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Active herbal ingredients and drug delivery design for tumor therapy: a review

HAN Jing[1Δ], SHEN Yanxi[2Δ], CAO Ruiying[2Δ], WANG Weiren[1], DUAN Jinao[1], DUAN Jialun[1*], BAO Chunjie[1, 2*]

[1] *National and Local Collaborative Engineering Center of Chinese Medicinal Resources Industrialization and Formulae Innovative Medicine, Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, Jiangsu Province Key Laboratory of High Technology Research, Nanjing University of Chinese Medicine, Nanjing 210023, China;*
[2] *School of Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, China*

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[ABSTRACT] Active herbal ingredients are gaining recognition for their potent anti-tumor efficacy, attributable to various mechanisms including tumor cell inhibition, immune system activation, and tumor angiogenesis inhibition. Recent studies have revealed that numerous anti-tumor herbal ingredients, such as ginsenosides, ursolic acid, oleanolic acid, and *Angelica sinensis* polysaccharides, can be utilized to develop smart drug carriers like liposomes, micelles, and nanoparticles. These carriers can deliver active herbal ingredients and co-deliver anti-tumor drugs to enhance drug accumulation at tumor sites, thereby improving anti-tumor efficacy. This study provides a comprehensive analysis of the mechanisms by which these active herbal ingredients-derived carriers enhance therapeutic outcomes. Additionally, it highlights the structural properties of these active herbal ingredients, demonstrating how their unique features can be strategically employed to design smart drug carriers with improved anti-tumor efficacy. The insights presented aim to serve as a reference and guide future innovations in the design and application of smart drug carriers for cancer therapy that leverage active herbal ingredients.

[KEY WORDS] Active herbal ingredients; Smart drug carriers; Anti-tumor therapy
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Introduction

Malignant tumors are characterized by rapid growth, high metastatic potential, and a significant propensity for recurrence post-treatment, presenting a substantial threat to human health. Recent advancements in anti-tumor therapy have highlighted the potential of active herbal ingredients, offering promising applications. Modern scientific and technological progress has enabled researchers to extract and identify active herbal ingredients with anti-tumor properties from various plants, including flavonoids, triterpenoids, and alkaloids [1]. These active herbal ingredients enhance anti-tumor effects primarily through two mechanisms: direct anti-tumor efficacy by inhibiting tumor cells, as observed with active herbal ingredients like paclitaxel (PTX) [2] and berberine (BBR) [3], and indirect anti-tumor efficacy by inhibiting tumor angiogenesis, such as ursolic acid (UA) [4] or activating the immune system, as seen with ginsenosides Rg3 [5].

However, many active herbal ingredients are characterized by low water solubility, which negatively impacts their bioavailability and therapeutic efficacy. Additionally, some ingredients are prone to degradation by metabolic enzymes, reducing their half-life and duration of action [6]. Recent studies have identified various anti-tumor herbal ingredients, including ginsenosides Rg3 [6], UA [7], oleanolic acid [8], and *Angelica sinensis* polysaccharide (ASP) [9], which can be utilized to construct smart drug carriers such as liposomes, micelles, and nanoparticles (Fig. 1). This approach enhances the water solubility of active herbal ingredients, enabling

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[*]**Corresponding author]** Emails: chunjie@njucm.edu.cn (BAO chunjie); jialun.duan@njucm.edu.cn (DUAN Jialun)
[Δ]These authors contributed equally to this work.
These authors have no conflict of interest to declare.

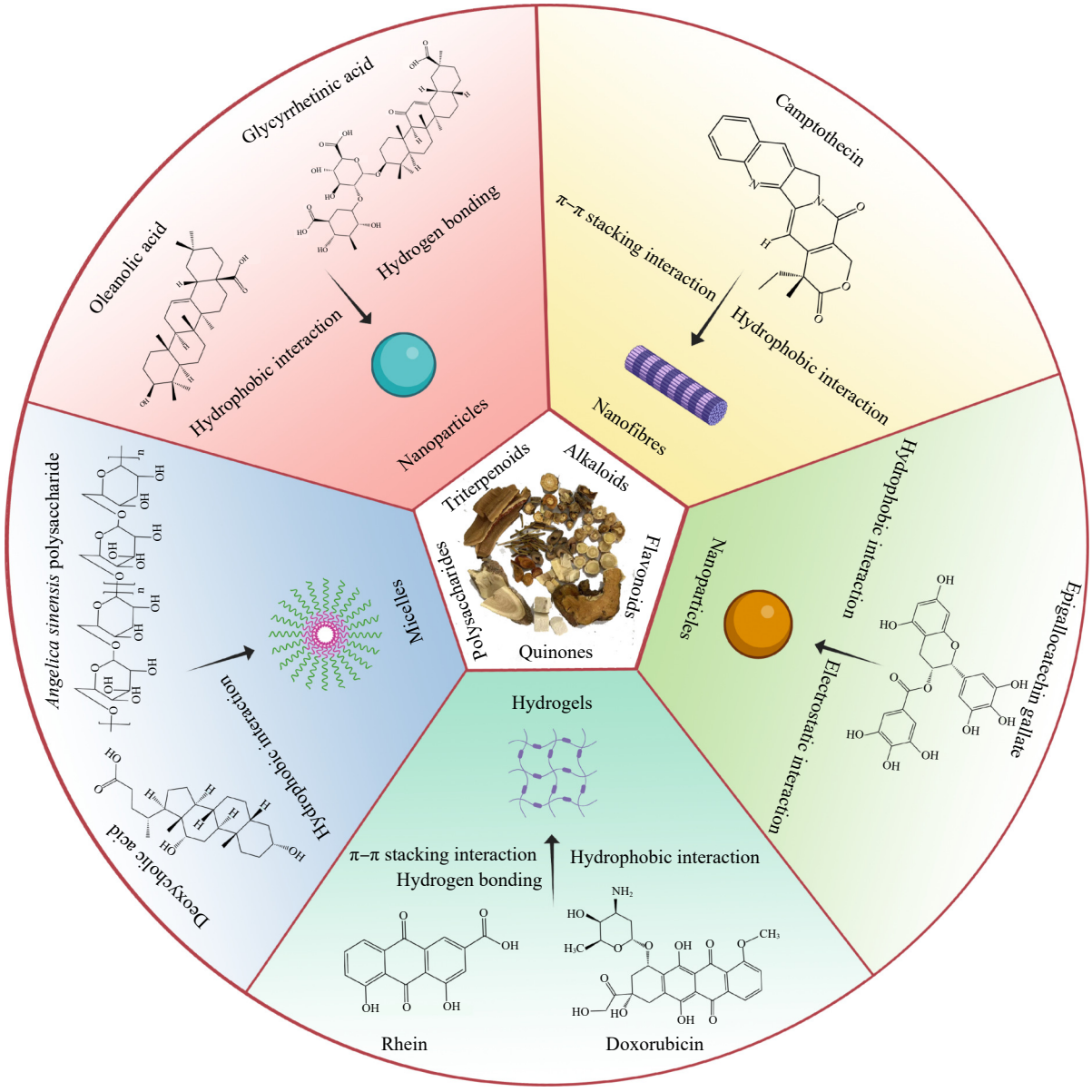

Fig. 1 Smart drug carriers developed by different types of active herbal ingredients and their main forces. Many types of active herbal ingredients could form into smart drug carries like hydrogels, micelles, nanoparticles, and nanofibers *via* multiple non-covalent bonding forces. Examples of each type of active herbal ingredients including quinones, polysaccharides, triterpenoids, alkaloids, flavonoids were given on the graph.

them to exert more potent pharmacological effects. Moreover, active herbal ingredients with specific structures, such as galactose-rich polysaccharides [10] and branched architectures, demonstrate high affinity for certain receptors like the salivary acid protein receptor (ASGPR) [11] prevalent in tumor cells, thus exhibiting significant natural targeting capability. Furthermore, smart carriers derived from active herbal ingredients can regulate drug release in a more controlled manner, achieving sustained and stable blood concentrations, thereby improving bioavailability [12]. In recent years, researchers have focused on the potential of these active ingredients in drug delivery, summarizing strategies for constructing delivery carriers for various active ingredients [13], and explored the application in fibroinflammatory diseases [14], cardiovascular diseases [15] and other conditions.

This article presents a comprehensive review of recent advancements in the application of active herbal ingredients as smart drug carriers for anti-tumor therapy. The focus is on elucidating the mechanisms by which these herbal ingredient-derived smart drug carriers enhance anti-tumor efficacy. Furthermore, the study provides an in-depth analysis of the structural characteristics of these herbal ingredients, demonstrating how these features can be utilized to develop intelligent drug delivery systems that augment anti-tumor effects.

Mechanisms for Enhancing Anti-tumor Efficacy

Recent research has increasingly acknowledged the ability of active herbal ingredients to self-assemble or co-as-

semble into smart drug delivery systems through various mechanisms. These active herbal ingredient-derived smart drug carriers can enhance their pharmacokinetic properties and increase their accumulation at tumor sites. Additionally, certain active herbal ingredients can exhibit direct tumor cell inhibition or indirect anti-tumor effects by stimulating immune responses, suppressing tumor angiogenesis, and other mechanisms (Fig. 2).

Improving drug enrichment

Active targeting

Some active herbal components possess intrinsic targeting capabilities. When these compounds self-assemble or co-assemble into carrier systems, they can actively target tumor tissues without necessitating complex chemical modifications.

Liposomes based on Ginsenoside Rg3 (Rg3-LPs) have demonstrated specific accumulation in tumor tissues by targeting Glucose transporter protein 1 (GLUT-1), a receptor overexpressed in malignant cells and the endothelial cells of tumor-associated vasculature [16, 17]. ASP, the primary active ingredient of *Angelica sinensis*, exhibits a strong affinity for asialoglycoprotein receptor (ASGPR), which is abundantly expressed in the liver [18]. Research has shown that ASP nanoparticles display excellent liver-targeting capabilities [19]. Furthermore, other natural polysaccharides, such as Arabinogalactan and branched-chain starch, have also demonstrated high affinity for ASGPR. These polysaccharide-based carriers show significant potential in delivering chemotherapy drugs for liver cancer treatment [20-22]. Additionally, BSP-based drug carriers have been shown to accumulate in the tumor microenvironment by targeting mannose receptors on M2-type macrophages [23, 24]. Certain active herbal ingredients, such as oleanolic acid (OA) and betulinic acid (BA), can bind to receptors on the blood-brain barrier (BBB) [25, 26]. Consequently, OA-based nanoparticles and BA-based drug carriers may be utilized to increase drug concentration for brain tumor treatment.

By employing these targeted components, medications can be concentrated in tumor tissue, thereby enhancing drug efficacy and improving anti-tumor effects. In addition to their intrinsic receptor-targeting capabilities, intelligent drug delivery systems derived from active herbal ingredients can be further enhanced with targeting ligands on the nanocarrier surface. Commonly utilized targeting ligands include folic acid [27], wheat germ agglutinins (WGA) [28], lactoferrin [29], DOCA [30], hyaluronic acid (HA) [31], mannan [32], and others.

Passive targeting

In addition to enhancing drug accumulation through active targeting, active herbal ingredients can also improve drug enrichment at tumor sites *via* passive targeting mechanisms, thereby augmenting anti-tumor efficacy. The high permeability of tumor vasculature and impaired lymphatic drainage contribute to the preferential accumulation and retention of nanoscale particles and macromolecular drugs within the tu-

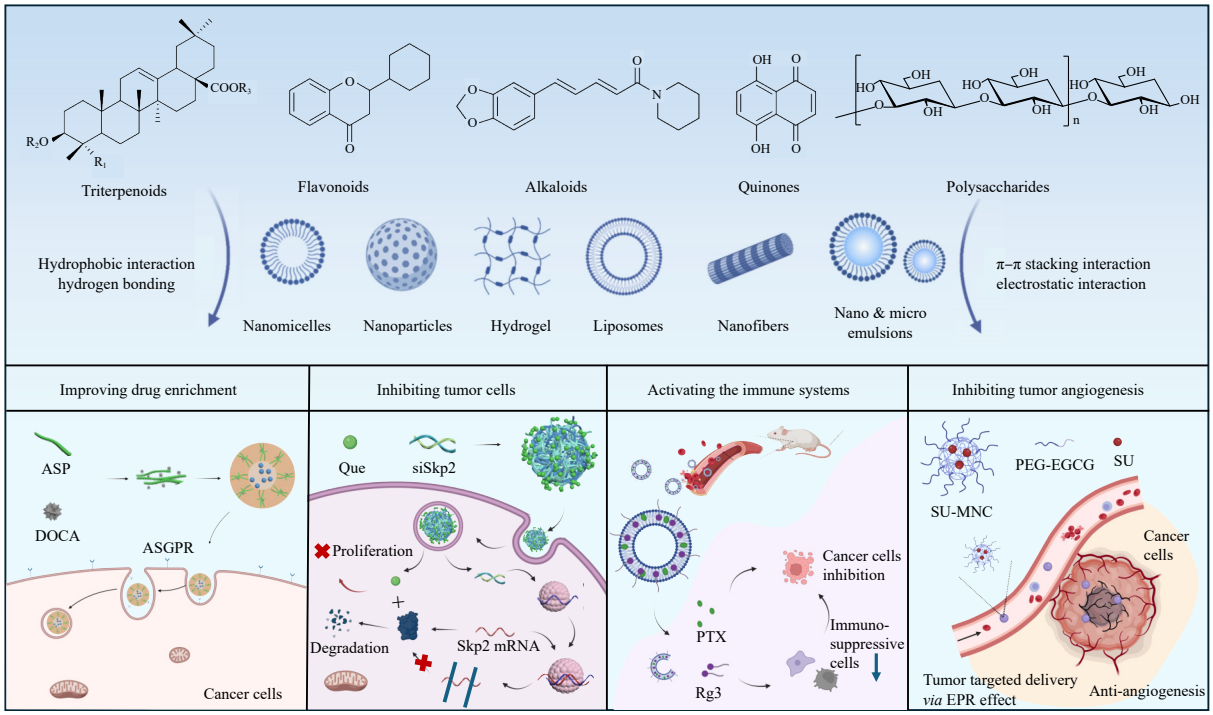

Fig. 2 The main mechanism by which smart drug carriers derived from active herbal ingredients enhance anti-tumor effects. Different kinds of active herbal ingredients can build smart drug carriers such as micelles, nanoparticles, liposomes and gels through hydrophobic interaction, hydrogen bonding, π-π interaction force and electrostatic interaction force, which can enhance anti-tumor effects by improving drug enrichment, inhibiting tumor cells, activating the immune systems, inhibiting tumor angiogenesis and other ways.

mor stroma, a phenomenon known as the Enhanced Permeability and Retention (EPR) effect. By leveraging the Enhanced Permeability and Retention (EPR) effect, smart drug carriers derived from active herbal ingredients at the nanoscale level, such as *Lycium barbarum* polysaccharides (LBP)-based nanoparticles and Camptothecin (CPT)-based nanofibers, have demonstrated increased concentration of chemotherapy drugs at tumor sites, thereby enhancing anti-tumor efficacy [33, 34].

