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REVIEW

Natural Products-Based Nanoformulations: A New Approach Targeting CSCs to Cancer Therapy

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Abstract: Cancer stem cells (CSCs) lead to the occurrence and progression of cancer due to their strong tumorigenic, self-renewal, and multidirectional differentiation abilities. Existing cancer treatment methods cannot effectively kill or inhibit CSCs but instead enrich them and produce stronger proliferation, invasion, and metastasis capabilities, resulting in cancer recurrence and treatment resistance, which has become a difficult problem in clinical treatment. Therefore, targeting CSCs may be the most promising approach for comprehensive cancer therapy in the future. A variety of natural products (NP) have significant antitumor effects and have been identified to target and inhibit CSCs. However, pharmacokinetic defects and off-target effects have greatly hindered their clinical translation. NP-based nanoformulations (NPNs) have tremendous potential to overcome the disadvantages of NP against CSCs through site-specific delivery and by improving their pharmacokinetic parameters. In this review, we summarize the recent progress of NPNs targeting CSCs in cancer therapy, looking forward to transforming preclinical research results into clinical applications and bringing new prospects for cancer treatment.

Keywords: cancer, cancer stem cells, nanoformulations, natural products, targeted therapy

Cancer remains a major public health problem worldwide, causing a huge disease burden. It is not only one of the leading causes of death globally but is also an important factor hindering the extension of human life expectancy, about 80% of tumor types derives from some solid cancers including prostate, breast, ovary, pancreas and lung.[1] With an estimated 19.3 million new cancer cases and nearly 10 million cancer deaths globally in 2020, the cancer death rate is expected to nearly double by 2040 due to the adverse effects of the COVID-19 pandemic.[2]

The lives of cancer patients have been significantly prolonged, the overall risk of cancer death has decreased by 32%, and approximately 3.5 million cancer deaths have been avoided owing to a series of revolutionary breakthroughs in early screening, surgical treatment, and immunotherapy in the past decade. Nonetheless, malignant cancer is still formidable, and the overall mortality rate is still high. Metastasis, recurrence, and multidrug resistance (MDR) are major challenges to current cancer treatment.[3,4]

Conventional cancer treatment has multiple drawbacks, including damage to healthy tissues, serious side effects, and MDR. Cancer stem cells (CSCs) are specialized cell subsets in tumor tissue with high self-renewal, multidirectional differentiation potential and tumorigenic ability and are the driving force of malignant proliferation, invasion, metastasis, drug resistance and recurrence of tumors.[5,6] As CSCs play a key role in treatment resistance, it has been difficult to significantly improve the overall clinical efficacy of Traditional oncology therapies from their current level. Undoubtedly, novel therapeutic strategies targeting CSCs will bring new approaches for cancer treatment.[7] By targeting the surface markers, signaling pathways, microenvironment, metabolic features and differentiation of CSCs, various inhibitors of CSCs have been investigated in preclinical studies or clinical trials.[8–10] Meanwhile, some existing inhibitors inevitably

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have certain side effects, such as dizziness and gastrointestinal reactions, which severely limit the clinical drug development of cancer therapies targeting CSCs.[11]

Increasing evidence has shown that many natural products (NP), such as curcumin, sulforaphane, quercetin, and berberine, have promising anticancer activity by targeting CSCs.[12,13] Although the incredible health benefits of NP have been elucidated, their widespread use in cancer therapy is severely restricted by limitations in terms of their water solubility, absorption, bioavailability, and targeting.[14] By specifically targeting the drug-resistant and aggressive CSCs in tumor tissues, nanoparticle-loaded drugs can improve patient survival while minimizing their side effects and alleviating patient suffering.[15] Therefore, the integration of NP and nanotechnology into cancer therapy could result in novel NP-based nanoformulations (NPNs) to target CSCs, which could improve the pharmacological response of patients and achieve better clinical benefits.[16,17] Accordingly, we aimed to systematically summarize the current new trends and development challenges of NPNs targeting CSCs for the treatment of cancer in this review.

CSCs

Cancer is a highly heterogeneous tissue, and different mechanisms contribute to its heterogeneity, such as genetic mutations, the microenvironment, and the presence of CSCs. CSCs maintain tumors in an immortalized or malignant clonal manner and differentiate into heterogeneous cancer cells, leading to the progression of primary tumors and the development of new tumors.[18,19] CSCs can be derived from self-renewing normal stem cells or progenitor cells that have acquired self-renewal capacity due to mutation or dedifferentiation of mature tumor cells. Studies have found that normal stem cells gradually develop into precancerous stem cells and CSCs after the first oncogenic mutation, and then further accumulate mutations under the effect of mutagens and the microenvironment to increase the tumor's heterogeneity, resulting in uncontrolled cell growth and promoting tumor development, metastasis, treatment resistance, and recurrence[20,21] (Figure 1).

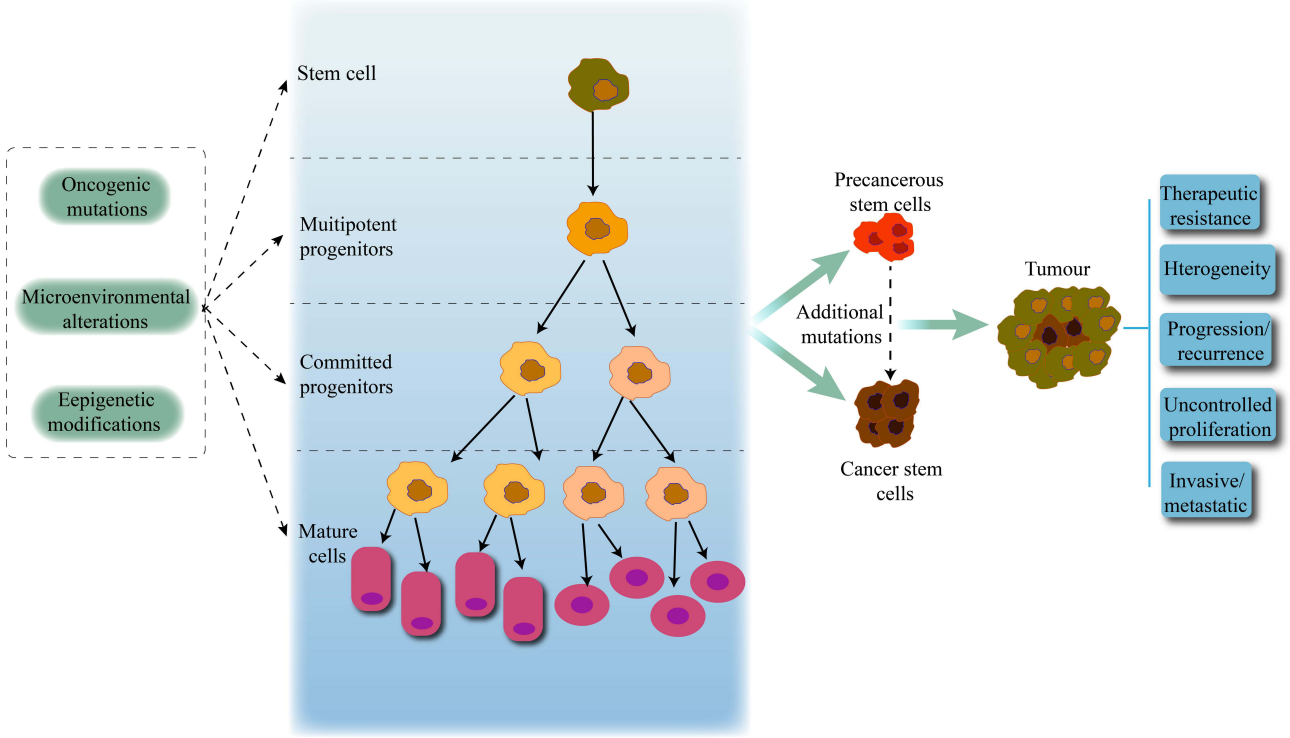

Figure 1 CSCs and tumor progression. Normal stem cells give rise to multipotent progenitor cells, committed progenitor cells, and mature differentiated cells. Oncogenic mutations, microenvironmental alterations, and epigenetic modifications lead to the emergence and abnormal proliferation of CSCs, promoting the development and progression of malignant tumors.

The earliest evidence for CSC models came from acute granulocytic leukemia. Dick et al isolated human acute myeloid leukemia stem cells with an immunophenotype of $CD34^{+}/CD38^{-}$ and confirmed the self-renewal ability of CSCs in immunodeficient mice.[22] The presence of CSCs in other solid tumors was then established, such as in breast, lung, pancreatic, prostate, and brain cancers.[23–25]

The most important feature of CSCs is their ability to continuously self-renew and maintain multidirectional tumor differentiation.[26] The self-renewal and differentiation pathways of normal stem cells are tightly regulated by Wingless-related integration site (Wnt), Notch, Hedgehog, Janus kinase–signal transducer and activator of transcription (JAK-STAT), Transforming growth factor (TGF)-β and other signaling pathways, and these pathways are significantly dysregulated in CSCs.[27–29] These signaling pathways do not individually act as single regulators but instead form an intertwined signaling network that together regulates the stemness of CSCs, resulting in the unlimited potential of CSCs for self-renewal, proliferation, and multidirectional differentiation, as well as initiating tumor formation, reconstituting tumor heterogeneity, and providing resistance to chemoradiotherapy.[13]

CSCs specifically express various stemness-related genes and markers, such as Krüppel-like factor 4 (Klf4), Nanog, Notch, CD24, CD26, CD44, CD133, CD166, aldehyde dehydrogenase (ALDH), and epithelial cell adhesion molecule (EpCAM). The expression of these stem cell-related genes and surface markers can significantly promote tumorigenesis and facilitate the isolation and identification of stem cells.[30,31] In addition, CSCs jointly maintain stemness characteristics by virtue of their biological characteristics (cell cycle arrest, DNA damage repair, drug efflux, epithelial-mesenchymal transition (EMT), etc.) and the protective effect of the tumor microenvironment (hypoxic environment, cancer-associated fibroblasts, chronic inflammation, etc.), which increases the difficulty of tumor treatment.[19,32] Moreover, CSCs have efficient DNA repair systems and represent a core-to-edge transition profile for enabling resistance and being protected within tumor microenvironment stem niches.[33–35] In addition, epigenetic mechanisms play critical roles in the formation and function of CSCs, tumor heterogeneity, tumorigenicity, tumor development, and metastasis. The interaction between epigenetic modifications and the tumor-surviving microenvironment modulates the plasticity of CSCs and shapes the architecture of tumors.[36–38] Therefore, the regulatory modes involved in CSCs interact and constitute a complex regulatory network of CSCs, which increases the difficulty of cancer treatment (Figure 2).

