

Nano-Drug Delivery Systems Based on Natural Products

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Abstract: Natural products have proven to have significant curative effects and are increasingly considered as potential candidates for clinical prevention, diagnosis, and treatment. Compared with synthetic drugs, natural products not only have diverse structures but also exhibit a range of biological activities against different disease states and molecular targets, making them attractive for development in the field of medicine. Despite advancements in the use of natural products for clinical purposes, there remain obstacles that hinder their full potential. These challenges include issues such as limited solubility and stability when administered orally, as well as short durations of effectiveness. To address these concerns, nano-drug delivery systems have emerged as a promising solution to overcome the barriers faced in the clinical application of natural products. These systems offer notable advantages, such as a large specific surface area, enhanced targeting capabilities, and the ability to achieve sustained and controlled release. Extensive in vitro and in vivo studies have provided further evidence supporting the efficacy and safety of nanoparticle-based systems in delivering natural products in preclinical disease models. This review describes the limitations of natural product applications and the current status of natural products combined with nanotechnology. The latest advances in nano-drug delivery systems for delivery of natural products are considered from three aspects: connecting targeting warheads, self-assembly, and co-delivery. Finally, the challenges faced in the clinical translation of nano-drugs are discussed.

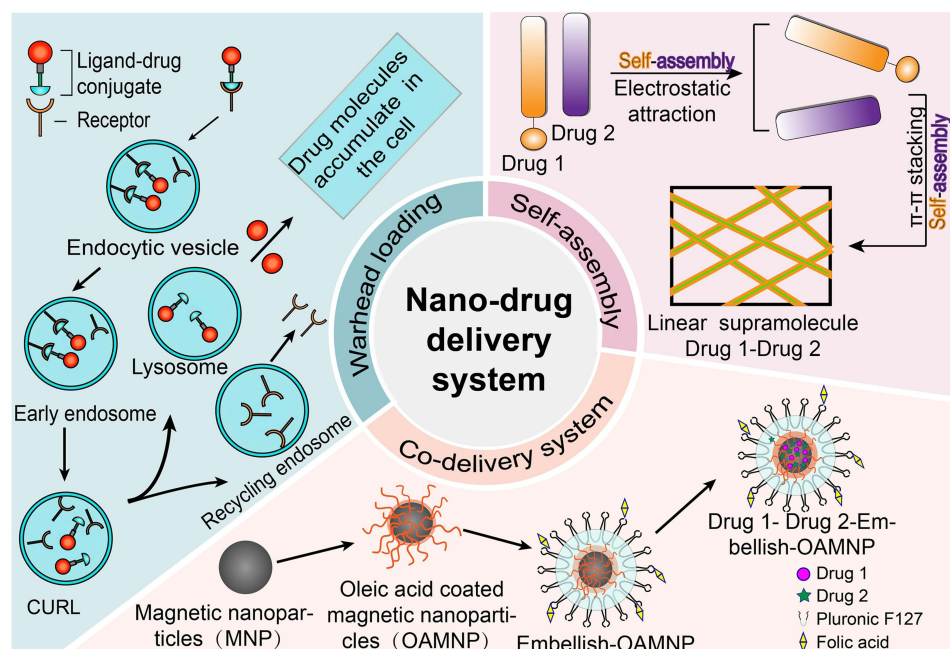
Keywords: natural products, nanotechnology, drug delivery, targeting

Introduction

Over the course of human evolution, natural products have been a source of necessities for human life. They have been used in numerous fields, ranging from ancient applications in paper-making to modern use in the production of perfumes and spices, and recently for the precaution and treatment of diverse diseases.^{1,2} With the continued advances in separation techniques and methods for evaluating pharmacological effects, an increasing number of active components have been identified in natural products. Due to the structural diversity of natural products and their biological activities on multiple tissues and molecular targets, modulating various signaling or functional pathways, they have significant clinical applications, especially in the treatment of complex diseases such as cancer and cardiovascular disorders.^{3,4}

The effectiveness of natural products in clinical trials, however, has not been particularly impressive, and most pharmaceutical companies are currently reluctant to pursue their development.⁵⁻⁷ This is mainly due to concerns regarding their poor solubility, limited biological distribution, or rapid metabolic clearance. These factors may result in drug plasma concentrations falling below therapeutic levels. Additionally, permeability and absorption across biological membranes and barriers can be challenging for compounds with relatively high molecular weight and low lipophilicity, resulting in poor drug transport efficiency and short half-lives. Therefore, finding new drug delivery methods may provide solutions to address these key issues.^{8,9} Currently, identifying the most effective means to maximize the efficacy of natural products is an important focus of research in the scientific community. These studies will lead to the emergence of more innovative drugs with fewer side effects.¹⁰

Graphical Abstract



Nano-Carriers

Nanotechnology has proven to be instrumental in connecting the realms of biological and physical sciences. Specifically, nano-drug delivery systems have garnered considerable interest within the pharmaceutical industry.^{7,11,12} Carriers based on nanostructures can facilitate drug delivery by encapsulating or attaching therapeutic agents and precisely targeting tissues or organs through controlled release.^{9,13} Compared to larger materials, nano-drugs designed at the atomic or molecular level have the ability to move more unrestrictedly within the human body, thus enabling them to attain therapeutic effects.^{14–19} However, the scope of application of these methods has huge limitations compared to the delivery of drugs through nanostructures. Drug delivery systems based on nanoparticles (NPs) not only improve the mean residence times of drugs in the body, but also have unique advantages, such as rapid extravasation and reduced likelihood of macrophage phagocytosis. Nanostructures can also be utilized successfully to co-load hydrophilic or hydrophobic substances. It has been reported that first-generation drugs based on nano-drug delivery systems have been approved for use by relevant authorities.²⁰ Liposomes and micelles containing inorganic NPs (such as gold NPs) have been developed, focusing on drug delivery, imaging, and therapeutic functions.²¹ Nano-formulations can incorporate natural products into nano-carriers using various methods, such as thin film hydration, high-pressure homogenization, nanoprecipitation, and self-assembly.²² These approaches represent significant advances in improving treatment outcomes by controlling drug release, enhancing drug solubility and permeability, improving drug targeting, reducing adverse reactions, and increasing physical and chemical stability. In summary, the application of nanotechnology offers substantial backing for the advancement of natural products and serves as a technological foundation for modernization (Figure 1).

Nano-Drug Delivery Systems and Natural Products

The application of nanotechnology in natural products is a rapidly developing field. The use of nanocarriers to successfully deliver drugs is increasingly considered a potential way to safely transport therapeutic agents to targeted areas within organs, specific tissues, or cells.⁶ The combination of natural products and nanotechnology holds promising prospects, as nanotechnology provides the possibility to load one or multiple natural products. The presence of nano-drug delivery systems can

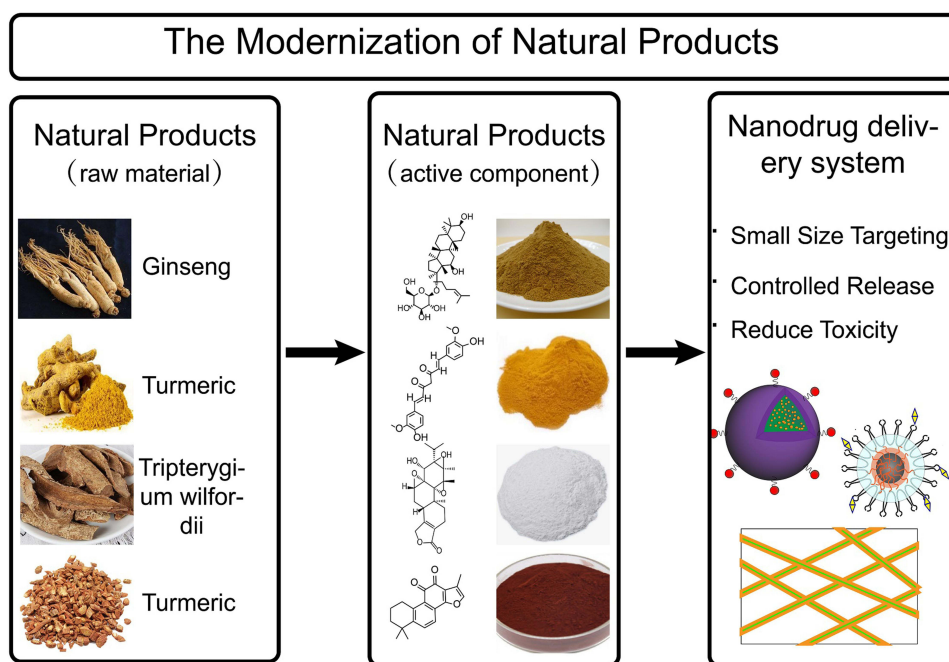


Figure 1 The combination of natural products and nanotechnology promotes the development of the pharmaceutical field.

enhance the bioavailability, targeting, and controlled release properties of natural products. This greatly improves the shortcomings in the clinical application of natural products and amplifies their pharmacological advantages, making significant contributions to clinical practice.

Design of the Review

This review covers strategies for developing natural product-based nano-drug delivery systems, which fall into the following three categories: connecting targeting warheads, self-assembly, and co-delivery. It specifically describes the characteristics of nano-systems applied to one or more natural product components, as well as their routes of administration. We summarize the in vitro and in vivo studies of natural product nano-drug delivery systems and highlight their potential advantages for improving biodistribution and efficacy and reducing adverse reactions and toxicity. Finally, the challenges faced in the clinical translation of nano-drugs are discussed. Table 1 provides a comprehensive summary of the natural products and their nano-drug delivery systems mentioned throughout the entire text, including the mechanisms of drug delivery or structural composition, treatment of diseases, and application dosages.

Study Design

In January 2023, we performed a literature search in PubMed for natural products, research on nanomedicine delivery systems, and systematic reviews. The search terms we used were “natural products” and “nano-carriers”, “natural products” and “targeting payload” and “targeting”, “natural products” and “self-assembly” or “carrier-free”, “natural products” and “co-delivery” and “nano” (since 2018.01–2022.12). Due to the classic and typical nature of the experimental content, three original research articles have been specially cited (2012, 2015, 2016).

Criteria for inclusion: Original articles related to the subject matter, scientific research in relevant fields, and key reference literature.

Criteria for exclusion: Irrelevant literature, duplicate publications, conference proceedings, lectures, letters to the editor, non-English publications.