Physicochemical targeting

The tumor microenvironment exhibits distinctive characteristics compared to normal tissues, including lower pH, elevated redox levels, and increased reactive oxygen species (ROS). Incorporating pH-responsive, glutathione-responsive, or ROS-responsive molecules into intelligent drug carriers derived from active herbal ingredients could facilitate precise release of anti-cancer drugs in tumor cells, thereby enhancing anti-cancer efficacy and reducing systemic toxicity. For example, micelles assembled from CA and ROS-responsive thioredoxin were utilized to deliver Doxorubicin (DOX). The findings demonstrated that these micelles degraded in cancer cells due to high ROS concentrations, enhancing the accumulation of CA and DOX at the tumor site, and achieving remarkable anti-tumor efficacy in breast and cervical cancer [35]. Furthermore, micelles assembled from BSP conjugated with disulfide bonds displayed significant redox-responsive release in pH 7.4 medium, with a cumulative DTX release of approximately 60% within 3 hours, substantially increasing drug accumulation at the tumor site [36, 37].

Local injection

In addition to systemic drug administration strategies that enhance tumor targeting, local injection has emerged as an effective approach for improving drug delivery to tumor sites. Recently, hydrogels derived from active herbal ingredients such as Cellulose and Alginate have gained widespread use in local tumor site injections due to their excellent hydrophilicity, non-toxicity, biodegradability, and biocompatibility. These active herbal ingredient-derived hydrogels can also be utilized to deliver anti-tumor drugs like DOX and achieve sustained drug release, resulting in increased local drug concentration and enhanced anti-tumor efficacy [38, 39].

Inhibiting tumor cells

Certain active herbal ingredients possess inherent anti-tumor properties, and smart drug carriers derived from these components can inhibit tumor cells through various mechanisms, including apoptosis induction and cell cycle arrest. For instance, OA has been demonstrated to induce apoptosis *via* multiple signaling pathways. OA-based nanoparticles loaded with PTX exhibited synergistic anti-tumor efficacy by preventing cell cycle progression and inducing both apoptosis and autophagy [25]. Furthermore, carrier-free nanoparticles composed of OA and chlorin e6 (Ce6) molecules, combined with chemotherapy and photodynamic therapy (PDT) or sonodynamic therapy (SDT), achieved a synergistic effect with a tumor inhibition rate of 82.5% in a 4T1 breast cancer model [40]. Similarly, carriers co-assembled by chemotherapy agents and active herbal ingredients such as CA[41], Epigallocatechin gallate (EGCG) [42, 43], *Astragalus* polysaccharide (APS) [44] and BA [45, 46] demonstrated synergistic inhibition of tumor cells.

Activating the immune systems

In recent years, tumor immunotherapy has emerged as a promising approach in cancer treatment. An increasing number of researchers have identified significant immunoregulatory functions in active herbal ingredients, demonstrating their potential in tumor immunotherapy. For example, ginsenoside Rg3, an active component of ginseng, has been shown to convert M2-type macrophages into anti-tumor M1-type macrophages. Ginsenoside Rg3-modified liposomes loaded with the chemotherapy agent PTX achieved a remarkable tumor inhibition rate of 90.3% through the dual mechanisms of tumor cell elimination and tumor microenvironment remodeling [17]. Certain ingredients, such as APS, have demonstrated the ability to activate antigen-presenting cells (APC) *via* dectin-1 and Toll-like receptors 2 and 4 [47]. Carriers derived from these ingredients and loaded with antigens exhibited superior anti-tumor efficacy by enhancing antigen cross-presentation, thereby increasing cytotoxic T-cell infiltration and improving anti-tumor effects [48]. Furthermore, some ingredients, like UA, not only activate the immune system but also directly eliminate tumor cells. Incorporating these molecules into the design of smart carriers could potentially achieve significant synergistic therapeutic effects [49].

Inhibiting tumor angiogenesis

Tumor angiogenesis is driven by the increased secretion of angiogenic factors and/or the downregulation of angiogenesis inhibitors. Inhibiting tumor angiogenesis by blocking the function of vascular endothelial growth factor (VEGF) is an established strategy for enhancing anti-tumor efficacy. Studies have shown that certain active herbal ingredients such as EGCG and UA can specifically inhibit the proliferation of tumor vascular endothelial cells, thereby producing synergistic anti-tumor effects when combined with other therapeutic agents [50-52]. These ingredient-based carriers have demonstrated synergistic anti-angiogenesis effects with common angiogenesis inhibitors like Sunitinib (SU) [53]. Furthermore, such ingredient-based carriers loaded with chemotherapeutic agents including PTX [54, 55], DOX [56] and methotrexate (MTX) [30] have been shown to significantly enhance anti-tumor efficacy by disrupting the nutrient supply to tumors.

The mechanisms by which active herbal ingredient-derived smart carriers enhance anti-tumor efficacy, as described in the preceding text, are summarized in Table 1.

Construction of Active Herbal Ingredients as Carriers

In recent years, numerous studies have demonstrated that active herbal ingredients can form sophisticated drug delivery systems based on fundamental forces. These systems include nanoparticles [64], micelles, liposomes [65], vesicles [66], and gels [67]. The subsequent section elucidates how various

active herbal ingredients have been employed in the development of smart drug carriers, focusing on their chemical structural properties.

Flavonoids-based carriers

Flavonoids, a class of compounds characterized by two benzene rings connected by three carbon atoms, are ubiquitous in plants such as baicalin, pueraria, glycine, soybean, and green tea [68]. Traditional anti-tumor drugs like Melittin and DOX face challenges including low solubility, poor stability, dose-dependent toxicity [69], and limited bioavailability. Flavonoid-based herbal ingredients such as EGCG, quercetin (QT), chrysin, morusin, and rhinocerosin possess structures analogous to phospholipids, lecithin, hydrophilic macromolecular proteins, or borates. Consequently, they can form amphiphilic compounds by attaching hydrophilic groups, which then self-assemble through hydrophobic interactions to create nanoparticles with enhanced water solubility and bioavailability [70].

Epigallocatechin gallate-based carriers

EGCG, a catechin derivative found in green tea, is renowned for its diverse pharmacological properties, notably its substantial anti-tumor activity. Extensive research has been conducted on EGCG's capacity to self-assemble into nanoparticles through various interactions.

EGCG demonstrates the ability to form nanoparticles through electrostatic interaction. Le *et al*. conducted a study investigating carrier-free self-assembled nanoparticles constructed using rapamycin and indocyanine green (ICG) [71]. The research utilized the trihydroxyphenyl functional group and the robust solid-liquid interfacial activity of EGCG for self-polymerization *via* hydrophobic and electrostatic interactions. This process resulted in the formation of a stable shell, which functioned as a scaffold for immobilizing Rapamycin. The study found that this method enhanced drug stability and prevented nanoparticle disintegration.

EGCG can be formulated into nanoparticles through hydrophobic interactions and hydrogen bonding. Chen *et al*. utilized EGCG as a hydrogen donor, interacting with the carbonyl group of poly (*N*-vinylpyrrolidone) (PVP) and CUR *via* hydrogen bonding to create EGCG/PVP nanoparticles loaded with CUR. This approach addressed CUR's limitations as a drug, such as low aqueous solubility, poor stability, and rapid metabolism. Another notable example is a novel "core-shell" co-assembled carrier-free nanosystem based on natural UA and EGCG, modified with EpCAM-aptamer. This system allowed EGCG to self-polymerize under basic pH, forming a homogeneous "shell" layer through hydrophobic interactions and hydrogen bonding to protect the "core" from degradation [72]. Dynamic light scattering measurements revealed that the diameter of UA nanoparticles increased threefold (from 123.6 to 216.3 nm) within 14 days, while the average diameters of fluorine nanoparticles encapsulated with UA remained relatively stable, indicating that the EGCG coating enhanced the stability of the self-assembled nanoparticles. Furthermore, EGCG can form nanoparticles through π-π interactions. EGCG was observed to cover the surface of the methyl hexadecane derivative MPa-TEG primarily through hydrogen bonding, π-π stacking, and hydrophobic interactions, preventing irregular aggregation and precipitation of MPa-TEG due to Ostwald ripening and improving drug solubility and stability [49]. Additionally, Han *et al*. developed a fluorinated assembly system of LFNPs/siTOX complexes in 2024 [73] to enhance the delivery efficiency of small interfering RNAs against TOX. EGCG's hydroxyl and benzene rings were employed to bind siRNA through hydrophobic interactions, hydrogen bonding, and π-π stacking interactions. EGCG can also form nanoparticles through other forces, such as ethyl bridge formation [74]. It is anticipated that the biocompatibility, stability, and cellular uptake efficiency of nanoparticles could be further optimized by modifying EGCG's surface properties, such as charge, hydrophilicity, or hydrophobicity, through chemical alterations. This approach may provide more effective and safer therapeutic options for cancer treatment and other diseases.

Furthermore, EGCG can be functionalized with additional groups to form nanoparticles. For example, Sun *et al*. [70] functionalized EGCG with a fluorinated bridge to produce fluorinated EGCG, which self-assembled with Melittin to create fluorinated nanoparticles. Liu *et al*. [75] introduced a hydrophobic small-molecule lipid-soluble compound, 9-fluorenyl methoxycarbonyl (Fmoc), to the phenolic hydroxyl functional group of EGCG, generating amphiphilic EGCG-Fmoc. This modification enhanced stability, self-assembling ability, and tumor cell absorption. *In vivo* anti-tumor assessments revealed that the tumor mass in mice treated with PTX-encapsulated nanoparticles was significantly reduced compared to the control group, indicating improved PTX delivery by this innovative drug carrier.

