054

105. Ekladious I, Colson Y, Grinstaff M. Polymer-drug conjugate therapeutics: advances, insights and prospects. *Nat Rev Drug Discov*. 2019;18(4):273–294. doi:10.1038/s41573-018-0005-0
106. boridy S, Soliman G, maysinger D. Modulation of inflammatory signaling and cytokine release from microglia by celastrol incorporated into dendrimer nanocarriers. *Nanomedicine*. 2012;7(8):1149–1165. doi:10.2217/nnm.12.16
107. Ding L, Wang X, Wang T, et al. Effect of lipophilic chains on the antitumor effect of a dendritic nano drug delivery system. *Molecules*. 2022;28(1):69. doi:10.3390/molecules28010069
108. Wang X, Chauhan G, Tacderas AR, et al. Surface-modified inhaled microparticle-encapsulated celastrol for enhanced efficacy in malignant pleural mesothelioma. *Int J Mol Sci*. 2023;24(6):5204.
109. Li Y, Yang L, Xu X, et al. Multifunctional size-expandable nanomedicines enhance tumor accumulation and penetration for synergistic chemo-photothermal therapy. *ACS Appl Mater Interfaces*. 2021;13(39):46361–46374. doi:10.1021/acsami.1c14170
110. Sanna V, Chamcheu J, Pala N, et al. Nanoencapsulation of natural triterpenoid celastrol for prostate cancer treatment. *Int J Nanomed*. 2015;10:6835–6846. doi:10.2147/ijn.s93752
111. Wei G, Chen J, Jing Z, et al. Glucose transporter 1 (Glut1)-targeting and hypoxia-activated mitochondria-specific chemo-thermal therapy via a glycosylated poly(amido amine)/celastrol (pamam/cel) complex. *J Colloid Interface Sci*. 2022;608(pt 2):1355–1365. doi:10.1016/j.jcis.2021.10.129
112. Zhong R, Talebian S, Mendes B, et al. Hydrogels for rna delivery. *Nat Mater*. 2023;22(7):818–831. doi:10.1038/s41563-023-01472-w
113. Chao D, Dong Q, Yu Z, et al. Specific nanodrug for diabetic chronic wounds based on antioxidase-mimicking mof-818 nanozymes. *J Am Chem Soc*. 2022;144(51):23438–23447. doi:10.1021/jacs.2c09663
114. Soni S, D'elia A, Alsasa A, et al. Sustained release of drug-loaded nanoparticles from injectable hydrogels enables long-term control of macrophage phenotype. *Biomater Sci*. 2022;10(24):6951–6967. doi:10.1039/d2bm01113a
115. Jang D, Heo J, Jannah F, et al. Stimulus-responsive tubular conjugated polymer 2D nanosheets. *Angew Chem*. 2022;61(43):e202211465. doi:10.1002/anie.202211465
116. Mousazadeh H, Bonabi E, Zarghami N. Stimulus-responsive drug/gene delivery system based on polyethylenimine cyclodextrin nanoparticles for potential cancer therapy. *Carbohydr Polym*. 2022;276:118747. doi:10.1016/j.carbpol.2021.118747
117. Ovais M, Mukherjee S, Pramanik A, et al. Designing stimuli-responsive upconversion nanoparticles that exploit the tumor microenvironment. *Adv Mater*. 2020;32(22):e2000055. doi:10.1002/adma.202000055
118. Jiang Q, Zhang S. Stimulus-responsive drug delivery nanoplatforms for osteoarthritis therapy. *Small*. 2023;19(23):e2206929. doi:10.1002/smll.202206929
119. An L, Li Z, Shi L, et al. Inflammation-targeted celastrol nanodrug attenuates collagen-induced arthritis through NF-κB and Notch1 pathways. *Nano Lett*. 2020;20(10):7728–7736. doi:10.1021/acs.nanolett.0c03279
120. Guo C, Diao N, Zhang D, et al. Achyranthes polysaccharide based dual-responsive nano-delivery system for treatment of rheumatoid arthritis. *Int J Biol Macromol*. 2023;234:123677. doi:10.1016/j.ijbiomac.2023.123677
