Review Articles

Acupuncture and Herbal Medicine

Emerging drug delivery strategies in natural products and traditional Chinese medicine research: from individual approaches to integrated design

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Abstract

Natural products and bioactive constituents derived from traditional Chinese medicine (TCM) are major sources of innovation in modern drug discovery and formulation because of their remarkable structural diversity and multidimensional pharmacological activities. However, their clinical translation is frequently hindered by poor solubility, limited stability, low systemic exposure, inefficient tissue delivery, and narrow therapeutic windows. In recent years, drug delivery technologies have advanced the field beyond conventional solubilization, stabilization, and encapsulation toward more integrated strategies that enable targeted delivery, barrier penetration, microenvironment-responsive release, and combination therapy. More importantly, certain natural products are no longer regarded solely as therapeutic cargoes but are increasingly repurposed as functional excipients that enhance structural assembly, delivery efficiency, targeting, and pharmacological synergy. This shift is driving a transition from formulation optimization centered on single active ingredients to integrated drug–excipient design. It also enables contemporary delivery science to reconnect with the holistic philosophy of TCM and the compatibility principles embodied in the monarch, minister, assistant, and guide framework. In this review, we examine the dual roles of natural products in drug delivery systems. We first summarize the developability barriers, delivery mechanisms, and representative optimization strategies associated with their application as therapeutic agents. We then highlight their emerging functions as excipients, focusing on key functional roles, construction paradigms, and recent advances in multifunctional delivery platforms integrating lipid nanoparticles, proteins, antibodies, nucleic acids, and living therapeutics. We further outline representative preclinical applications in cancer, neurodegenerative, metabolic, inflammatory, and immune-related diseases. Collectively, research on natural product–based delivery systems is evolving from single-formulation optimization toward integrated design guided by disease context, material functionality, and the holistic principles of TCM, thereby providing new conceptual and technological foundations for formulation innovation and clinical translation.

Keywords: Drug delivery systems, Integrated design, Natural products, Preclinical studies, Traditional Chinese medicine research

Introduction

Natural products, derived from plants, animals, microorganisms, and endogenous metabolites, have long served as foundational resources for drug discovery and the modernization of traditional Chinese medicine (TCM) research[1–4]. Landmark examples, including paclitaxel[5], camptothecin[6,7], and artemisinin[8], demonstrate that nature-derived molecules not only provide a rich reservoir of chemical scaffolds but also continue to reveal novel therapeutic targets and mechanistic insights for the treatment of complex diseases[6–8]. From the perspective of TCM research, natural products are particularly characterized by their multicomponent, multitarget, and multipathway modes of action[9–12] and have shown broad therapeutic potential in cancer[1,4], inflammation[9], neurodegenerative disorders[11], and metabolic dysregulation[10].

Despite their therapeutic promise, the translation of natural products from pharmacological discovery to clinical application remains challenging[4,11,13]. Many natural products are characterized by poor aqueous solubility, high crystallinity, chemical instability, low oral absorption, extensive first-pass metabolism, short circulation times, and inadequate tissue selectivity[4,14–19]. Their effective delivery is further hindered by physiological

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and pathological barriers, including the tumor microenvironment[20], the blood–brain barrier[21–24], the intestinal mucus barrier[25,26], and inflammatory lesion barriers[27]. Consequently, drug delivery systems have evolved from supportive formulation tools into central enabling technologies for the modern translation of natural products and bioactive compounds derived from TCM[1,4,11]. Recent advances have expanded the field far beyond solubility enhancement and encapsulation optimization to include targeted delivery[15,16,18,28,29], stimuli-responsive release[9,30,31], lesion-specific accumulation[20,29], combination therapy[9,32], and biomimetic delivery[29,30], thereby more systematically reshaping the *in vivo* fate and therapeutic performance of natural products[4,11].

For decades, the modernization of TCM has largely centered on isolating active constituents from complex medicinal materials or formulations and developing them into evaluable and scalable drug products using modern pharmaceutical technologies[33–37]. This strategy has substantially advanced both the understanding of the material basis underlying TCM activity and the development of modern pharmaceutics[1,4,38]. However, it has also shifted attention from holistic compatibility toward single-compound optimization, resulting in a partial disconnect from the TCM principles of systemic regulation and synergistic intervention. With the emergence of the drug–excipient combination paradigm and integrated design concepts[29,30,32,39], this landscape is now changing. Selected natural products are no longer regarded merely as passive cargoes; instead, they are increasingly incorporated directly into delivery systems as structural units[40,41], interfacial modulators[42,43], targeting components[44,45], and synergistic pharmacological agents[46,47], thereby establishing tighter functional coupling between the carrier and the therapeutic payload[30,32]. This narrative review was developed through a focused literature search of PubMed, Web of Science, Scopus, and Google Scholar covering publications from 2006 to 2026. The search combined terms related to natural products, traditional Chinese medicine, drug delivery systems, nanomedicine, functional excipients, biomimetic delivery, nucleic acid delivery, living therapeutics, and disease-specific applications. Reference lists of relevant review articles and key primary studies were also screened to identify additional publications. Studies were selected based on their relevance to the developability barriers, delivery mechanisms, functional roles, preclinical efficacy, safety, and translational potential of natural product-based delivery systems. This article is intended as a narrative review and was not designed as a systematic review or meta-analysis; therefore, no formal risk-of-bias assessment or quantitative data synthesis was performed.

From the TCM perspective, this transition is particularly significant. Drug–excipient combination strategies do not merely increase material complexity; they also re-establish functional division and synergistic interactions among components within a modern delivery framework[30,32]. While the therapeutic cargo provides the principal pharmacological effect, functional excipients can confer stabilization, targeting capability, protection, potentiation, toxicity mitigation, and tissue