Due to the complex characteristics of the CSCs described above, conventional cancer treatment options can only kill cancer cells with limited proliferative potential, while enriched CSCs lead to tumor reconstruction.[39] The presence of CSCs has inspired the design of innovative therapeutic strategies against cancer aimed at eliminating CSCs. Therefore, targeting CSCs is considered a more promising approach to improve therapeutic outcomes, whether it is the development of monoclonal antibodies against surface antigens, self-renewal pathways of CSCs, or the induction of differentiation and modulation of the CSC microenvironment, as possible new therapeutic strategies targeting CSCs.[40,41]

NanoMaterials

Nanomaterials are defined as particles with particle sizes <100 nm or materials with particle sizes of 100 nm to 1000 nm but exhibiting nanoparticle properties. Due to their specificity in spatial dimensions, nanomaterials possess properties that are different from those of macroscopic materials, such as surface effects and small size effects.[42] These properties not only endow nanomaterials with high catalytic activity to enhance the bioavailability of drugs but also endow nanomaterials with good protection and penetration, which can protect drugs from enzymatic degradation and facilitate drug absorption, thus enabling targeted delivery to tumor tissues and improved drug delivery efficiency. Nanomaterials as delivery carriers can increase drug loading, prolong their circulation time, improve their bioavailability and achieve drug enrichment in specific organs or tissues due to their unique physicochemical properties, pharmacokinetic characteristics and modifiable biodistribution.[43–45] In particular, nanomaterials deliver drugs mainly to malignant regions rather than healthy ones, thus minimizing toxic off-target effects and maximizing efficacy.[46] Therefore, nanoMedicine plays an important role in tumor therapy.[47]

The particle size, shape, arrangement, surface charge distribution, and surface chemistry of nanomedicine carriers are the key factors that determine their physicochemical properties and interactions with the biological environment (molecules, cells, tissues, etc.).[48,49] The first generation of nanoMedicines was based on the enhanced permeability and retention (EPR) effect of the tumor vasculature to load traditional small-molecule antitumor drugs with liposomes

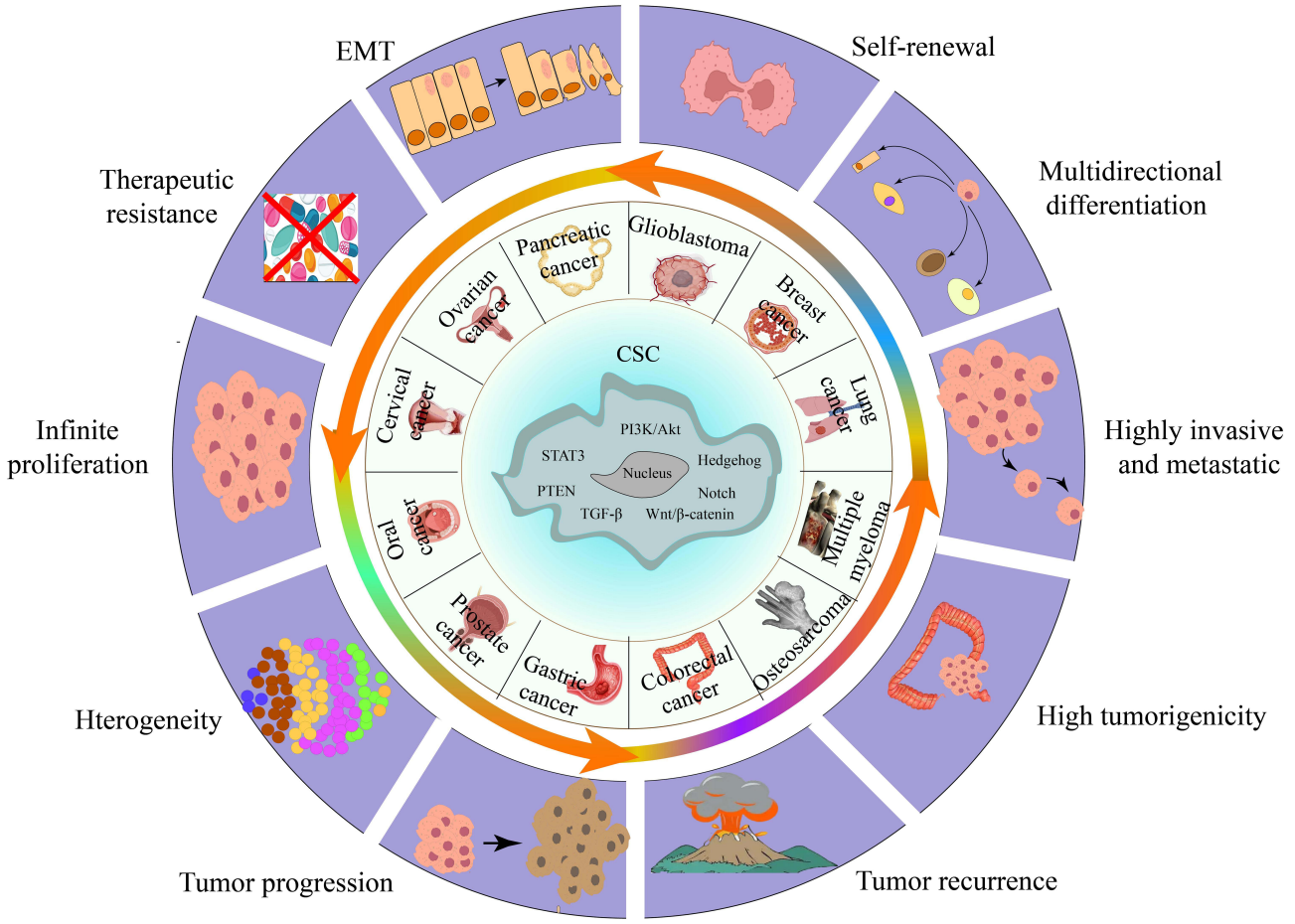

Figure 2 CSC-related malignant tumor behavior. CSCs are cells in tumors that can self-renew and generate heterogeneous tumor cells, such as breast cancer and gastric cancer. The presence of CSCs promotes tumorigenesis, growth, metastasis, EMT, drug resistance, and recurrence.

as carriers to achieve drug enrichment in tumors. Liposomal doxorubicin (Doxil) became the first nanomedicine approved by the Food and Drug Administration(FDA), achieving a breakthrough in the field of nanomedicine applied as tumor therapy.[50] The preparation of subsequent nanomedicines is more diversified in terms of carrier types and drug type selection, with albumin-bound paclitaxel (Abraxane) and paclitaxel polymer micelles (Genexol-PM) being the most representative.[51,52] In recent years, a variety of novel nanocarriers have also become a hotspot in the field of nanomedicines, showing stronger specificity than Traditional carriers.[53,54] The choice of nanocarriers loaded with NP affects the strength of antitumor effects and the potential to target CSCs (Figure 3).

Liposomes

Liposomes are hollow spherical vesicles formed by the self-assembly of amphiphilic molecules containing a lipid bilayer and an internal aqueous core that allow liposomes to carry and target the delivery of hydrophilic and hydrophobic drugs, respectively, and protect the activity of the drug during slow drug release. Liposomes are inherently biocompatible and biodegradable because their main components are phospholipids and cholesterol, naturally present in cell membranes. Ordinary liposomes are rapidly cleared by the liver and spleen, resulting in a short half-life and circulation time in the body. Modification of liposomes with hydrophilic polymers such as polyethylene glycol (PEG) and chitosan can prolong their in vivo circulation time and enhance their tumor enrichment. In addition, liposomes modified with sugar residues, receptor ligands, antibodies, hormones and other ligands can bind specifically to tumor cell target proteins and enter the cells through receptor-mediated endocytosis, accelerating the application of nanomedicine delivery to tumors.[41–44]

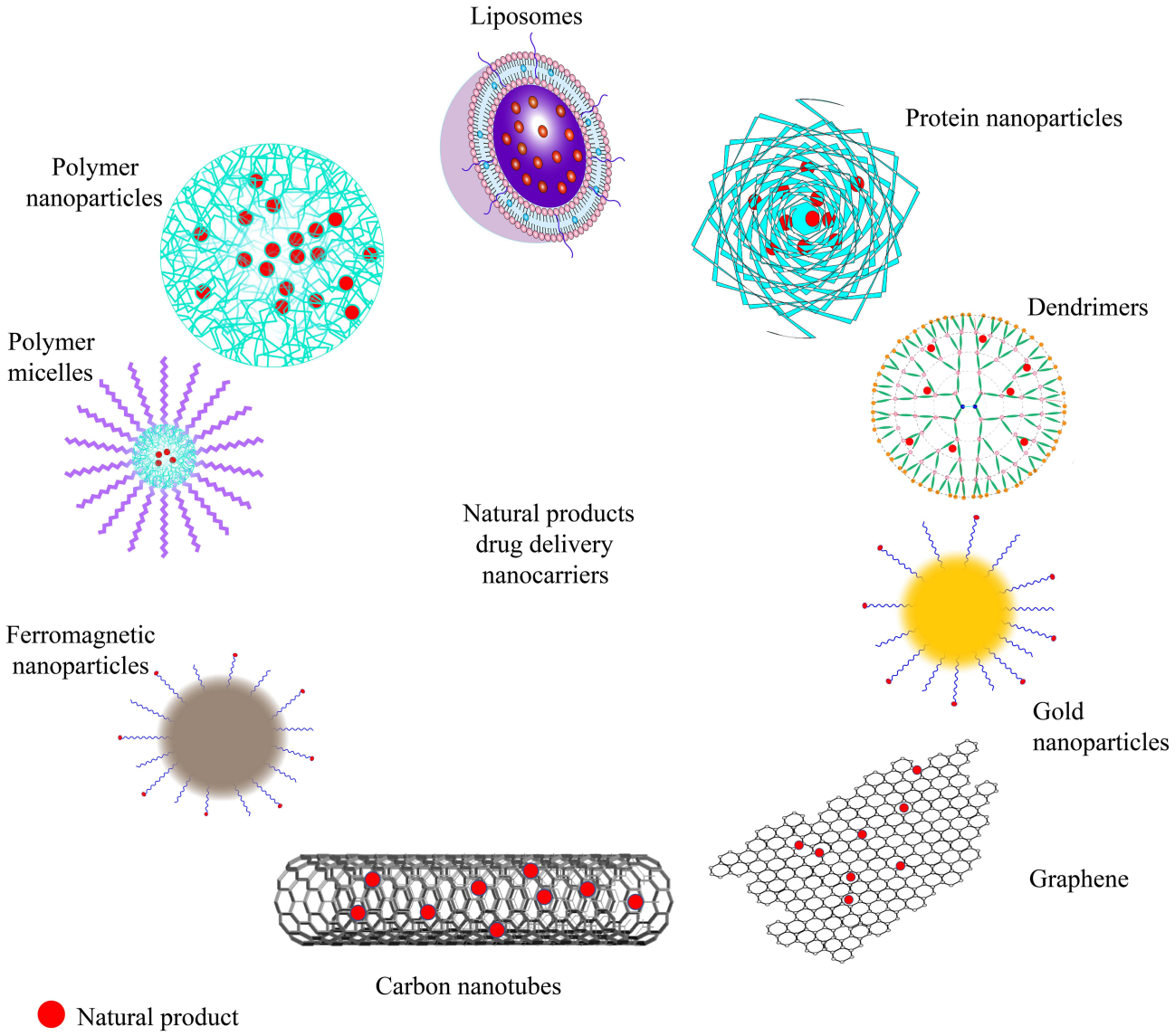

Figure 3 Drug delivery nanocarriers for NP.