121. Zhao X, Huang C, Su M, et al. Reactive oxygen species-responsive celastrol-loaded: bilirubin nanoparticles for the treatment of rheumatoid arthritis. *AAPS J*. 2021;24(1):14. doi:10.1208/s12248-021-00636-3
122. Choi K, Han H, Lee E, et al. Hyaluronic acid-based activatable nanomaterials for stimuli-responsive imaging and therapeutics: beyond cd44-mediated drug delivery. *Adv Mater*. 2019;31(34):e1803549. doi:10.1002/adma.201803549
123. Ding H, Tan P, Fu S, et al. Preparation and application of pH-responsive drug delivery systems. *J Control Release*. 2022;348:206–238. doi:10.1016/j.jconrel.2022.05.056
124. Gannimani R, Walvekar P, Naidu V, et al. Acetal containing polymers as ph-responsive nano-drug delivery systems. *J Control Release*. 2020;328:736–761. doi:10.1016/j.jconrel.2020.09.044
125. Jin T, Wu D, Liu X, et al. Intra-articular delivery of celastrol by hollow mesoporous silica nanoparticles for ph-sensitive anti-inflammatory therapy against knee osteoarthritis. *J Nanobiotechnol*. 2020;18(1):94. doi:10.1186/s12951-020-00651-0
126. Zheng Z, Chen X, Ma Y, et al. Dual H(2) O(2) -amplified nanofactory for simultaneous self-enhanced nir-ii fluorescence activation imaging and synergistic tumor therapy. *Small*. 2022;18(37):e2203531. doi:10.1002/smll.202203531
127. Chen Y, Guo M, Qu D, et al. Furin-responsive triterpenine-based liposomal complex enhances anticervical cancer therapy through size modulation. *Drug Deliv*. 2020;27(1):1608–1624. doi:10.1080/10717544.2020.1827086
128. Chen S, Zhao L, Chen Z, et al. Self-delivery biomedicine for enhanced photodynamic therapy by feedback promotion of tumor autophagy. *Acta Biomater*. 2023;158:599–610. doi:10.1016/j.actbio.2022.12.059
129. Zhu H, Luo H, Chang R, et al. Protein-based delivery systems for rna delivery. *J Control Release*. 2023;363:253–274. doi:10.1016/j.jconrel.2023.09.032
130. Ding B, Wahid M, Wang Z, et al. Triptolide and celastrol loaded silk fibroin nanoparticles show synergistic effect against human pancreatic cancer cells. *Nanoscale*. 2017;9(32):11739–11753. doi:10.1039/c7nr03016a
131. Rabbani G, Ahn S. Structure, enzymatic activities, glycation and therapeutic potential of human serum albumin: a natural cargo. *Int J Biol Macromol*. 2019;123:979–990. doi:10.1016/j.ijbiomac.2018.11.053
132. Tao H, Wang R, Sheng W, et al. The development of human serum albumin-based drugs and relevant fusion proteins for cancer therapy. *Int J Biol Macromol*. 2021;187:24–34. doi:10.1016/j.ijbiomac.2021.07.080
133. Fan N, Zhao J, Zhao W, et al. Celastrol-loaded lactosylated albumin nanoparticles attenuate hepatic steatosis in non-alcoholic fatty liver disease. *J Control Release*. 2022;347:44–54. doi:10.1016/j.jconrel.2022.04.034
134. Fan N, Zhao J, Zhao W, et al. Biodegradable celastrol-loaded albumin nanoparticles ameliorate inflammation and lipid accumulation in diet-induced obese mice. *Biomater Sci*. 2022;10(4):984–996. doi:10.1039/d1bm01637g
135. Hakala T, Davies S, Toprakcioglu Z, et al. A microfluidic co-flow route for human serum albumin-drug-nanoparticle assembly. *Chemistry*. 2020;26(27):5965–5969. doi:10.1002/chem.202001146