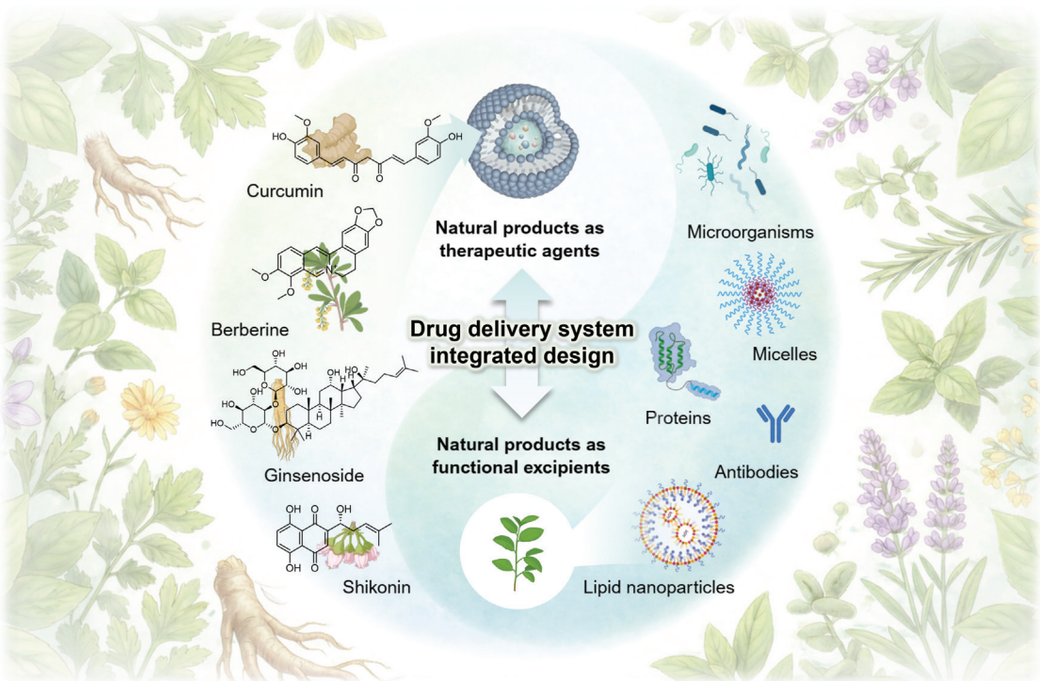


Figure 1. Drug delivery strategies in natural product and traditional Chinese medicine (TCM) research are evolving from a conventional focus on natural products as therapeutic cargoes toward an integrated design framework that harnesses their dual roles as both therapeutics and functional excipients, thereby advancing targeted delivery and providing new opportunities for the innovation and translation of modern TCM formulations. Created with BioRender.

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adaptability[30,32,46]. This logic is methodologically consistent with the monarch, minister, assistant, and guide principles in TCM, which emphasize hierarchical cooperation, synergistic enhancement, and the moderation of undesirable properties[34,48–51]. Consequently, natural product delivery research is moving beyond formulation optimization centered on single active ingredients toward a more integrated design philosophy that is increasingly aligned with the holistic principles of TCM[30,32,39,52]. Against this background, this review examines the dual roles of natural products as both therapeutic entities and functional excipients. It provides a systematic overview of recent progress and emerging trends in integrated delivery design to inform the development of innovative modern formulations for TCM (Figure 1).

Natural products as therapeutic agents: drug delivery systems enhance their developability

Developability barriers of natural products and the interventional roles of drug delivery systems

Physicochemical properties

Natural products are structurally complex and exhibit wide variations in polarity. Their developability is often constrained by poor aqueous solubility, high crystallinity, limited chemical stability, and sensitivity to light, heat, and oxidative conditions[4,14–16]. Flavonoids and polyphenols, such as curcumin, resveratrol, quercetin, and fisetin, are typically highly hydrophobic and prone to rapid *in vitro* degradation, resulting in a narrow formulation window[21,53–57]. Curcumin, for example, has a half-life of less than 1 hour at neutral pH and is highly sensitive to light and heat, which can compromise its bioactivity before it reaches the target tissue[58,59]. Alkaloids, including berberine, camptothecin, and evodiamine, frequently present the dual challenge of poor solubility and insufficient structural stability[7,17,60–62]. Terpenoids and saponins, such as andrographolide, ginsenosides, astragaloside IV, oleanolic acid, and ursolic acid, are likewise often limited by low membrane permeability and poor formulation compatibility[14,63–70]. To address these physicochemical barriers, drug delivery systems can modify the physical state of natural products through nanosizing, encapsulation, complexation, and self-assembly, thereby improving their apparent solubility, dispersibility, and chemical stability[4,15,16,18]. For instance, Zhang et al.[71] developed a disodium glycyrrhizinate-enabled curcumin self-micellar solid dispersion that converted crystalline curcumin into a more soluble dispersed state and markedly improved its bioavailability. Liao et al.[72] incorporated baicalein into a phospholipid complex-based self-microemulsifying system, thereby enhancing its dissolution, lipid stability, and subsequent absorption.

Pharmacokinetics

Beyond physicochemical limitations, natural products often face pharmacokinetic constraints, including poor oral absorption, extensive first-pass metabolism, short plasma half-life, and suboptimal tissue distribution[4,11,14,15,17]. Li et al.[60] developed a self-nanoemulsifying system for berberine to improve oral absorption and overcome the insufficient systemic exposure that limits its therapeutic efficacy following oral administration. Similarly, although curcumin and resveratrol possess well-established anti-inflammatory and neuroprotective properties, their rapid metabolism and clearance *in vivo* make it difficult to maintain therapeutically effective concentrations[21,55,56,73]. In addition, cytochrome P450-mediated metabolism and biliary excretion can further shorten the systemic retention time of certain natural products[74]. In brain disorders, inflammatory bowel disease, and solid tumors, barriers such as the blood–brain barrier, intestinal mucus layer, and tumor microenvironment further restrict delivery to the site of action[20–22,25,27,75]. To address these pharmacokinetic barriers, drug delivery systems can systematically reshape the transport pathways and therapeutic windows of natural products by prolonging circulation time, enhancing transmembrane transport, promoting target tissue accumulation, and improving local retention[4,11,76]. For instance, Meng et al.[22] designed a lactoferrin-modified, low-density lipoprotein-mimicking nanostructured lipid carrier for curcumin delivery, in which the biomimetic lipid composition and surface ligands jointly enhanced brain targeting and facilitated transport across the blood–brain barrier.

Efficacy and safety

Although natural products often enable multitarget regulation, their low systemic exposure and limited efficacy frequently necessitate high doses, creating a persistent trade-off between therapeutic benefit and toxicity[4,11,13,77]. Camptothecin and its derivatives, for example, exhibit well-established cytotoxic activity; however, their development has long been constrained by adverse effects and a narrow therapeutic window[7,61,78]. Likewise, triptolide and celastrol demonstrate potent anti-inflammatory and antitumor activities, but systemic administration can cause severe hepatotoxicity and nephrotoxicity, substantially limiting their clinical application[79–82]. Therefore, improving the developability of natural products requires not only enhancing intrinsic pharmacological activity but also rebalancing efficacy, systemic exposure, and safety. Drug delivery systems can address this challenge through controlled release, targeted delivery, and local accumulation, thereby enhancing therapeutic effects at diseased sites while reducing dose requirements and improving safety[67,83–86]. For example, Cheng et al.[87] co-encapsulated cisplatin and curcumin in liposomes for hepatocellular carcinoma treatment and showed that curcumin enhanced chemosensitivity, whereas the liposomal platform helped reduce cisplatin-associated nonspecific toxicity. For highly toxic Tripterygium-derived compounds, poly(ethylene glycol)-poly(ε-caprolactone) (PEG–PCL) micelles and other nanosystems can similarly reduce systemic exposure and mitigate safety concerns during inflammatory disease treatment[80–82].