Table I Natural Product Nano-Drug Delivery System Drug Delivery/Structure Composition Mechanism, Dosage

Natural Products	Nano-Drug Carrier/ Delivery System	Applicable Disease	Drug Delivery / Structural Composition Mechanism	Dosage
Triptolide (TP)	Galactosylated-chitosan-TP-nanoparticles (GC-TP-NPs)	Hepatocellular carcinoma	Triptolide is delivered to hepatocellular carcinoma cells by asialoglycoprotein receptor mediated cell uptake with galactose group as target head and chitosan as carrier to play therapeutic role.	In vitro:50µg/mL In vivo: 6.76 mg/kg GC-TP-NPs (GC-TP-NP-low group), 16.90 mg/kg GC-TP-NPs (GC-TP-NP-high group) (TP equivalent)
	Folate(FA)- Pluronic F127/P123 nanoparticles (FP-TP-NPs)	Renal Ischemia/ Reperfusion Injury	The vector Pluronic F127/P123 was modified by folic acid ligand, and FA had a high affinity with folic acid receptors highly expressed on the proximal renal tubule epithelial cells, thus achieving renal targeting of Triptolide through folic acid receptor-mediated endocytosis	In vivo dose:0.5mg/Kg (TP equivalent)
Ginsenosides	A54-PEG-DA-OCMC polymer CK-loaded micelle (APD-CK) (DA-OCMC: deoxycholic acid-O-carboxymethyl chitosan)	Liver cancer	A54 peptide is a hepatocellular carcinoma specific binding peptide. It is attached to the carrier deoxycholic acid-O-carboxymethyl chitosan as the target head to construct ginsenoside K-loaded micelles, thus enhancing the anticancer activity	Cellular uptake dose:100µg/mL (CK equivalent)
Gambogic acid (GA)	Hyaluronic acid (HA)-coated redox-sensitive chitosan-based nanoparticle (HA(HECS-ss-OA)/GA)	Non-small-cell lung cancer	Ga-containing HA (HECS-ss-OA) nanoparticles (HA (HECS-ss-OA) /GA) are stably transported in blood circulation, selectively accumulate in tumor sites, effectively internalize into tumor cells via CD44-mediated endocytosis, and complete GSH-triggered GA release in cytoplasm	In vivo dose:8.0mg/Kg (GA equivalent)
Baicalin (BAI)	Bovine serum albumin (BSA)	Breast cancer	FA-BSA-BANPs achieves mammary targeting by adjusting particle size, surface charge, and encapsulation material	In vivo dose:2, 4, 8mg/Kg (BAI equivalent)
	RVG29 peptide-modified polyethylene glycol-polylactic acid-co-glycolic acid nanoparticles (PEG-PLGA RNPs)	Neuroprotection in cerebral ischemia (CI)	With the brain-targeting peptide RVG29 as the targeting warheads, nanoparticles are modified with the polyethylene glycol poly(lactic acid-co-glycolic acid) nanoparticles through the specific binding of RVG29 peptide with the acetylcholine receptor on neurons in the brain. Thus, the neural targeted delivery of baicalin in brain was realized.	In vivo dose:9mg/mL (BAI equivalent)
Resveratrol (RES)	Transferrin moieties-modified PEGylated liposomes (TF-RES-L)	Glioblastomas (GBMs)	Because the transferrin (TFR) receptor is highly expressed on the surface of cancer cells and modifies transferrin on the surface of resveratrol loaded liposomes, TFR targets drug delivery to malignant tumor cells through reticuloprotein-mediated endocytosis	In vivo dose:10mg/Kg (Injection volume: 200µL) (RES)

Curcumin (Cur)	Hyaluronic acid (HA)-propylene glycol-based ethosomes	Psoriasis	The overexpressed CD44 protein in psoriatic skin was used as a potential target for active targeting nanocarriers, and HA was used as the targeting warheads to bond with propylene glycol-based ethosomes to construct a novel local drug delivery system (HA-ES) for curcumin, and the accumulation of curcumin at the focal site was achieved through CD44 receptor-mediated endocytosis	45mg/cm ² (Cur equivalent)
Paclitaxel (PTX)	α configurational N-acetylgalactosamine (Tn) modified nanoliposomes loaded with PTX (Tn-Lipo-PTX)	Hepatocellular carcinoma	The pegylated paclitaxel nano-liposomes were modified with α -acetylgalactosamine as the targeting warheads, and the concentration of PTX in hepatocellular carcinoma cells was accumulated through the specific binding of N-acetylgalactosamine to sialoglycoprotein receptor (ASGPR)	In vitro dose:50 ng/mL (PTX equivalent)
	tLyP-I-human H chain ferritin (HFtn) - PTX	Tumor	tLyP-I fuses with the N-terminal of human H-chain ferritin (Hfnt), and packages PTX in Hfnt nanocagnets to construct a double-targeted nano-drug delivery system, with tLyP-I as the targeting warheads and TFR1 and NRP-1 as double receptors	In vivo: 1 mg/mL (PTX equivalent)
Ursolic acid (UA)	Carrier-free	Protects the liver and inhibits tumor growth	UA molecules self-assemble into carrier-free nanostructures through electrostatic and hydrophobic interactions	In vitro:30 μ M In vivo:8mg/Kg (UA equivalent)
Rhein (Rhe)	Carrier-free	Neuroinflammatory	Rhein was directly self-assembled into three dimensional network supramolecular hydrogels with nanofibers through intermolecular π - π interaction and hydrogen bonding	—
Ursolic acid (UA) + Paclitaxel (PTX)	Carrier-free	Anti-tumor and liver protection	UA and PTX form stable high-drug-loading nanocomplexes through hydrogen bonding and hydrophobic interaction	In vivo:5mg/Kg (PTX equivalent)
Berberine (Ber)+ Rhein(Rhe)	Carrier-free	Bacterial infection	Ber and Rhe formed a nanoparticle with Rhe as the basic skeleton and Ber embedded in the layer gap through π - π interaction and electrostatic interaction	Minimum inhibitory concentration (MIC):0.05 mmol/mL (S.aureus). Minimal bactericidal concentration (MBC):0.1 mmol/mL (S.aureus)
Berberine (Ber) +Tannin acid(TA)	Carrier-free	Ulcerative colitis	Ber and TA are self-assembled into stable nanoparticles in aqueous solution through π - π packing and hydrogen bonding interactions, wrapped in hyaluronic acid, and delivered by CD44 receptor-mediated endocytosis	In vivo:20mg/Kg (Ber equivalent)
Paclitaxel (PTX)	Self-assembling peptide: FER-8 peptide	Anti-tumor	The FER-8 peptide self-assembles to form a stable nanohydrogel at a pH of 7.4, which acts as a carrier for loading paclitaxel. The accumulation of drug concentration in tumor tissues is completed through the response of drug delivery system to the acidic environment of tumor tissues	In vivo:10mg/Kg (PTX equivalent)

(Continued)

Table 1 (Continued).

Natural Products	Nano-Drug Carrier/ Delivery System	Applicable Disease	Drug Delivery / Structural Composition Mechanism	Dosage
Emodin	Self-assembling peptide: RADA16-I/ RVDV16-I	—	Two ionic complementary self-assembling peptides RADA16-I and RVDV16-I were used to construct suspended in-situ hydrogels with emodin respectively through hydrophobic action	—
Shikonin	Carrier-free	Tumors	Iron (III) - Shikonin is a metal-polyphenol complex supramolecular nanomedical drug. Under the action of high concentration of glutathione (GSH) in tumor cells, the nanomedical drug is decomposed into Fe^{2+} and Shikonin, which stimulates the death of tumor cells through iron apoptosis and necrosis apoptosis	In vivo: 10mg/Kg (Shikonin equivalent)
Curcumin (Cur)	Carrier-free	Tumors	Curcumin and Gd^{3+} coordination with indocyanine green (ICG) drove self-assembly of curcumin- Gd^{3+} nanoparticles containing indocyanine green (ICG@cur-Gd NP), which resulted in cancer-specific release of curcumin, Gd^{3+} and ICG due to their acidic pH triggering degradation properties	In vitro: 10 μ g/mL (ICG equivalent) In vivo: 4mg/Kg (ICG equivalent)
Myricetin (Myr) Quercetin (Que) Fisetin (Fis) Luteolin (Lut)	Carrier-free	—	The four natural products were self-assembled with Fe^{3+} films to form metal phenolic network, respectively	—
Tanshinone (TAN) +Puerarin (PUE)	PUE-prodrug and TAN co-loaded solid lipid nano-particles (SLN) (PUEp/TAN-SLN)	Myocardial infarction (MI)	PUE- prodrug was synthesized by esterification reaction between mPEG-COOH and PUE, and PUEp/TAN-SLN was prepared by single emulsification-solvent evaporation method,	In vivo: 25mg/KgPUE+25mg/KgTAN (PUEp/TAN-SLN)
Paclitaxel (PTX) +Naringenin (NAR)	Solid nanolipoids co-loaded with PTX and NAR modified with cyclic peptide cRGD	Glioblastoma multiforme	Through the targeted action of cRGD on tumor cells, the drug can accumulate in tumor cells, so as to effectively respond to Glioblastoma multiforme	In vivo: 5mg/KgPTX+50mg/KgNAR (SLN)
Paclitaxel (Ptx) +Tanshinone IIA (TanIIA)	FA-LB-MSNs loaded with Ptx and TanIIA ((Ptx + TanIIA) @FA-LB-MSNs)	Acute promyelocytic leukemia	Ptx mainly triggered the apoptosis of NB4 cells, while TanIIA mainly induced the differentiation of NB4 cells, that is, TanIIA and Ptx played a synergistic role in NB4 cells	In vivo: 5mg/Kg (Ptx + TanIIA) @FA-LB-MSNs (PTX equivalent; PTX: TanIIA=1 (molar ratio))
Ginsenoside Rg3 (Rg3) +Paclitaxel (Ptx)	Rg3-PTX Liposomes (Rg 3-PTX-LPs)	Breast cancer	Rg 3-PTX liposomes were prepared from ginsenoside Rg 3 by thin film hydration method. Rg 3-PTX-LPs can specifically target both MCF-7/T cells and tumor microenvironment through GLUT-1 recognition	In vivo: 20 mg/ kg PTX + 40 mg/kg Rg 3 (Rg 3-PTX-LPs)

Artemisinin (Art) + Chrysin (Chr)	Art and Chr are co-encapsulated in PEG-PLGA nanoparticles (Art/ CR-PLGA /PEG NPs)	Breast cancer	Art and Chr were co-encapsulated in PEG-stabilized PLGA nanoparticles (NPs) by multi-emulsion method (W/O/W)	In vivo: 40 μ M Art/ CR-PLGA /PEG NPs showed higher cytotoxicity
Paclitaxel (PTX) + Honokiol (HK)	A glutathione (GSH)/reactive oxygen species (ROS) dual-responsive hybrid PMs composed of PTX and honokiol (HK) prodrug	Laryngeal carcinoma	A cocktail polymeric prodrug micelle (PHPPM) was developed using an oxidation and reduction dual-responsive polymeric paclitaxel (PTX) and polymerichonokiol (HK) prodrugs. Both of them were obtained by covalently conjugating the drug to dextran via diselenium bonds.	In vivo: 6mg/Kg (PTX equivalent)
Paclitaxel (PTX)+ Curcumin (Cur)	Folic acid (FA) Modified Pluronic F127 (PF 127) Stabilized oleic acid (OA) coated iron oxide nanoparticles (OAMNPPF 127 FA)	Cancer	Fe ₃ O ₄ nanoparticles were synthesized by coprecipitation method under alkaline conditions. Oleic acid-coated nanoparticles were dispersed in water by folic acid-modified Pluronic F127 and Pluronic F127 mixtures. With folic acid as the target head, Pluronic F127 is connected to Pluronic F127 by diethylene glycol bis (3-amino-propyl) ether spacer, and the final loading of paclitaxel and curcumin forms a nanodrug delivery system	In vivo IC ₅₀ :0.7377 μ g/mL

Natural Product-Based Nano-Drug Delivery Systems with Targeting Warheads

Mechanisms and Advantages

The world is entering a new era of personalized healthcare, where drugs are prepared based on patient needs and then targeted and delivered to non-healthy cells. This is currently a research hotspot.²³ Nano-drug delivery systems, prepared through innovative nanotechnology, have received widespread attention for their capacity to enhance the bioavailability of drugs that are insoluble. To further optimize the nano-drug delivery system, researchers often attach targeting warheads to the nano-carriers through different strategies. These warheads can selectively deliver the drug to pathological cells through receptor-mediated endocytosis.^{24,25} The attachment of targeting warheads can be achieved using various reaction mechanisms, including nucleophilic addition, nucleophilic substitution, and addition elimination.²⁶ Among them, nucleophilic addition and addition-elimination are the two most widely used mechanisms. These mechanisms make it possible for drugs to be selectively delivered; for example, aromatic electrophilic substitution occurs only with tyrosine and tryptophan.²⁶