EGCG, besides forming nanoparticles, can also create nanoemulsions through hydrophobic interactions, hydrogen bonds, covalent bonds, and intermolecular forces. A notable example is the conjugation of EGCG with Polyethylene Glycol (PEG) to form PEG-EGCG, which functions as a high-performance carrier. Liang *et al*. [69] employed PEG-EGCG as a shell to self-assemble with DOX through hydrophobic interactions and intermolecular forces, resulting in micellar nanocomplexes. Furthermore, PEG-EGCG demonstrated the capacity to load sunitinib [53], enhancing drug delivery efficacy with a drug loading capacity (DLC) reaching 88%. Ki *et al*. [31] developed a HA-EGCG conjugate that utilized the hydrophobic nature of EGCG molecules and the hydrophilic properties of HA, enabling spontaneous self-assembly and providing an optimal environment for cisplatin encapsulation. Simultaneously, the polyphenolic structure of EGCG interacted with cisplatin through hydrophobic interactions and hydrogen bonds, improving drug solubility and stability. EGCG could be covalently bonded to the thiol end of HA, after which the HA-EGCG conjugate self-assembled with daunorubicin through intermolecular forces to form micellar nanocomplexes. In comparison to the HA/DNR complex, this mi-

Table 1 The mechanism for enhancing anti-tumor efficacy

Active ingredients	Carriers	Mechanisms	Reference
Alginate	Hydrogel	Improving drug enrichment by localized drug delivery	[57]
Angelica sinensis polysaccharide	Nanoparticles with active targeting function	Activating the immune system by restoring Th1/Th2-type immune response; inhibiting tumor cells	[58]
	Nanoparticles with active targeting function	Improving drug enrichment by targeting asialoglycoprotein receptor on the HepG2 cell	[19]
	Nanoparticles with pH-responsive and active targeting function	Improving drug enrichment by targeting asialoglycoprotein receptor on the HepG2 cell	[30]
Astragalus polysaccharide	Nanocomplexes	Activating the immune systems by stimulating the maturation of DCs	[48]
Betulinic acid	Nanoparticles with passive targeting function	Inhibiting tumor cells	[46]
	Nanoparticles with glutathione responsiveness	Improving drug enrichment	[59]
Bletilla hyacinthina polysaccharide	Micelles with dual pH and redox responsiveness	Improving drug enrichment	[37]
	Conjugates with active targeting function	Improving drug enrichment by targeting mannose receptor on tumor-associated macrophages; inhibiting tumor angiogenesis	[24]
Berberine	Nanoparticles with passive targeting function	Improving drug enrichment by enhanced EPR effect; inhibiting tumor cells	[60]
Camptothecin	Nanofibers with passive targeting function	Improving drug enrichment by enhanced EPR effect	[34]
Cellulose	Hydrogel	Improving drug enrichment by localized drug delivery	[38]
Cinnamaldehyde	Nanoparticles with reactive oxygen species responsiveness	Inhibiting tumor cells	[41]
	Nanoparticles with reactive oxygen species responsiveness	Inhibiting tumor cells	[35]
Epigallocatechin gallate	Nanoparticles	Activating the immune systems by decreasing Programmed Cell Death Ligand 1 expression	[41]
	Nanocomplexes with passive targeting function	Inhibiting tumor angiogenesis	[53]
	Micellar nanocomplexes with active targeting function	Inhibiting tumor cells	[31]
Ginsenoside	Multi-functional liposomes with active and passive targeting function	Improving drug enrichment by targeting glucose transporters type 1 on gastric cancer cells and enhanced EPR effects	[16]
	Multi-functional liposomes with active targeting function	Improving drug enrichment by targeting glucose transporters type 1 on tumor-associated macrophages; activating the immune systems by inhibiting the IL-6/STAT3/p-STAT3 pathway	[17]
Lycium barbarum polysaccharide	Couplers with passive targeting properties	Improving drug enrichment by enhanced EPR effect	[33]
Oleanolic acid	Nano-sensitizers with active targeting function	Inhibiting tumor cells	[40]
	Nanoparticles with active and passive targeting function	Improving drug enrichment by targeting cannabinoid receptor 1 on breast cancer brain metastases cell and enhanced EPR effects; inhibiting tumor cells	[25]
Rhein	Hydrogel	Improving drug enrichment by localized drug delivery	[61]
	Hydrogel	Improving drug enrichment by localized drug delivery; inhibiting tumor cells	[62]
Ursolic acid	Nanoparticles with active targeting function	Improving drug enrichment by targeting ASGPR on the HepG2 cell	[63]
	Nanoparticles with passive targeting function	Improving drug enrichment by EPR effects; inhibiting tumor angiogenesis	[55]
	Carrierless Nanosystems	Activating the immune systems by activating the innate and acquired immunity	[29]
Wheat Germ agglutinin	Nanoparticles with active targeting function	Improving drug enrichment by targeting the glycoproteins on the colon cancer cell; inhibiting tumor cells	[28]
Zein	Nanoparticles with active targeting function	Improving drug enrichment by targeting lactoferrin receptor on MCF-7 breast cancer cells	[29]

cellar nanocomplex exhibited approximately 10.6 times higher drug loading efficiency (DLE) and 7.5 times higher drug content [76].

Moreover, EGCG demonstrates potential as a smart drug carrier, capable of forming nanogels. For example, researchers developed a novel ternary nanogel by reacting an Alanine-hybridized EGCG dimer with the carboxyl group of HA through a condensation reaction, followed by self-assembly with linear Polyethyleneimine and Granzyme B in an aqueous environment [77]. In this system, EGCG facilitated protein binding through physical interactions, resulting in a stable nanogel with reduced particle size (approximately 0.7 times that of the HA group) and improved particle size distribution uniformity (with a polydispersity index about two-thirds of the control group). In another study, Ding J et al. designed a drug carrier wherein EGCG was linked to siRNA *via* non-covalent interactions and subsequently encapsulated by an HA shell [78].

Quercetin-based carriers

QT, a polyphenolic flavonoid compound, is abundantly present in red wine, grapefruit, onions, apples, and black tea, with lower concentrations in green leafy vegetables and legumes [79]. Its structure, characterized by multiple phenolic hydroxyl groups with redox activity, contributes to its diverse biological properties, including anti-oxidant, anti-inflammatory, and notably, cancer-preventive effects.

QT demonstrates the ability to form nanoparticles through hydrogen bonding and π-π stacking interactions. Sunoqrot *et al* [80]. developed QT@CUR nanoparticles *via* spontaneous oxidative polymerization of QT under basic conditions, resulting in colloidal aggregates functionalized with surface ligands, such as amine-terminated PEG and DOX. The hydrogen bonding and π-π stacking interaction between QT and DOX facilitated PEGylation and drug loading, conferring the nanoparticles with a high loading capacity of 91.0% and prolonged release time. In a separate study, Hong Liang and colleagues [81] engineered nanoparticles with T- or F-shaped π-π stacking interactions between the aromatic ring of QT and the RNA bases in the minor groove and terminus of siRNA (siSkp2), which silenced the Skp2 gene. Furthermore, multiple hydrogen bonds formed between QT and the RNA bases. QT also exhibited the capability to self-assemble through parallel stacking, forming π-rich mediated bridges that further enhanced the assembly with siSkp2.

In addition to nanoparticle generation, QT demonstrates potential to enhance drug-loading properties through nanocluster formation. For example, QT was modified by reacting with citraconic anhydride (CA) to produce the QT-CA ester. Subsequently, chitosan (CS) was reacted with the carboxyl group of the QT-CA ester *via* a carbodiimide reaction, resulting in the QT-CA-CS conjugate. This conjugate self-assembled in aqueous solution through hydrophobic interaction, forming nano micelles with a critical micelle concentration of 0.034 mg·mL^{-1}. This low concentration indicated strong resistance to dissociation upon dilution, leading to high encapsulation efficiency (EE) for DOX. Moreover, this advanced drug carrier significantly enhanced the cellular uptake of DOX by MCF-7/ADR cells. According to Yuzhi Mu and colleagues [82], the uptake rate was nearly eight times higher compared to free DOX.

Other flavonoids-based carriers

Beyond the two primary categories previously discussed, various plant-derived flavonoids such as Myricetin, Proanthocyanidins, Baicalin, Rhinocerosin, Morusin, and others can self-assemble into nanoparticles through π-π stacking and coordination bonding [83]. For example, Zheng *et al*. [84] immobilized chrysin on the terminal groups of methoxy PEG. Chrysin functioned as a lipophilic molecule, facilitating π-π interaction with the anti-tumor drug DOX, thereby enhancing stability. The mPEG2000-Chrysin nanoparticles demonstrated superior DLC (18.7%) and EE (> 50%) compared to previously reported PEGylated cinnamic acid or PEGylated cinnamic acid conjugated nanoparticles. Furthermore, Tie *et al*. [85] engineered nanocarriers utilizing the Mannich reaction between the phenolic hydroxyl group of Proanthocyanidins, the aldehyde group of Vanillin, and the amino group of Phycocyanidin. These nanocarriers effectively delivered active herbal ingredients, such as Lutein, exhibiting a uniform spherical distribution, high EE, and good bio-compatibility. Additionally, nanoparticles can serve dual roles as both chemotherapeutic and photothermal agents. Liu *et al*. [86] designed an innovative drug carrier that incorporated a supramolecular photothermal effect through lignocerol liganded with iron ions.

The development of intelligent drug carriers for cancer treatment utilizing flavonoids is summarized in Table 2. These carriers substantially improve drug solubility and stability, thus enhancing bioavailability and providing an effective drug delivery system for cancer therapy and other pathological conditions. In contrast to traditional drug delivery systems, carriers derived from flavonoid-active herbal components demonstrate the capacity to reduce inflammatory responses and oxidative stress within the tumor microenvironment. This mitigation enhances the therapeutic efficacy of anticancer agents while simultaneously reducing the adverse effects associated with chemotherapeutic drugs [87, 88]. Notably, carriers incorporating DOX have demonstrated the ability to not only enhance the antitumor efficacy of DOX but also to mitigate neurotoxicity and other chemotherapy-related side effects, attributed to the antioxidant properties of quercetin [89, 90].

Quinones-based carriers

Quinones are organic compounds characterized by a six-membered cyclic diketone structure with two carbonyl groups and two double bonds. These compounds exhibit exceptional biocompatibility, redox properties, and modifiability, displaying distinctive chemical characteristics. For instance, they frequently incorporate conjugated π-electron systems, such as benzene rings, which can form stable nanoparticles through π-π stacking. Additionally, they often contain polar functional

groups like hydroxyl (-OH) and carboxyl (-COOH), which facilitate intermolecular hydrogen bond formation, promoting nanoparticle formation and stabilization. Moreover, quinones demonstrate multiple biological activities, including antibacterial, antiviral, and notably antitumor properties, making them suitable as intelligent drug carriers for efficient drug delivery, controlled release, and enhanced drug bioavailability.

Rhein-based carriers

Rhein, an anthraquinone compound extracted from the Chinese medicinal herb *Rheum palmatum*, exhibits diverse biological activities, including the stimulation of intestinal motility, anti-inflammatory, antioxidant, antibacterial, and antitumor properties. The molecular structure of Rhein comprises two hydroxyl groups and two carboxyl groups, enabling its self-assembly into nanoparticles and nanogels through various interactions, such as electrostatic attraction, hydrogen bonding, π-π stacking, and hydrophobic interactions.

Rhein exhibits the capacity to form nanoparticles through electrostatic attraction, hydrogen bonding, and π-π stacking interactions [91]. Utilizing BBR from CR and Rhein from Rhubarb as raw materials, researchers developed a novel carrier-free nano-assembly with a three-dimensional porous framework crystal structure *via* supramolecular self-assembly [92]. This innovation presents a promising potential carrier for drug delivery systems. Wang *et al*. engineered co-delivery nanoparticles through the self-assembly of Rhein and DOX molecules [93]. The robust interactions between DOX and Rhein created a hydrophobic core, while the hydrophilic daunosamine head of DOX remained unbound, enhancing the nanoparticles' dispersibility. The encapsulation efficiencies of Rhein and DOX in the nanoparticles were 50% and 93%, respectively, demonstrating superior drug-loading capacity compared to other co-delivery nanoparticles.

Beyond nanoparticles, Rhein can self-assemble into nanogels through intermolecular π-π interactions and hydrogen bonding. For example, the Rhein-DOX nanogel self-assembles based on hydrogen bonding, π-π stacking interactions, and hydrophobic interactions, achieving a DLE of 100%. The carboxyl groups of Rhein form hydrogen bonds with DOX, and the supramolecular aggregate self-assembles into one-dimensional nanofibers through van der Waals forces and hydrogen bonds provided by the carbon framework. Several one-dimensional fibers form two-dimensional fibers, which cross-link with the solvent to create a three-dimensional fiber network [94]. Other studies have reported that Rhein can self-assemble into a nanofiber network-based hydrogel in the pH range of 8.0 to 9.4, allowing for the slow release of Rhein [61]. Furthermore, under weakly basic conditions, some Rhein molecules can deprotonate to form Rheinate salts, as evidenced by spectroscopic analysis, circular dichroism, X-ray diffraction, and theoretical calculations. Rhein monomers and Rheinate salts can form dimers through π-π stacking. Due to electrostatic repulsion between carboxylate ions, the two molecules tend to arrange in opposite directions. Subsequently, the dimers further assemble into trimers, tetramers, and higher-order aggregates, ultimately cross-linking to form a 3D network.

Shikonin-based carriers

Shikonin, an anthraquinone compound prevalent in plants of the comfrey family, possesses multiple hydroxyl groups (-OH) that facilitate the formation of inter-molecular hydrogen bonds, thereby enhancing nanoparticle stability. The anthraquinone rings, containing conjugated π-electron systems, contribute to the formation of stable nanoparticles through π-π stacking. For instance, Shikonin and CUR can self-assemble into homogeneous nanoparticles *via* π-π stacking and hydrophobic interactions. To further improve stability, DSPE-PEG2k was incorporated [95]. The resulting self-assembled nanoparticles exhibited significantly enhanced drug-carrying capacity, with encapsulation efficiencies (EEs) of CUR and Shikonin reaching 71.89% ± 0.92% and 60.64% ± 0.84%, respectively, approximately 1.4 times higher than the original formulations.

Rhein and Shikosin represent common quinone-active herbal ingredients suitable for developing smart drug delivery carriers. Quinone compounds, characterized by their distinctive chemical structures with conjugated π-electron systems and polar functional groups, can form stable nanoparticles through π-π stacking and intermolecular hydrogen bonding. This property enhances drug solubility and bioavailability [96-98]. Moreover, quinones demonstrate significant biocompatibility and modifiability, enabling the formation of nanoparticles and nanogels *via* self-assembly. These attributes contribute to effective drug encapsulation and controlled release, thereby enhancing the efficacy of drug delivery systems [98].

Herbal polysaccharides-based carriers

Herbal polysaccharides comprise sugar chains and branches of varying lengths, containing numerous hydrophilic groups such as hydroxyl, carboxyl, and aldehyde groups [99-101]. Amphiphilic polymers can be synthesized by conjugating hydrophobic groups to polysaccharide molecules, which spontaneously aggregate into nanoparticles or micelles. For example, chitosan (CS), alginate, starch, and their derivatives can self-assemble or co-assemble into nanocarriers through electrostatic interactions and hydrogen bonding [102]. These materials are frequently utilized in the design of smart drug carriers due to their high biocompatibility, biodegradability, and low toxicity. They have been extensively applied in antimicrobial treatments, gene therapy, photodynamic therapy, and insulin transport, with particular emphasis on cancer treatment [103].