Delivery strategies for distinct classes of natural products

Flavonoids and polyphenols

Flavonoids and polyphenols are among the most extensively studied classes in natural product delivery research. Although they are often limited by pronounced hydrophobicity, poor *in vivo* stability, and rapid metabolic clearance, their antioxidant, anti-inflammatory, antitumor, and neuroprotective activities make them attractive candidates

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for therapeutic development[21,53–56]. For curcumin, nanostabilization, lipid-biomimetic targeting, and co-loaded liposomal systems have been employed to enhance brain delivery, improve *in vivo* persistence, and support combination therapy[87]. For quercetin, polymeric micelles and poly(lactic-co-glycolic acid) (PLGA)-based nanoparticles have been utilized to improve oral bioavailability, sustained release, and intracellular delivery[88]. Resveratrol has been incorporated into natural protein–polysaccharide hybrid nanoparticles[73], whereas fisetin has been formulated into lipid carriers and nanocrystals[89]. Collectively, these examples demonstrate that delivery platforms for flavonoids and polyphenols can be tailored to address distinct developability barriers, including poor solubility, limited stability, insufficient absorption, restricted cellular uptake, and inadequate tissue delivery.

Alkaloids

Alkaloid natural products often combine potent pharmacological activity with substantial developability constraints, making drug delivery systems particularly important for their successful translation[7,17,60,61]. Berberine is among the most representative examples and has been formulated into chitosan/alginate nanogels, self-nanoemulsifying systems, and pH-activated oral nanobombs to improve cellular uptake, systemic exposure, and lesion-localized release[20,90]. Nitidine chloride has been delivered using folate-modified D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) micelles and MIL-100(Fe) metal–organic framework carriers, illustrating how targeting strategies and carrier engineering can improve tumor delivery while reducing toxicity[91,92]. For camptothecin and its derivatives, advances in prodrug design, nanoscale formulations, and self-delivering systems are expanding the potential to transform highly potent toxic alkaloids into more clinically manageable candidates[61,78,93].

Terpenoids and saponins

Terpenoids and saponins are highly relevant to TCM and possess substantial value in modern pharmacology, making them another major focus of natural product delivery research[63–65,67–69,86,94–96]. These compounds often exhibit well-defined bioactivities but are limited by poor membrane permeability, inefficient tissue delivery, or rapid *in vivo* clearance[97–100]. Saponins such as ginsenoside Rg3, ginsenoside Rb1, and astragaloside IV have been incorporated into polymeric nanoparticles, lipid nanocapsules, and ligand-modified chitosan nanoparticles to improve formulation stability, local retention, and barrier-crossing delivery[64,68,94,95,101,102]. Among triterpenoids, oleanolic acid and ursolic acid have been incorporated into PEGylated liposomes, calcium carbonate nanoparticles, and stimuli-responsive phytosomes to improve biodistribution, achieve controlled release, and enhance therapeutic performance[69,86]. Likewise, andrographolide delivery has evolved from conventional nanoformulation approaches toward lesion-microenvironment-matched design, as exemplified by oxidation-responsive micelles developed for atherosclerotic plaques[96]. These studies indicate that delivery strategies for terpenoids and saponins are increasingly designed according to both chemical class characteristics and disease-associated transport barriers.

Quinones

Although quinone natural products have been less extensively studied than the classes discussed earlier, they demonstrate considerable potential for delivery-based optimization. Thymoquinone, indirubin, shikonin, and aloe-emodin have been formulated into microcarriers, microemulsion gels, thermosensitive micelles, and solid lipid nanoparticles, respectively, to improve solubility, tumor accumulation, and local administration[103–106]. These compounds often combine pronounced redox activity with intrinsic cytotoxicity, and drug delivery systems can help balance therapeutic efficacy, stability, and safety. Notably, Liu et al.[107] identified shikonin as a natural product with potent antiplatelet activity and engineered an Rg3-stabilized, platelet membrane–coated biomimetic liposomal system, shikonin-loaded platelet membrane-coated liposome (SK-PLT), that integrates membrane stabilization, immune evasion, and thrombus-targeted accumulation. This study demonstrates that biomimetic delivery platforms can reshape the *in vivo* fate of quinone natural products and expand their therapeutic potential.

These examples are summarized in Table 1, which compares representative delivery engineering strategies across major classes of natural products and illustrates how formulation design addresses class-specific barriers related to solubility, stability, targeting, and therapeutic performance.

Natural products as functional excipients: integrated design for drug delivery systems

Enabling properties of natural products as functional excipients

Physicochemical properties

Some natural products possess amphiphilic scaffolds, aromatic conjugated structures, or abundant functional groups, such as hydroxyl, carboxyl, and glycosyl moieties, enabling stable supramolecular assembly through hydrogen bonding, hydrophobic interactions, electrostatic interactions, and π–π stacking[30,39,109,110]. For example, ginsenosides and glycyrrhizic acid combine hydrophobic backbones with hydrophilic sugar chains or polar groups, making them intrinsically suitable for interfacial assembly[32,111,112]. Polyphenols, which are rich in aromatic rings and phenolic hydroxyl groups, readily form complex networks and facilitate rapid assembly[46,113,114]. In contrast, plant polysaccharides often exhibit film-forming ability, adhesiveness, and chemical modifiability, enabling them to function as natural structural frameworks for drug delivery[115–117]. Cyclodextrins, which are cyclic oligosaccharides derived from starch, are notable for their hydrophobic cavities that can encapsulate diverse hydrophobic or poorly soluble compounds, thereby improving aqueous solubility, stability, and bioavailability[118,119].

Pharmacological activity

Unlike conventional inert excipients, natural products can exhibit anti-inflammatory, antioxidant,

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Table 1

Representative delivery engineering strategies for natural products as therapeutic agents