Drug delivery systems loaded with targeting warheads have many advantages over their non-targeted counterparts. Firstly, targeted systems can selectively deliver effective therapeutic drugs to particular organs or tissues, thereby avoiding non-specific uptake and toxicity in healthy cells.²⁷ Secondly, when drugs administered in the non-targeted form at the MTD show no significant efficacy, efficacy may be improved by connecting them to highly effective therapeutic warheads.²⁷ For example, nano-conjugates of polyethylene glycol or methoxy polyethylene glycol-modified with the targeting peptide T7 and covalently linked to podophyllotoxin (PPT) (Pep-SS-NPs) have been developed to target the transferrin receptor, resulting in a significant increase (5.3 times) in the MTD compared with free PPT.²⁸ Last advantage is that the targeting warheads can be connected to diagnostic agents, such as imaging agents, which can be used to identify overexpression of target receptors in pathological cells.²⁹ In the context of drug delivery using drug carriers containing warheads that specifically target folate receptors, successful development has taken place in the creation of folate-linked ^{99m}Tc and ⁶⁸Ga radiopharmaceutical imaging agents. These agents serve the purpose of identifying whether tumor cells in patients exhibit an ample expression of folate receptors, which is necessary for the absorption of therapeutic drug doses.^{30–33}

Currently, warheads that specifically bind to receptors are being synthesized and studied in both in vitro and in vivo experiments. Integrins ($\alpha_2\beta_3$, $\alpha_v\beta_3$, and $\alpha_5\beta_1$) and aminopeptidase N (CD13) have been identified as the most common targets in tumor neovascular systems. They can be recognized by derivatives of cyclic RGD peptide and linear NGR peptide, respectively.³⁴ Another example that is commonly referred to is the specific targeting of the folate receptor, which can be found on the outer membrane of different types of breast cancer cells.³⁵ In this case, the folate receptor is targeted by synthesizing FA-drug conjugates and grafting FA onto nano-carriers to promote internalization by cancer cells. Focusing on natural products, this section presents an extensive overview of advancements in the investigation of nano-drug delivery systems containing targeting warheads. Table 1 presents the clinical applications of natural products and the advantages of nano-drug delivery systems loaded with targeting warheads.

Natural Products Delivered by Nano-Drug Delivery Systems with Targeting Warheads

Terpenoids

Terpenoids are widely used in diversified industries, such as medicine, and food. They are consisted of several C_5H_8 units.³⁶ In the late 1990s, research on the separation and purification of active ingredients, component analysis, and structural research of terpenoids received widespread attention. Research has highlighted their prominent role in medicine, with terpenoids exhibiting multiple pharmacological effects, including anti-tumor, anti-inflammatory, anti-microbial, antiviral properties, and utility for treatment of cardiovascular diseases.^{37–41} This section discusses research on nano-drug delivery systems for typical natural terpenoid products, triptolide and ginsenoside, aiming to provide a theoretical basis for subsequent studies.

Triptolide (TP), derived mainly from *Tripterygium wilfordii* Hook.f., is considered to be a potential candidate for the next “blockbuster” anticancer drug. It is a highly oxidized diterpenoid trioxide that has analgesic, anti-inflammatory, and

immunomodulatory activities. Several triptolide derivatives have entered clinical research.^{22,42,43} With the advancement of research, a variety of drug delivery systems have been developed to optimize the clinical adverse factors of TP (Figure 2). One study⁴⁴ focused on the design of galactosylated chitosan-triptolide NPs with a high capacity for loading the drug, aiming for targeted delivery to hepatocellular carcinoma. As anticipated, the GC-TP-NPs demonstrated sustained release properties. In laboratory experiments, the NPs were internalized by cells through the asialoglycoprotein receptor (ASGPR), and in vivo they accumulated significantly in liver tumors. Furthermore, compared with free drug administration, nanoparticle-based delivery with targeting warheads resulted in less systemic toxicity and reduced male reproductive toxicity. The galactose moiety of the NPs attached specifically to receptors on liver cancer cells, enabling significant uptake of TP through ligand-receptor interactions. This dramatically demonstrates the superiority of nano-drug delivery systems with targeting warheads. Hydrophobic toxic drugs can be conjugated with specific targeting warheads, which enhance the drug concentration inside cells by receptor-mediated endocytosis on the membrane of liver cancer cells, reducing nonspecific distribution and significantly improving drug safety. Huang et al⁴⁵ also conducted research on delivery of TP and developed Pluronic F127/P123 NPs (TP-FPNPs) with folate as a targeting moiety, modified with the toxic drug TP. The drug-loaded NPs exhibited high kidney targeting, prolonged in vivo residence, and improved cellular uptake. TP-FPNPs gave significantly better therapeutic effects on renal ischemia/reperfusion injury (IRI) than TP alone. The NPs entered cells by binding to folate receptors on the renal tubular cell membrane via the folate moiety. TP was slowly released from TP-FPNPs by a controlled diffusion process, followed by degradation of the NPs, thereby affecting treatment of renal IRI. This indicates that folate-functionalized drug-loaded NPs have potential as delivery platforms for hydrophobic drugs in the treatment of renal diseases.

Ginsenosides is also known as triterpenoid saponin, which mainly is found in the dried root of ginseng. Due to their chemical structure and biological effects similar to glucocorticoids, they have huge potential for application. However, their unsatisfactory solubility and bioavailability greatly impede their clinical application.^{46,47} Many nano-drug delivery systems have been utilized to maximize the pharmacological effects of these compounds.⁴⁸ Zhang et al⁴⁹ employed A54 peptide to construct micelles loaded with ginsenoside compound K (CK) for liver targeting. The vehicle used for this purpose was deoxycholic acid-O-carboxymethyl chitosan. Compared with the use of CK alone, polymer micelles significantly enhanced their anti-proliferative effect on two types of liver cancer cell lines, exhibiting better anti-cancer effects. This is because A54 peptide is a liver cancer-specific binding peptide that enables modified drug nano-

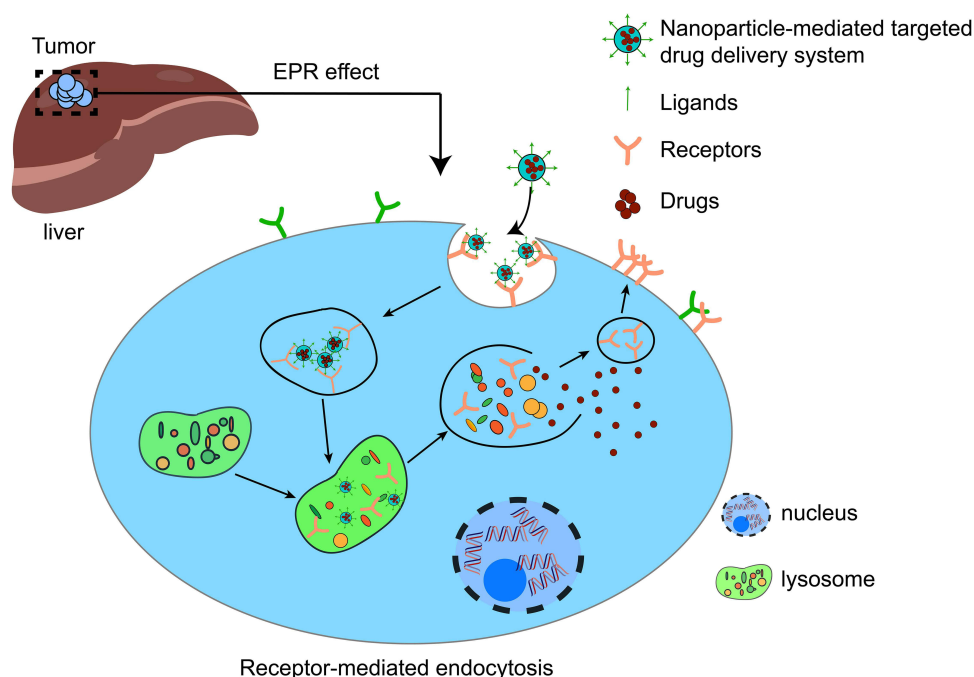


Figure 2 Nano-formulated triptolide for hepatocellular through EPR effect and active targeting.

systems to recognize specific cell surface receptors, targeting liver cancer cells, and being rapidly absorbed. As CK is gradually released from the micellar carrier into solution, its residence time in the bloodstream is increased, which improves bioavailability (Figure 3).

Flavonoids

Flavonoids have a C_{15} backbone and contain two phenyl rings ($C_6-C_3-C_6$). Flavonoids have a wide range of therapeutic applications and can help delay the aging of various life systems and organs to varying degrees. They also help prevent cardiovascular diseases, Alzheimer's disease and breast cancer.^{50–52} For these reasons, many methods have been taken to increase their solubility, improve gastrointestinal absorption, and reduce metabolic clearance. In addition, when consumed with other food components, flavonoids can undergo enhanced complexation or precipitation, ultimately leading to degradation by microbial flora and reducing their stability and bioavailability. To overcome these limitations, researchers have focused on developing nano-carrier systems to deliver flavonoid compounds to specific target sites. This approach has significantly improved the pharmacokinetics and pharmacodynamics of the drugs by altering their free form.^{53,54} Haroon Khan et al⁵⁵ have extensively discussed the improved bioavailability of flavonoid nano-drugs and their safety implications. Paola Aiello and his team⁵⁶ evaluated in vivo studies of dietary flavonoid NPs with anticancer activity. This section focuses on the recent progress made in nano-drug delivery systems for flavonoid compounds, with the specific mention of two flavonoids, gambogic acid, and baicalin.

Gambogic acid (GA) is a novel flavonoid-based anticancer drug that has been found to exhibit strong tumor activity against colon, pancreatic, and breast cancers.^{57–60} Unfortunately, its clinical use is hindered by inadequate solubility, brief duration of action within the body, toxicity that is dependent on the dosage, and discomfort experienced at the site of injection.^{61,62} Therefore, there have been many attempts to construct new GA nano-formulations to improve bioavailability and clinical efficacy. In a study,⁶³ hyaluronic acid (HA) was used to modify redox-sensitive chitosan NPs. By controlling a well-established synthesis procedure, HA-coated redox-sensitive chitosan NPs (HA(HECS-ss-OA)/GA) were prepared for tumor-specific intracellular delivery of GA (Figure 4). The system exhibited excellent loading of GA,

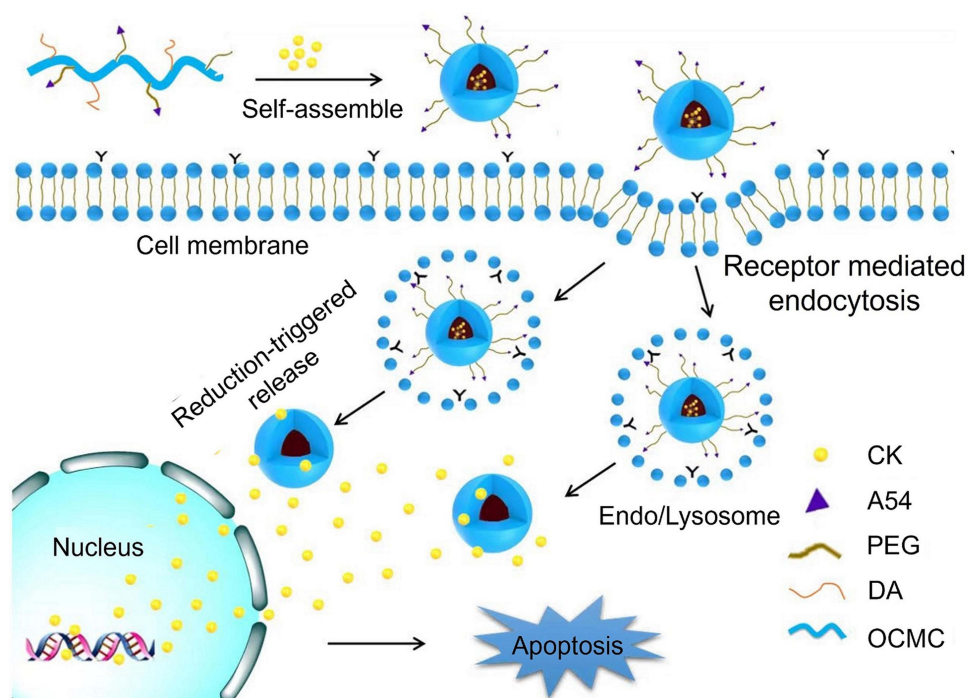


Figure 3 Schematic diagram of the preparation of polymer micelles, cellular uptake of CK, and the anticancer mechanism.