Polymeric Nanoparticles

Polymeric nanoparticles are colloidal nanoparticles composed of natural or synthetic polymeric materials, mainly classified as nanocapsules (cavities surrounded by polymeric membranes or shells) or nanospheres (solid matrix systems) according to their morphology and further classified as polymeric vesicles, micelles and dendrimers. The drug can be encapsulated inside the polymer or coupled to the polymer surface, and further modification of ligands on the surface can achieve targeted drug delivery. However, polymeric nanoparticles have the potential risk of increased toxicity and particle aggregation, so polymers with high biocompatibility and degradability, such as poly (lactic acid) (PLA), poly (lactic acid-hydroxyacetic acid) (PLGA), and polycaprolactone (PCL), are being developed.[45–47]

Proteins

Proteins of plant and animal origin or recombinant proteins are attractive nanocarriers that are important in clinical therapy, especially in targeted tumor therapy, because of their good biocompatibility, biodegradability, nontoxicity, high stability and drug delivery.[48] Protein-based drug carriers such as albumin and ferritin are commonly used. Albumin is an ideal carrier for delivering hydrophobic drugs, and paclitaxel albumin nanoconjugated particles (Abraxane) use human

serum albumin as a carrier to rapidly distribute and aggregate in tumor tissues through the natural transport pathway of albumin in the body, which increases the efficacy of chemotherapy and reduces toxicity at the same time.[49,50] Ferritin is the major iron storage protein in the body, and its specific affinity for transferrin receptor 1 (TfR1) allows for drug encapsulation and specific targeting of tumors, especially brain tumors, without additional modifications.[51] However, high temperature, light, strong acid, strong alkali and other factors in the environment can denature and inactivate proteins, and the limitations of proteins as a carrier have limited their further development in clinical applications.[52]

Inorganic Nanoparticles

Inorganic nanoparticles, which have the advantages of simple preparation, a high drug loading rate, good stability, good photothermal and photodynamic effects, and easy surface modification, mainly include carbon nanomaterials (carbon nanotubes, fullerenes, graphene and graphene oxide), gold nanoparticles, ferromagnetic oxide nanoparticles, silica nanoparticles, calcium nanomaterials, etc.[53,54] Typical representatives such as Aurmine (CYT6091), a gold nanoparticle carrying tumor necrosis factor (TNF), carry toxic but highly effective doses of the anticancer agent TNF into tumor tissues to destroy their blood vessels, rather than releasing it into healthy tissues, allowing subsequent chemotherapy to penetrate the tumor and kill the cancer cells inside.[55] However, the low water solubility and high toxicity of inorganic materials are still important issues that cannot be ignored when considering clinical applications, such as oxidative stress and DNA damage induced by iron oxide nanomaterials. In contrast, carbon quantum dots, as emerging carbon-based nanomaterials with good biocompatibility and low cytotoxicity, are widely used in biofluorescence imaging, tumor diagnosis and treatment and may be the most ideal nanomedicine or carrier for the integration of tumor diagnosis and treatment.[56–58]

NPNs Targeting CSCs

Numerous clinical trials have shown that NPNs can improve the antitumor efficacy of NP.[55–58] Nanocarriers enable NP, such as curcumin, paclitaxel, cyclopamine, all-trans retinoic acid, resveratrol, and silibinin (Figure 4), to maintain a stable form before reaching their target organs, and their controllable release of NP to precisely target CSCs significantly improves their therapeutic effect against tumors.

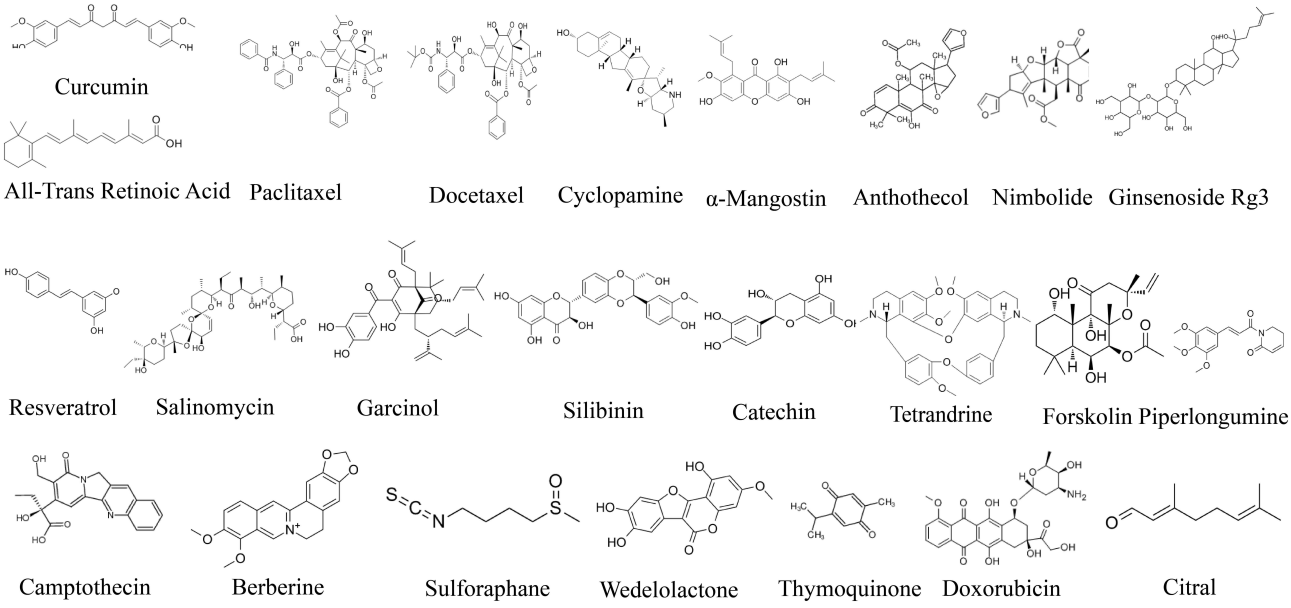

Figure 4 Chemical structure of NPs targeting CSCs.

Curcumin

Curcumin contained in *Curcuma longa* L. is a natural polyphenolic compound. With the increasing amount of research on curcumin, it has been found that curcumin has a wide range of pharmacological activities, such as antitumor, anti-inflammatory, antioxidant, antiviral, and anti-infection activities.[59,60] Curcumin exerts excellent antitumor effects by inhibiting proliferation, inducing apoptosis, and reversing MDR.[61,62] Curcumin can inhibit CSCs in numerous types of cancers, such as glioma and breast, colorectal, pancreatic, brain, and esophageal cancers.[63–66] Even so, its therapeutic potential is limited by its poor bioavailability. Nanotechnology-based drug delivery systems, such as nanoparticles and liposomes, could facilitate curcumin targeting CSCs, thereby improving its bioavailability, cellular uptake, and antitumor activity (Figure 5, Table 1).

Although gemcitabine is the first-line chemotherapy regimen for pancreatic cancer, drug resistance invariably develops, significantly limiting its clinical efficacy.[67] Khan et al prepared a superparamagnetic iron oxide nanoparticle formulation of curcumin (SP-CUR) that could effectively deliver curcumin to pancreatic tumors, target the tumor microenvironment, and improve gemcitabine uptake and efficacy by inhibiting the C-X-C chemokine receptor type 4 (CXCR4)/C-X-C motif chemokine ligand 12 (CXCL-12)/sonic hedgehog signaling pathway. More importantly, the combination therapy of SP-CUR and gemcitabine inhibited CSC growth and self-renewal by regulating pluripotent maintenance stem cell factors and limiting tumor sphere formation.[65] These results indicated that SP-CUR has great potential for the clinical treatment and management of pancreatic cancer.

Glioblastoma is the most common and fatal central nervous system malignancy, originating from glial cells and accounting for one-third of all central nervous system tumors. Glioblastoma is almost impossible to cure, prone to recurrence and has a high lethality rate. Even with surgery plus postoperative chemoradiotherapy, the median survival of patients is only approximately 15 months, and the 5-year survival rate is less than 10%.[68,69] The poor transport of drugs across the blood–brain barrier (BBB) and glioblastoma stem cells play key roles in the occurrence, invasion and recurrence of the disease. Curcumin nanoparticles have been found to inhibit the growth of multiple glioblastoma cell

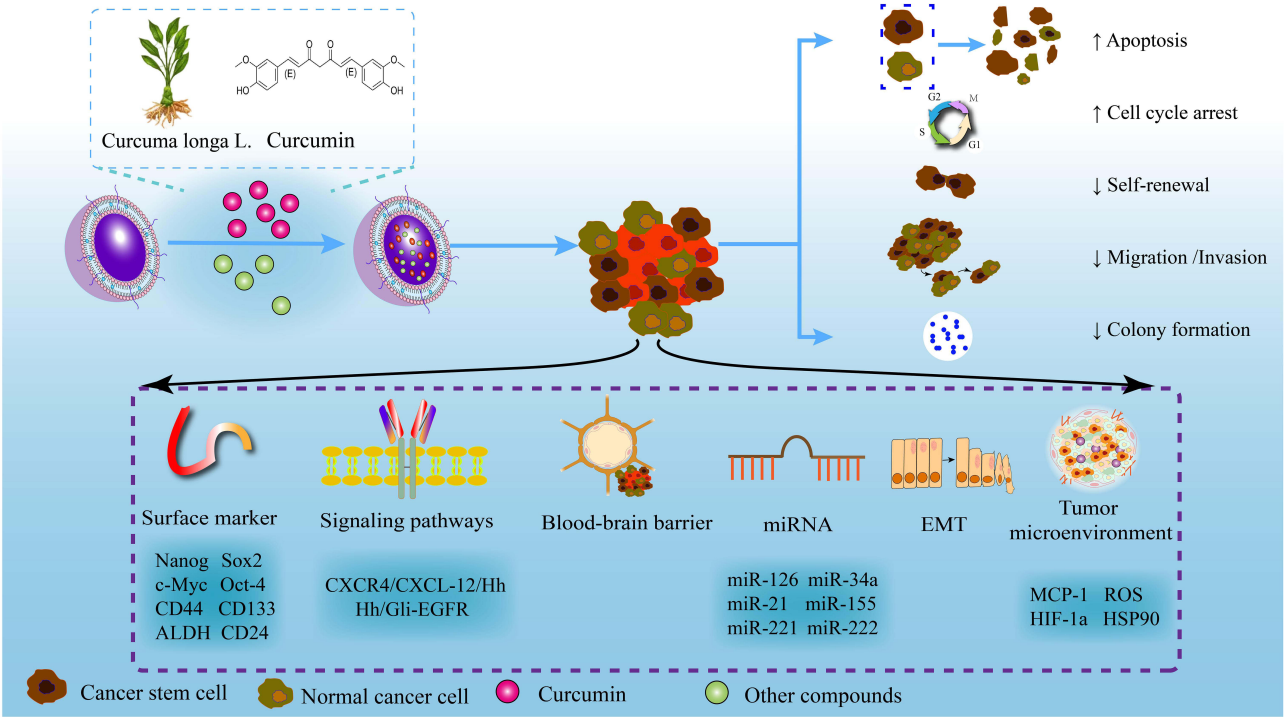

Figure 5 Mechanism of targeting CSCs by curcumin nanoformulations. A nanotechnology-based drug delivery system can improve the bioavailability and antitumor activity of curcumin and promote the targeting of curcumin to CSCs. By regulating surface markers, signaling pathways, the tumor microenvironment, EMT, and other mechanisms of CSCs, curcumin nanoformulations have shown excellent efficacy against pancreatic cancer, breast cancer, colorectal cancer, glioma, and other cancers.