Class	Representative natural product	Representative delivery strategy	Main optimization objective	Representative application	Ref.
Flavonoids/ polyphenols	Curcumin	Brain-targeted LDL-mimicking lipid carrier	Enhances blood–brain barrier transport and brain accumulation	Neurodegenerative diseases	[22]
		High-stability nanoparticles	Enhances intracerebral delivery and neuroprotection	Alzheimer's disease	[53]
		Cisplatin co-loaded liposomes	Combines delivery optimization with chemosensitization	Combination cancer therapy	[87]
	Quercetin	Soluplus/P407 polymeric micelles	Improves oral bioavailability and sustained release	Diabetes	[54]
		PLGA nanoformulation	Enhances mitochondria-mediated apoptosis and antitumor efficacy	Cancer	[88]
	Resveratrol	Zein/fucoidan self-assembled nanoparticles	Improves stability and bioaccessibility	Oral delivery/ anticancer therapy	[73]
	Baicalein	Phospholipid complex–based self-microemulsion	Promotes oral absorption and lymphatic transport	Oral delivery	[72]
	Fisetin	Nanostructured lipid carriers; nanocrystals	Improves stability, cellular uptake, and antitumor activity	Cancer	[89,108]
Alkaloids	Berberine	Self-nanoemulsion	Improves oral absorption and systemic exposure	Acute myeloid leukemia	[60]
		Chitosan/alginate nanogels	Enhances cellular uptake and apoptosis induction	Hepatocellular carcinoma	[90]
		pH-activated oral nanobomb	Enables lesion-localized release and colonic accumulation	Ulcerative colitis	[20]
	Nitidine chloride	Folate-modified TPGS micelles	Improves tumor targeting and cellular uptake	Cancer	[91]
		MIL-100(Fe) metal–organic framework carriers	Reduces toxicity and enhances efficacy	Cancer	[92]
	Camptothecin and derivatives	Prodrug, nanoformulation, and self-delivering systems	Improves clinical usability through detoxification and controlled release	Cancer	[61, 78, 93]
Terpenoids and saponins	Ginsenoside Rg3	PLGA nanoformulation	Amplifies neuroprotective efficacy	Alzheimer's disease	[64]
	Ginsenoside Rb1	Nanoformulation	Enhances anti-inflammatory effects	Gouty arthritis	[95]
	Astragaloside IV	Ultrasmall lipid nanocapsules	Improves posterior-segment ocular delivery	Dry age-related macular degeneration	[68]
		β-Asarone–modified chitosan nanoparticles	Promotes nose-to-brain delivery	Multiple sclerosis	[94]
	Ursolic acid	Dual-stimuli-responsive phytosomes	Improves tumor targeting and release control	Cancer	[86]
	Andrographolide	Oxidation-responsive micelles	Enables lesion-microenvironment-matched delivery	Atherosclerosis	[96]
	Oleanolic acid	PEGylated liposomes	Improves biodistribution and antitumor efficacy	Cancer	[69]
		Cisplatin co-loaded calcium carbonate nanoparticles	Functions as a functional bioactive component in combination therapy	Cancer	[67]
Quinones	Thymoquinone	Microcarriers	Improves delivery performance and translational feasibility	Local/systemic delivery	[103]
	Indirubin	Microemulsion gel	Enhances lesion responsiveness and optimizes release	Smart delivery	[105]
	Aloe-emodin	Solid lipid nanoparticles	Improves solubility, stability, and pharmacological performance	Cancer/local delivery	[106]
	Shikonin	Thermosensitive micelles	Enhances suitability for local administration	Local therapy	[104]
		Rg3-stabilized platelet membrane-biomimetic liposomal SK-PLT	Enhances membrane stability, immune evasion, and thrombus-targeted accumulation	Antithrombotic therapy	[107]

LDL: Low-density lipoprotein; PEG: Polyethylene glycol; PLGA: Poly(lactic-co-glycolic acid); SK-PLT: Shikonin-loaded platelet membrane-coated liposome; TPGS: D-α-tocopheryl polyethylene glycol 1000 succinate.

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immunomodulatory, resistance-reversing, and tissue-protective activities while simultaneously contributing to carrier construction[9,29,32,46,113,120]. Wang et al.[46] proposed the concept of a nanomedicine-cum-carrier, in which natural small molecules co-assemble into systems that integrate delivery and therapeutic functions within the carrier itself, demonstrating that active excipients can pharmacologically reconfigure, rather than merely replace, conventional materials. A review of the dual drug–carrier roles of ginsenosides further highlighted that saponins can function not only as nanostructural scaffolds but also as direct contributors to antitumor therapy by inducing apoptosis, enhancing immune regulation, and reversing drug resistance[32].

Major functional roles of natural products as functional excipients

Structural components

The most direct functional role of natural products is to act as lipid-like components, hydrophobic scaffolds, or crosslinking units for nanostructure construction[30,32,40,109]. With the growing integration of natural products into biotechnological therapeutics, this role is no longer limited to the encapsulation of small-molecule drugs. For example, Chen et al.[41] employed a metal–polyphenol coordination strategy to co-assemble natural phenolic ligands, metal ions, siRNA, and multiple proteins into uniform nanoparticles, demonstrating that polyphenolic natural products can serve as key structural building blocks and mild assembly interfaces for biomacromolecular therapeutics while preserving biological activity. Qu et al.[121] further constructed supramolecular polyphenol–DNA microparticles from tannic acid and DNA, enabling the co-delivery of CpG adjuvant sequences and ovalbumin, and demonstrating that natural polyphenols can serve as scaffold materials for nucleic acid vaccine platforms.

Delivery enhancement

Natural products can also enhance delivery efficiency by improving interfacial stability, promoting adhesion, and facilitating transmembrane uptake[122–126]. Yang et al.[127] developed a multicomponent nano-co-delivery system using Astragalus polysaccharides, which improved the dissolution, permeation, and absorption of flavonoid-related constituents derived from Astragalus, illustrating that natural polysaccharides can function as active delivery enhancers rather than merely as encapsulating matrices. In addition, Shen et al.[43] systematically compared the effects of plant polyphenols, including epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), and gallic acid, on small interfering RNA (siRNA) transport and found that EGCG most effectively promoted siRNA condensation and delivery through low-molecular-weight cationic polymers. These results suggest that natural polyphenols can enhance nucleic acid loading, complex stability, and intracellular transport through hydrogen bonding and hydrophobic interactions. Fan et al.[42] further demonstrated that a cationic polycatechol polymer, P1, incorporating natural catechol motifs markedly improved siRNA binding, serum stability, cellular uptake, and gene-silencing efficiency (Figure 2A).

Targeting functions

Some natural products and their derivatives can endow delivery systems with organ- or lesion-targeting capabilities[130–133]. Xu et al.[134] developed dual-responsive, Angelica polysaccharide-based colon-targeted nanoparticles for inflammatory bowel disease, demonstrating that TCM-derived polysaccharides can function not only as carrier scaffolds but also as targeting components that exploit disease-associated microenvironmental cues to promote local accumulation. For liver targeting, glycyrrhetinic acid– and glycyrrhizic acid–derived structures have shown promise as natural ligands because of their favorable interactions with hepatocyte surface receptors[135,136]. In integrated systems combining natural products with biotherapeutics, polyphenols can further confer tissue tropism to proteins and peptides through surface functionalization. For example, Shin et al.[45] used tannic acid–mediated TANNylation to target protein and peptide therapeutics to the myocardium by promoting binding to elastin and collagen within the cardiac extracellular matrix (Figure 2B). Zhao et al.[44] further engineered erythrocytes, macrophages, natural killer cells, and T cells with polyphenol-functionalized bioactive nanocomposites, thereby creating the Cellnex hybrid-cell system and enabling efficient organ delivery of proteins, DNA, mRNA, and viral vectors.

Pharmacological synergy

A key advantage of using natural products as functional excipients is their capacity to generate therapeutic synergy with the primary drug[137]. Yi et al.[113] constructed antioxidant nanoparticles from amino acids and tea polyphenols, enabling the carrier itself to modulate oxidative stress rather than functioning as an inert packaging material. This advantage is even more evident when natural products are integrated with gene therapeutics. Ding et al.[47] developed a stealth nanogel through the self-assembly of EGCG, siRNA, and protamine, followed by the incorporation of hyaluronic acid and a tumor-homing, membrane-penetrating peptide, which produced markedly greater cytotoxicity against drug-resistant breast cancer cells than EGCG-based chemotherapy alone. Chen et al.[138] designed an ellagic acid-assisted interleukin (IL)-10 mRNA delivery system, demonstrating that natural polyphenols can both stabilize mRNA delivery and synergize with IL-10–mediated anti-inflammatory therapy, thereby suppressing inflammation while promoting mucosal repair and cytoprotection in acute and chronic colitis models.