Bletilla Striata polysaccharide-based carriers

BSP, a naturally occurring hydrophilic polymer extracted from the dried rhizomes of *Bletilla Striata*, is composed of *α*-mannose, *β*-mannose, and *β*-glucose. Its main chain consists of aldose pyranosyl residues linked by (1→4) connections. BSP exhibits potential as a material for drug carriers

Table 2 The construction of smart drug carriers for cancer treatment by flavonoids

Flavonoids	Carrier construction process	Drugs delivered	Cancers treated	Reference
Epigallocatechin gallate (EGCG)	Self-assembly of Fluorinated EGCG with MPI *via* hydrogen bonding	Melittin	Liver cancer	[70]
	Co-assembly of EGCG with Indocyanine Green and Rapamycin *via* hydrophobic and electrostatic interactions	Rapamycin and indocyanine green	Liver cancer, lung cancer, breast cancer	[71]
	Co-assembly of EGCG as Hydrogen Donor with PVP's Carbonyl and Curcumin *via* hydrogen bonding	Curcumin	Colon cancer	[72]
	Co-assembly of EGCG-Encapsulated Ursolic acid nanoparticles *via* hydrophobic and hydrogen bonding interactions	Ursolic acid	Liver cancer	[49]
	Self-assembly of EGCG and MPa-TEG *via* hydrogen bonding, π-π stacking, and hydrophobic interactions	Methyl-epiflorone derivatives MPa-TEG	Cervical cancer	[73]
	Self-assembly of EGCG with chitosan *via* Ethyl Bridge	Lycopene	Skin cancer, prostate cancer	[74]
	Self-assembly of EGCG-Fmoc *via* π-π interactions	Paclitaxel	Breast cancer	[75]
	Co-assembly of Sunitinib with EGCG *via* intermolecular interactions	Sunitinib	Kidney cancer	[53]
	Self-assembly of Hyaluronic acid-EGCG *via* hydrophobic and hydrogen bonding	Hyaluromic acid and *cis*-platinum	Ovarian cancer	[31]
	Co-assembly of HA-EGCG conjugate with Daunorubicin *via* covalent and intermolecular forces	Daunorubicin	Leukaemia	[76]
	Binding of EGCG with proteins *via* physical interactions	Granzyme B	Colon cancer	[77]
	Self-assembly of EGCG with small interfering RNA *via* non-covalent interactions	siRNA and hyaluronic acid	Drug-resistant breast cancer	[78]
Quercetin	Self-assembly of Quercetin *via* hydrogen bonds and π-π stacking for spontaneous oxidative polymerization	Curcumin	Colon cancer	[80]
	Self-assembly of Quercetin-CA-CS conjugate *via* hydrophobic interactions	Doxorubicin and quercetin	Breast cancer	[89]
	Self-assembly of Quercetin with siSkp2 *via* hydrogen bonds and π-π stacking	siRNA	Prostate cancer	[81]
	Self-assembly of methoxy polyethylene Glycol-Salicin conjugate *via* π-π interactions	Doxorubicin	Liver cancer	[84]
Morusin	Self-assembly of Indocyanine Green, Copper Ions (Cu^{2+}), and Morin *via* coordination and π-π stacking	Morusin	/	[83]
Rhinocerosin	Self-assembly of Luteolin with Iron Ions *via* coordination bonds	Rhinocerosin	/	[86]

due to its biocompatibility [104], bio-degradability [105], and the abundance of hydroxyl groups in its molecular chain, facilitating chemical modification to form amphiphilic polymers [106]. In its unmodified form, BSP is typically used to create hydrogels, while chemically modified BSP is primarily employed in the preparation of micelles, microspheres, nanoparticles, and nanofibers [107].

BSP can form nano-micelles through covalent bonds, disulfide bonds, and electrostatic interactions [108]. For instance, micelles formed *via* covalent bonds between BSP's hydroxyl groups and vitamin E succinate's carboxyl groups demonstrated a high EE of 91.15% ± 0.05%, addressing Andrographolide's poor water solubility, low bioavailability, and short half-life [109]. Liu *et al*. synthesized amphiphilic polymers by connecting BSP with Stearic acid (SA) through covalent bonds, which self-assembled into core-shell structured micelles in the medium. This approach enhanced the bioavailability and improved the solubility of the hydrophobic drug DOX, achieving a maximum EE of 91.9% [110]. Moreover, electrostatic interactions mediated the self-assembly of SA-modified BSP and Folic acid, resulting in highly stable and safe nano-micelles [111]. Disulfide bonds facilitated the self-assembly of SA and cysteine, encapsulating DTX. The DTX-loaded micelles exhibited an optimal mean particle size of 158.2 ± 1.7 nm in an aqueous medium. Introducing cholesterol increased BSP's hydrophobicity, enabling its self-assembly into nanoparticles in aqueous solutions [112].

Angelica Sinensis polysaccharide-based carriers

ASP, a water-soluble plant polysaccharide extracted from *Angelica Sinensis* of the Umbelliferae family, demonstrates favorable characteristics including excellent water solubility, biodegradability, and biocompatibility [113]. It exhibits diverse pharmacological activities, encompassing hematopoietic, immunomodulatory, anti-inflammatory, antioxidant, anti-aging, antiviral, hepatoprotective, and antitumor properties. Its ability to target hepatocellular carcinoma cells makes it a frequent component in targeted drug carrier development. ASP can self-assemble into nanoparticles through hydrophobic interaction and covalent bonding. In a recent investigation, Zhang *et al*. introduced ASP as a hydrophilic group and DOCA as a hydrophobic group, which self-assembled to form an amphiphilic conjugate *via* hydrophobic interaction

and encapsulated DOX to form nanoparticles [114]. The results revealed that DOX/ASP-DOCA (1/10) demonstrated high drug delivery efficacy with a DLC of 4.86% and a DLE of 68.08%. Furthermore, ASP showed the ability to form a conjugate with DOCA through covalent bonding, facilitating ORI delivery [30]. The nanoparticle DLE was determined to be 63.6% ± 0.24%. Additionally, it could form nanoclusters through covalent bonding. For instance, Liu *et al*. designed micelles formed by encapsulating CUR through an azobenzene junction connected to ferrocene and covalently modifying the side chains with Arachidonic acid [115]. These ASP-based micelles exhibited an EE and DLE of CUR of 45.9% and 4.97%, respectively, indicating the high drug-carrying capacity of these smart drug carriers.

Cellulose and its derivatives-based carriers

Cellulose $(C_6H_{10}O_5)_n$ is the most abundant naturally occurring polysaccharide on Earth. It constitutes a significant component of plant cell walls, demonstrating excellent biodegradability and biocompatibility. The structure of cellulose comprises hundreds to thousands of linear chains of D-glucose units linked by *β*-(1,4) bonds. Owing to its remarkable biocompatibility and biodegradability [116], cellulose, particularly in its nanoform, shows substantial potential for future biomedical applications. However, cellulose is insoluble in water and many organic solvents, necessitating efforts to modify it into suitable derivatives to address the issue of poor solubility [117]. Advantageously, the hydroxyl groups present in cellulose nanomaterials facilitate chemical modification and conjugation with drugs. This chemical modifiability offers versatility in the design of drug carriers. Notable examples include CMC, Nanocrystalline Cellulose, Cellulose nanofibers, and Bacterial Nanocellulose [118].

Chemical modification of cellulose through the introduction of carboxymethyl groups results in the formation of CMC. Compared to cellulose, CMC demonstrates enhanced water solubility, high biocompatibility [119], and increased drug-carrying capacity [120], collectively indicating significant potential and advantages in smart drug carrier applications. CMC can self-assemble into hydrogels through various mechanisms, including covalent bonding, chemical cross-linking, electrostatic interaction, hydrogen bonding, and van der Waals forces. For instance, Chen *et al* [121]. constructed a hydrogel utilizing the Schiff base bond, a covalent bond, between MC-NH_2 (hydrazine-modified CMC) and CMC-CHO (oxidized CMC) to facilitate CMC self-assembly for DOX delivery, achieving high encapsulation efficiency. Moreover, CMC can self-assemble with bovine serum albumin *via* electrostatic interaction, forming hybridized hydrogels [122]. Additionally, hydrogen bonding and electrostatic interactions can promote the self-assembly of CS and CMC, thereby enhancing drug stability and release [123]. Atallah M *et al*. [124] co-delivered the anti-metabolite drug Pemetrexed (PMT) and the herbal polyphenol rhodiola rosea using nanogels formed by Lactoferrin and CMC through electrostatic interaction. Subsequently, they employed chemical cross-linking for self-assembly, achieving an encapsulation efficiency of 66.67%.

Nanocrystalline Cellulose is a nanoscale crystalline region extracted from Cellulose through chemical or physical methods. Its high specific surface area and pore structure [125], biocompatibility, and abundance of surface hydroxyl groups facilitating modification, renewability, and biodegradability make it a promising candidate for nanomedicine applications [126]. For instance, Sevil Vaghefi Moghaddam and colleagues developed a nanoparticle system self-assembled from Nanocrystalline Cellulose and l-lysine amino acid *via* covalent bonding [127]. This system effectively co-released MTX and CUR into MCF-7 and MDA-MB-231 cells, with encapsulation efficiencies of 33% for MTX and CUR, and 75% for CUR alone.

Cellulose nanofibers, derived from plant cellulose, exhibit a filamentous structure with diameters ranging from 5 to 20 nm and lengths spanning several hundred nanometers to tens of micrometers. The three-dimensional nanofibrillar network structure of cellulose nanofibers confers exceptional mechanical properties and stability [128], which contributes to maintaining drug stability and controlling release during the drug delivery process. Shiyu Zong *et al*. developed a smart hydrogel with dual redox and temperature-responsive properties for targeted DOX delivery [129]. In this system, cellulose nanofibers were uniformly distributed throughout the hydrogel network, interwoven and connected by hydrogen bonding and van der Waals forces, enhancing the strength of the N-isopropyl acrylamide hydrogel. The compressive strength of the hydrogel reached 1.98 MPa at 0.5 wt% of cellulose nanofiber, 3.16 times greater than that of the pure NIPAM hydrogel.

Pectin-based carriers

Pectin, a polysaccharide abundantly present in plant cell walls, is predominantly extracted commercially from citrus and apple fruits [130]. The molecular structure of pectin comprises diverse structural domain units, including polygalacturonic acid, *Rhamnogalacturonic* acid glycans of types I and II (RG-I and RG-II), xylose galacturonic acid glycans, and others. These domains are interconnected by covalent bonds, enabling pectin's optimization as a drug carrier through various chemical modifications. The functional groups in pectin, such as hydroxyl, methyl, carboxyl, and amide, can be modified to produce a wide array of derivatives, including pectin-encapsulated nanogels, micelles, and particulate systems.

Pectins can form nanoparticles through various mechanisms, including electrostatic, hydrophobic, hydrogen, covalent, and ionic bonding. For example, pectin can create stable nanoparticles by binding to *β*-lactoglobulin through ionic and hydrogen bonding interactions. The complementary charges of these components contribute to the colloidal stability of the nanoparticles. *β*-lactoglobulin-pectin nanoparticles loaded with Pt (II) complexes exhibited a zeta potential of −19 ± 0.2 mV. This significant negative value indicates strong electrostatic repulsion between nanoparticles, preventing aggrega-

tion in solution and enhancing stability [131]. Additionally, Silant'ev *et al*. demonstrated the formation of pectin-CS polyelectrolyte nanoparticles through electrostatic, hydrogen bonding, and ionic interactions between oppositely charged CS and pectic polysaccharides [132]. The drug temozolomide was adsorbed onto these nanoparticles *via* chemical interaction. In these examples, pectin enhanced drug delivery efficiency, achieving a DLE of 84.1% ± 4.7%. Liu *et al*. developed novel core-shell structured Pectin-octa-armed poly (ethylene glycol)-arbutinic acid/hydroxy Camptothecin (HCPT) nanoparticles to improve water solubility [133]. Covalent bonds facilitated the self-assembly of Pectin with multi-armed PEG (8arm-PEG). The nanoparticles demonstrated a drug loading of 9.22 wt% UA and an EE of 16.51 wt% HCPT, significantly higher than the control. This study expands the potential applications of pectin as a drug carrier. Furthermore, the development and implementation of additional functional groups on conjugates represent a critical area of investigation in this research domain, requiring comprehensive exploration and resolution.

Pectin can self-assemble into nanoclusters through the formation of covalent bonds. For instance, Bai *et al*. utilized Pectin as a backbone and conjugated it with curcumin (CUR), a hydrophobic drug, at the core *via* an esterification reaction. Following UV irradiation, the residual amount of free CUR was 25% [134], while the residual amount of this nanocolloid exceeded 50%. This finding indicates that CUR conjugated with Pectin exhibits enhanced stability in aqueous solution. The Pectin-based nanoparticle platform demonstrates significant potential for drug delivery. Its hydrophobic core provides a versatile carrier for encapsulating various hydrophobic drug molecules. Future research exploring additional hydrophobic drug molecules may facilitate the development of more effective and safer therapeutic options for cancer and other treatments.