Table 1 Characteristics of NP-Based Nanoformulations with Curcumin

Nanocarrier	Co-Loaded	Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)	Target CSCs	Mechanism	Refs
Superparamagnetic iron oxide nanoparticle	-	120-140	0.244 ± 0.03	-7	-	-	Pancreatic cancer	↓ Tumorsphere formation, self-renewal, C-X-C chemokine receptor type 4/C-X-C motif chemokine ligand 12 /sonic hedgehog signaling pathway ↑ Gemcitabine uptake and efficacy	[65]
Polymeric nanoparticle	-	-	-	-	-	1.5	Glioblastoma	↓ $CD133^+$ stem-like population, STAT3	[70, 71]
Niosome nanoparticle	-	90	0.2 ± 0.002.	-35	80	-	Glioblastoma	↓ Proliferation, viability, migration, invasion and colony forming ↑ Apoptosis and necrosis	[72]
P-aminophenyl-α-D-mannopyranoside-targeting curcumin plus quinacrine liposomes	Quinacrine	119.7 ± 0.17	0.22 ± 0.01	−2.73 ± 0.74	94.32 ± 0.71	-	Glioblastoma	↑ Apoptosis, uptake and endocytic effects ↑ Cross the blood-brain barrier	[73]
Chitosan- PLGA nanoparticles	-	187.50 ± 5.08	-	21.57 ± 3.73	82.67 ± 2.02	2.5	Glioblastoma	↓ Proliferation ↑ Cross the blood-brain barrier	[74]
PH-sensitive core-shell nanoparticle	Doxorubicin	160.8 ± 8.64	-	-30.6 ± 4.98	85.07 ± 2.86	4.46 ± 0.87	Glioma	↓ $CD133^+$ stem-like population	[75]
Hybrid lipid capsules	-	Three different sizes: 27 ± 3/78 ± 5/149 ± 8	0.247 ± 0.016/ 0.271 ± 0.017/ 0.247 ± 0.024	-10 ± 2 /-14 ± 2/-19 ± 1	90	4	Breast Cancer	↓ Mammosphere size/number and stemness	[76]
Sterically stabilized phospholipid nanomicelles	-	11.5 ± 2.0	-	-	86.0 ± 4.8	-	Breast Cancer	↓ Tumorsphere formation ↑ Uptake, water solubility and stability of curcumin	[77]
Folic acid functionalized nanoliposomes	-	83 ± 17	<0.2	-27 ± 2	68 ± 4	3.3 ± 0.3	Breast cancer	↓ Enrichment, growth, proliferation, mammosphere growth and epithelial-mesenchymal transition	[78]
Phosphorylated amphiphilic calixarene micelles	-	3.86 ± 0.32	0.125 ± 0.078	−25.18 ± 5.74	95.40 ± 4.50	17.10 ± 1.25	Triple-negative breast cancer	↓ Tumorsphere formation, proliferation, invasion and migration ↓ $CD44^+$ /$CD133^+$ breast CSCs	[80]
Glucose nanogold particles	-	15	-	-	-	-	Breast cancer	↓ Tumorsphere formation, proliferation, hypoxia-inducible factor 1α and heat shock protein 90 ↑ Apoptosis and reactive oxygen species	[82]
HA-PLGA hybrid NPs	Paclitaxel	347.6	0.12	-26.5	44.6	-	Breast cancer	↓ Mammosphere formation, population and migration of CSCs	[83]
PH multistage responsive micellar	Paclitaxel	79.4 ± 3.4	0.112 ± 0.15	-2.26 ± 3.9	30.9 ± 2.4	37.1 ± 2.9	Breast cancer	↑ Cellular uptake and deep tumor penetration ↓ Formation and growth of mammospheres	[84]

Oligosaccharides of hyaluronan -histidine-menthone 1,2-glycerol ketal	Paclitaxel	120.6	-	-	-	-	Breast cancer	↓ $CD44^+$ breast CSCs	[85]
PH-sensitive polymeric nanoparticles of mPEG-PLGA-PGlu with hybrid core	Doxorubicin	103.4 ± 0.3	-	-11.7 ± 0.1	80.30 ± 1.82	1.91 ± 0.13	Breast cancer	↓ Percentage of CSCs	[86]
Hyaluronic acid conjugatedPLGA-PEG-NH2 co-polymer	Salinomycin	153.4 ± 4.6	-	−32.6 ± 2.5	82	-	Breast cancer	↑ G1 cell cycle arrest ↓ Epithelial-mesenchymal transition	[87]
PLGA nanoparticles	GANT61	347.4 ± 2.75	0.318 ± 0.02	-21.3 ± 0.23	99.97 ± 0.09	28.6 ± 2.05	Breast cancer	↓ Self-renewal ↑ Autophagy and apoptosis	[88]
Stearic acid-g-chitosan oligosaccharide	-	114.7 ± 16.9	0.57 ± 0.02	18.5 ± 0.4	29.9 ± 2.9	-	Colorectal cancer	↓ $CD44^+/CD24^+$ CSCs, tumorsphere formation and proliferation ↑ Uptake of curcumin	[89]
Polymersome nanoparticles	-	259.5 ± 1.5	0.465 ± 0.012	-8.74 ± 0.2	97.18 ± 0.05	16.08 ± 0.07	Colorectal cancer	↓ $CD44^+/CD24^+$ /$CD133^+$ CSCs ↑ Apoptosis and S cell cycle arrest	[90]

Abbreviations: PDI, polydispersity index; ↑, increase or promote; ↓, decrease or inhibit; -, no data available.

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lines by reducing CSCs.[70,71] Negah et al designed a curcumin-loaded niosomal nanoparticle (CM-NP) to target curcumin delivery to CSCs, showing stronger anti-CSC ability than free curcumin. CM-NP have good physicochemical stability and effectively target and inhibit the survival, proliferation, migration, invasion and colony formation of CSCs by regulating cell cycle arrest, apoptosis, reactive oxygen species (ROS) generation, and monocyte chemoattractant protein-1.[72] An ability to penetrate the BBB is an essential characteristic of the anti-glioblastoma efficacy of NPNs. Wang et al designed liposomes coloaded with curcumin and quinacrine modified by mannose, which contributed to curcumin and quinacrine crossing the BBB and significantly enhanced the curcumin uptake effect, endocytosis effect and induction of apoptosis in glioblastoma cells and CSCs.[73] Sialic acid can improve the hydrophilicity of curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles and inhibit the proliferation of CSCs by allowing it to cross the BBB.[74] In addition, curcumin combined with chemotherapy drugs is also an effective method for the treatment of GBM. Xu et al developed a pH-sensitive core-shell nanoparticle for the proportional delivery of curcumin/doxorubicin to target both CD133+ CSCs and differentiated cancer cells, showing a synergistic therapeutic effect between curcumin and doxorubicin.[75] These data suggest that nanocarriers can efficiently deliver curcumin across the BBB to inhibit glioblastoma CSCs, thereby improving the clinical efficacy of glioblastoma treatment.

Breast cancer is the leading cancer affecting women in terms of both incidence and mortality, and chemotherapy resistance and disease recurrence associated with breast CSCs remain serious challenges.[2] Yadava et al developed curcumin-loaded nanostructure hybrid lipid capsules (CMN-nHLCs) to optimize their physicochemical properties and anticancer efficacy for the co-elimination of CSCs and cancer cells. CMN-nHLCs effectively prevented the enrichment, growth, and proliferation of CSCs by downregulating the expression of ALDH-1 and led to the disintegration or size/number reduction of mammospheres with an anticancer activity 2.5 times higher than that of free curcumin.[76] Gülçür et al found that the vasoactive intestinal peptide (VIP) receptor is an attractive molecular target overexpressed in breast CSCs, and VIP-modified curcumin sterically stabilized phospholipid nanomicelles (C-SSM-VIP) were designed to enhance cell-selective and intracellular drug uptake, actively targeting VIP receptors to inhibit CSCs.[77] Similarly, folate receptor (FR)-targeted nanoliposomes promoted curcumin internalization into FR-positive CSCs, thereby preventing CSC enrichment, growth, proliferation, spheroid formation, and epithelial-mesenchymal transition.[78]

Triple-negative breast cancer (TNBC) is a heterogeneous and difficult-to-treat type of breast cancer for which there are currently no effective targeted therapies.[79] Phosphorylated calixarene POCA4C6 is not only an excellent carrier for the delivery of curcumin, but itself has good anticancer activity. Studies have shown that curcumin-loaded POCA4C6 micelles (CPMs) can induce cell cycle arrest and apoptosis and decrease β-catenin nuclear activity and androgen receptor levels. More importantly, these NPNs can significantly destroy the formation of CD44+/CD133+ breast CSCs and tumor spheroids without causing obvious systemic toxicity,[80] which provides new hope for the targeted therapy of TNBC.

It was also found that gold nanoparticles showed good radiosensitizing ability.[81] Yang et al prepared curcumin combined with glucose gold nanoparticles (Glu-GNPs), which showed great potential in alleviating the hypoxic tumor microenvironment and improving the radiosensitivity of breast CSCs by inhibiting the expression of hypoxia-inducible factor 1α (HIF-1α) and heat shock protein 90 (HSP90) and increasing the level of ROS.[82] Surprisingly, the nanoformulations prepared by combining curcumin with chemotherapeutic drugs such as paclitaxel,[83–85] doxorubicin,[86] salinomycin,[87] and the Hh/Gli-EGFR signaling pathway inhibitor GANT61[88] also showed superior tumor suppressive activity and CSC killing ability, which provides a potential strategy for drugs combined with targeted therapy to improve the treatment of breast cancer.