136. Abdelmoneem M, Abd Elwakil M, khattab S, et al. Lactoferrin-dual drug nanoconjugate: synergistic anti-tumor efficacy of docetaxel and the NF-κB inhibitor celastrol. *Mater Sci Eng C Mater Biol Appl*. 2021;118:111422. doi:10.1016/j.msec.2020.111422
137. Xu Y, Fourniols T, Labrak Y, et al. Surface modification of lipid-based nanoparticles. *ACS Nano*. 2022;16(5):7168–7196. doi:10.1021/acsnano.2c02347

138. Tiwari P, Yadav K, Shukla R, et al. Surface modification strategies in translocating nano-vesicles across different barriers and the role of bio-vesicles in improving anticancer therapy. *J Control Release*. 2023;363:290–348. doi:10.1016/j.jconrel.2023.09.016
139. Zhao Z, Ukidve A, Kim J, et al. Targeting strategies for tissue-specific drug delivery. *Cell*. 2020;181(1):151–167. doi:10.1016/j.cell.2020.02.001
140. Soe Z, Thapa R, Ou W, et al. Folate receptor-mediated celastrol and irinotecan combination delivery using liposomes for effective chemotherapy. *Colloids Surf b Biointerfaces*. 2018;170:718–728. doi:10.1016/j.colsurfb.2018.07.013
141. Law S, Leung A, Xu C. Folic acid-modified celastrol nanoparticles: synthesis, characterization, anticancer activity in 2d and 3d breast cancer models. *Artif Cells Nanomed Biotechnol*. 2020;48(1):542–559. doi:10.1080/21691401.2020.1725025
142. Niemelä E, Desai D, Lundsten E, et al. Quantitative bioimage analytics enables measurement of targeted cellular stress response induced by celastrol-loaded nanoparticles. *Cell Stress Chaperones*. 2019;24(4):735–748. doi:10.1007/s12192-019-00999-9
143. Niu W, Wang J, Wang Q, et al. Celastrol loaded nanoparticles with ros-response and ros-inducer for the treatment of ovarian cancer. *Front Chem*. 2020;8:574614. doi:10.3389/fchem.2020.574614
144. Hu Y, Chen X, Xu Y, et al. Hierarchical assembly of hyaluronan coated albumin nanoparticles for pancreatic cancer chemoimmunotherapy. *Nanoscale*. 2019;11(35):16476–16487. doi:10.1039/c9nr03684a
145. Xia F, Lu Y, Gong Z, et al. Cancer immunotherapy based on the bidirectional reprogramming of the tumor microenvironment by a "brakes off/step on the accelerator" core-shell manganese phosphate/sipd-l1 modulator. *Exploration*. 2025;5(3):270009. doi:10.1002/exp.70009
146. Wang S, Zhou L, Tian H, et al. Site-specific nanomodulator capable of modulation apoptosis for enhanced colorectal cancer chemo-photothermal therapy. *J Nanobiotechnol*. 2023;21(1):24. doi:10.1186/s12951-023-01779-5
147. Xia Q, Zhang Y, Li Z, et al. Red blood cell membrane-camouflaged nanoparticles: a novel drug delivery system for antitumor application. *Acta Pharm Sin B*. 2019;9(4):675–689. doi:10.1016/j.apsb.2019.01.011
148. Zhang M, Cheng S, Jin Y, et al. Membrane engineering of cell membrane biomimetic nanoparticles for nanoscale therapeutics. *Clin Transl Med*. 2021;11(2):e292. doi:10.1002/ctm2.292
149. Yang N, Li M, Wu L, et al. Peptide-anchored neutrophil membrane-coated biomimetic nanodrug for targeted treatment of rheumatoid arthritis. *J Nanobiotechnol*. 2023;21(1):13. doi:10.1186/s12951-023-01773-x