Notes: Reprinted from *Carbohydrate Polymers*, Volume 230, Zhang J, Jiang Y, Li Y, et al. Micelles modified with a chitosan-derived homing peptide for targeted intracellular delivery of ginsenoside compound K to liver cancer cells, Pages 115576, Copyright 2020, with permission from Elsevier.⁴⁹

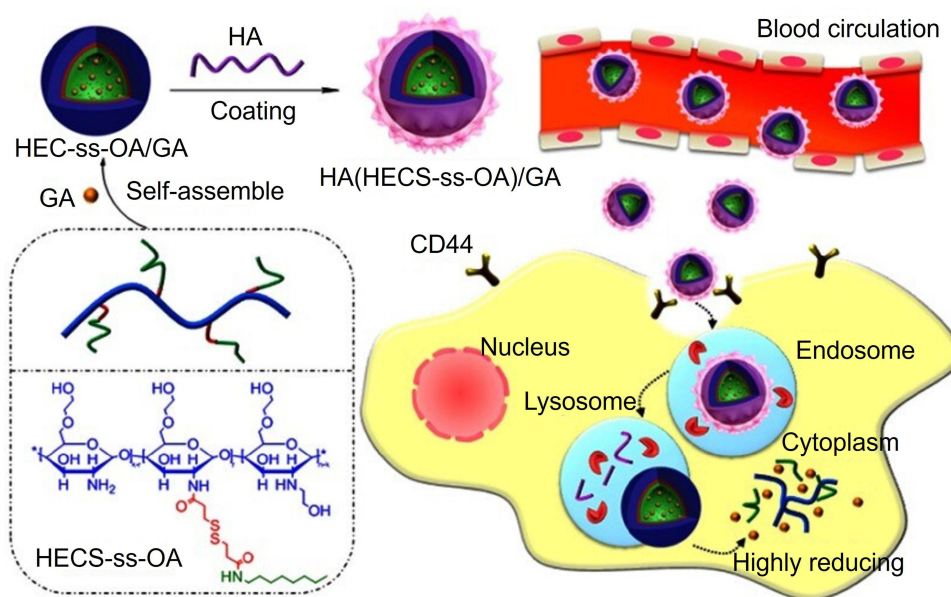


Figure 4 The design and targeted delivery of HA(HECS-ss-OA)/GA nanoparticles for tumor treatment.

Notes: Copyright ©2013. Dove Medical Press. Reproduced from Xu W, Wang H, Dong L, et al. Hyaluronic acid-decorated redox-sensitive chitosan micelles for tumor-specific intracellular delivery of gambogic acid. *Int J Nanomed*. 2019;14:4649–4666.⁶³

and in vivo and in vitro experiments demonstrated that compared with the non-sensitive control and HA-uncoated counterparts, HA(HECS-ss-OA)/GA NPs exhibited the strongest anti-tumor efficacy. The low-solubility and toxic drug GA can be efficiently delivered into cells by binding of the surface-modified hyaluronic acid to the CD44 receptor on cancer cells. This approach not only greatly enhances drug safety but also underscores the need to develop nano-drug delivery systems that utilize natural products as targeting agents. It provides a promising new avenue for effective tumor treatment.

Baicalin (BAI) is derived from the roots and stems of *Scutellaria baicalensis*. Extensive research has demonstrated its remarkable ability to inhibit the growth and proliferation of different types of cancer cells, including those found in breast and ovarian cancers.^{64–66} Researchers⁶⁷ have developed folate-conjugated bovine serum albumin NPs (FA-BSANPs /BAI) with BAI as a model drug, using the desolvation-crosslinking method. The folate-modified albumin delivery system prolongs the in vivo residence of BAI and enhances its tumor-targeting ability. By making use of the elevated levels of folate receptors present on the superficial breast cancer cells, targeted recognition and folate receptor-mediated endocytosis substantially enhance the concentration of hydrophobic medications within tumor cells. As a result, this approach significantly improves the efficacy of breast cancer treatment. Research team⁶⁸ optimized a nano-carrier for neuroprotective agents by obtaining RVG29 peptide-modified polyethylene glycol-poly(lactic acid-co-glycolic acid) nanoparticles with favorable physicochemical properties. The carrier provided drug stability and continuous release, thus enhancing the effectiveness of neuroprotective agents for delivering medication from the nose to the brain. It was discovered that administering BAI-PEG-PLGA RNPs through the nasal route resulted in significant improvement in neurological function in rats with ischemic brain injury. The RVG29 peptide, derived from the rabies virus glycoprotein with a sequence of 29 amino acids, serves as a brain-targeting molecule and is incorporated into the drug delivery system. It exploits receptor-mediated endocytosis through binding of the RVG29 peptide to receptors on the BBB to transport the hydrophobic baicalin from the bloodstream to the brain, achieving brain-targeted drug delivery. BAI-PEG-PLGA RNPs effectively delivered BAI in rats, and the safety of the delivery system was improved.

Polyphenols

Polyphenols are widely recognized as highly effective natural substances for the clinical use of chronic diseases due to their exceptional antioxidant and anti-inflammatory characteristics.⁶⁹ They are substances found in various vascular

plants that consist of numerous hydroxyl groups on the aromatic ring.⁷⁰ For the past few years, clinical research on the pharmacological effects of polyphenols has gradually expanded, and they have been found to have antioxidant, anti-inflammatory, anti-cancer, hepatoprotective, and anti-obesity properties.^{71–75} Despite their significant potential, polyphenols have a tendency to become structurally unstable when exposed to alkaline, light, and thermal conditions. This instability is attributed to the presence of multiple hydroxyl groups. Moreover, the majority of polyphenols have low solubility, leading to limited gastrointestinal absorption and bioavailability. Consequently, these limitations restrict their usage as pharmaceuticals and functional foods.⁷⁶ To address these difficulties, nano-drug delivery systems have been created to counteract the occurrence of precipitation, quick degradation, and elimination of natural polyphenolic compounds. A substantial body of studies has demonstrated the successful development of nano-carrier systems for polyphenolic compounds, thereby improving their stability and bioavailability.^{77,78} This section provides an overview of recent advances in nano-drug delivery systems, focusing on two polyphenolic natural compounds, resveratrol and curcumin. These findings lay a theoretical foundation for future research in this field.

Resveratrol (RES) is a polyphenol antioxidant of natural origin, characterized by its trans-3,4',5-trihydroxystilbene structure. It is present in different plants, including grapes, mulberries, peanuts, and rhubarb roots. RES plays a crucial role in safeguarding blood vessels and DNA against oxidative harm, making it an important element in the precaution and treatment of chronic diseases associated with inflammation. Nevertheless, the limited physicochemical properties of RES pose significant constraints on its application as a standalone medication.⁷⁹ Encapsulation and controlled release of RES using different carriers have emerged as promising strategies to overcome the limitation of low bioavailability.⁸⁰ Jhaveri et al⁸¹ first used transferrin-modified polyethylene glycol liposomes (Tf-RES-L) as a delivery system for RES. Compared with free drugs, functionalized drug-loaded liposomes significantly increased apoptosis of glioblastoma multiforme cells (GBMs) by activating the caspase 3/7 pathway. Since transferrin receptors (TfRs) are upregulated in GBMs, the surface modification of liposomes with transferrin confers cancer cell specificity. In the presence of excess free transferrin, competitive inhibition confirmed that Tf-RES-L exploits the receptor-mediated endocytosis pathway mediated by TfRs for cell internalization. As expected, Tf-RES-L exhibited uniform size distribution and zeta potential, and its stability increased. The effectiveness of Tf-RES-L is largely attributed to the surface modification by transferrin. This also demonstrates that the increased bioavailability and targeting of natural product accumulation are due to the cumulative effects of the nano-drug delivery system targeting warheads.

Curcumin (Cur) is a polyphenol isolated from the rhizome of *Curcuma longa*. It demonstrates remarkable antioxidant, wound healing, and anticancer properties.^{82,83} However, the use of it is restricted due to low bioavailability, high hydrophobicity, and vulnerability to degradation when exposed to light. One approach to address these issues is to enclose natural plant metabolites within biodegradable and biocompatible NPs. Feng and colleagues⁸⁴ developed a CD44-targeted drug delivery system by covalently linking hyaluronic acid to propylene glycol-based ethosomes (HA-ES). The HA-ES surface was coated with a HA gel network, resulting in decreased leakage and release of curcumin. This improved the targeted delivery of Cur to inflamed psoriatic skin that overexpressed CD44 protein, thereby enhancing the therapeutic effect on the affected area. By encapsulating lipophilic natural products within the gel structure, the stability of the drug is ensured, as well as its safety in non-target tissues. This promising local drug delivery system, which releases the drug in areas of inflamed skin that highly express CD44 protein, can also be used to enhance the accumulation of other drugs.

Alkaloids

Alkaloids are generally small nitrogenous organic compounds, derived from amino acids, that are isolated from plants. They can be categorized into 80 groups according to their chemical core structures, such as isoquinoline alkaloids, quinoline alkaloids, indole alkaloids, and pyridine alkaloids.⁸⁵ A significant number of studies conducted in vivo and in clinical settings have shown that alkaloids possess diverse pharmacological properties, including anti-cancer, antiviral, anti-inflammatory.^{86–88} Many alkaloid drugs have been developed and are widely used in clinical practice, such as camptothecin and paclitaxel for anticancer therapy, and berberine hydrochloride for antibacterial therapy. However, research has shown that despite their significant pharmacological activities, alkaloids often exhibit poor pharmacokinetic characteristics, incompatibility in biological media, and the formation of aggregates that can hinder cellular uptake, thus limiting their clinical applications.^{89,90} A prominent focus of contemporary scientific investigation lies in the

advancement of nano-drug delivery systems. These systems possess distinctive physical and chemical attributes that safeguard encapsulated drugs from enzymatic and mechanical deterioration, heighten permeability, and exhibit retention effects. Such properties offer an array of advantages in drug delivery.^{91,92} Consequently, designing novel nano-drug delivery systems to improve the therapeutic effects of alkaloids in diseases such as cancer holds great potential. In this section, we have chosen the natural product paclitaxel as a representative drug and discuss recent research on relevant delivery systems.