Colorectal cancer is the third most common type of gastrointestinal cancer in the world and the second leading cause of cancer-related mortality. Targeting the inhibition of the malignant biological behavior of CSCs is an important strategy for colorectal cancer treatment.[2] Wang et al prepared curcumin encapsulated in stearic acid-g-chitosan oligosaccharide polymeric micelles to increase the accumulation of curcumin in cancer cells through endocytosis, and the NPNs not only reduced the tumor volume but also inhibited the expression of the colorectal CSC marker CD44+/CD24+.[89] Pakizehkar et al encapsulated curcumin with polyribosomal nanoparticles, which significantly inhibited the proliferation of CSCs and induced apoptosis by modulating colorectal CSC surface markers (CD133, CD24, and CD44), miRNAs (miR-126, miR-34a, miR-21, miR-155, miR-221, and miR-222) and the expression of apoptosis targets such as P53, CASP9, CASP8,

CASP3, BAX and BCl-2.[90] This suggests that nanocarrier-loaded curcumin can eliminate CSCs as well as bulk cancer cells, which has significant advantages in cancer therapy.

Paclitaxel

Paclitaxel (PTX) is a natural secondary metabolite isolated and purified from the bark of *Taxus chinensis*.[91] PTX has been proven to have good antitumor effects, especially on ovarian cancer, uterine cancer, and breast cancer. The anticancer mechanism of PTX is mainly to inhibit the depolymerization of tubulin and promote its polymerization, inhibit cell division and proliferation, and eventually lead to tumor cell apoptosis. Although PTX can eliminate most tumor cells and reduce the size of tumors, it also enriches the CSC population, leading to acquired drug resistance, recurrence, metastasis, and progression.[92,93] Therefore, reducing tumor cells while targeting CSCs is a key strategy to improve the anticancer efficiency of PTX (Figure 6, Table 2).

PTX Nanoformulations

Researchers have found that the presence of vasculogenic mimicry (VM) and CSCs inevitably leads to the malignant progression of gliomas. VM transports nutrients and blood to the extravascular areas of tumors, while CSCs are associated with drug resistance and glioma recurrence. Therefore, the key to glioma treatment is to inhibit VM and CSCs.[94] Liu et al prepared multifunctional tandem peptide R8-c (RGD)-modified PTX liposomes for targeted inhibition of VM and CSCs. RGD specifically promotes the contact of CSCs with liposomes, thereby increasing the uptake of liposomes by CSCs. Both in vitro and in vivo experiments demonstrated that PTX-loaded liposomes effectively inhibited the proliferation and induced apoptosis of CSCs and induced the destruction of VM channels, thereby cutting off the nutrient transport channels and preventing glioma recurrence.[95] ElNaga et al prepared PTX-loaded PLGA nanoparticles to target ovarian CSCs by recognizing FR. In vitro experiments showed that the inhibition efficiency of the NPNs on ovarian CSCs was much higher than that of free PTX. A xenograft model was established by subcutaneous injection of CSCs in the backs of nude mice, and PLGA nanoparticles enhanced the targeted antitumor ability of PTX

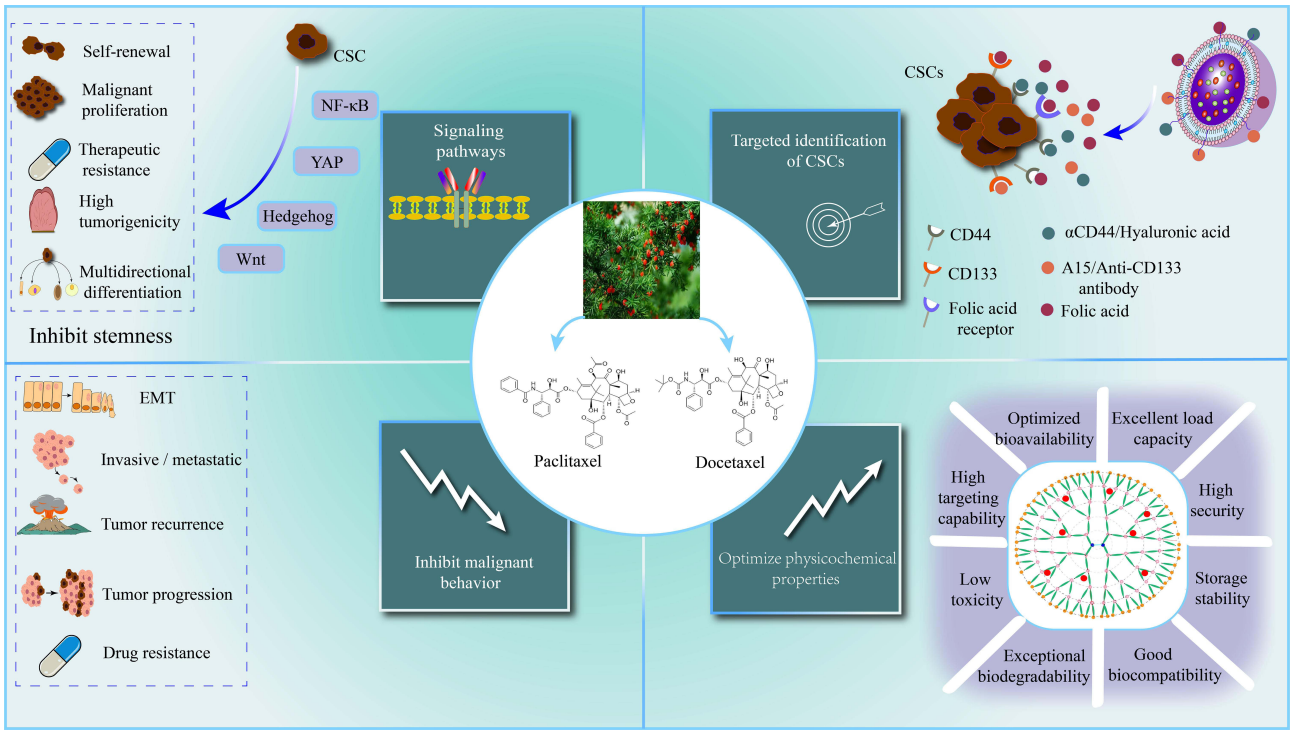

Figure 6 Mechanism and advantages of paclitaxel and docetaxel nanoformulations. Nanoformulations of paclitaxel and docetaxel significantly improved their physicochemical properties. By modulating key signaling pathways, surface markers and other mechanisms of CSCs, nanoformulations of paclitaxel and docetaxel significantly inhibited cancer migration, invasion, progression, recurrence, and drug resistance.

Table 2 Characteristics of NP-based nanoformulations with paclitaxel or docetaxel

Natural Products	Nanomaterials	Co-loaded	Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)	Target CSCs	Mechanism	Refs
Paclitaxel	Multifunctional tandem peptide modified Liposomes	-	100.8 ± 1.5	0.201 ± 0.018	−7.36 ± 0.32	92.37 ± 4.91	-	Glioma	↓ Proliferation ↑ Apoptosis and destruction of VM channels	[95]
	PLGA nanoparticles, conjugated with folic acid	-	294.7	-	-	73	1.46	Ovarian cancer	↓ ATP-binding cassette sub-family G-2 (ABCG2) and multidrug resistance-1 (MDR1) ↑ Caspase-3 and p53	[96]
	Anti-CD44-Conjugated Olive Oil Liquid Nanocapsules	-	110 ± 20	0.25 ± 0.01	-35	81.1	2.2	Pancreatic Cancer	↓ CD44 ↑ Uptake of paclitaxel	[98]
	CD133-targeted nanoparticles	-	318.6	0.228	-8.3	91	11.9 ± 0.6	Breast cancer	↓ Formation of tumor spheres, CD133	[99]
	Albumin nanoparticle	-	-	-	-	-	-	Triple-negative breast cancer	↑ Uptake of CSCs	[101]
	Lipid nanocapsules	Salinomycin	89 ± 3	0.08 ± 0.002	-6 ± 1	98	0.202	Breast cancer	↓ Formation of tumor spheres, CD44 ↑ Apoptosis	[104]
	PLGA nanoparticles	Salinomycin	116.71 ± 4.31	0.257 ± 0.08	68.2 ± 2.2	59.7 ± 5.7	5	Breast cancer	↑ Cellular uptake ↓ Population of $CD44^+$ cells	[105]
	Liquid crystal nanoparticles	Forskolin	90	-	-15.3	60-90	-	Breast cancer	↑ Epithelial-mesenchymal transition ↓ Wnt/β-catenin pathway, stemness	[107]
	Lipid-polymer hybrid nanoparticles	Verteporfin	80-100	-	-3	67	0.56	Triple-negative breast cancer	↓ NF-κB, Wnt, and YAP signaling pathways ↓ $CD44^+/CD24^-$ and $ALDH^+$ CSCs	[111]
	Dual-modified cationic liposomes	Survivin-siRNA	118.7 ± 6.3	0.134 ± 0.082	11.5 ± 0.6	98.2 ± 0.6	2.7 ± 0.4	Glioma	↑ Apoptosis and differentiation of CSCs	[113]

Docetaxel	Gelatinase-stimuli nanoparticles	Salinomycin	214.5 ± 2.6	0.186 ± 0.013	-	10.26 ± 3.9	61.57 ± 3.9	Cervical cancer	↓ CD133/CD44 ↓ Epithelial-mesenchymal transition, tumorigenicity and tumor growth rate	[117]
	Polylactide-co-glycolide/D-alpha-tocopherol polyethylene glycol 1000 succinate	Salinomycin	73.83 ± 3.59	0.193 ± 0.021	−25.7 ± 2.03	53.28 ± 8.96	4.08 ± 0.86	Breast cancer	↑ The circulation time ↓ Mammospheres	[118]
	Hyaluronan modified mesoporous silica nanoparticles -supported lipid bilayers	8-Hydroxyquinoline	189.9 ± 3.428	0.092 ± 0.015	-54.2 ± 0.372	8.23 ± 0.91	8.51 ± 0.15	Breast cancer	↓ CD44 ↑ Uptake	[121]
	HA-modified polymeric nanoparticles	Photosensitizer mesotetraphenyl chlorine disulfonate	205 ± 3	0.2	−37.2 ± 3	96 ± 4	4.8	Breast cancer	↓ Self-renewal capacity, CD44	[122]
	Liposomes	Telmisartan	133.2 ± 11.7	0.207 ± 0.0113	-	96.4 ± 2.45	-	Lung cancer	↑ Apoptosis and reactive oxygen species ↓ CD44, SOX2, ABCC1 and ABCG2	[126]

Notes: PDI, polydispersity index;↑, increase or promote;↓, decrease or inhibit; -, no data available.