Major construction paradigms for drug delivery systems using natural products as functional excipients

Lipid delivery systems built with natural products as lipid components

Some natural products exhibit lipid-like interfacial behavior and can therefore be directly incorporated into liposomes, micelles, and lipid-like nanosystems[139]. Guo et al.[111] demonstrated that saponin-based liposomes can partially replace conventional membrane-forming materials while conferring lung-targeting properties. Yang et al.[112] used glycyrrhizic acid to develop an oral paclitaxel delivery system, highlighting the advantages of amphiphilic triterpenoid

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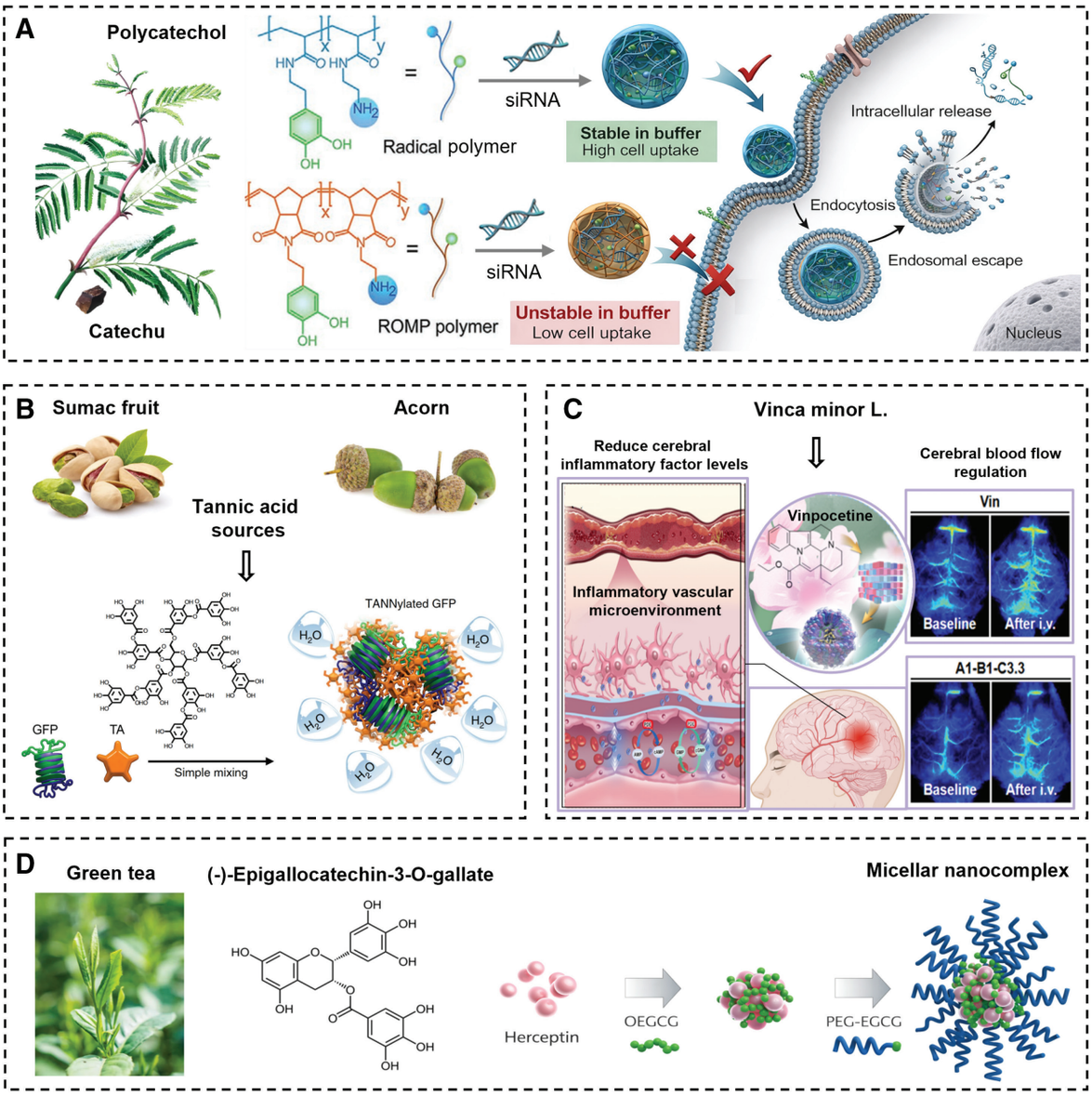


Figure 2. Representative drug delivery systems constructed using natural products. A, Structures of the designed polymers and the proposed gene-silencing mechanism for intracellular siRNA delivery. Reproduced from Fan et al.[42]. B, Schematic diagram illustrating the preparation of TANNylated GFP. Reproduced from Shin et al.[45]. C, Schematic diagram of a vinpocetine-derived lipid delivery system for brain targeting and modulation of cerebral microcirculation. Reproduced from Bian et al.[128]. D, Schematic illustration of the self-assembly process used to form the MNCs, which are generated through two sequential self-assembly steps in an aqueous solution: complexation of OEGCG with proteins to form the core, followed by complexation of PEG–EGCG around the preformed core to generate the shell. Reproduced from Chung et al.[129] GFP: Green fluorescent protein; MNCs: Mononuclear cells; OEGCG: Oligomeric epigallocatechin-3-gallate; PEG-EGCG: Polyethylene glycol-conjugated epigallocatechin-3-gallate; ROMP: Ring-opening metathesis polymerization; siRNA: Small interfering RNA; TA: Tannic acid.

saponins in micellization and drug solubilization. A related review further indicated that ginsenosides can function as both structural components and antitumor synergists in liposomal and biomimetic nanosystems, making them representative examples of integrated delivery design[32]. More recently, this paradigm has been extended to natural alkaloids. Bian et al.[128] developed brain-targeted lipid nanoparticles based on vincamine/vinpocetine-like alkaloid scaffolds, demonstrating that alkaloid-derived lipid-like materials can serve as nucleic acid carrier components while retaining pharmacological functions that regulate cerebral microcirculation, facilitate blood–brain barrier transport, and synergize with siRNA, mRNA, and small-molecule drugs (Figure 2C). In a subsequent study, Bian et al.[140] used the tetrahydroisoquinoline scaffold of protoberberine alkaloids to construct berberine-inspired lipid nanoparticles, demonstrating that natural alkaloid scaffolds can function as lipid-like structural units in lipid nanoparticles (LNPs), enhance nucleic acid loading and stability through poly(A) interactions, and enable brain-targeted delivery *via* D3 receptor-mediated endocytosis.