Paclitaxel (PTX), a natural compound derived from the bark of *Taxus brevifolia*, is known for its remarkable anti-tumor properties, especially in the treatment of ovarian and uterine cancers.^{93,94} However, because of its limited ability to dissolve in water, tendency to become unstable, propensity to precipitate, and toxic nature, its application in clinical settings has proven to be quite difficult.^{95,96} To address these drawbacks, researchers⁹⁷ have successfully devised and produced an innovative Tn-Lipo-PTX, a PEGylated paclitaxel nano-liposome with ASGPR targeting capabilities, specifically tailored for the treatment of hepatocellular carcinoma. A configurationally defined N-acetylgalactosamine was synthesized and used as a targeting warhead, significantly enhancing the cytotoxicity of paclitaxel towards liver cancer cells. This study highlights the superiority of nano-carriers with warhead-modifications for delivery of lipophilic drugs. Human H-chain ferritin (HFtn), with its excellent solubility in water, biodegradability, multifunctionality, and uniform size distribution, has gained increasing attention in drug delivery applications.^{98–101} Ma et al¹⁰² confirmed that the N-terminus of human HFtn can be functionalized with the C-terminal cyclic peptide tLyP-1 as the targeting moiety for PTX delivery. By adjusting the pH, PTX was encapsulated into HFtn NPs through disassembly/reassembly, forming a dual-targeting NP delivery system. This method greatly improved the ability of PTX to inhibit cancer cells and demonstrated the promise of utilizing protein-functionalized targeting peptides as vehicles for delivering hydrophobic drugs to tumor tissues. The hydrophobic drugs are encapsulated within functionalized proteins, maintaining relative stability under normal physiological conditions, and then released from the nanostructures (Figure 5).

Natural Product-Based Self-Assembled Nano-Drug Delivery Systems

Self-assembly refers to the process in which fundamental units, such as molecules and nano-structured materials, spontaneously come together to form a stable and closely-knit structure. This process is primarily propelled by feeble non-covalent interactions, encompassing hydrogen bonding, van der Waals forces, π - π stacking, and electrostatic

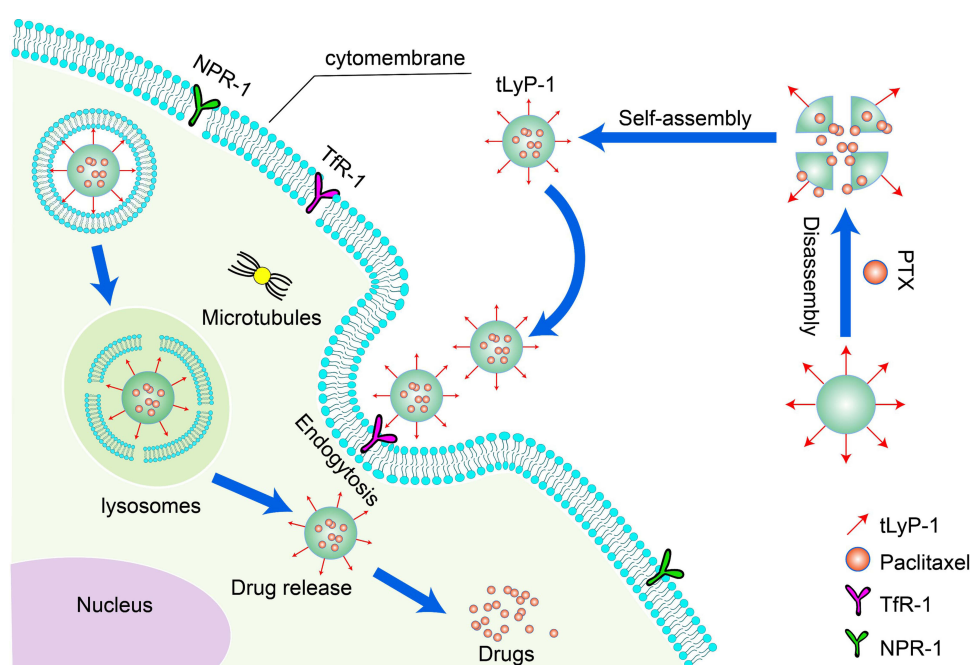


Figure 5 Method for preparing PTX nanoparticles; schematic illustration of the tLyP-1 peptide functionalized HFtn for targeted delivery.

interactions, with the intention of generating durable self-assembled systems featuring distinct structures. The resulting products can take forms such as micelles, liposomes, or helical belts.^{103,104} In 1993, Ghadiri and others¹⁰⁵ first used self-assembly techniques to synthesize peptide nanotubes from a novel cyclic peptide. Subsequently, Zhang and others¹⁰⁶ discovered ionizable short peptides that could undergo self-assembly, and the field of peptide self-assembly gradually developed. Natural product self-assembly has shown apparent advantages in terms of low cost, low energy consumption, and low pollution in the field of nanomaterials, and can also improve drug solubility, targeting, and other properties.

In recent years, supramolecular self-assembly technology has attracted wide attention both domestically and internationally because of its ability to prepare nanomaterials with unique physical and chemical properties. Research has found that nano-drug delivery systems may suffer from problems such as non-ideal biocompatibility and biodegradability in clinical applications. Therefore, researchers are dedicated to developing biologically safe drug carrier materials and formulating drugs with minimal side effects. The construction of nanostructures mainly abides by two strategies: top-down and bottom-up approaches (Figure 6). Top-down strategies involve creating nanostructures of specific shapes and sizes from larger structures. On the other hand, bottom-up methods produce the desired nanostructures by using basic components and utilizing molecular recognition and self-assembly processes. The latter approach heavily relies on the interactions between these basic units to form highly organized structures. Consequently, by effectively controlling the structure of self-assembled molecular units, it becomes possible to manipulate the formation of nanostructures at the atomic or molecular level.¹⁰³ This section provides an overview of the study and practical uses of various types of self-assembled nano-carriers.

Drug Self-Delivery Systems Based on Natural Small-Molecule Drugs

Drug Self-Delivery Systems (DSDSs) are novel ways to deliver drugs that do not require additional nano-catalysts to achieve drug delivery.¹⁰⁷ The self-assembled drugs serve as both carriers and medications, resulting in an increased rate of drug encapsulation and drug loading capacity, while also minimizing drug wastage. This technology eliminates the necessity for additional nano-catalysts, thus preventing drug degradation, metabolism, and excretion, while also avoiding any potential toxicity or immunogenicity caused by the carriers. As a result, the drug remains protected from damage, and the system demonstrates excellent biocompatibility and is relatively safe.^{108,109} Optimization of key characteristics such as size, surface properties, and circulatory stability in vivo of the nanomaterials allows effective improvement of their clinical safety, enabling timely application in clinical practice.¹¹⁰

Ursolic acid (UA) is a pentacyclic triterpenoid compound commonly found in plants and food. It has promising biotechnology applications and pharmacological activity. UA exhibits potent anticancer effects by inhibiting tumor cell differentiation, angiogenesis, invasion, and metastasis through various pathways with low toxicity to normal cells.^{111–114} In the realm of drug delivery, self-assembled peptide-based nano-drug delivery The progress and utilization of this compound encounter obstacles such as inadequate drug levels within the body and unsatisfactory distribution throughout the body. Nano-drug delivery systems hold promise in augmenting the pharmacokinetics, bioavailability, and therapeutic efficacy of targeted medications. Based on the robust hydrophobic interactions and hydrogen bonding interactions among UA molecules, certain scholars have employed self-assembly technology to devise a carrier-free and highly loaded nano-drug system.¹¹⁵ UA allows

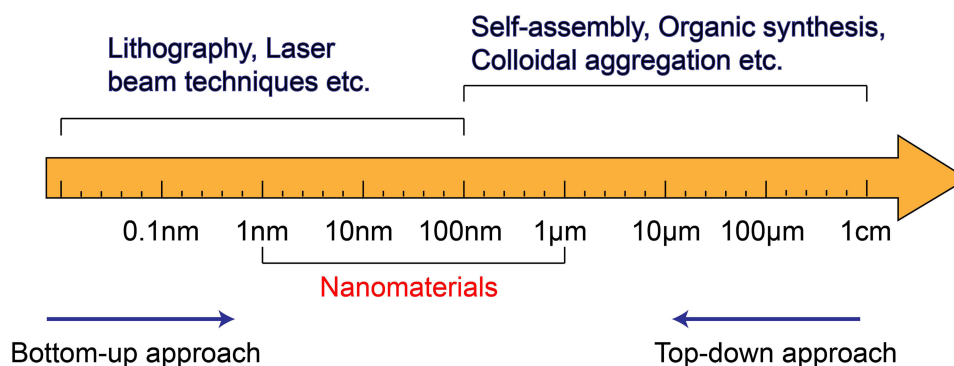


Figure 6 Two strategies for self-assembly: top-down and bottom-up.

for self-assembly at a small size and negative charge without any additional assistance, which helps improve its solubility and concentration-dependent inhibition of HeLa and A549 cell growth. Additionally, it significantly increases the deposition of UA in tumor tissues. This suggests that the novel carrier-free nano-drug delivery system holds potential as a strategy to improve the efficacy of unsatisfactory solubility of anticancer drugs. Hydrophobic drugs have the ability to spontaneously form Drug Self-Assembled Delivery Systems (DSDSs) by means of intermolecular interactions. These drugs can then gather at the specific site of the disease, influenced by the permeability of blood vessels and the EPR effect that tumors exhibit. The systems could release load in response to the acidic tumor microenvironment. Several reports have described the successful development of supramolecular hydrogels containing drug complexes in the laboratory, which have been used for alleviating inflammation, wound healing, and other applications.^{116–119} Rhein (Rhe) is an anthraquinone compound extracted from the dried roots and rhizomes of *Rheum palmatum* L. or *Rheum tanguticum* Maxim, which has been provided evidence of its remarkable potential in the field of medical imaging, as well as in the treatment of neurodegenerative diseases.^{120–123} However, the difficulties faced in clinical development of Rhe arise from its limited solubility in water and low bioavailability. To settle these problems, nano-drug delivery systems have been employed to improve the pharmacological effectiveness of Rhe. Zheng and his group¹¹⁶ have successfully fabricated a controlled-release hydrogel by means of the directed self-assembly of Rhe molecules, which is facilitated through π - π stacking and hydrogen bond interactions. The hydrogel has good biological stability and exhibits sustained release and stimulus responsiveness, which is attributed to its stability and fiber brittleness. The self-assembly of Rhe monomers, devoid of any structural modification or delivery carriers, provides significant insights into the self-assembly mechanisms of other small molecules. Ke and others¹²⁴ found that licorice protein could self-assemble into NPs and load 28.2% aconitine at pH 5 and 20–25 °C. The preparation of high-bioavailability protein NPs expands the application of protein components and provides a basis for preparation and targeted action of self-assembled NPs of active ingredients from natural products.

In one study,¹²⁵ the concept of a “self-contained bioactive nano-carrier” system has been proposed, revealing that van der Waals forces and electrostatic interactions are important driving forces in the assembly of UA and PTX, and that the drugs are almost fully loaded. The experiments have indicated a time-dependent effect, resulting in a tumor inhibition rate of 90.2%. Furthermore, the experimental data provide convincing evidence for the biocompatibility of UA. UA initially forms a double-layered vesicle structure, providing hydrophobic positions for the self-assembly of UA and PTX. The self-assembly of the two drugs compensates for the lack of bioactivity of the nano-carrier, endowing it with excellent therapeutic activity, and achieving synergy of the carrier and drug treatment. Tian et al¹²⁶ constructed a nano-drug delivery system based on self-assembly of the natural products Rhe and Berberine (Ber) to enhance antibacterial activity against *Staphylococcus aureus*. The experimental results showed that at the lowest bactericidal concentration of 0.1 $\mu\text{mol/mL}$, Ber-Rhe NPs gave significantly higher inhibition of *S. aureus* compared with the same concentration of free drugs. That is, after Ber and Rhe were self-assembled into NPs, the synergistic antibacterial effect was significantly enhanced, and good biocompatibility and safety were demonstrated. These molar complex NPs relying on ectopic stacking and electrostatic interactions could form stable layered stacking three-dimensional configurations in an aqueous solution (Figure 7). The weak bond-driven effective structural self-assembly offers several advantages over nano-carriers. These advantages include enhanced drug delivery efficiency and the ability to evade the potential metabolism and toxicity issues relevant to nano-carriers. Chen and others¹²⁷ investigated the thermodynamic mechanism of the interaction between the active components of rhubarb and *Coptis chinensis*, tannic acid and berberine, and found that their combination was a spontaneous process. They constructed a supramolecular self-assembly system of tannic acid-berberine host molecules and drug conjugate HA for active targeted delivery to the colon. The constructed nano-drug delivery system exhibited a powerful synergy of the two drugs, enhanced uptake and accumulation of drugs in lesions, suppressed levels of pro-inflammatory cytokines, and showed substantial anti-inflammatory effects against acute colitis induced by dextran sodium sulfate. In comparison to previously reported drug carriers, these possess distinct benefits in preventive healthcare, highlighting the promising growth potential of self-assembly in utilizing natural products.