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and minimized systemic toxicity. Surprisingly, the tumors in the xenograft mice completely disappeared after injection of PTX-loaded folic acid (FA)/PLGA nanoparticles, the possible mechanism being the appearance of reactive lymphoid follicles, high expression of caspase-3 and P53 promoting apoptosis and suppression of the expression of chemoresistant genes.[96]

Lipid liquids are also excellent nanocarriers for drug delivery.[97] Marchal et al developed olive oil liquid nanocapsules (O2LNCs), which covalently linked specific immuno-γ-globulin to the surface of O2LNCs, thereby preparing a new immunonanoformulation. Its internal hydrophobic domain was used to encapsulate PTX, and the outer shell was covalently conjugated with an anti-CD44-fluorescein isothiocyanate antibody (αCD44) to specifically deliver PTX to CD44-overexpressing pancreatic CSCs. Both in vitro and in vivo experiments showed that pancreatic CSCs with high uptake of PTX-loaded αCD44-O2LNCs were four times more effective than free PTX against cancer.[98] This immuno-nanoformulation innovatively optimizes the ability of conventional nanomaterials to target CSCs with IgG, providing a new idea for the advancement of nanodrug delivery systems. Similarly, Swaminathan et al combined an anti-CD133 monoclonal antibody with nanoparticles formulated with poly (D, L-lactide-co-glycolide) polymers to load PTX to achieve targeted killing of breast CD133+ CSCs.[99]

Abraxane, an albumin nanoparticle of PTX, has been approved by the FDA as a first-line treatment for metastatic breast cancer, advanced non-small cell lung cancer, and advanced pancreatic cancer.[100] In patients with metastatic breast cancer, Abraxane was significantly more effective than free PTX. Yuan et al found that the plasma concentration of Abraxane was much lower than that of paclitaxel, but the tumor/plasma drug concentration ratio of Abraxane was 10 times higher, explaining its targeting and high efficacy. PTX enriches CSCs in residual tumors while eliminating breast cancer cells. In contrast, Abraxane increased drug uptake by CSCs 3- to 15-fold and dramatically improved its anticancer activity by eliminating CSCs,[101] suggesting that NPNs can optimize the efficacy of existing chemotherapy drugs and reverse drug resistance and cancer recurrence.

Nanocarriers Coloaded with PTX and Other Molecules

Many small-molecule compounds (such as salinomycin and doxorubicin) and plant-derived compounds (such as curcumin, piperine, epigallocatechin gallate, and sulforaphane) have been shown to be effective in eliminating CSCs.[102] Therefore, the establishment of nanoformulations coloaded with PTX and other natural anti-CSC compounds, may ameliorate their respective limitations, reduce their side effects, and enhance their anticancer efficacy due to their different modes of action.

Among the various anti-CSC natural compounds screened, salinomycin isolated from *Streptomyces albicans* has proven to be a perfect candidate for killing CSCs.[103] Basu et al developed lipid nanocapsules (LNCs) coloaded with PTX and salinomycin, which showed superior drug loading capacity and storage stability. Its lipid properties facilitate efficient cellular uptake, delivering drugs to breast cancer cells and CSCs simultaneously. The intervention of free PTX led to an increase in the number of CSCs (increased expression of $CD44^{+}/CD24^{-}$ and ALDH), while the presence of salinomycin reduced the stemness of CSCs. The combined application of these two natural compounds significantly induced CSC apoptosis and tumor mammosphere growth, showing superior cytotoxicity and anti-CSC properties.[104] Hyaluronan was coated on the surface of polymeric nanoparticles coloaded with PTX and salinomycin, which actively targeted CD44 receptors overexpressed on CSCs and eradicated tumors by killing the cancer cells and CSCs.[105] This suggests that combination therapy with conventional chemotherapeutic agents and CSC inhibitors may be a promising approach to overcome cancer recurrence caused by drug-resistant cell populations.

Forskolin, a diterpene extracted from the roots of *Coleus forskohlii*, induces the differentiation of CSCs through cAMP signaling, causing them to lose their mesenchymal state and acquire a nonstem cell-like epithelial state.[106,107] Singh et al prepared liquid crystal nanoparticles coloaded with forskolin and PTX, and they could target both differentiated CSCs and bulk tumor cells, resulting in overall tumor targeting, thus significantly improving the therapeutic efficacy.[107] Conventional PTX therapy has been shown to upregulate the NF-κB, YAP, and Wnt signaling pathways, while inhibition of these signaling pathways by the photosensitizer verteporfin may abolish the PTX-induced enrichment of CSCs.[108–110] Sulaiman et al developed coloaded PTX and verteporfin hybrid nanoparticles (PV-NPs) targeting TNBC patient-derived xenografts and

CSCs. PV-NPs accumulated in tumors, coinhibited the NF-κB, Wnt, and YAP signaling pathways, and exhibited synergistic effects in inhibiting tumor growth and $CD44^+/CD24^-$ and $ALDH^+$ CSC populations.[111]

Survivin, an important protein involved in the regulation of apoptosis, is strongly expressed in glioma tissues (especially CSCs) and is an ideal molecular target for glioma therapy. The combination of PTX with survivin-siRNA represents a potentially useful chemotherapeutic gene therapy strategy.[112] Sun et al designed dual-modified cationic liposomes (DP-CLPs) linking two receptor-specific ligands, angiopep-2 and A15. DP-CLPs durably and stably bound glioma cells and brain microvascular endothelial cells and delivered drugs (survivin-siRNA/PTX) to $CD133^+$ glioma CSCs. In vivo experiments showed that DP-CLPs significantly inhibited tumorigenesis and improved survival of tumor-bearing nude mice by inducing apoptosis of $CD133^+$ CSCs without therapeutic toxicity.[113] This suggests that dual-targeting ligands targeting CD133 can be used to develop safe and efficient nanoformulations.

Docetaxel

By enhancing tubulin polymerization and inhibiting microtubule depolymerization, docetaxel leads to the formation of stable nonfunctional microtubule bundles and destroys the process of mitosis in tumor cells.[114] Docetaxel is one of the first-line chemotherapeutic drugs for the treatment of recurrent or metastatic cervical cancer. However, it leads to the enrichment of CSCs and the decreased expression of E-cadherin associated with EMT, resulting in treatment failure.[115] The preparation of docetaxel nanoparticles targeting CSCs could address the above problems (Figure 6, Table 2).

Salinomycin is one of the key NP that could be used to change this situation. Wang et al synthesized salinomycin nanoparticles, showing their advantages of specific aggregation in tumors, anti-CSCs and low toxicity.[116] Then, salinomycin-docetaxel-loaded gelatinase-stimuli nanoparticles (Sal-Doc-SE-NP) were designed. Sal-Doc-SE-NP improves the therapeutic efficacy while minimizing side effects and recurrence, not only enhancing the antitumor effect of docetaxel but also significantly inhibiting CSCs and non-CSCs in cervical cancer xenograft mice by suppressing EMT and CD133/CD44 expression.[117] The nanoparticles codelivered salinomycin and docetaxel to tumor tissues to inhibit breast cancer cells and CSCs with better tumor targeting and antitumor activity.[118]

8-Hydroxyquinoline (8-HQ), an organic compound with preferential activity against CSCs, showed promising anticancer activity in combination with docetaxel.[119,120] Wang et al combined 8-HQ-loaded HA-modified mesoporous silica nanoparticles-supported lipid bilayer (HA-MSS) and docetaxel-loaded MSS. In vivo and in vitro experiments demonstrated that docetaxel-loaded MSS was more cytotoxic to MCF-7 cells, whereas 8-HQ-loaded HA-MSS was more cytotoxic to CSCs. Therefore, the combined treatment with the two nanoformulations killed both breast cancer cells and CSCs, showing the best antitumor activity.[121] Combining chemotherapy and photodynamic therapy, Gaio et al made HA-modified polymeric nanoparticles to simultaneously deliver docetaxel and the photosensitizer mesotetraphenyl chlorine disulfonate, showing excellent ability to target and kill CD44+ breast CSCs.[122]

Telmisartan, as an antifibrotic agent, was found to disrupt the tumor interstitial barrier and promote the distribution of docetaxel nanoparticles within lung cancer tissues and to penetrate CSCs to enhance the anticancer effect.[123–125] Pretreatment with telmisartan significantly increased the uptake of docetaxel liposomes by lung CSCs and enhanced the anticancer effect by improving the hypoxic conditions of the tumor microenvironment, inducing ROS generation and apoptosis, and downregulating drug resistance genes and marker expression of CSCs.[126]

Cyclopamine

Cyclopamine (CYP), a steroidal alkaloid extracted from *veratrum*, can inhibit the proliferation, invasion and metastasis of cancer cells by suppressing the hedgehog signaling pathway. The hedgehog signaling pathway is closely related to the self-renewal and maintenance of stem cells, so the targeted inhibition of the pathway by cyclopamine can eliminate CSCs, and its nanoformulation can improve its high hydrophobicity, systemic toxicity and poor pharmacokinetics to expand its clinical applications[127–129] (Table 3).

Hu et al synthesized HA-cystamine-polylactic-co-glycolic acid (HA-SS-PLGA) dual drug-loaded particles loaded with cyclopamine and the chemotherapeutic drug doxorubicin. The dual drug-loaded particles with hyaluronic acid targeting showed redox-responsive drug release characteristics, releasing cyclopamine and doxorubicin on demand,

Table 3 Characteristics of NP-Based Nanoformulations with Cyclopamine or All-Trans Retinoic Acid

Natural Products	Nanomaterials	Co-Loaded	Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)	Target CSCs	Mechanism	Refs
Cyclopamine	Hyaluronic acid functional amphipathic and redox-responsive polymer particles	Doxorubicin	245.3	0.11	-	58.2/70.6	-	Breast cancer	↓ The number and size of tumor spheres	[130]
	N-(2-hydroxypropyl) methacrylamide copolymer	-	-	-	-	-	-	Prostate cancer	↓ CD133	[131]
	N-(2-hydroxypropyl) methacrylamide copolymer-cyclopamine/ docetaxel conjugate	-	-	-	-	-	6.6/7.2	Prostate cancer	↑ Apoptosis ↓ $CD133^{+}$CSCs	[132]
	mPEG-b-PCC-g-PTX/CYP-g-DC	Paclitaxel	76.37 ± 0.15	0.273	-	14.50 ± 1.60	5.36 ± 0.07	Prostate cancer	↓ Hedgehog signaling and colony formation ↑ Tumor suppressor miRNA expression	[133]
All-trans retinoic acid	Nanoparticles	Doxorubicin	151.6	-	1.8	40.01	3.05	Breast cancer	↑ Differentiation of CSCs	[137]
	Albumin nanoparticles	-	180.63 ± 0.38	0.180 ± 0.007	32.1 ± 0.42	93	8.37	Lung cancer	↑ Uptake of ATRA, apoptosis ↓ Cell growth	[138]
	Lipid-polymer nanoparticles	-	125.2 ± 9.9	0.18 ± 0.08	-16.3 ± 7.2	86.4 ± 5.6	10.5 ± 4.5	Osteosarcoma	↓ $CD44^{+}$ CSCs	[139]
	Nanoparticles	-	106.7 ± 8.7	0.17 ± 0.18	-11.5 ± 5.3	84.5 ± 6.9	8.4 ± 3.4	Gastric cancer	↓ $CD44^{+}$ and $CD133^{+}$ gastric CSCs	[140]
	FA-modified chitosan (CSO)-derived polymer micelles	Doxorubicin	73.34	0.209	25.4	-	-	Breast cancer	↑ Apoptosis ↓ Stemness and metastasis	[142]
	Stealth liposomes	-	81.1 ± 0.8 nm	0.18 ± 0.01	-6.1± 1.4	>90	9.3 ± 0.1	Breast cancer	↑ Differentiation and cell cycle arrest ↓ Proliferation	[143]
	Electrospun polycaprolactone nanofibers	-	929	-	-	86.2	12.17	Glioblastoma	↑ Differentiation ↑ Effect of photothermal therapy	[144]
	Gold nanostars-dendritic polyglycerol	-	68.1	-	13.9	-	54.5	Breast cancer	↓ Stemness gene expression, tumor sphere formation, self-renewal and tumor growth	[145]