Natural product–polymer/protein hybrid delivery systems

Integrating natural products with polymers, proteins, or polysaccharides is one of the most common approaches

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for constructing drug delivery systems through integrated design. In this paradigm, natural polysaccharides and protein-based materials can function as carrier scaffolds, stabilizing matrices, or absorption-enhancing components[141]. Representative examples include astragalus polysaccharide-based nano-co-delivery systems, xiancao polysaccharide/zein nanoparticles for curcumin delivery, and zein/fucoidan nanoparticles for resveratrol delivery, which collectively demonstrate the ability of natural polymer composites to improve the stability and gastrointestinal utilization of poorly soluble polyphenolic compounds[73,127,142]. In the context of biotherapeutic delivery, this strategy also extends to metal–polyphenol composite nanoparticles, highlighting the broad compatibility of natural polyphenol–polymer/protein hybrid systems with nucleic acids and protein therapeutics[41].

Self-assembled delivery systems driven by natural products

Self-assembled systems most clearly exemplify the transition of natural products from therapeutic agents to multifunctional materials. Huang et al.[39] proposed a self-assembling nanostrategy for TCM, demonstrating that certain natural small molecules within compatibility systems can form nanoscale assemblies during decoction or coexistence, thereby influencing therapeutic outcomes. Huang et al.[52] further provided a thermodynamic interpretation of phytochemical self-assembly, linking morphological evolution to efficacy enhancement and providing a mechanistic basis for the nanoformulation of TCM compatibility systems. Beyond naturally occurring or coexisting assemblies, drug-derived carriers such as poly(ursolic acid) nanomedicines and curcumin self-micellar solid dispersions illustrate two related modes of self-assembly: carrier-as-therapeutic design and solubility-enhancing self-association[40,71]. Chung et al.[129] constructed a self-assembled micellar nanocomplex from green tea catechin derivatives, in which oligomeric EGCG and Herceptin formed the core and PEG–EGCG formed the shell. This design protected the protein therapeutic during delivery, enabled recovery of activity after dissociation, and improved tumor accumulation, circulation time, and antitumor efficacy both *in vitro* and *in vivo* (Figure 2D). More broadly, self-assembly strategies offer scalable and adaptable approaches for integrating natural products with biotherapeutics.

Living drug delivery systems mediated by natural products

Natural products are also emerging as building blocks for living drug delivery systems. Pan et al.[143] used tannic acid and Fe^{3+} to construct a single-cell nano-coating, termed nanoarmor, on probiotic surfaces, demonstrating that polyphenols can form transient protective shells that improve antibiotic tolerance, intestinal survival, and colonization, thereby enhancing therapeutic efficacy against antibiotic-associated diarrhea. Building on this strategy, Zhu et al.[144] developed an inflammation-responsive nanoarmor-assisted probiotic system that protects probiotics during delivery and degrades within inflamed tissues to restore probiotic activity, thereby improving targeted delivery and intestinal colonization. Hu et al.[145] used nanostructured polyphenols to modify probiotics while co-delivering drugs, thereby creating a synergistic platform for inflammatory bowel disease that combines microenvironmental remodeling, drug synergy, and probiotic amplification. Qi et al.[146] further designed core–shell microneedles that sequentially release tannic acid–magnesium complexes and Lactobacillus-derived extracellular vesicles, illustrating how polyphenols can provide early antibacterial and reactive oxygen species–scavenging effects while synergizing with probiotic-derived vesicles to promote angiogenesis, collagen remodeling, and infected wound repair.

Other paradigms

Beyond the strategies outlined earlier, plant-derived nanovesicles and plant-based nanomaterials represent another important approach[147–149]. Plant-derived nanovesicles combine natural membrane architectures with endogenous bioactive components, conferring favorable biosafety profiles and cross-kingdom regulatory potential[29,150–152]. Self-stabilized Pickering emulsions based on drug nanocrystals represent another emerging paradigm, in which natural bioactive compounds or their nanocrystals, including curcumin, glycyrrhizic acid, diosgenin, luteolin, dihydromyricetin, ursolic acid, and ginkgo extracts, can generate self-stabilized emulsions[153]. These systems highlight the capacity of natural products to provide interfacial stabilization, high drug loading, and reduced reliance on exogenous surfactants[154]. In biotherapeutic delivery, this direction continues to expand. Yu et al.[155] used tannic acid to crosslink urokinase-type plasminogen activator and a thrombin-cleavable peptide on a template surface, thereby constructing bioresponsive polyphenol-based thrombus-targeting nanoparticles. This work demonstrates that natural polyphenols can enable lesion-responsive protein release while reducing uptake by the mononuclear phagocyte system[155].

Table 2 consolidates these construction paradigms, illustrating how natural products can be incorporated as lipid-like components, polymer/protein partners, self-assembly drivers, living-system interfaces, or other functional excipients to support integrated drug–excipient design.

Preclinical progress of natural product–based drug delivery systems

Cancer

Cancer remains the most extensively explored application area for natural product–based drug delivery systems[19,156–161]. Lipid carriers and nanocrystal formulations have been developed for fisetin to improve its stability, cellular uptake, and antitumor activity[89,108]. PLGA nanoparticles have likewise been used to enhance the mitochondria-mediated antitumor efficacy of quercetin[88]. Other examples, including folate-modified nitidine chloride micelles, nitidine chloride-loaded metal–organic framework carriers, and ursolic acid phytosomes, further illustrate a broader shift toward improving the therapeutic index of anticancer natural products through targeting strategies, stimuli-responsive release, and combinatorial design[86,91,92].

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Table 2

Major construction paradigms and representative systems using natural products as functional excipients