Pectin can also form nanogels through electrostatic interaction. For example, researchers prepared stable MTX-loaded nanogels by self-assembling pectin, lysozyme, and MTX through electrostatic interaction, followed by heat-induced lysozyme gelation. These nanogels demonstrated a high MTX loading capacity of up to 17.58% ± 0.85% [135].

Alginate-based carriers

Alginate, a natural polysaccharide extracted from brown algae, consists of two units: *β*-D-mannuronic acid (M unit) and *α*-L-guluronic acid (G unit). These units are linked by 1,4-*β*-D glycosidic bonds, forming GM, MM, and GG fragments in varying ratios to create copolymers. Alginate's ability to cross-link with divalent or trivalent ions (*e.g.*, calcium ions) to form stable hydrogel structures makes it an excellent candidate for smart drug carriers [136]. Through physical or chemical interactions, alginate can self-assemble or covalently bond to form microcapsules, hydrogels [137], and nanoparticles [138, 139]. For example, Louhana M. Rebouças *et al.* utilized alginate and guar gum, connected through physical forces, to create microcapsule structures [140]. This approach resulted in encapsulation efficiencies of 98.15% and 99% for orange peel extract and white oak extract, respectively, demonstrating effective drug protection and release capacity with a 76% efficiency rate. Additionally, Wang *et al*. observed the self-assembly of Sodium Alginate with calcium ions (Ca^{2+}) and Gallic acid facilitated by ionic and hydrogen bonds [141]. Non-covalent interactions, such as hydrogen bonding and hydrophobic effects, can also mediate the self-assembly of folate-cholesterol-Sodium Alginate into nanocapsules [137]. Furthermore, ion-bridging and hydrogen bonding interactions can facilitate the self-assembly of Sodium Alginate, Cisplatin and DOX into a hydrogel [142].

The construction of smart drug carriers for cancer treatment by herbal polysaccharides mentioned in this section was summarized in Table 3. Traditional polysaccharides such as CS [143-146], HA [147], gelatin [148], glucomannan [149, 150] along with their derivatives, have shown promising results and clinical potential in various applications including cancer treatment, antibacterial therapies, insulin delivery, and vaccine administration. In comparison to these established drug delivery carriers, herbal polysaccharides demonstrate superior biocompatibility, biodegradability, and reduced toxicity [151]. These polysaccharides can undergo chemical modification to form amphiphilic polymers, which subsequently self-assemble into nanoparticles, microcapsules, hydrogels, and other structures through mechanisms such as electrostatic interactions, hydrogen bonding, covalent bonding, and ionic bonding [152, 153]. This versatility enhances their drug encapsulation and delivery capabilities. Furthermore, herbal polysaccharides often possess intrinsic biological activities that can enhance therapeutic efficacy. For example, certain herbal polysaccharides exhibit immunomodulatory, anti-inflammatory, and antioxidant properties, providing additional therapeutic benefits alongside drug delivery. Moreover, specific herbal polysaccharides, such as ASP, can target receptors in tumor cells or the tumor microenvironment, thereby improving drug targeting and efficacy [154].

Plant Proteins-based carriers

Plant proteins represent a significant class of biomolecules, ubiquitous in the natural world, particularly abundant in plant seeds, legumes, and cereals. These proteins exhibit diverse chemical structures and are more cost-effective and accessible than their animal-derived counterparts. Furthermore, they are amenable to modification and functionalization [156]. Plant protein nanocarriers possess several advantageous properties, including low cytotoxicity, derivation from multiple renewable sources, and high drug-binding capacity. These characteristics have facilitated their development as sophisticated drug delivery systems, encompassing nanospheres, nanocapsules, micelles, and nanofibers [157].

Zein-based carriers

Zein, an alcohol-soluble glutenin derived from corn, is characterized by its high proline content and hydrophobic amino acid sequence. These properties confer excellent self-assembly capabilities and the potential to form stable nano-

Table 3 The construction of smart drug carriers for cancer treatment by herbal polysaccharides

Herbal polysaccharides	Carrier construction process	Drugs delivered	Cancers treated	Reference
Bletilla striata polysaccharide	Self-assembly of stearic acid and cystamine *via* disulfide bonds	Docetaxel	Liver cancer	[155]
	Self-assembly of folate and stearic acid modified *Bletilla striata* polysaccharide *via* electrostatic interactions	Doxorubicin	Liver cancer	[111]
	Self-assembly of *Bletilla striata* polysaccharide and vitamin E succinate polymer *via* covalent bonds	Doxorubicin	Colon cancer	[108]
	Self-assembly of *Bletilla striata* polysaccharide with stearic acid *via* hydrophobic forces	Doxorubicin	Colon cancer	[110]
	Co-assembly of *Bletilla striata* polysaccharide and stearic acid copolymer *via* hydrophobic interactions	Doxorubicin	Breast cancer	[114]
Astragalus polysaccharide	Co-assembly of *Astragalus* polysaccharide and OVA *via* intermolecular interactions	Tumor nanovaccine	/	[48]
Angelica sinensis polysaccharide	Self-assembly of *Angelica sinensis* polysaccharide-deoxycholic acid *via* hydrophobic interactions	Orcinolone acetonide	Melanoma Cancer	[30]
	Self-assembly of hydrophilic portion of *Angelica sinensis* polysaccharide with hydrophobic ferrocene *via* covalent bonds	Curcumin	Liver cancer	[115]
Carboxymethyl cellulose	Co-assembly of carboxymethyl cellulose and bovine serum albumin *via* electrostatic interactions	Camptothecin	/	[122]
	Co-assembly of chitosan and carboxymethyl cellulose *via* hydrogen bonds and electrostatic interactions	Quercetin	Brain cancer	[123]
	Self-assembly of carboxymethyl cellulose *via* schiff base bonds formed by reaction between hydrazine-modified carboxymethyl cellulose (MC-NH_2) and oxidized carboxymethyl cellulose	Doxorubicin	Cervical cancer	[121]
	Co-assembly of lactoferrin and carboxymethyl cellulose *via* electrostatic interactions and chemical crosslinking	Pemetrexed and polyphenol rhodiola	Breast cancer	[124]
Nanocrystalline cellulose	Self-assembly of lysine and nanocrystalline cellulose *via* covalent bonds	Methotrexate and curcumin	Breast cancer	[126]
Cellulose nanofibers	Self-assembly of cellulose nanofibers and *N*-isopropylacrylamide *via* hydrogen bonds and van der waals forces	Doxorubicin and berberine	/	[129]
Pectin	Co-assembly of chitosan and pectin polysaccharide *via* electrostatic interactions, hydrogen bonds, and Ionic interactions	Temozolomide	Brain cancer	[132]
	Self-assembly of pectin and curcumin *via* covalent bonds	Curcumin	/	[134]
	Self-assembly of pectin with multi-arm polyethylene glycol (8arm-PEG) *via* covalent bonds	Ursolic acid/Hydroxycamptothecin	Breast cancer	[133]
	Self-assembly of lactoferrin, pectin, and methotrexate *via* electrostatic interactions	Methotrexate	/	[135]
Alginate	Co-assembly of carboxyl groups in G-blocks of alginate, rich in α-1,4-L-guluronic acid, with calcium ions (Ca^{2+}) through coordination bonds	Doxorubicin	/	[140]
	Co-assembly of alginate and guar gum *via* physical forces	Hesperidin and betulinic acid	Leukaemia	[141]
	Self-assembly of folic acid-cholesterol-sodium alginate *via* non-covalent interactions (*e.g.*, hydrogen bonds and hydrophobic interactions)	Metformin and doxorubicin	Malignant melanoma	[139]
	Self-assembly of Sodium alginate, cisplatin, and doxorubicin *via* ionic crosslinking and hydrogen bonding	Doxorubicin and cisplatin	Breast and ovarian cancer	[142]
	Co-assembly of sodium alginate with calcium ions (Ca^{2+}) and glycyrrhizic acid *via* ionic bonds and intermolecular hydrogen bonds	Glycyrrhizin and doxorubicin	Liver cancer	[137]
	Co-assembly of alginate with calcium ions *via* coordination bonds	Doxorubicin	/	[138]

particles. As a drug carrier, Zein's hydrophobic core provides an optimal environment for encapsulating hydrophobic drugs, thereby enhancing their solubility and bioavailability. Furthermore, Zein's amphiphilic nature facilitates the formation of nanoparticles through self-assembly, which exhibit high drug-loading capacity and sustained-release properties. Additionally, Zein's molecular structure contains reactive functional groups, such as amino and carboxyl groups, enabling

covalent binding and surface modification of drugs. The biocompatibility and biodegradability of Zein are advantageous for its application as a drug carrier, as these properties mitigate the risk of potential immunogenicity and toxicity [158]. Consequently, Zein has emerged as a highly promising plant protein widely utilized in the fabrication of smart drug carriers, including nanoparticles [159], nano micelles [160], and nanofibers [161].

Zein can form nanoparticles through various interactions, including static electricity, hydrophobicity, hydrogen bonds, covalent bonds, and molecular forces [162]. Sarah *et al*. developed Zein nanospheres where Zein assembled into the core of the nanoparticles in water *via* hydrophobic interaction and hydrogen bonding [163]. The addition of polyethylene glycolyzed phospholipids (*e.g*., DSPE-PEG 2000) to the Zein nanoparticles' surface enhanced their hydrophilicity and stability while reducing non-specific interaction with serum proteins. Electrostatic adsorption facilitated the decoration of positively charged lactoferrin on Zein nanoparticles, improving their specificity for tumor cells. The results showed an EE ranging from 61.8% to 88.3%, indicating effective drug encapsulation in Zein nanoparticles. Furthermore, Xiang Li's research team developed a targeted multifunctional nanoparticle based on corn protein/HA/Tannin (TA)/Cu^{2+} loaded with IR7800 [164]. The molecular interaction was mediated by the carboxylic acid group of Sodium Alginate and the hydrophobic amino acids in corn protein. The presence of Zein enhanced drug delivery efficiency, with the EE reaching 89%. Hou *et al*. created a novel drug carrier by combining PTX and corn protein through disulfide bonding, followed by self-assembly into nanoparticles [165]. The DLE and EE of the resulting nanoparticles reached 98.3% and 16.4 $mg \cdot g^{-1}$ respectively.

In the case of GA-loaded corn protein nanoparticles, the self-assembly process was facilitated by covalent bonds [166]. Similarly, for corn protein-egg lecithin hybrid nanoparticles, the self-assembly of Zein and the drug was enabled by hydrogen bonds, electrostatic interactions, and hydrophobic interactions [167].

Zein demonstrates versatility in nanoparticle formation and can self-assemble into nanogels through non-covalent bonds, hydrogen bonds, and hydrophobic interactions. Pang *et al*. developed a system combining Zein and L-lysine, where Zein partially formed a nanogel structure through these interactions, effectively encapsulating siRNA molecules [168]. In a separate study, Sally and colleagues utilized corn protein as a hydrophobic core, chemically bonding it with the hydrophilic protein lactoferrin [29]. This research team encapsulated the hydrophilic drugs Rapamycin and Wogonin within a dual-drug corn protein-lactoferrin complex. The EE of Wogonin reached 98.00% ± 4.90%, while Rapamycin achieved an EE of 61.90% ± 3.10%.

Other herbal proteins-based carriers

In addition to corn proteins, various herbal proteins, including Soy Protein, Radix *Pseudostellariae* Protein [169], Pea Proteins [170], and WGA, demonstrate potential as smart carriers for anti-tumor drugs. For instance, Soy protein can self-assemble into nanostructures, such as nanoparticles [171] and nano gels [172], through physical adsorption and chemical cross-linking. This process has been shown to offer several benefits, including enhanced bioavailability of active herbal ingredients [173] and improved aqueous dispersibility and stability of drugs [172]. Moreover, multiple studies suggest that this method may enhance drug delivery efficacy. WGA [174] can be covalently bonded to form nanoparticles by binding to CS polymers using glutaraldehyde cross-linking. This approach enables WGA to function as a ligand with specific affinity for certain glycoproteins in colorectal cancer tissues. It enhances the EE of drugs (EE% of 78.21% ± 1.07% and 62.58% ± 0.13% for EGCG and 5-FU, respectively).