Notes: PDI, polydispersity index;↑, increase or promote;↓, decrease or inhibit; -, no data available.

targeting CD44-overexpressing breast CSCs and breast cancer cells, significantly reducing the number and size of tumor spheres, and almost completely inhibiting tumor growth, showing an excellent synergistic antitumor effect.[130]

The selective inhibitory effect of N-(2-hydroxypropyl)methacrylamide(HPMA) copolymer cyclopamine conjugate (P-CYP) on prostate CSCs was stronger than its effect on ordinary tumor cells, and the proportion of $CD133^+$ cells among the surviving cancer cells was significantly reduced by attenuating CD133 expression and CSCs activity.[131] Zhou's team then engineered an HPMA copolymer docetaxel conjugate (P-DTX) to kill bulk tumor cells, but not CSCs. P-DTX and P-CYP together showed superior synergistic effects against prostate tumors.[132] Likewise, the combined use of cyclopamine and PTX polymer-drug conjugates alleviated PTX resistance and inhibited prostate cancer colony formation by inhibiting Hh signaling and upregulating tumor suppressor miRNA expression.[133] This suggests that the use of two or more drugs with independent mechanisms of action on cancer cells can achieve synergistic therapeutic effects.

All-Trans Retinoic Acid

All-trans retinoic acid (ATRA) is the major natural metabolite of vitamin A. As a low toxicity cell differentiation agent, the anticancer efficacy of ATRA has been extensively studied in various malignancies. By activating retinoic acid receptors and retinoid X receptors to regulate gene transcription, induce stem cell differentiation and regulate stem cell maintenance-related signaling pathways, ATRA has shown excellent ability to target CSCs.[134–136] However, due to the low solubility and stability of ATRA, it is rapidly cleared, resulting in a rapid decrease in the concentration of ATRA in plasma and serious dose-dependent side effects. ATRA encapsulated in nanoparticles is expected to protect it from degradation, and targeting ATRA to CSCs may stimulate CSCs to shift to a more differentiated state, resulting in a better response to chemotherapy[137] (Table 3).

Li et al developed an HA-functionalized cationic albumin-based targeted nanoparticle-delivered ATRA to target CD44-overexpressing CSCs. Due to the HA modification, $CD44^+$ CSCs promoted the uptake of ATRA and exhibited a strong inhibitory effect on cell growth and induction of apoptosis. In vivo imaging revealed that drug-loaded nanoparticles inhibited the tumorigenicity of CSCs, showed targeted accumulation in mouse tumor-bearing lungs and significantly inhibited tumor growth.[138] Similarly, the use of an anti-CD133 antibody can increase the efficient and specific delivery of ATRA-loaded lipid-polymer nanoparticles to osteosarcoma stem cells for higher therapeutic efficacy.[139] However, cancers often have multiple CSCs populations with different phenotypes, suggesting that targeting just one CSCs population is not enough to eliminate CSCs completely, and therefore targeting multiple CSCs sub-populations simultaneously would yield better outcomes. Chen et al prepared ATRA-loaded poly(lactide-co-glycolide)-lecithin-PEG nanoparticles (ATRA-PLPN), and combined anti-CD44 and anti-CD133 antibodies with the nanoparticles to transport ATRA specifically to $CD44^+$ and $CD133^+$ gastric CSCs, thereby enhancing the growth inhibition of gastric CSCs. In contrast, ATRA-PLPN cannot target any CSCs population due to a lack of anti-CD44 or anti-CD133 antibodies.[140] It can be expected that better efficacy will be achieved by simultaneously targeting more phenotypic populations of CSCs.

The chemotherapeutic drug doxorubicin has been used to treat a variety of cancers, but CSCs in many solid tumors are resistant to it, which may also further enrich CSCs after treatment, leading to chemoresistance, tumor recurrence, and metastasis.[141] Sun et al prepared nanoparticles simultaneously encapsulating ATRA and doxorubicin, which effectively increased the drug's enrichment in tumor tissues and CSCs and reduced CSCs in breast tumors in a synergistic manner. ATRA and doxorubicin were simultaneously delivered to the CSCs. ATRA induced differentiation of the CSCs, thereby attenuating their tumor-initiating ability and subsequently enhancing the cytotoxicity of doxorubicin, without triggering CSCs enrichment after treatment. At the same time, in vivo experiments also confirmed the significant synergistic inhibitory effect of the combined administration of ATRA and doxorubicin on tumor growth.[137] Liu et al developed an FA-modified chitosan (CSO)-derived polymer (FA-CSOSA). FA modification can promote the uptake of nanoparticles by cancer cells through FA receptor-mediated cellular internalization, and thus they synthesized ATRA and doxorubicin-loaded micelles (FA-CSOSA-DOX/ATRA). Simultaneous use of these two micelles induces cancer cell apoptosis and inhibits the breast cancer stemness and metastasis induced by doxorubicin treatment.[142] Li et al encapsulated ATRA in pegylated liposomes (stealth liposomes) through the EPR effect, resulting in better accumulation in tumors and

significant inhibition of tumor formation and growth. Compared with regular cancer cells, breast CSCs are more sensitive to ATRA stealth liposomes and they prevent rapid proliferation of CSCs in the mitotic stage by inducing CSCs differentiation and cell cycle arrest in G0/G1 phase. At the same time, the combination of ATRA stealth liposomes and low-concentration vinorelbine stealth liposomes showed a stronger ability to kill CSCs, providing a new strategy for the treatment and prevention of the recurrence of breast cancer.[143]

In addition, a combination of ATRA and heat therapy is also an effective strategy for the removal of CSCs. The combination of hydroxylated multiwalled carbon nanotubes (MWCNTs-OH) and ATRA in an electrospun polycaprolactone (PCL) nanofiber system can disrupt the stemness of CSCs and reduce their tolerance to heat therapy to improve its effectiveness. Both in vivo and in vitro experiments showed that after ATRA induced CSCs differentiation, multiwalled carbon nanotubes generated heat under near-infrared, significantly inhibited the activity of glioma stem cells, and killed more CSCs.[144] Similarly, Pan et al developed a gold nanostars-dendritic polyglycerol nanoplatform loaded with retinoic acid (RA) to specifically and multivalently target breast CSCs. RA induces CSCs differentiation, combined with photothermal therapy in a synergistic inhibitory manner to inhibit stemness gene expression, CSCs-driven tumor sphere formation, CSCs self-renewal, and tumor growth.[145] This points the way to improving the efficacy of existing cancer treatments, including photothermal therapy, to specifically eliminate CSCs.

Flavonoids

Flavonoids are widely found in natural plants and are produced by the secondary metabolism of natural polyphenolic compounds. Studies have shown that dietary intake of rich flavonoids will reduce the risk of colon cancer, prostate cancer, breast cancer and other cancers, and play an effective role in inhibiting the growth and spread of tumor cells at multiple stages.[146–148] The current main research direction is focused on the structural modification and optimization of natural flavonoids, and targeting cancer cells and CSCs through drug delivery systems may achieve more clinically meaningful effects (Table 4).

α-Mangostin is a bioactive flavonoid in *Garcinia mangostana*, and it has been proven to have good antitumor properties.[149] α-Mangostin-coated PLGA nanoparticles (Mang-NPs) were readily taken up by CSCs and cancer cells to inhibit cell viability, proliferation, colony formation, EMT, and induce apoptosis without affecting normal epithelial cells. More importantly, by inhibiting the expression of Notch, sonic hedgehog pathways and their downstream targets, stem cell markers (CD24, CD133, CD44, Musashi and Lgr5) and pluripotent maintenance factors (Oct4, Sox-2, Klf-4, c-myc and Nanog), Mang-NPs significantly inhibited the self-renewal ability of CSCs, suggesting the great potential of nanotechnology targeting CSCs signaling pathways in blocking cancer progression, metastasis, drug resistance and recurrence.[150,151] Likewise, garcinol is a polyisoprenylated benzophenone derivative that is highly abundant in the genus *Garcinia*. Hyaluronic acid-modified PLGA nanoparticles loaded with garcinol reduced its toxicity to normal tissues and improved drug accumulation in tumors. By downregulating hypoxia-inducible factors (HIF-1α and HIF-2α) and the Notch pathway to induce apoptosis and inhibit CSCs proliferation, garcinol nanoformulations were able to inhibit CD44+ breast CSCs growing in a hypoxic microenvironment.[152]

Silibinin is a flavonoid compound isolated from the fruit and seeds of *milk thistle* (*Silybum marianum* L. Gaertn), and it has been widely used in clinical practice as a hepatoprotective drug.[153] In recent years, the anticancer and tumor preventive effects exhibited by silibinin have shown great potential for development and improved bioavailability with nanomaterials.[154,155] Coloaded carbazole and silibinin cationic liposomes can kill prostate cancer cells and CSCs simultaneously.[156] Furthermore, aberrant up-/down- regulation of microRNAs (miRNA or miR) has been identified in different cancers and it plays an important role in the self-renewal and differentiation of stem cells.[157,158] Therefore, upregulation of tumor suppressor miR and downregulation of tumor miR expression by NP with anticancer effects may be a novel approach to target CSCs. Tehrani et al found that by inhibiting tumor miR (miR-21, miR-155, and miR-221) and inducing tumor suppressor miR (miR-34a, miR-126, and miR- let7b) and their targeted expression, a nanoformulation of silibinin induced apoptosis and inhibited the migration and proliferation of pancreatic cells and CSCs.[159,160] This suggests that targeting CSCs by modulating the function of miRNAs associated with stem cells is a feasible and promising approach.