Construction paradigm	Representative natural product/material	Functional role	Representative integrated object/system	Representative advantage or use	Ref.
Lipid delivery systems built with natural products as lipid components	Platycodon–glycyrrhiza herb-pair saponins	Lipid-component replacement + structural stabilization + lung targeting	Liposomes in which saponins replace cholesterol	Lung cancer–targeted delivery exemplifies the materialization of TCM herb-pair compatibility	[111]
	Glycyrrhizic acid	Amphiphilic functional excipient + micellar component	Paclitaxel–glycyrrhizic acid micelles	Improves oral delivery while providing intrinsic bioactivity	[112]
	Ginsenosides	Dual-function drug/nanocarrier	Multifunctional lipidic/biomimetic nanosystems incorporating saponins	Provides structural support, membrane interactions, and antitumor synergy	[32]
	Vincamine/vinpocetine-like alkaloids	Lipid-like core component + pharmacological synergy	Brain-targeted LNPs	Retains microcirculation regulation, blood–brain barrier transport, and synergy with siRNA, mRNA, small molecules	[128]
	Protoberberine alkaloids	Key lipid-like structural unit + nucleic acid stabilization	Berberine-inspired brain-targeted LNPs	Enhances poly(A)-associated nucleic acid loading and stability and enables D3 receptor-mediated brain targeting	[140]
Natural product–polymer/protein hybrid delivery systems	Astragalus polysaccharides	Carrier scaffold + co-delivery facilitator	Multicomponent nano-co-delivery systems	Improves dissolution, permeation, and absorption of poorly soluble or poorly permeable actives	[127]
	Mesona polysaccharide–zein	Composite stabilization + delivery enhancement	Self-assembled composite nanoparticles for curcumin	Improves stability and gastrointestinal utilization of hydrophobic natural products	[142]
	Zein–fucoidan	Composite stabilization + delivery enhancement	Self-assembled composite nanoparticles for resveratrol	Improves resveratrol stability, bioavailability, and delivery efficiency	[73]
	Tannic acid	Surface functionalization + tissue targeting	TANNylated protein/peptide therapeutics	Enhances binding to myocardial elastin and collagen for heart-targeted protein delivery	[45]
	Natural phenolic ligands/metal–polyphenol networks	Mild assembly interface + biomacromolecule compatibility	Metal–polyphenol composite nanoparticles integrating siRNA and multiple proteins	Enables mild assembly, broad compatibility, and preservation of biomacromolecular activity	[41]
Self-assembled delivery systems driven by natural products	TCM small-molecule coexisting systems	Self-assembly scaffold + synergistic enhancement	TCM self-assembled nanosystems	Demonstrates that natural small molecules can form nanoscale assemblies under coexisting conditions and modulate efficacy	[39, 52]
	Poly(ursolic acid)	Self-active carrier scaffold	Poly(ursolic acid) nanomedicines	The carrier itself exhibits anticancer activity, exemplifying carrier-as-therapeutic design	[40]
	Disodium glycyrrhizinate	Self-assembly promoter	Curcumin self-micellar solid dispersion	Improves curcumin bioavailability and cytotoxic activity	[71]
	Green tea catechins	Self-assembly scaffold + protein protection + pharmacological synergy	Herceptin/IFN-loaded micellar nanocomplexes	Enhances protein stability, tumor accumulation, and antitumor activity; exemplifies carrier–protein synergy	[129]

(Continued)

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Table 2
(Continued)

Construction paradigm	Representative natural product/material	Functional role	Representative integrated object/system	Representative advantage or use	Ref.
Living drug delivery systems mediated by natural products	Tannic acid/Fe^{3+}	Single-cell nanoencapsulation + cellular protection	Nanoarmor probiotic single-cell nanoencapsulation	Improves antibiotic tolerance, intestinal survival, and colonization of probiotics	[143]
	Nanostructured polyphenols	Microenvironment remodeling + drug synergy + probiotic amplification	Polyphenol-modified probiotic co-delivery platform	Combines drug synergy, intestinal microenvironment regulation, and amplified probiotic therapy	[145]
	Tannic acid–magnesium complexes	Antibacterial/reactive oxygen species scavenging + living-vesicle synergy	Core–shell microneedles sequentially releasing tannic acid–magnesium complexes and Lactobacillus-derived extracellular vesicles	Promotes infected wound repair and synergistically enhances angiogenesis and collagen remodeling	[146]
Other	Plant-derived nanovesicles	Natural membrane carriers + cross-kingdom regulation	Plant-derived nanovesicle delivery systems	Favorable biosafety with natural membrane architecture and endogenous bioactive cargo background	[29,150,151]
	Curcumin, glycyrrhizic acid, diosgenin, luteolin, dihydromyricetin, ursolic acid and ginkgo extracts	Interfacial stabilization + high drug loading	Pickering emulsions/self-stabilized drug-nanocrystal emulsions	Reduces reliance on exogenous surfactants while improving loading and safety	[16,154]

IFN: Interferon; LNP: Lipid nanoparticles; mRNA: Messenger RNA; siRNA: Small interfering RNA; TANN: Tannylated nanoparticles (tannic acid-modified nanoparticles); TCM: Traditional Chinese medicine.

Neurodegenerative diseases

In neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, natural product delivery strategies primarily aim to cross the blood–brain barrier and prolong intracerebral therapeutic activity[162–166]. Lactoferrin-modified low-density lipoprotein (LDL)-mimicking carriers and highly stable nanoparticles have improved curcumin brain delivery through biomimetic targeting and nanostabilization, respectively[53]. PLGA nanoparticles have also enhanced the neuroprotective effects of ginsenoside Rg3 while improving the brain uptake and sustained release of schisandrin A[167]. In Parkinson's disease models, andrographolide-loaded PLGA nanoparticles can penetrate the blood–brain barrier and accumulate in the substantia nigra, thereby supporting targeted intervention against neuroinflammation. Additional systems, including β-asarone–modified chitosan nanoparticles for astragaloside IV and brain-targeted microemulsions or solid lipid nanoparticles for piperine, further indicate that the neurological translation of natural products depends critically on precise barrier-crossing design[94,168,169].

Diabetes and metabolic syndrome

Natural product delivery research for diabetes and metabolic syndrome has primarily focused on glycemic control, antioxidant and anti-inflammatory effects, and the prevention of complications[170]. Quercetin micelles enhanced antidiabetic efficacy by improving oral bioavailability and sustained release[54], whereas nanoformulated oleanolic acid alleviated diet-induced metabolic disturbances, suggesting that nanosizing can enhance systemic regulation mediated by triterpenoids[63]. Flavonoid-based solid lipid nanoparticles, such as EGCG-loaded solid lipid nanoparticles (SLNs), protect EGCG from gastrointestinal degradation, enhance intestinal permeability, and improve oral absorption. In a mouse model of type 2 diabetes, EGCG-loaded SLNs reduced fasting blood glucose levels and improved insulin sensitivity by activating antimicrobial peptide (AMP)-activated protein kinase, a key regulator of glucose metabolism[171]. Nanoformulated curcumin and ferulic acid have also shown promise in pancreatic islet protection and the prevention of diabetes-related injury[172,173]. Celastrol-loaded micelles further alleviated obesity-associated inflammation and lipid metabolic dysregulation, underscoring the importance of delivery systems in balancing potency, efficacy, and safety in metabolic disease[80].

Autoimmune and inflammatory diseases

Autoimmune and inflammatory diseases, including inflammatory bowel disease, arthritis, and psoriasis, represent rapidly expanding application areas for natural product–based drug delivery systems[174–178]. In ulcerative colitis, butyrate-derived polymeric nanoparticles for magnolol, andrographolide/carbon monoxide donor nanotherapeutics, reactive oxygen species (ROS)-responsive luteolin nanoparticles, and pH-activated berberine nanobombs illustrate a shift from simple drug administration toward lesion-responsive intervention, mucosal repair, and microenvironmental regulation[20,25,27,83]. Dual-responsive Angelica polysaccharide-based colon-targeted nanoparticles and pH-sensitive glycyrrhizic acid-loaded PLGA nanoparticles further demonstrate

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how natural polysaccharides and small molecules can be harnessed for localized colonic delivery[134,179]. In arthritis and psoriasis, nanoformulated ginsenoside Rb1, andrographolide-loaded mesoporous silica systems, and indirubin microemulsion gels improve local retention and suppress inflammatory responses[84,95,104]. In wound models, exosome-like nanoparticles derived from the medicinal insect Periplaneta americana L. further highlight the potential of natural bioactive vesicles to modulate inflammatory microenvironments[180].