Self-Assembled Nano-Drug Delivery Systems Based on Natural Products and Peptides

Peptides are bioactive compounds situated between proteins and amino acids, which are generated by linking numerous amino acids in a specific sequence through amide bonds. Although peptides have simple structures and are small, they

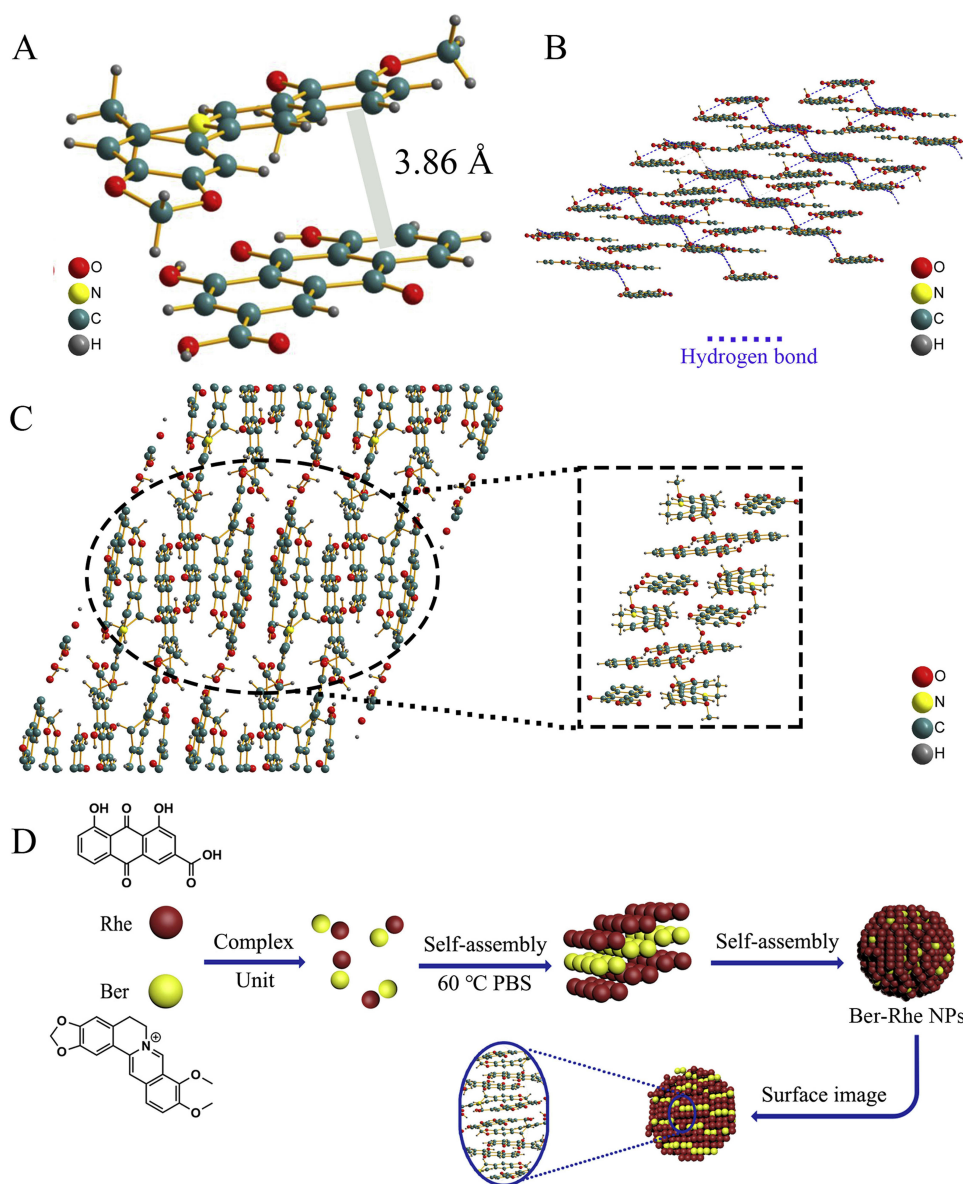


Figure 7 (A) The basic unit of the crystal formed by the π - π bond of Ber-Rhe nanoparticles; (B) the layered skeletal structure formed under the hydrogen bonding by Rhe; (C) the accumulation structure of Ber-Rhe NPs crystals; (D) schematic diagram of self-assembly of Ber and Rhe.

Notes: Reproduced with permission from Tian X, Wang P, Li T, et al. Self-assembled natural phytochemicals for synergistically antibacterial application from the enlightenment of traditional Chinese medicine combination. *Acta Pharm Sin B*. 2020;10(9):1784–1795.¹²⁶ © 2020 Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences. Production and hosting by Elsevier B.V.

often have important biological functions. Compared to traditional biomedical materials, peptides possess excellent biocompatibility and chemical versatility. They are also biodegradable and exhibit remarkable self-assembly characteristics.^{128,129} By modifying the pH and ion strength, and incorporating enzymes or light, it becomes feasible to initiate self-assembly and create a variety of distinct nanostructures. These nanostructures have been found utility in the realm of controlled drug delivery.¹³⁰ Peptide-based NPs have unique advantages, such as customizable molecular design, effective functional regulation, and peptide-specific biomolecular recognition capabilities, making them stand out among many nano drugs.^{131,132} There have been numerous studies on the design, synthesis, and application of peptide-based nano-drugs. For example, in their comprehensive review, Wang et al¹³³ concisely outline the design methodologies employed in the development of self-assembled peptide nano-drug delivery systems. The authors place particular emphasis on elucidating the various strategies utilized for drug delivery, all of which are based on the self-assembly

properties of peptides. In the realm of drug delivery, self-assembled peptide-based nano-drug delivery systems have gained significant traction. This can be attributed to their remarkable attributes, such as their ability to carry a large quantity of drugs, heightened bioavailability, effective targeting capabilities, and capacity to permeate cellular structures.

The diverse chemical properties of non-covalent interactions have promoted rapid development of self-assembly for drug delivery. Sis and Webber¹³⁴ provide a deep-going overview of the basic design of peptide self-assembled systems and methods. Amphiphilic peptides have extended the application of self-assembling peptides in drug delivery. Hsieh and Liaw¹³⁵ proposed safety measures to ensure the precise size and length of nanotubes for effective delivery of active drug ingredients utilizing multifunctional cyclic peptides. In a separate study, Ji Hwan Park et al¹³⁶ formed amphiphilic peptides R7L10 by self-assembly of additional arginine and leucine residues at the amino and carboxyl ends of peptide R3L6, which stably self-assembles with plasmid DNA to form complexes. The model drug curcumin, a lipophilic anti-inflammatory drug, was loaded into the hydrophobic core of the complex formed by the amphiphilic peptide R7L10 and plasmid DNA, significantly improving the solubility. Additionally, the system enhanced cellular uptake in a model of acute lung injury without inducing hepatotoxicity, demonstrating its potential.

Peptide-based hydrogels are a class of drug delivery carriers that involve encapsulation of drugs and covalent linkage of therapeutic agents. Typically, small peptide molecules generally form specific secondary structures in solution and have the ability to spontaneously form fibrous networks in response to different physical factors.^{137–139} Hydrogels are hydrophilic networks with strong water-retaining capacity that resemble biological tissues.¹⁴⁰ Based on supramolecular chemistry, Faisal Raza and his colleagues¹⁴¹ designed a pH-responsive octapeptide, FER-8, for targeted delivery of the anti-tumor drug PTX. As a consequence of the compatibility of the peptide self-assembly and cross-linking with physiological conditions, FER-8 hydrogel exhibited exceptional efficacy as a drug carrier. It effectively increased accumulation of PTX in tumor cells, prolonged residence time, and reduced systemic side effects through intratumoral injection. This suggests the superiority of peptide self-assembling hydrogels as carriers for insoluble natural products. Drugs loaded in hydrogels exhibit biphasic release behavior and diffuse from the surface pores of the hydrogel. Wei et al¹⁴² confirmed that the self-assembling peptides RADA16-I and RVDV16-I interacted with emodin. Both of these peptides that assemble themselves formed hydrogels in aqueous solution with emodin while being influenced by magnetic stirring. The hydrogels significantly increased the effectiveness of inhibiting tumor cells *in vitro* compared to emodin on its own. This also fully showcases the capability of self-assembling peptides as carriers for hydrophobic drugs. Hydrophobic drugs are enclosed within the self-assembled peptides, ensuring their stability in the circulatory system, and then released from the hydrogel.

Self-Assembly Based on Metal-Coordinated Polyphenols

Recently, researchers have discovered that natural polyphenols can coordinate with metals to self-assemble into metal-polyphenol nanonetworks (MPNs) with a thickness of two nanometers. Like most self-assembled systems, MPNs can not only exist as thin films but also take on various other forms as a consequence of their flexible structures.¹⁴³ Polyphenols exhibit a range of powerful physical, chemical, and biological properties, such as antioxidant activity, high adhesion, and the ability to absorb ultraviolet radiation.^{144,145} Adriamycin, peroxidases, and some natural products can be stably embedded in the MPN framework. Many natural polyphenols, such as catechin, shikonin, curcumin, epigallocatechin, and tannic acid, have been utilized for constructing MPNs in cancer treatment.¹⁴⁶ Feng et al¹⁴⁷ constructed a Fe (III)-shikonin metal-polyphenol-coordinated supramolecular nanomedicine (FSSN) for comprehensive tumor therapy involving iron-dependent apoptosis and necroptosis (Figure 8). The preparation of FSSN not only improved the solubility and loading of shikonin but also reduced toxicity to normal cells. When the FSSN is engulfed by tumor cells, Fe^{3+} is reduced by glutathione, causing decomposition of the FSSN and release of the drug, triggering the effective biological activity of tumor cell deferrization. This demonstrates the promising potential of nano-drug delivery systems derived from metal-polyphenol coordination interactions. Wen et al¹⁴⁸ reported a degradable carrier-free curcumin-based MPN theranostic agent (ICG @Cur-Gd NPs) combining indocyanine green (ICG), Cur, and Gd^{3+} . In the tumor microenvironment, ICG @Cur-Gd NPs were degraded, resulting in the release of Cur, ICG, and Gd^{3+} to enhance therapeutic efficacy and reduce biotoxicity. *In vivo* experiments confirmed that laser treatment in combination with ICG @Cur-Gd NPs significantly inhibited tumor growth without apparent cytotoxicity, indicating great