The construction of smart drug carriers for cancer treatment using plant proteins, as discussed in this section, is summarized in Table 4. These plant protein-based carriers enhance drug bioavailability, water dispersion, and stability, while exhibiting attributes such as low cytotoxicity, renewable sourcing, high drug binding affinity, and targeted delivery potential [175]. These properties make them highly suitable for drug delivery systems. Historically, protein-based carriers such as albumin [176-178] and collagen [179] have been employed in various drug delivery systems, particularly for on-

Table 4 The construction of smart drug carriers for cancer treatment by plant proteins

Plant proteins	Carrier construction process	Drugs delivered	Cancers treated	Reference
Corn protein	Co-assembly of corn protein and glycyrrhizic acid *via* covalent bonds	Glycyrrhizic acid	Breast cancer	[167]
	Co-assembly of tannic acid with corn protein *via* intermolecular forces	IR780	Breast cancer	[165]
	Co-assembly of paclitaxel with corn protein *via* disulfide bonds	Paclitaxel	Cervical cancer	[166]
	Self-assembly of corn protein *via* hydrophobic and hydrogen bonding interactions	Exemestane and luteolin	Breast cancer	[164]
	Self-assembly of corn protein *via* hydrophobic and hydrogen bonding interactions (repeated entry)	siRNA	Osteosarcoma	[168]
	Self-assembly of corn protein-lactoferrin *via* covalent bonds and hydrophobic interactions	Rapamycin and wogonen	Breast cancer	[29]
Wheat germ agglutinin	Self-assembly of wheat germ agglutinin covalently with chitosan polymer *via* covalent bonds	5-FU and EGCG	Colon cancer	[28]

cology, cardiovascular diseases, vaccine delivery, and skin repair. For instance, albumin-bound PTX (Abraxane) has received FDA approval for the treatment of breast cancer and non-small cell lung cancer [180, 181]. Compared to these traditional protein carriers, plant proteins derived from natural sources offer improved biocompatibility and reduced toxicity. As drug carriers, these plant proteins can reduce immune rejection and side effects. Additionally, these plant proteins often possess intrinsic properties including anti-oxidant, anti-tumor, anti-inflammatory, and immunomodulatory effects [182]. Consequently, drug delivery systems utilizing these plant protein carriers can provide synergistic benefits with the drugs they deliver, potentially enhancing the overall efficacy of cancer treatments.

Triterpenoids-based carriers

Triterpenoids can be extracted from various plant components, including roots, stems, leaves, flowers, and fruits, and are widely distributed in nature. These compounds consist of six isoprene units, forming a basic skeleton with five or six rings and multiple stereoisomers [183]. The presence of functional groups such as carboxyl and hydroxyl groups enables triterpenoids to self-assemble or co-assemble into nanostructures. These nanostructures can serve as smart carriers to enhance drug efficacy and safety [184].

Oleanolic acid-based carriers

OA, a common pentacyclic triterpenoid, is primarily derived from the leaves of *Olea europaea* and *Swertia mileensis* [4]. It demonstrates diverse pharmacological effects, including anti-inflammatory, antioxidant, antitumor, and antiviral properties. OA molecules contain hydroxyl and carboxyl groups, which function as hydrogen bond donors and acceptors. These groups facilitate the spontaneous aggregation of intermolecular non-covalent bonds, resulting in the formation of drug-carrying uniform spherical nanoparticles. Bao et al. applied this principle to obtain nanoparticles and utilized them for drug encapsulation. The drug-carrying nanoparticles, formed by loading PTX into nanoparticles, were employed in the treatment of breast cancer and brain metastases [25]. Additionally, OA can self-assemble with photosensitizers (Ce6) through π-π stacking and hydrophobic interactions to form carrier-free nanoparticles. These nanoparticles achieve controlled drug release and can be utilized in chemotherapy and sono-photodynamic therapy (SPDT) for cancer treatment [40]. Moreover, OA can co-assemble with other natural active herbal ingredients, demonstrating high drug-loading capacity. Wang *et al*. developed stable nanoparticles through the direct co-assembly of OA and GA *via* non-covalent interactions, such as hydrogen bonding and hydrophobic interactions. These nanoparticles exhibited a drug-loading capacity of up to 15% [185]. Through comparison of different OA and GA ratios, it was determined that nanoparticles displayed the highest EE when the mass ratio of OA to GA was 5 : 2.

Ursolic acid-based carriers

UA, a pentacyclic triterpenoid with pharmacological activity, is widely extracted from medicinal plants, fruits, and vegetables [186, 187]. Research has demonstrated that UA exhibits a range of biological properties, including anti-inflammatory, antioxidant, antitumor, and hepatoprotective effects [188]. UA can be synthesized into nanoparticles through the interaction of its molecular charge and hydrophobic properties. These nanoparticles have been shown to enhance UA's solubility, thereby demonstrating superior anti-proliferative activity compared to free UA. Moreover, hydrogen bonding and hydrophobic interaction facilitate the encapsulation of chemotherapeutic agents, such as PTX [54, 55], DOX [56], and MTX [189], into UA nanoparticles to form drug-carrying nanoparticles. In addition to chemotherapeutic drugs, UA can also be co-assembled with other compounds to form nanoparticles. Li *et al*. demonstrated that Aspirin could be co-assembled with UA through hydrophobic interaction to form spherical nanoparticles [190]. By combining chemotherapeutic drugs, photosensitizers, and targeting molecules through self-assembly, it is possible to develop nanoparticles with targeted, stable, and controllable properties. Chao and colleagues developed a novel carrier-free nanodrug based on hydrophobic interaction, π-π stacking, and electrostatic interaction [63]. This nanodrug was formed by the self-assembly of lactobionic acid with UA and the photosensitizer ICG *via* a simple green self-assembly method. The incorporation of UA enhanced the solubility and molecular activity of the drug, consequently improving the drug delivery efficiency.

Betulinic acid-based carriers

BA, also known as white birch oil, is a natural substance widely distributed in various plants, including the bark of larch, eucalyptus, and walnut trees. It is a pentacyclic triterpenoid with a similar structure to UA but with different stereochemical properties [191]. BA exhibits pharmacological activities such as anti-tumor [192], anti-inflammatory [193], antiviral [194], and anti-diabetic effects [191]. Its self-assembling capability has garnered significant attention. Researchers developed a method to form BA nanoparticles through self-assembly, which enhanced BA's solubility and demonstrated good stability and biocompatibility *in vitro* [46]. This approach addressed the hydrophobicity and solubility challenges of BA, improving its dispersion and stability in water. Transmission electron microscopy and scanning electron microscopy analysis revealed rod-like nanoparticles with an average diameter of 60 nm and length of 400 nm. After 7 days of storage at room temperature, 85% of the nanoparticles maintained their morphology. Jiacheng Wang and colleagues successfully constructed a superior biocompatible and low-toxicity supramolecular nano-assembly [195]. *Beech Tannic* acid and PTX were assembled through hydrogen bonding and hydrophobic interaction. The research group led by Cheng Jianjun investigated the co-assembly of biologically active natural small molecules and photosensitive drugs [59, 196, 197]. They screened 17 natural small molecules of the triterpenoid class and identified 11 that could form regulated drug-sized nanoparticles with Ce6, a photosensitive agent. The research team

designed and synthesized three prodrugs. Using BA as a representative example, they designed and synthesized three carrier-free precursors: co-assembled from BC and Ce6; co-assembled from modified GSH containing disulfide bonds, responsive natural BA, and Ce6; and self-assembled from BA, water-soluble CS oligosaccharides and Ce6. The formation was primarily driven by π-π stacking and hydrophobic interaction between BA and Ce6 molecules, with hydrogen bonding also contributing. The introduction of BA enhanced the water solubility and cellular uptake of Ce6, thereby improving the drug's delivery efficiency.

Other triterpenoids-based carriers

Other terpenoids, such as GA [198], Corosolic acid [199], Disodium glycyrrhizinate [200] and Ginsenoside [201], can also self-assemble to form smart nanocarriers through π-π stacking and hydrophobic interaction. GA is a naturally occurring triterpenoid extracted from the roots of the plant *Glycyrrhiza uralensis* [198]. It demonstrates a range of biological properties, including anti-inflammatory, anti-tumor, anti-microbial, anti-viral, and anti-oxidant effects. GA is a bifunctional triterpenoid capable of self-assembling into micelles in aqueous solutions. The interaction between the hydrophilic head and the hydrophobic tail of GA molecules facilitates micelle formation at low concentrations (10^{-5}–10^{-3} mol·L^{-1}) [202]. GA primarily forms dimers, while at higher concentrations (greater than 10^{-3} mol·L^{-1}) it forms larger aggregates comprising four or more molecules. For example, Zhang *et al*. utilized a GA-transparent acid conjugate for co-loading PTX [203]. The self-assembly of PTX into stable liquid-crystalline dispersions demonstrated high stability and favorable biocompatibility.

Zhi *et al*. extracted a triterpenoid natural product with a tricyclic to pentacyclic skeletal structure from maple trees [204]. This compound exhibits self-assembly properties, forming gels through a multi-step process. Initially, it develops into one-dimensional fibers *via* van der Waals forces, π-π stacking, and hydrogen bonding. These fibers subsequently form nanogels with three-dimensional network structures in the presence of solvents, enabling the encapsulation of antitumor drugs such as DOX and PTX. The resulting nano gel scaffold demonstrates excellent self-healing ability, controlled gelation, good safety, and sustained release properties. Moreover, it achieves synergistic tumor therapy through the incorporation of bioactive natural products.

The development of smart drug carriers for cancer treatment utilizing triterpenoids, as discussed in this section, is summarized in Table 5. These natural compounds demonstrate the ability to self-assemble into micelles within aqueous environments, positioning them as a central focus in drug carrier research [205]. In contrast to conventional drug delivery systems, triterpenoids generally exhibit enhanced biocompatibility and biodegradability due to their natural origins. This characteristic mitigates potential toxicity and immunogenicity concerns often associated with synthetic carriers. Moreover, triterpenoids possess intrinsic biological activities, including anti-inflammatory, antioxidant, antitumor, and hepatoprotective effects. When co-assembled with therapeutic agents, triterpenoids can augment drug efficacy and produce synergistic therapeutic outcomes, thus offering a multifaceted approach to drug delivery [206].

Alkaloids-based carriers

Alkaloids constitute a diverse class of nitrogen-containing secondary metabolites found in plants. These compounds are characterized by their complex ring structures, often incorporating nitrogen atoms within the rings. However, a subset of alkaloids, known as organic amine alkaloids, feature nitrogen atoms outside the ring system. These nitrogen atoms can engage in hydrogen bonding or participate in ionization processes, contributing to the diverse biological activities and pharmacological properties of alkaloids. Additionally, alkaloids possess multiple conjugated aromatic rings connected by rigid planar structures. Alkaloids and their derivatives have emerged as innovative components in the development of various nano-drug delivery systems. These systems have demonstrated remarkable capabilities in drug encapsulation and exhibited favorable bio-safety profiles in *in vivo* experiments.

Camptothecin and its derivatives-based carriers

CPT, originally isolated from the plant *Camptotheca acuminata* Decne, is a naturally occurring tetracyclic alkaloid. As the first natural product identified as a topoisomerase I inhibitor, it exhibits remarkable anti-tumor properties [208-210]. However, the clinical application of CPT has been constrained due to poor water solubility and stability concerns. Researchers have developed various CPT derivatives that self-assemble into multiple smart drug carriers to enhance their efficacy and reduce side effects. These modifications improved the pharmacokinetic properties of CPT while preserving their pharmacological activity. For instance, derivatives of CPT (CPT-arginine, CR) were synthesized by modifying CPT with endogenous hydrophilic arginine to enhance its water solubility [34]. CR self-assembled into helical nanofibers through intermolecular π-π stacking and hydrophilic-hydrophobic interactionCR self-assembled into helical nanofibers through intermolecular π-π stacking and hydrophilic-hydrophobic interaction [211]. The cationic modified CR nanofibers complexed with anionic cisplatin-polyglutamic acid *via* electrostatic interaction to form a CPT and cisplatin co-delivery system. Results indicated that the carrier demonstrated high delivery efficacy, with a DLE exceeding 99%. Additionally, CPT could be modified by *β*-cyclodextrin (*β*-CD) to increase water solubility, and subsequently mixed with modified HA. Nanoparticles with a hydrophilic HA shell and a hydrophobic CPT core were then constructed through strong non-covalent interactions between *β*-CD and adamantane as well as supramolecular amphiphilic interaction. Mu X *et al*. developed a tumor heterogeneity-activated prodrug by linking amphiphilic Rhodamine and CPT via disulfide bonds [212]. Data revealed that the prodrug nanoparticles exhibited longer circulation time (half-life of approximately 4.4 h) and superior anti-tumor activity (tumor inhibition effect of

Table 5 The construction of smart drug carriers for cancer treatment by terpenoids