To integrate these disease-specific advances, Table 3 summarizes representative preclinical natural product–based drug delivery systems across cancer, neurodegenerative, metabolic, and inflammatory diseases, highlighting their delivery platforms, disease contexts, and principal translational value.

Conclusions and perspectives

Overall, research on natural product delivery in TCM is advancing along two intertwined trajectories. The first treats natural products as therapeutic agents and employs lipid-based, polymeric, protein/polysaccharide, and biomimetic platforms to improve their solubility, stability, systemic exposure, and tissue delivery. The second repurposes selected natural products as functional excipients that contribute to structural assembly, delivery enhancement, targeting, and pharmacological synergy, thereby shifting delivery systems from simple cargo-loading platforms toward integrated drug–excipient design. Compared with conventional exogenous excipients, this strategy more effectively captures the intrinsic coupling among chemical structure, interfacial behavior, and biological function in natural bioactive compounds while aligning with the TCM principles of holistic regulation, multicomponent synergy, and compatibility-based efficacy enhancement. When integrated with lipid nanoparticles, protein therapeutics, antibodies, nucleic acid medicines, and cell-engineering systems, natural products can further expand the delivery boundaries of biotherapeutics.

In parallel, natural product-mediated living delivery systems are emerging as a new frontier. Through polyphenol-based interfacial engineering, metal–polyphenol networks, stimuli-responsive protective shells, and cooperation with naturally derived vesicles, living therapeutics, including cells, microorganisms, viruses, and bacteriophages, are being redefined from passive carriers into engineered therapeutic systems with lesion colonization, environmental responsiveness, active migration, and functional amplification. This transition positions natural products not only as functional excipients in conventional nanomedicine but also as enabling materials for the engineering and controllable deployment of living therapeutics.

The evolution of natural product delivery research reflects a broader shift in the modernization of TCM. Earlier strategies largely focused on isolating individual active constituents from complex systems and standardizing them using modern pharmaceutical technologies for

Table 3

Representative preclinical advances in natural product–based drug delivery systems

Disease area	Representative natural product	Delivery platform	Indication/ disease context	Main translational value	Ref.
Cancer	Fisetin	Nanostructured lipid carriers	Advanced/ metastatic melanoma	Overcomes the delivery limitations of the free drug and enhances the antitumor potential	[89]
	Cisplatin + oleanolic acid	Co-loaded calcium carbonate nanoparticles	Hepatocellular carcinoma	Co-delivers a chemotherapeutic agent and a natural triterpenoid to enhance synergistic tumor suppression	[67]
Neurodegenerative diseases	Curcumin	LDL-mimicking lipid carriers/ high-stability nanoparticles	Alzheimer's disease	Improves blood–brain barrier transport and brain bioavailability	[22,53]
	Ginsenoside Rg3	PLGA nanoformulation	Alzheimer's disease	Enhances neuroprotection and formulation stability	[64]
	Astragaloside IV + Nesfatin-1	Multi-ligand–modified liposomes	Parkinson's disease	Enhances brain targeting and combination therapy potential through multi-ligand engineering	[65]
Diabetes and metabolic syndrome	Quercetin	Soluplus®/P407 micelles	Diabetes	Improves *in vivo* utilization and glucose-lowering efficacy	[54]
	Celastrol	PEG–PCL nanomicelles	Diet-induced obesity/insulin resistance	Improves safety and gastrointestinal tolerability while enhancing efficacy	[80]
Autoimmune and inflammatory diseases	Angelica polysaccharides	Dual-responsive colon-targeted nanoparticles	Ulcerative colitis	Combines lesion-responsive release with intestinal immune and microbiota modulation	[134]
	Indirubin	Microemulsion gels	Psoriasis	Enhances transdermal delivery and antipsoriatic activity	[104]

LDL: Low-density lipoprotein, PEG–PCL: Poly(ethylene glycol)-poly(ε-caprolactone), PLGA: Poly(lactic-co-glycolic acid).

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drug development. Although this approach has improved controllability and enabled clinical translation, it has also directed research toward single-compound pharmacology and one-dimensional technical optimization. By contrast, integrated drug–excipient design refocuses attention on component synergy, functional division, and systemic regulation. The relationship between therapeutic cargo and functional excipients is no longer a simple loading arrangement, but rather an organized system with multiple functional layers, including principal therapeutic action, auxiliary modulation, delivery enhancement, and toxicity attenuation. This transition from a single-compound perspective to integrated design renews the connection between modern delivery science and the holistic philosophy of TCM, providing the compatibility logic embodied by the monarch, minister, assistant, and guide principles with a material basis and practical realization in nanomedicine and biotherapeutic delivery.

Despite this progress, the field remains rapidly evolving, and several priorities are essential for higher-level translation. First, classification should move beyond conventional chemical taxonomy toward delivery-oriented functional categorization, with greater emphasis on amphiphilicity, self-assembly potential, chemical modifiability, and microenvironment responsiveness. Second, systematic studies are needed to establish connections among structural features, assembly behavior, *in vivo* fate, and therapeutic outcomes rather than relying primarily on particle size, surface charge, and *in vitro* release profiles. Third, the links between TCM compatibility principles and modern drug delivery systems should be investigated more deeply, particularly in multicomponent formulae, self-assembled particles, and the synergistic mechanisms of naturally derived functional components. Such work could translate empirical knowledge into verifiable and scalable formulation principles. Finally, greater attention should be directed toward quality control, scalable manufacturing, long-term safety, and clinical evaluation frameworks to advance natural product–based drug delivery systems from proof-of-concept studies toward standardized translational applications.

Looking ahead, the next major advances in natural product and TCM delivery should move beyond the nanoformulation of an expanding repertoire of bioactive molecules. Future progress will depend on mechanism-driven integrated design guided by disease context, route of administration, material function, and compatibility relationships. Only through more precise alignment among natural bioactive components, functional excipients, delivery systems, and disease microenvironments can the modernization of TCM progress beyond single-compound optimization toward system-level innovation and beyond incremental technological layering toward a deeper convergence of theory and methodology.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Zhongjie Tang, Ying Li, Kaicheng Tang, and Feiyan Gao drafted the manuscript. Xiaoyi Chen revised the manuscript. Chong Li supervised and guided the review. All authors have read and approved the final version of the manuscript.

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Data availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Declaration of generative AI in scientific writing

Generative AI was used solely to improve language clarity, sentence coherence, and punctuation. It was not used to generate scientific content or references. All citations were independently identified and verified by the authors, who thoroughly reviewed and revised the manuscript and take full responsibility for its content.

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