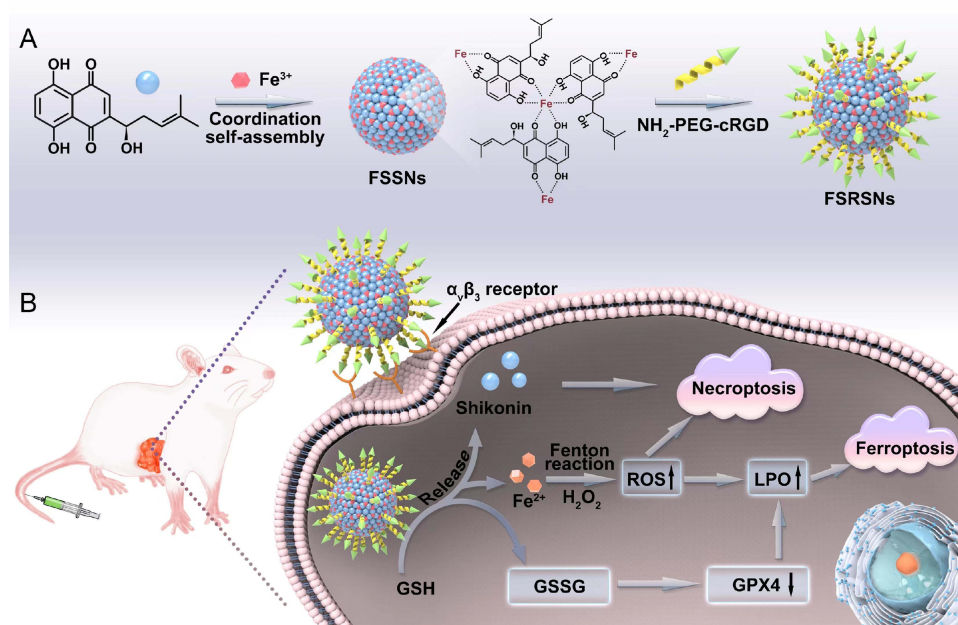


Figure 8 (A) Schematic diagram illustrating the supramolecular nano-drug FSSNs formed by Shikonin and Fe^{3+} , as well as further modifications; **(B)** FRSN specifically binds to the $\alpha_v\beta_3$ receptor, significantly enhancing its accumulation in tumor cells.

Notes: Reproduced with permission from Feng W, Shi W, Liu S, et al. Fe(III)-Shikonin Supramolecular Nanomedicine for Combined Therapy of Tumor via Ferroptosis and Necroptosis. *Adv Healthc Mater.* 2022;11(2):90.¹⁴⁷ © 2021 Wiley-VCH GmbH.

potential for clinical applications. This investigation presents an innovative and efficient approach for the development of tumor imaging-guided therapeutic drugs, without the need for carrier molecules.

Dietary flavonoids have a wide range of biological functions, including acting as antioxidants, contributing to pigmentation, and providing defense against radiation damage. Flavonoids have garnered considerable interest due to their notable advantages for human health, with applications in areas such as cancer treatment, prevention of cardiovascular diseases, and mitigation of inflammation. Nadja Bertleff-Zieschang et al¹⁴⁹ assembled four flavonoids containing a common ortho-dihydroxybenzene structure, namely myricetin (Myr), quercetin (Que), fisetin (Fis), and luteolin (Lut), into solid surface coatings by coordinating with Fe (III). The mechanism is based on pH-dependent rapid coordination assembly between the flavonoid ligands and Fe (III). The results indicated that the films formed by Que, Myr, Lut, and Fis had free radical scavenging activity (Figure 9), and could be reused in multiple cycles.

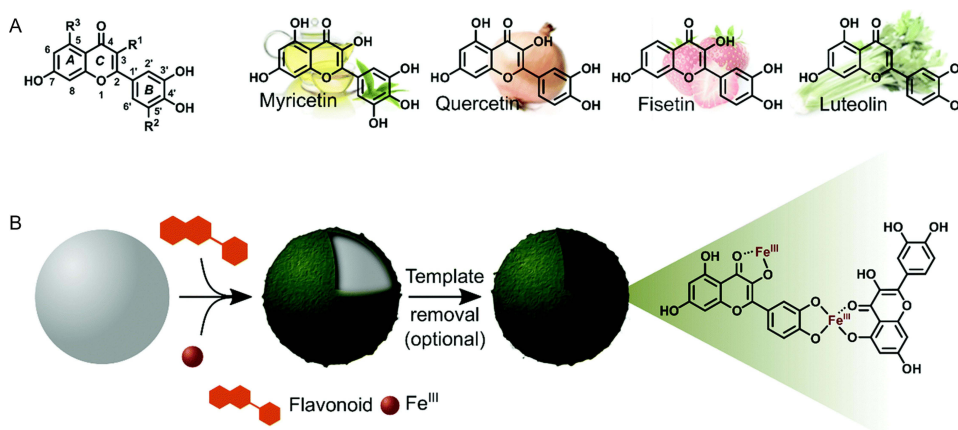


Figure 9 (A) Molecular structure of flavonoids and their main sources; **(B)** schematic diagram of the self-assembly of flavonoids and Fe^{3+} on the template surface.

Notes: Reproduced from Bertleff-Zieschang N, Arifur Rahim M, Ju Y, et al. Biofunctional metal-phenolic films from dietary flavonoids. *Chem Commun.* 2017;53(6):1068–1071.¹⁴⁹

Co-Delivery Nano-Drug Delivery Systems Based on Natural Products

Natural products exhibit therapeutic effects in clinical applications through the comprehensive actions of multiple components. The fundamental aspect of this is the role played by the pharmacologically bioactive constituents. The key to preventing and treating diseases lies in effective delivery of multiple natural small-molecule components. Consequently, taking advantage of modern nanotechnology to achieve effective delivery and distribution of multiple components, leveraging synergistic effects, reversing multidrug resistance, and reducing toxicity is a scientifically rational choice. Modern research has found that co-delivery systems based on nano-carriers clearly demonstrate potential to overcome problems associated with the use of single drugs or traditional treatment methods. Nano-drug co-delivery systems are specifically developed for clinical purposes, wherein a minimum of two drugs possessing distinct physicochemical and pharmacological characteristics are incorporated into a system.¹⁵⁰ According to reports, co-delivery technologies have numerous advantages, such as administration of different natural products in specific ratios and doses, controlled release, and potential synergistic effects.^{151,152} The combination of nanotechnology and co-delivery strategies has not only become an ideal drug delivery approach but also represents one of the cutting-edge research areas in the quest for effective drug delivery systems.^{153–155} The segment furnishes a thorough review and analysis of the present state of research and utilization of nano delivery carriers for drug co-delivery. Its objective is to establish a theoretical foundation for nano systems that can effectively transport multiple natural active ingredients concurrently.

Solid Lipid Nano-Carriers

The application of lipid NPs is an emerging field at the forefront of rapidly developing nanotechnology.^{156,157} In the early days, solid lipid nanoparticles (SLNs) were formulated as colloidal vehicles for drug delivery, exhibiting a particle size distribution spanning from 50 to 1000 nanometers.¹⁵⁸ They offer numerous advantages, such as reducing adverse reactions, permitting encapsulation and entrapment of various molecules, accelerating targeted delivery of therapeutic drugs to specific tissues and cells, and feasibility of large-scale production.^{159,160} SLNs could be composed of a mixture of solid lipids or lipids and surfactants. In addition, aqueous phases, co-surfactants, and cryoprotectants may also be present.^{161–163} Hydrophobic drug combinations are encapsulated in a solid lipid matrix to protect the drugs from chemical degradation, thereby increasing their stability.

In a scholarly investigation,¹⁶⁴ the objective was to elevate the therapeutic effectiveness of tanshinone (TAN) and achieve a synergistic effect with puerarin (PUE). This was accomplished by co-encapsulating PUE-prodrug and TAN in solid lipid nanoparticles (SLNs) to treat myocardial infarction. Compared with administration of free TAN and PUE, SLNs loaded with both drugs were significantly more efficacious in the treatment of infarction. Single emulsification and solvent evaporation methods were employed for the formulation of co-loaded solid lipid nanoparticles (SLNs), resulting in reduced cytotoxicity and extended-release characteristics attributed to the incorporation of PEG. This significantly improved drug safety, demonstrating significant advantages of co-delivery nano-drug delivery systems with synergistic effects. The drugs, present independently on the surface layer of the particles, were released by rapid dissolution from the surface of the SLN. In another study, Wang et al¹⁶⁵ formulated solid lipid nanoparticles (SLNs) loaded with paclitaxel and naringenin in order to address glioblastoma multiforme. To enhance the targeting efficiency towards cancerous sites, the SLNs were modified with cyclic RGD peptide sequences. The research demonstrated that the pharmacokinetic properties of the peptide-functionalized SLNs, including maximum plasma concentration (C_{max}), time to C_{max} , and relative bioavailability, outperformed those of regular SLNs and drug suspensions. Furthermore, the functionalized SLNs exhibited greater cytotoxicity against U87MG glioma cells in comparison to the free drug suspension. This study highlights the immense benefits of co-delivery nano-drug delivery systems in the context of cancer treatment.

Liposomes

Some of the most important nanotechnology carrier systems are lipid-based,¹⁶⁶ including widely used liposomes, and closely related lipid nanodiscs. Lipid-based vesicles such as liposomes are highly attractive for drug delivery because of their high drug-loading capacity, ability to deliver both hydrophilic and hydrophobic drugs, good biodegradability and biocompatibility, prolonged residence in the body, and ease of controlling drug delivery.¹⁶⁷ Liposomes are primarily composed of phospholipids

that allow self-assembly of non-ionic surfactants and other amphiphilic chemicals, or are composed of amphiphilic lipids, which form spherical vesicles. This structure creates two microenvironments, facilitating co-delivery of drugs.^{168,169} The drug encapsulation efficiency of liposomes is contingent upon factors such as the size and quantity of bilayers, as well as the vesicle size. Modifying the structure of liposomes can be an effective method to attain the desired therapeutic outcome.^{170,171}

According to recent research,¹⁷² it has been discovered that the combination of paclitaxel and tanshinone IIA (TanIIA) has a cooperative effect on the induction of apoptosis in human acute promyelocytic leukemia NB4 cells. For the sake of enhancing the effectiveness of this combination and minimizing any adverse effects, the authors of the study developed a drug delivery system using mesoporous silica nanoparticles that were coated with FA-modified PEGylated lipid-bilayer membranes. It was found that the NPs exhibited sustained release characteristics, with both paclitaxel and TanIIA being released simultaneously from the carrier. This finding highlights the potential of nano-carrier systems to accommodate multiple hydrophilic and hydrophobic drugs while maintaining a high drug-loading capacity. Through specific binding between ligands and receptors, multiple drugs enter cells through endocytosis to exert synergistic anticancer effects. Wang et al¹⁷³ used ginsenoside Rg3 as a membrane material to prepare unique Rg3-based liposomes loaded with PTX and evaluated their stability, anticancer activity, and mechanisms. The study showed that Rg3-PTX-LPs were specifically distributed to human breast cancer cells and the tumor microenvironment synchronously. Compared with conventional liposomes, Rg3-PTX-LPs exhibited significantly improved reversal of drug resistance and in vivo antitumor efficacy.

Polymeric Nanoparticles

Polymer nanoparticles (PNPs) offer several advantages as drug carriers in terms of controlled release, protection of drugs and bioactive molecules from environmental factors, and enhancement of bioavailability and therapeutic index.^{167,174} Various methods can be employed to produce PNPs for drug delivery, depending on the specific drug and its administration requirements. These methods can be broadly categorized into two main strategies that are commonly utilized in the field. The first strategy involves the dispersion of preformed polymers, while the second strategy involves the polymerization of monomers. The selection of the appropriate method depends on the type of drug to be loaded into the PNPs and the desired pathway of administration.^{175,176} To extend the duration of drug circulation in the body and minimize their interaction with blood proteins, PEG can be employed to modify the drugs or carriers. PEGylation of PNPs considerably prolongs drug circulation in the body and enhances their stability.¹⁷⁷

Leila Khoshrovan Azar et al¹⁷⁸ co-encapsulated two natural products, artemisinin (Art) and chrysin (Chr), in PEG-modified poly (lactic-co-glycolic acid) NPs to investigate their combined effects against T47D breast cancer cells. The administration of the Art/Chr-PLGA/PEG NPs demonstrated superior synergistic effects in inhibiting cell proliferation when compared to the individual drugs administered separately. The modification reduced the size of the co-delivery system, which significantly improved drug solubility and showed good stability. Co-encapsulation of the two natural products in PEG-PLGA biodegradable NPs significantly amplified the synergistic anti-tumor effects of artemisinin and chrysin while ensuring drug safety.