Terpenoids	Carrier construction process	Drugs delivered	Cancers treated	Reference
Oleanolic acid	Self-assembly of oleanolic acid *via* electrostatic, π-π stacking, or hydrophobic interactions	Carrier-free nano-sensitizer	Breast cancer	[40]
	Self-assembly of oleanolic acid *via* hydrophobic interactions and hydrogen bonds	Paclitaxel	Breast cancer, brain metastases (BCBMs)	[25]
Ursolic acid	Co-assembly of ursolic acid and paclitaxel *via* hydrogen bonds and hydrophobic interactions	Paclitaxel	Breast cancer	[54]
	Co-assembly of ursolic acid and doxorubicin *via* π-π interactions, hydrophobic interactions, and electrostatic interactions	Ursolic acid and Doxorubicin	Breast cancer	[56]
	Co-assembly of aspirin and ursolic acid *via* hydrogen bonds and hydrophobic interactions	Aspirin and ursolic acid	/	[190]
	Co-assembly of ursolic acid, liver-targeting molecule lactose acid, and photosensitizer indocyanine green *via* π-π stacking, hydrophobic interactions, and electrostatic interactions	Ursolic acid	Liver cancer	[63, 189]
	Co-assembly of ursolic acid and sora *via* hydrophobic interactions and hydrogen bonds	(Sorafenib) Sora, Rapamycin	Liver cancer	[207]
	Co-assembly of methotrexate and ursolic acid *via* electrostatic and hydrophobic interactions	Methotrexate	Breast cancer	[189]
	Self-assembly of ursolic acid *via* electrostatic and hydrophobic interactions	Ursolic acid	Breast cancer	[188]
	Self-assembly of ursolic acid *via* strong intermolecular hydrogen bonds	Paclitaxel	Glioblastoma	[55]
Betulinic acid	Co-assembly of betulinic acid, chlorin e6, and chitosan *via* π-π stacking and hydrophobic interactions	Betulinic acid	Breast cancer	[196]
	Co-assembly of betulinic acid and paclitaxel *via* hydrogen bonds and hydrophobic interactions	Paclitaxel	Breast cancer	[195]
	Co-assembly of terpenoid molecules and chlorin e6 *via* π-π stacking and hydrophobic interactions	Betulinic acid	Breast cancer	[197]
	Co-assembly of betulinic acid and photosensitizer chlorin e6 *via* π-π stacking and hydrophobic interactions	Chlorin e6	Breast cancer	[59]
	Self-assembly of betulinic acid *via* hydrogen bonds	Betulinic acid	Glioblastoma	[46]
Glycyrrhizic acid	Self-assembly of glycyrrhizic acid *via* hydrophobic forces and hydrogen bonds	Paclitaxel	Ovarian cancer	[202]
	Co-assembly of glycyrrhizic acid and hyaluronic acid *via* hydrophobic forces, covalent bonds, and hydrogen bonds	Paclitaxel	Ovarian cancer, breast cancer, non-small cell lung cancer	[203]
Glycyrrhizic acid, Oleanolic acid	Co-assembly of glycyrrhetinic acid and oleanolic acid *via* hydrogen bonds and hydrophobic interactions	Adriamycin	Breast cancer	[185]
Corosolic acid	Co-assembly of paclitaxel and corosolic acid *via* hydrophobic forces	Paclitaxel	Breast cancer, ovarian cancer, lung Cancer	[199]
Disodium glycyrrhizinate	Self-assembly of disodium glycyrrhizic acid *via* hydrogen bonds	Camptothecin	Ovarian cancer, metastatic Breast cancer, non-small cell lung cancer	[200]
Ginsenoside	Co-assembly of celastrol and ginsenoside *via* π-π stacking and hydrophobic interactions	Celastrol and ginsenosides	Breast cancer	[201]
	Co-assembly of ginsenoside with paclitaxel *via* hydrophobic forces	Paclitaxel	Stomach cancer	[16]
Three triterpenoids with tricyclic to pentacyclic skeletal structures	Self-assembly of triterpenoid compounds *via* Van der Waals forces, π-π interactions, and hydrogen bonds	Doxorubicin	Breast cancer	[204]

about 77.4%, which was 1.5-fold that of the free CPT group (about 51.2%) compared to free CPT *in vivo*.) Furthermore, CPT could be modified by Lac through disulfide bonds to form Lac-SS-CPT molecules, and Lac-SS-CPT spontaneously formed nano-vesicular structures in aqueous solution through intermolecular interactions, efficiently rupturing and releasing CPT and DOX [34]. (In GSH solution, the release rates of CPT and DOX were 76% and 86% respectively).

Fei Chen and colleagues developed an innovative co-delivery system that effectively combined HCPT and DOX within a single nanocarrier through non-covalent interactions, including hydrogen bonding, π-π stacking, and van der Waals forces [213]. The co-assembly process initially involved HCPT molecules self-assembling into nanorod structures in an aqueous solution. Upon introduction of DOX, these HCPT nanorods disassembled, transformed into intermediates, and ultimately reassembled into stable spherical nanoparticles. This approach successfully addressed the limitation in clinical applications where direct mixing of HCPT and DOX injections would typically result in reduced therapeutic efficacy.

Furthermore, CPT and its derivatives can be co-loaded with photosensitizers to enhance drug stability. For instance, 7-ethyl-10-hydroxy CPT (SN38) and HCPT were co-assembled with Ce6 to form carrier-free nanoparticles. Chemical thermodynamic methods and molecular dynamics simulations revealed that this process primarily relied on hydrophobic interactions (π-π stacking) and hydrogen bonding [214]. Additionally, Ao *et al*. utilized inter-molecular hydrophobic interaction and π-π stacking to combine CPT with photo thermite infrared 820 (IR820) *via* a redox-responsive disulfide bond, creating an amphiphilic drug-drug conjugate. This conjugate self-assembled into nanoparticles in aqueous solution with high DLC, facilitating efficient co-delivery of chemotherapeutics and photosensitizers, while demonstrating low systemic toxicity and good biocompatibility *in vivo* [215, 216].

Berberine and its derivatives-based carriers

BBR, characterized by a two-conjugated isoquinoline core structure comprising a six-membered ring and a partially oxidized isoquinoline ring, is a naturally occurring isoquinoline alkaloid found in various plants. The functional groups, such as hydroxyl and methyl groups, in the BBR molecule enhance its water solubility and provide opportunities for derivatization. This enables the improvement of pharmacokinetic properties and bioavailability of the drug through chemical modification [217]. Furthermore, the planar polycyclic structure of BBR facilitates interactions with biomolecules such as DNA and proteins, offering advantages as a drug carrier [216]. The planar structure of BBR molecules promotes the formation of stable complexes with other molecules through π-π stacking. Yun and colleagues developed a self-assembled nanoparticle based on BBR, combining BBR with GA or Artesunate [218]. The ammonium ions in BBR molecules formed electrostatic interactions with the carboxyl groups in GA or Artesunate molecules, while GA and Artesunate molecules possessed hydrophobic backbones and multiple chiral centers, allowing them to form ordered aggregates with BBR. BBR could also form nanodrugs with DOX through intermolecular interactions, including π-π stacking and hydrophobic interaction, resulting in typically spherical nanodrugs with a diameter of approximately 100 nm [60]. Song *et al*. constructed self-assembled mitochondria-targeted nanodrugs from a 9-*O*-octadecyl-substituted BBR derivative (BD) [219]. In this system, BD molecules formed nanoparticles through electrostatic interaction, HA covered the surface of PEG/BD NDs *via* electrostatic interaction, and π-π stacking and hydrophobic interaction further stabilized this nanodrug. BD could also self-assemble with DOX to form nanodrugs for breast cancer treatment. The hydrophobicity of BBR and DOX molecules promoted their aggregation, while electrostatic interaction led to stable structures during the self-assembly process. In conclusion, BBR can be utilized to construct smart drug carriers through self-assembly techniques, forming spontaneously by exploiting interactions between drug molecules (*e.g*., electrostatic interaction, hydrophobic interaction, π-π stacking).

Paclitaxel-based carriers

PTX, a complex secondary metabolite extracted from the *Picearubra* plant, exhibits significant anti-tumor activity. Its chemical structure is uniquely complex, featuring a 6-8-6-4 tetracyclic backbone and 11 stereochiral centers. The PTX molecule inherently possesses poor water solubility; however, the introduction of hydrophilic groups could modify the interactions between PTX molecules. Consequently, these modifications could facilitate its self-assembly in aqueous solutions, forming stable nanoparticles and enhancing its solubility and drug delivery efficiency in organisms. Researchers have successfully induced PTX self-assembly in combination with various compounds [220-228], including curcumin, poly (L-glutamic acid)-graft-methoxy Polyethylene Glycol, Baicalin, Doxorubicin, Dihydroartemisinin, Sunitinib, Mifepristone, and PEG, utilizing hydrophobic forces, π-π stacking, and electrostatic interactions. Furthermore, investigators covalently bound PTX to the TAR peptide to form a prodrug coupling. Due to its amphiphilic nature, this compound self-assembled into core-shell nanoparticles in water [229]. In this configuration, PTX was linked by acid- and esterase-sensitive ester bonds, enabling the nanoparticles to maintain stability in physiological environments while releasing PTX in the tumor micro-environment. In another study, DTX and Gemcitabine were conjugated using PEG as a linker arm to form amphiphilic nano-molecules. DTX served as the hydrophobic head, while PEG and Gemcitabine acted as hydrophilic tails. These molecules spontaneously formed *via* π-π stacking and hydrogen bonding to co-deliver DTX and Gemcitabine [230]. The results demonstrated a low critical micelle concentration and exhibited enhanced cellular uptake and efficacy. Concurrently, drug stability improved due to the hydrophilicity and steric hindrance/cryptosis phenomenon of PEG, reducing the conversion rate to its in-

active metabolite 2'-deoxy-2',2'-difluorouridine in plasma.

The development of smart drug delivery systems for cancer treatment utilizing alkaloids, as discussed in this section, is summarized in Table 6. These compounds employ various intermolecular forces, including electrostatic and hydrophobic interactions, as well as π-π stacking, to create stable structures that enhance drug encapsulation efficiency, prolong circulation time, and improve anti-tumor efficacy [231]. Compared to conventional carriers, alkaloid-based systems generally exhibit enhanced biocompatibility and reduced toxicity, thus minimizing adverse effects associated with drug delivery. Furthermore, alkaloids demonstrate superior biodegradability and high affinity for target tissues, enabling more precise targeting of specific cells or organs [232]. The combination of alkaloids with therapeutic agents not only enhances drug stability and bioavailability but also extends the drug's half-life in the body, thereby increasing therapeutic efficacy [233].

Table 6 The construction of smart drug carriers for cancer treatment by alkaloids

Alkaloids	Carrier construction process	Drugs delivered	Cancers treated	Reference
Camptothecin and its derivative	Self-assembly of camptothecin and curcumin *via* hydrophobic forces, hydrogen bonds, and π-π stacking	Curcumin and Camptothecin	Ovarian, cervical and lung cancer	[210]
	Self-assembly of camptothecin with amphiphilic poly (ethylene glycol)-b-poly(ε-caprolactone) *via* hydrophobic forces and π-π stacking	Camptothecin	Breast cancer	[209]
	Self-assembly of rhodamine and camptothecin conjugate *via* hydrophobic forces, π-π stacking, and hydrogen bonds	Camptothecin	Breast cancer	[212]
	Self-assembly of camptothecin and photothermal agent indocyanine green (IR820) conjugate *via* π-π stacking interactions and hydrogen bonds	Camptothecin	Breast cancer	[216]
	Self-assembly of camptothecin with poly (L-glutamic acid)-graft-methoxy polyethylene glycol and CPT *via* hydrophobic forces and electrostatic interactions	Doxorubicin	Breast cancer	[214]
	Co-assembly of *β*-cyclodextrin modified camptothecin (CPT-CD) and adamantane modified hyaluronic acid	Camptothecin and Adamantane	Colon cancer	[211]
	Co-assembly of doxorubicin and 10-hydroxycamptothecine *via* hydrophobic forces, hydrogen bonds, and π-π stacking	Doxorubicin and hydroxycamp-tothecine	Breast cancer	[214]
	Co-assembly of 10-hydroxycamptothecine with photosensitizer chlorin e6 *via* hydrophobic forces and π-π stacking	10-Hydroxycamp-tothecin and Ce6	/	[217]
	Co-assembly of 10-hydroxycamptothecine (SN38) and chlorin e6 *via* hydrophobic forces and hydrogen bonds	7-Ethyl-10-hydroxycamptothecin and Ce6	Breast cancer	[215]
Berberine derivative	Self-assembly of berberine derivative and doxorubicin *via* hydrophobic forces, π-π stacking, and electrostatic interactions	Berberine and doxorubicin	Metastatic breast cancer	[234]
	Co-assembly of 9-*O*-Octadecyl berberine derivative, DSPE-PEG2000, and hyaluronic acid *via* hydrophobic forces, π-π stacking, and charge interactions	9-*O*-octadecyl substituted berberine derivatives	Lung cancer	[219]
Paclitaxel and its derivative	Self-assembly of paclitaxel by conjugating platinum peptides with peptide arginine-glycine-aspartic acid and succinic acid as a linker	Tetrandrine	Stomach cancer	[220]
	Self-assembly of paclitaxel and baicalin *via* hydrophobic forces and charge effects	Baicalin and paclitaxel	Paclitaxel Resistant lung cancer	[222]
	Co-assembly of paclitaxel and evans blue conjugated camptothecin *via* hydrophobic forces and weak intermolecular forces	Paclitaxel and camptothecin	/	[208]
	Co-assembly of doxorubicin conjugate and paclitaxel conjugate *via* hydrophobic forces, π-π stacking, and electrostatic interactions	Doxorubicin and paclitaxel	Breast cancer	[223]
	Co-delivery of paclitaxel and dihydroartemisinin *via* hydrophobic forces	Paclitaxel and dihydroartemisi-nin	Rectal cancer	[224]
	Co-delivery of paclitaxel and sunitinib *via* hydrophobic forces and π-π stacking	Paclitaxel and sunitinib	Triple negative breast cancer	[225]
	Co-assembly of paclitaxel-SA and mifepristone *via* hydrophobic forces	Paclitaxel and mifepristone	Breast cancer	[212]
	Co-assembly of paclitaxel and TAR peptide conjugate *via* hydrophobic forces	Paclitaxel	Triple negative breast cancer	[229]
	Self-assembly of PEGylated paclitaxel *via* hydrophobic forces	Paclitaxel	Breast cancer	[228]
	Co-assembly of docetaxel, gemcitabine, and polyethylene glycol *via* hydrophobic forces, van der Waals forces, and hydrogen bonds	Docetaxeland gemcitabine	Breast cancer	[230]

Other classes of active herbal ingredients-based carriers

Beyond the aforementioned compounds, various other active herbal constituents, including diketones, phenolic ethers, and essential oils, remain in the early phases of investigation within the domain of intelligent drug delivery systems. These substances demonstrate considerable potential for further exploration, attributable to their distinctive physicochemical characteristics. Such properties encompass stability, multi-functionality, amenability to modification and synthesis, low toxicity, and promising biocompatibility.