150. Zhou X, Yu R, Cao X, et al. Bio-mimicking nanoparticles for targeted therapy of malignant melanoma. *J Biomed Nanotechnol*. 2019;15(5):993–1004. doi:10.1166/jbn.2019.2739
151. Cao X, Hu Y, Luo S, et al. Neutrophil-mimicking therapeutic nanoparticles for targeted chemotherapy of pancreatic carcinoma. *Acta Pharm Sin B*. 2019;9(3):575–589. doi:10.1016/j.apsb.2018.12.009
152. Zhou X, Cao X, Tu H, et al. Inflammation-targeted delivery of celastrol via neutrophil membrane-coated nanoparticles in the management of acute pancreatitis. *Mol Pharmaceut*. 2019;16(3):1397–1405. doi:10.1021/acs.molpharmaceut.8b01342
153. Zhou M, Liao J, Lai W, et al. A celastrol-based nanodrug with reduced hepatotoxicity for primary and metastatic cancer treatment. *Ebiomedicine*. 2023;94:104724. doi:10.1016/j.ebiom.2023.104724
154. Zhu S, Sun F, Zhao P, et al. Brain-targeting biomimetic nanoparticles for codelivery of celastrol and ly2157299 for reversing glioma immunosuppression. *Int J Pharm*. 2022;619:121709. doi:10.1016/j.ijpharm.2022.121709
155. Yu C, Liu H, Guo C, et al. Dextran sulfate-based mmp-2 enzyme-sensitive sr-a receptor targeting nanomicelles for the treatment of rheumatoid arthritis. *Drug Deliv*. 2022;29(1):454–465. doi:10.1080/10717544.2022.2032482
156. Gong T, Tan T, Zhang P, et al. Palmitic acid-modified bovine serum albumin nanoparticles target scavenger receptor-a on activated macrophages to treat rheumatoid arthritis. *Biomaterials*. 2020;258:120296. doi:10.1016/j.biomaterials.2020.120296
157. Deng L, Zhang H, Zhang Y, et al. An exosome-mimicking membrane hybrid nanoplatform for targeted treatment toward kras-mutant pancreatic carcinoma. *Biomater Sci*. 2021;9(16):5599–5611. doi:10.1039/d1bm00446h
158. Elhasany K, khattab S, Bekhit A, et al. Combination of magnetic targeting with synergistic inhibition of nf-κb and glutathione via micellar drug nanomedicine enhances its anti-tumor efficacy. *Eur J Pharm Biopharm*. 2020;155:162–176. doi:10.1016/j.ejpb.2020.08.004
159. Zhu S, Luo C, Feng W, et al. Selenium-deposited tripterine phytosomes ameliorate the antiarthritic efficacy of the phytomedicine via a synergistic sensitization. *Int J Pharm*. 2020;578:119104. doi:10.1016/j.ijpharm.2020.119104
160. Park S, Kang S, Veach A, et al. Self-assembled nanoplatform for targeted delivery of chemotherapy agents via affinity-regulated molecular interactions. *Biomaterials*. 2010;31(30):7766–7775. doi:10.1016/j.biomaterials.2010.06.038
161. Qian Y, Zhang J, Xu R, et al. Nanoparticles based on polymers modified with ph-sensitive molecular switch and low molecular weight heparin carrying celastrol and ferrocene for breast cancer treatment. *Int J Biol Macromol*. 2021;183:2215–2226. doi:10.1016/j.ijbiomac.2021.05.204
162. Liu Y, Li J. Self-assembling nanoarchitectonics of size-controllable celastrol nanoparticles for efficient cancer chemotherapy with reduced systemic toxicity. *J Colloid Interface Sci*. 2023;636:216–222. doi:10.1016/j.jcis.2022.12.162
163. Geng Y, xiang J, Shao S, et al. Mitochondria-targeted polymer-celastrol conjugate with enhanced anticancer efficacy. *J Control Release*. 2022;342:122–133. doi:10.1016/j.jconrel.2022.01.002