Polymeric Micelles

Polymer-based delivery systems present themselves as stable and dependable substitutes for carriers based on lipids.^{179,180} Polymer micelles (PMs) are biodegradable, flexible, and spherical nanoparticles formed by combining different amphiphilic diblock or triblock copolymers. The hydrophobic interior of PMs provides sufficient space for water-insoluble drugs, while the exterior shell effectively safeguards the drugs from the external environment, thus impeding rapid degradation.¹⁸¹ Research has shown that PMs are versatile drug carriers due to increased drug solubility, excellent biocompatibility, enhanced permeability, and reduced toxicity.¹⁸² Commonly used hydrophilic segments in PMs include PEG and poly-N-isopropyl acrylamide, while hydrophobic segments include polypropylene glycol and polycaprolactone.¹⁸³

Zhou et al¹⁸⁴ successfully constructed glutathione (GSH)/reactive oxygen species (ROS) dual-responsive hybrid PMs composed of PTX and honokiol (HK) prodrug that self-assembled. The resulting micelles inhibited the growth of laryngeal cancer. Following optimization and characterization, PTX and HK were precisely loaded in the PMs in a defined mass ratio, enabling proportional drug loading and synchronous drug release in response to the high ROS

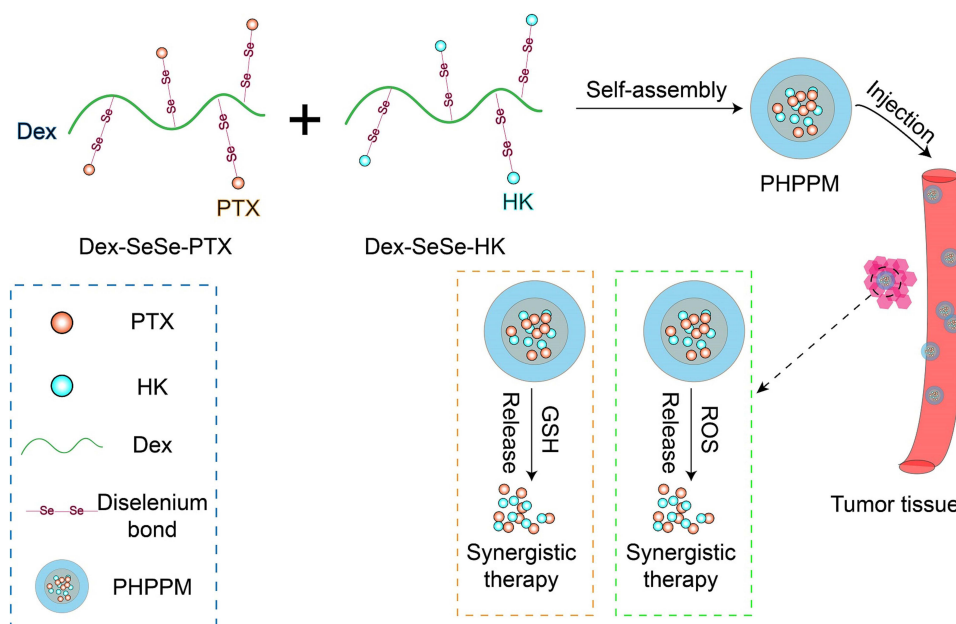


Figure 10 The preparation of PHPPM and the schematic illustration of the intracellular glutathione/reactive oxygen species (ROS) dual-responsive drug delivery system.

and GSH levels in tumor cells. The PMs exhibited prolonged circulation and significantly increased accumulation in tumors (Figure 10). Through the covalent linkage of different drugs with biocompatible polymers that possess diselenium bonds, the result was the formation of amphiphilic polymers. These polymers, in turn, exhibited self-assembly properties, leading to the creation of core-shell micelles when placed in an aqueous solution. This significantly increased the drug loading capacity of the nano-drug delivery system while maintaining excellent biomimetic properties and demonstrating the advantages of multi-drug co-delivery and synergistic effects.

Metal Nanoparticles

Many studies have reported the potential of metal nanoparticles (MNPs) with different compositions, such as platinum, gold, silver, iron, selenium, and their oxides, for disease treatment through various mechanisms, including controlled drug release and localized hyperthermia.^{185,186} These NPs possess remarkable attributes such as surface plasmon resonance properties, structural variability, minimal toxicity, and remarkable compatibility with biological systems.¹⁵⁸ These characteristics render them well-suited for drug encapsulation through non-covalent attractive interactions or covalent bonding. Moreover, scientific investigations have demonstrated that MNPs exhibit exceptional capabilities in targeting specific areas, gene silencing, and facilitating drug transport.^{167,187} Various MNPs that have been used for disease treatment include gold nanoparticles (Au NPs), silver nanoparticles (Ag NPs), and iron oxide nanoparticles (IO NPs).¹⁸⁸

Iron oxide nanoparticles (IO NPs) have garnered considerable attention in the emerging field of magnetic nanoparticle technologies due to their remarkable ability to selectively target specific areas under the influence of external magnetic fields.¹⁸⁹ In a study by Hiremath C. et al¹⁹⁰ folate-modified Pluronic F127-coated oleic acid-stabilized IO NPs were developed as a means of concurrently delivering PTX and Cur to combat breast cancer. The modification of the NPs resulted in enhanced toxicity towards cancer cells, which was further augmented when an external magnetic field was applied, indicating an increased uptake of the NPs by the cancer cells. The transportation of medications by IO NPs is facilitated by the interaction between the hydrophobic cavities of the NPs and hydrophobic drugs. Through the specific binding of folate to folate receptors on the surface of breast cancer cells, a substantial amount of medication enters the cells, resulting in synergistic effects that induce apoptosis in the cancer cells. This underscores the significance of developing co-delivery systems.

Conclusions

It has been discovered that natural products have significant pharmacological effects against most diseases. Despite their great therapeutic potential, the less-than-ideal physicochemical and pharmacokinetic properties of these natural product compounds have limited clinical application. Nanotechnology-based delivery systems have successfully resolved concerns related to natural products through the enhancement of tissue targeting, reduction of off-target side effects, and improvement of local bioavailability. It is anticipated that nano-drugs will emerge as a viable method for diagnosis, imaging, as well as the treatment and control of diverse diseases, representing a significant advancement in the modernization of natural product research. The utilization of nano-drug delivery systems alters the particle size of natural products, elevates drug solubility, and enhances cellular or tissue absorption. Combining natural products with different nano-carriers can solve most of the challenges they face. Nano-carriers not only reduce the hydrophobicity of natural products but also enhance component stability and bioavailability.

Nevertheless, research on natural product-based nano-drug delivery systems is still in its early stages, and foundational research is currently weak. The pharmacological mechanisms of natural products in the treatment of certain diseases are not yet clear, making their clinical application relatively complex. The loading or modifying of natural products with nanomaterials may enhance their effectiveness, but it may also lead to new adverse reactions. Nanotechnology has fundamentally improved the physical or chemical properties of some natural products, resulting in significant uncertainty regarding their composition. It is crucial to better understand the metabolic pathways and choose appropriate and safe nano-carriers. The widespread application of nanotechnology provides new opportunities for the modernization of natural products. However, foundational and exploratory research still needs to be strengthened. Immaturity in modern separation techniques for natural products, lagging nano-drug preparation techniques, and imperfect methods for evaluating pharmacological efficacy are key issues that need to be addressed. Currently, there are numerous controversies surrounding the effectiveness and safety of nano-carriers. Some nano-drugs lack specific targeting in disease treatment, and the EPR effect fails to achieve drug accumulation at the site of the lesion. Nano delivery rates need to be improved, but current research is mainly focused on assembly of the carriers, with insufficient in-depth research on the interaction of drugs involved in the assembly process. Although binding to specific receptors may somewhat enhance targeting, off-target effects and other issues still exist. Henceforth, it is imperative to give precedence to the advancement of carrier materials that possess heightened tissue targeting specificity, superior biocompatibility, and augmented stability. Insufficient understanding of nanotoxicity is an important issue that requires further research to improve efficacy and safety, enabling safer application of these drugs. Currently, the basic knowledge of nano delivery systems and the evaluation of their effectiveness and safety are continuously expanding. Therefore, cautious design of these nano-systems may help address issues associated with their use. Figure 11 is employed to demonstrate the constraints observed in current clinical utilization of natural products, the benefits offered by nanotechnology, the clinical

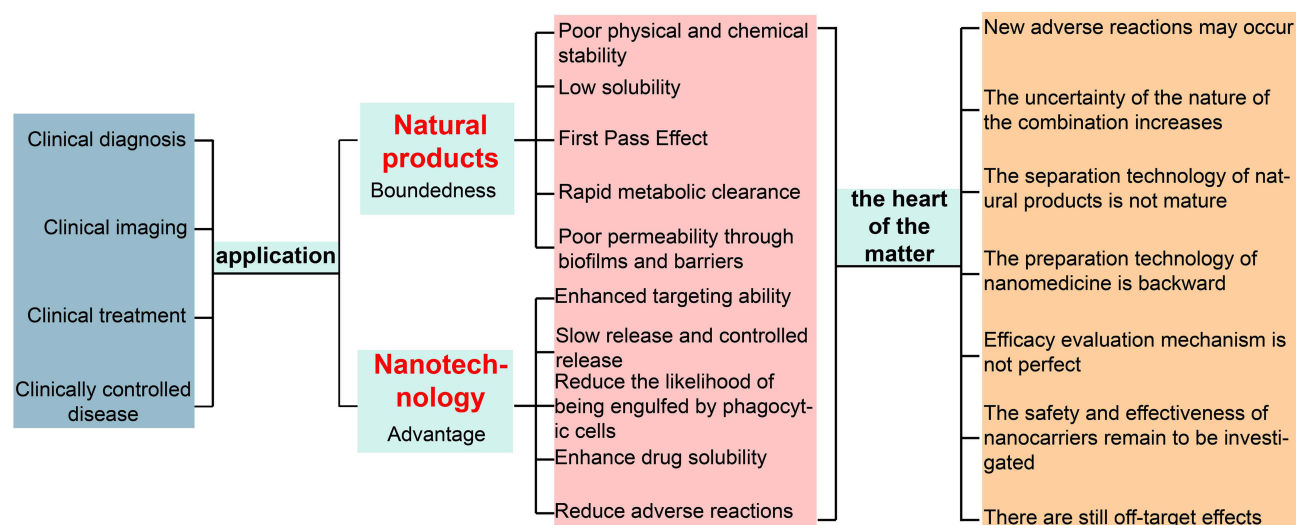


Figure 11 The limitations of clinical application of natural products, the advantages of nanotechnology, the clinical application of nano-drug delivery system based on natural products and the key problems to be solved.

implementation of nano-drug delivery systems derived from natural products, and the pressing concerns that require immediate attention.

Advances in technology will undoubtedly become an important driving force for the modernization of natural products. In the field of natural product research, once the key issues of nanotechnology are overcome, tremendous social and economic benefits can be achieved through clinical application of natural products, promoting their continuous development.

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Disclosure

The authors report no conflicts of interest in this work.

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