Diketones, exemplified by CUR, contain two ketone groups in their chemical structure, which can be further derivatized to enhance the multi-functionality of drug carriers by introducing different substituents or interacting with other molecules through hydrogen bond formation. CUR and erlotinib were linked by PEG to form an amphiphilic conjugate, which self-assembled in water to form a homogeneous nano assembly with a critical micelle concentration of 1.95 μmol·L^{-1}. This low concentration facilitates micelle formation, contributing to the drug's solubility and stability [235]. Additionally, CUR and Gd^{3+} could drive self-assembly to form carriers through ligand interaction. ICG was subsequently loaded into these CUR-gadolinium complex nanoparticles *via* electrostatic attraction, providing a novel and highly efficient strategy for constructing carrier-free therapeutic agents [236].

Phenolic ethers, exemplified by Honokiol, a natural phenolic compound derived from *Magnolia officinalis*, exhibit a diverse range of biological activities, including anti-inflammatory, antioxidant, and anti-tumor properties. The Thujaplicin molecule comprises two aromatic rings connected by a central chain, providing multiple functional groups such as phenolic hydroxyl groups and olefinic bonds. These structural features facilitate chemical modifications to enhance drug solubility and stability. Furthermore, Thujaplicin's lipophilic nature promotes its ability to traverse biological membranes, thereby improving drug bioavailability and cell permeability. In drug carrier design, Thujaplicin's chemical structure enables self-assembly with drug molecules to form stable nanoparticles through hydrogen bonding, π-π stacking, and hydrophobic interactions, facilitating controlled release and targeted drug delivery [237, 238]. Additionally, the antioxidant capacity of Thujaplicins aids in protecting drug molecules from degradation by reactive oxygen species *in vivo*, while its anti-inflammatory effects may mitigate adverse reactions during drug delivery [239].

Volatile oil, a term encompassing a class of volatile oily constituents extracted from plants, is prevalent in families such as Asteraceae and Rutaceae. These oils primarily comprise terpenoids, aromatic compounds, and their oxygenated derivatives, exhibiting a range of pharmacological effects including anti-tumor, anti-inflammatory, anti-allergic, anti-microbial, and anti-mutagenic properties. Due to their lipophilic nature and low water solubility, volatile oils are frequently formulated into hydrogels, microcapsules, liposomes, nanoemulsions, and other advanced drug carriers to enhance drug stability, bioavailability, and targeting [240, 241]. However, the complex chemical composition, instability, high volatility, and low bioavailability of volatile oils present significant challenges [242]. Currently, many related technologies are in their early stages, necessitating further research and development to fully realize the potential of volatile oils in smart drug carriers and to create safer, more effective drug delivery platforms.

Comparison Between Active Herbal Ingredients-derived Smart Drug Carriers and Traditional Carriers

In comparison to conventional drug delivery systems, smart drug carriers derived from active herbal ingredients offer notable advantages. These include natural origins, reduced toxicity, diverse biological activities, targeting capabilities, and immunomodulatory functions (as illustrated in Table 7). These distinctive features demonstrate significant potential for applications in areas such as anti-tumor therapy, anti-inflammatory treatments, and immune regulation. Furthermore, they provide innovative approaches for personalized treatment strategies and precision medicine.

Disease treatment

In contrast to conventional drug delivery systems, smart drug carriers derived from active herbal ingredients exhibit multiple pharmacological properties. Certain active herbal components possess inherent anti-cancer effects and, when combined with chemotherapeutic agents, can produce synergistic therapeutic outcomes.

Research has demonstrated that numerous active herbal ingredients possess anti-tumor properties and are utilized in cancer treatment medications, including PTX, CPT, and Baicalein. PTX has been clinically proven to exhibit effective anti-tumor properties, particularly against ovarian, uterine, and breast cancers, which have high incidence rates. Its mechanism of action primarily involves promoting tubulin polymerization and inducing the expression of genes and cytokines that inhibit tumor cell growth and apoptosis [243]. CPT, a plant-derived anti-tumor drug, is clinically employed to treat primary liver cancer, gastrointestinal cancer, head and neck cancer, lung cancer, leukemia, and bladder cancer. Its anti-tumor mechanism primarily involves inhibiting DNA topoisomerase I (TOPO I). Baicalein has been extensively utilized as an anti-oxidant, anti-inflammatory, anti-hepatotoxic, antiviral, and anti-tumor agent. Several studies have identified Baicalein as a significant candidate for treating lung cancer. Its mechanism of action encompasses regulation of cell proliferation, metastasis, apoptosis, and autophagy [244]. When these active herbal ingredients are employed as carriers for drug delivery, a synergistic therapeutic effect is generated between the carrier and the drug. This combination has the capacity to inhibit tumor cell cycle, suppress proliferation, induce cell apoptosis, promote autophagy, inhibit tumor cell invasion and metastasis, enhance efficacy, or reduce drug res-

Table 7 Differences between the active herbal ingredients-derived smart drug carriers and the traditional drug delivery carriers

Characteristics	Active herbal ingredients-derived smart drug carriers	Traditional drug delivery carriers
Source of carrier components	Flavonoid, quinones, polysaccharides, proteins, etc.	Artificially synthesizing polymer materials, nanoparticles, liposomes, proteins, etc.
Biocompatibility	High biocompatibility, low toxicity, and natural ingredients are easily metabolized in the body.	Good biocompatibility, but some synthetic materials may trigger immune reactions or toxicity.
Collaborative therapeutic effect	The carrier itself has pharmacological activities, such as antioxidant, anti-inflammatory, and immune regulatory functions.	The carrier itself has no pharmacological activity and is mainly used for drug loading and delivery.
Degradation products	The degradation products are non-toxic and easily metabolized and utilized by the body.	Some synthetic materials may produce toxic or difficult to metabolize by-products after degradation.
Drug release characteristics	Controllable release, the carrier itself has the ability to regulate the drug release rate and has good long-term efficacy.	Depending on the design of the carrier structure, the release rate of some carriers is difficult to control.
Versatility	It has multiple biological activities and can simultaneously serve as a drug carrier and therapeutic ingredient.	Single function, mainly used for drug delivery, requires additional design to achieve specific functions.
Personalized treatment	Different active herbal ingredients can be selected according to different pathological needs for personalized combination.	Mainly relying on physical and chemical properties adjustment, personalized treatment has limited effectiveness.
Cost and Production	Some plant components have abundant sources and low costs, but the extraction and preparation processes may be complex.	The production process is relatively mature, and the cost of synthetic materials and carriers is gradually decreasing.

istance, effectively impeding cancer progression and extending patient survival.

Furthermore, combining carriers derived from active herbal ingredients with chemotherapy drugs can mitigate the development of drug resistance. This approach demonstrates enhanced anti-cancer efficacy and reduced toxic side effects compared to monotherapy with chemotherapy or targeted drugs.

The smart drug carriers derived from active herbal ingredients can also facilitate personalized and controllable treatment. The physicochemical properties of these active herbal ingredients can be modulated through straightforward methods, such as altering molecular weight or modifying functional groups, to address various drug delivery requirements. Additionally, controlled drug release can be achieved by adjusting the composition and structure of active herbal ingredients and exposing them to specific stimuli.

Biocompatibility and safety

Active herbal ingredients demonstrate a high affinity for human tissues, which enhances the stability and bioavailability of drugs administered *in vivo*. Moreover, due to their low toxicity and established safety profile resulting from long-term natural selection, smart drug delivery systems incorporating these ingredients can reduce immunogenicity and inflammatory responses, thereby mitigating the toxic side effects associated with drug delivery. In comparison to synthetically produced polymer materials, active herbal ingredients generate fewer harmful byproducts during *in vivo* degradation processes.

In comparison to conventional carrier systems, smart drug carriers derived from active herbal ingredients offer a broader spectrum of therapeutic potential and enhanced safety. This is particularly evident in contemporary Chinese medicine research, demonstrating significant promise for future applications.

Cost and sources

Active herbal ingredients are derived from diverse sources, including plants, Chinese herbs, and algae, enhancing their accessibility and reducing production costs. Furthermore, sustainable production can be achieved through agricultural cultivation of specific plants, facilitating large-scale application.

Conclusion and Prospect

Active herbal ingredients demonstrate significant anti-tumor properties and exhibit considerable potential as matrices for developing smart drug delivery systems [245-247]. This study systematically investigates the transformation of active herbal ingredients and their derivatives into sophisticated drug carriers, based on their chemical structures. Additionally, it analyzes the mechanisms through which these carriers enhance anti-tumor efficacy.

Smart drug carriers derived from herbal active ingredients play a crucial role in anti-tumor drug delivery. These carriers offer several advantages. Firstly, certain active herbal ingredients can self-assemble into carriers due to their inherent physical and chemical properties, facilitating their delivery to tumor sites [101]. For instance, Honokiol can self-assemble into nanoscale particles through hydrogen bonds and hydrophobic interactions [238]. It functions both as a drug carrier and a pharmacologically active agent, effectively enhancing drug loading capacity without additional excipients. Secondly, carriers derived from active herbal ingredients can deliver other anti-tumor drugs like DOX, achieving a synergistic anti-tumor effect through multiple mechanisms. Berberine derivatives and DOX can be formulated into nanomedicines for cancer treatment using self-assembly technology [234]. Berberine derivatives induce apoptosis *via* the

mitochondrial pathway, inhibiting tumor cell proliferation and invasion. Simultaneously, DOX, a chemotherapeutic agent, induces apoptosis by inhibiting topoisomerase. These agents work synergistically, promoting apoptosis through distinct pathways, thereby enhancing overall therapeutic efficacy. Thirdly, active herbal ingredients often exhibit multiple anti-tumor mechanisms, which helps reduce drug resistance and may mitigate side effects. In PTX-loaded OA/GA co-assembled nanoparticles [185], OA induces tumor cell apoptosis and autophagy by activating caspases and kinases while inhibiting certain drug efflux transporters, such as P-gp, to increase the intracellular concentration of PTX. This enhances the anti-tumor effect while reducing the dosage of chemotherapeutic drugs and alleviating side effects. Fourthly, smart drug carriers derived from active herbal ingredients are commonly prepared using the precipitation method, which typically involves mild reaction conditions and the use of water as a solvent or a poor solvent, reducing dependence on organic solvents and benefiting environmental protection [214].

Smart drug carriers derived from herbal active ingredients demonstrate significant potential in anti-tumor drug delivery, yet they face several challenges. Primarily, the low abundance of these active ingredients in plants necessitates complex extraction and purification processes. Current extraction methods include solvent extraction, ultrasonic-assisted extraction, distillation, and supercritical fluid extraction, while purification techniques involve adsorption column chromatography and thin-layer chromatography [248-250]. These resource-intensive processes require substantial time, labor, and financial investment, significantly increasing production costs. To address these challenges, researchers are investigating the use of synthetic biology to produce natural compounds through microbial cell factories. For instance, constructing high-activity biosynthesis pathways in microorganisms could facilitate the green biomanufacturing of non-natural ginsenosides [251]. Additionally, studies have shown that the mechanisms by which active herbal ingredients form drug delivery carriers are closely related to their structural features. For example, polyhydroxy-structured compounds, such as quercetin, can coordinate with metal ions to form chelate assemblies, while herbal polysaccharides, rich in hydrophilic groups, can self-assemble by covalently binding hydrophobic groups to form amphiphilic polymers [251]. Moreover, compounds like Rhein, with their benzene ring and planar structure, facilitate self-assembly through π-π stacking [46, 252, 253]. These principles, derived from previous studies, provide valuable insights, and it is crucial for researchers to comprehensively understand the relationships between molecular structures and functions before application. Furthermore, computational chemistry and molecular simulation techniques could predict the assembly behavior and performance of compounds, which could then be validated through experiments to design novel smart drug carriers [254]. Despite numerous reports on active herbal ingredients-derived smart drug carriers, there remains a lack of in-depth research, with many carriers still at the laboratory research stage [255]. Therefore, during the clinical translation process, it is essential to address key issues such as ensuring consistent quality standards, long-term stability, and traceable, sustainable sources [245]. Overcoming these barriers will significantly enhance the application of active herbal ingredients in the medical field.

Smart drug carriers derived from active herbal ingredients demonstrate significant potential in anti-tumor drug delivery. These ingredients offer novel strategies for designing drug delivery systems due to their inherent biological activity. Future research could focus on developing integrated multifunctional smart carriers that achieve targeting, stimulus response, and precise control of drug release within the tumor microenvironment, enhancing precision therapy. Moreover, these carriers can be combined with advanced treatment technologies such as gene therapy and immunotherapy to achieve synergistic anti-tumor effects. For instance, co-delivering active herbal ingredients with immunomodulators like CRISPR-Cas9 gene-editing systems or immune checkpoint inhibitors may lead to innovative therapies with multiple therapeutic effects. Given their natural properties, active herbal ingredients potentially offer advantages in biodegradability and environmental compatibility. Consequently, future research could explore the development of biodegradable and environmentally friendly drug delivery carriers based on these ingredients, potentially mitigating toxicity issues and environmental pollution associated with traditional synthetic materials.

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