164. Zhao M, Li J, Chen F, et al. Engineering nanoparticles boost tnbc therapy by CD24 blockade and mitochondrial dynamics regulation. *J Control Release*. 2023;355:211–227. doi:10.1016/j.jconrel.2023.01.075
165. You C, Wu H, Gao Z, et al. Subcellular co-delivery of two different site-oriented payloads based on multistage targeted polymeric nanoparticles for enhanced cancer therapy. *J Mat Chem B*. 2018;6(42):6752–6766. doi:10.1039/c8tb02230e
166. Yin J, Wang P, Yin Y, et al. Optimization on biodistribution and antitumor activity of tripterine using polymeric nanoparticles through res saturation. *Drug Deliv*. 2017;24(1):1891–1897. doi:10.1080/10717544.2017.1410260
167. Chen S, Zhu F, Nie Z, et al. pH-Activatable charge-reversal polymer-based nanocarriers for targeted delivery of antihepatoma compound. *Langmuir*. 2023;39(38):13588–13598. doi:10.1021/acs.langmuir.3c01604
168. Qin S, Wu B, Gong T, et al. Targeted delivery via albumin Corona nanocomplex to renal tubules to alleviate acute kidney injury. *J Control Release*. 2022;349:401–412. doi:10.1016/j.jconrel.2022.07.013
169. Deng C, Zhang Q, He P, et al. Targeted apoptosis of macrophages and osteoclasts in arthritic joints is effective against advanced inflammatory arthritis. *Nat Commun*. 2021;12(1):2174. doi:10.1038/s41467-021-22454-z
170. Gong T, Zhang P, Deng C, et al. An effective and safe treatment strategy for rheumatoid arthritis based on human serum albumin and kolliphor ® HS 15. *Nanomedicine*. 2019;14(16):2169–2187. doi:10.2217/nnm-2019-0110

171. Guo L, Luo S, Du Z, et al. Targeted delivery of celastrol to mesangial cells is effective against mesangioproliferative glomerulonephritis. *Nat Commun*. 2017;8(1):878. doi:10.1038/s41467-017-00834-8
172. Choi J, Ramasamy T, Kim S, et al. Pegylated lipid bilayer-supported mesoporous silica nanoparticle composite for synergistic co-delivery of axitinib and celastrol in multi-targeted cancer therapy. *Acta Biomater*. 2016;39:94–105. doi:10.1016/j.actbio.2016.05.012
173. Hu Y, Miao Z, Zhang X, et al. Preparation of microkernel-based mesoporous (sio(2)-cdte-sio(2))@sio(2) fluorescent nanoparticles for imaging screening and enrichment of heat shock protein 90 inhibitors from tripterygium wilfordii. *Anal Chem*. 2018;90(9):5678–5686. doi:10.1021/acs.analchem.7b05295
174. Choi J, Gupta B, Ramasamy T, et al. Pegylated polyaminoacid-capped mesoporous silica nanoparticles for mitochondria-targeted delivery of celastrol in solid tumors. *Colloids Surf B Biointerfaces*. 2018;165:56–66. doi:10.1016/j.colsurfb.2018.02.015
175. Niemela E, Desai D, Nkizinkiko Y, et al. Sugar-decorated mesoporous silica nanoparticles as delivery vehicles for the poorly soluble drug celastrol enables targeted induction of apoptosis in cancer cells. *Eur J Pharm Biopharm*. 2015;96:11–21. doi:10.1016/j.ejpb.2015.07.009
176. Zhou R, You J, Zha Z, et al. Biotin decorated celastrol-loaded zif-8 nano-drug delivery system targeted epithelial ovarian cancer therapy. *Biomed Pharmacother*. 2023;167:115573. doi:10.1016/j.biopha.2023.115573
177. Maysinger D, Moquin A, Choi J, et al. Gold nanourchins and celastrol reorganize the nucleo- and cytoskeleton of glioblastoma cells. *Nanoscale*. 2018;10(4):1716–1726. doi:10.1039/c7nr07833a