Table 4 Characteristics of NP-Based Nanoformulations with Flavonoids or Alkaloids

Natural Products	Nanomaterials	Co-loaded	Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)	Target CSCs	Mechanism	Refs
α-Mangostin	PLGA nanoparticle	-	186.3 ± 6.42	-	0.03 ± 0.005	51.16 ± 2.61	-	Pancreatic cancer	↓ Sonic hedgehog pathway, epithelial-mesenchymal transition, self-renewal, proliferation, colony formation ↑ Apoptosis	[150]
	PLGA nanoparticles	-	-	-	-	-	-	Colorectal cancer	↓ Notch pathway ↓ Epithelial-mesenchymal transition and self-renewal capacity	[151]
Garcinol	HA-coated GA-loaded PLGA nanoparticles	-	158.8	0.192	47.4	60.31	5.02	Breast cancer	↓ Hypoxia-inducible factors (HIF-1α and HIF-2α) ↓ Notch pathway	[152]
Silibinin	Liposomes	Carbazole	63.0 ± 1.0	0.26 ± 0.007	10.7 ± 0.3	99.1 ± 0.02	10	Prostate cancer	↓ Colony formation and migration ↑ Apoptosis and G2/M phase arrest	[156]
	Polymersome	-	221.7 ± 59.23	0.32	-	94.86 ± 0.07	15.81 ± 0.57	Pancreatic cancer	↑ Apoptosis ↓ Migration and proliferation	[159]
	Polymersome	-	219.2	0.32	-12.15	94.86	15.81	Pancreatic cancer	↑ Apoptosis ↓ Migration and proliferation	[160]
Catechin	Carbon nanotubes	-	11	0.354	-	-	-	Prostate cancer	↑ Radiosensitivity ↓ Nanog, Oct4 and β-catenin	[162]
Resveratrol	Liposomes	-	-	-	-	-	-	Glioblastoma	↑ Caspases 3/7	[163]
	Liposomes	-	200	-	-	-	-	Glioblastoma	↑ Apoptosis	[164]
	Nanoparticle.	-	198.5 ± 0.28	0.196 ± 0.020	3.40 ± 0.976	-	-	Oral cancer	↑ Cytokines ↓ Invasion, proliferation and growth of CSCs	[165]

(*Continued*)

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Table 4 (Continued).

Natural Products	Nanomaterials	Co-loaded	Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)	Target CSCs	Mechanism	Refs
Camptothecin	Nanoparticle	-	-	-	-	-	-	Breast Cancer	↓ Hypoxia-inducible factor 1α	[169]
	Nanoparticle	All-trans retinoic acid	150	-	-	-	6.7	Breast Cancer	↓ Hypoxia-inducible factor 1α ↑ Differentiation of CSCs into non-CSCs, reactive oxygen species	[170]
	Nanocapsules	Fluorouridine and lovastatin	107.72 ± 10.78	0.152 ± 0.013	-26.45 ± 5.33	67.6	68.3	Triple-negative Breast Cancer	↓ Growth and metastasis of CSCs	[171]
Berberine	Liposomes	-	96.88 ± 1.81	0.20 ± 0.01	-8.98 ± 0.96	93.5 ± 3.14	-	Breast Cancer	↓ ABC transporters (ABCC1, ABCC2, ABCC3, ABCG2) and Bcl-2 ↑ Apoptosis	[174]
Piperlongumine	PLGA based nanoparticle	-	251	0.3	-	95	9.5	Triple-negative Breast Cancer	↓ Self-renewal, stemness, chemoresistance, epithelial-mesenchymal transition and aggressiveness ↓ STAT3	[175]
Tetrandrine	Liposomes	Vinorelbine	102.05 ± 0.99	0.193 ± 0.003	24.35 ± 4.76	89.453 ± 1.86	-	glioma	↑ Apoptosis	[176]

Note: ↑, increase or promote;↓, decrease or inhibit; -, no data available.
Abbreviation: PDI, polydispersity index

Catechin, a flavonoid found in various plants, including green tea, is widely considered an adjuvant in cancer treatment.[161] Carbon nanotubes deliver catechin specifically targeting CSCs, inhibit the expression of related transcription factors and regulators (including Nanog, Oct4, and β-catenin), and significantly increase the radiosensitivity of cancer cells, which is expected to eradicate prostate CSCs through synergistic effects and radiosensiticity.[162] In addition, resveratrol is a well-known natural polyphenolic organic compound that is widely found in grapes, peanuts, knotweed, blueberries, and other plants, and has multiple health benefits such as anti-inflammatory, anticancer, cardiovascular and cerebrovascular protection, and anti-aging.[66] The targeted delivery of resveratrol encapsulated in nanocarriers to CSCs can induce apoptosis (regulate caspases 3/7, P53), regulate the production of inflammatory cytokines (such as TNF-α, IL-6, IL-1β, etc.), and decrease the expression of metastasis (CD133, ALDH1, CXCR4, etc.) and angiogenic markers (matrix metalloproteinases, inducible nitric oxide synthase, vascular endothelial growth factor -A, etc.) in xenograft mouse model systems.[163–165]

Alkaloids

In recent years, alkaloids such as camptothecin, berberine, piperlongumine, and tetrandrine have been found to have good therapeutic effects on multiple types of cancer[166] (Table 4). The combination of camptothecin with anti-angiogenic drugs and differentiation inducers is an effective therapeutic strategy against CSCs-derived tumor heterogeneity. The induction of hypoxia and concomitant upregulation of HIF-1a stimulates tumor angiogenesis, invasion, metastasis, resistance to anti-angiogenic drugs and self-renewal of CSCs, and the alkaloid camptothecin is a powerful inhibitor of HIF-1a activity.[167,168] The camptothecin nanoformulation (CRLX101) blocks hypoxia-induced accumulation of CSCs and HIF-1a in breast cancer cells while enhancing the efficacy of anti-angiogenic drugs.[169] Shen et al prepared nanoparticles for the combined delivery of ATRA and camptothecin. The nanoparticles differentially released the two drugs to maximize their synergistic anticancer efficacy and eliminate both CSCs and bulk tumor cells.[170] In addition, Zhang et al innovatively combined statins with chemotherapeutic agents to design nanocapsules loaded with a lovastatin-camptothecin-fluorouridine conjugate for simultaneous drug delivery to tumor sites showing encouraging synergistic anticancer and antimetastatic potential.[171] This nanodelivery system provides a simple and synergistic strategy to significantly reduce chemotherapy resistance, recurrence, and metastasis associated with CSCs.

Conventional chemotherapeutic drugs will enrich CSCs while destroying cancer cells and generate drug resistance, which in turn leads to cancer recurrence and metastasis. The overexpression of cell membrane ATP-binding cassette (ABC) transporter proteins and mitochondrial apoptosis-related proteins is the main cause of drug resistance in CSCs.[172,173] Berberine liposomes can cross the membranes of CSCs, downregulate the expression of ABC transporter proteins (ABCC1, ABCC2, ABCC3, ABCG2) and selectively accumulate in mitochondria, which in turn induces the death of CSCs due to acute cytotoxic injury and the induction of apoptosis.[174] PLGA-based piperlongumine nanoparticles (PL-NPs) similarly induced apoptosis in CSCs via the mitochondria pathway and inhibited self-renewal, stemness, chemoresistance, EMT, and invasiveness of CSCs by downregulating STAT3.[175] The multifunctional targeting of vinorelbine plus tetrandrine liposomes enhances drug targeting across the BBB to aggregate in brain tumor sites, penetrate and destroy CSCs, and induce apoptosis in CSCs by activating relevant apoptotic proteins.[176] These results suggest that targeted modulation of CSCs apoptosis may improve chemotherapy drug resistance and reduce the consequent risk of cancer recurrence and metastasis.

Other NP

Sulforaphane (SFN), a natural isothiocyanate, can inhibit CSCs and CSCs-like properties through a variety of mechanisms, such as blocking self-renewal signaling (Wnt/b-catenin, Hedgehog, and Notch signaling.), activating apoptotic and autophagic pathways, and altering miRNAs (miR-140, 21 and 29).[66,177,178] However, SFN is highly hydrophobic and has poor stability to light and oxygen, which limit its efficacy and wide application.[179] Gu et al developed mineralized hyaluronic acid-SS-tetradecyl nanocarriers that are responsive to highly reducing and mildly acidic tumor microenvironments, and could rapidly deliver SFN and target CD44+ breast CSCs via HA, enhancing the efficacy of SFN in inhibiting CSCs-like properties and significantly inhibit CSCs invasion, self-renewal and tumor growth.[180] Likewise, by targeting the Wnt/β-catenin signaling pathway, the SFN-loaded nanoparticles significantly inhibited the self-renewal of breast CSCs and improved their chemotherapy sensitivity, and its combination with doxorubicin can eliminate both cancer cells and CSCs, thus effectively eradicating breast cancer.[181]

ALDHs maintain intracellular environmental homeostasis by catalyzing the conversion of toxic aldehydes to nontoxic carboxylic acids, which are essential for maintaining the self-renewal of normal and cancer stem cells. Members of the ALDH1A family (ALDH1A1, ALDH1A3) are closely associated with cancer development, metastasis, and drug resistance, hence targeting ALDH1A associated with CSCs may be an effective adjuvant cancer therapy.[182–184] Natural coumestan wedelolactone-encapsulated PLGA nanoparticles enhanced drug retention and sustained release in CSCs by downregulating the expression of drug resistance genes SOX2 and ABCG2, thereby significantly reducing self-renewal, pluripotency, invasiveness and increasing sensitivity to PTX in $ALDH1A1^+$ breast CSCs (which are known to be resistant to breast CSCs).[185] CaCO3 nanoparticles codeliver thymoquinone and doxorubicin to significantly eliminate breast CSCs by inhibiting ALDH activity.[186] In addition, citral extracted from lemongrass oil is a natural inhibitor of ALDH1A1 and ALDH1A3, and the nanodelivery system improves the stability of citral and maintains its ability to specifically inhibit ALDH1A1 and ALDH1A3 activity to significantly block CSCs self-renewal, colony formation, drug resistance, and metastatic potential, while its combination with PTX shows strong synergistic effects.[187,188]

Realgar is a mineral that has been used in China for more than 3000 years and its main active ingredient is tetraarsenic tetrasulfide (As_4S_4). In recent years, many studies have shown that As_4S_4 can induce apoptosis in various cell lines such as leukemia cell lines and lung cancer cell lines.[189–191] Grinding the realgar coarse powder into nanoparticles showed higher efficacy and less toxicity, significantly eliminating CSCs and reducing their clonogenic ability.[192] Moreover, realgar nanoparticles inhibited glucose metabolism, lung CSCs viability, and tumor growth by inhibiting metabolic reprogramming, which may be associated with the downregulation of HIF-1α expression via the PI3K/Akt/mTOR pathway.[193]

Nanomaterials delivering triterpenoids such as anthothecol, nimbolide, and ginsenoside Rg3 similarly showed excellent ability to target CSCs. The use of nanoparticle graphene oxide loaded with ginsenoside Rg3 significantly inhibited the malignant progression of osteosarcoma, inhibited the sphere formation of CSCs, and improved the effect of photodynamic therapy.[194] Anthothecol-coated PLGA nanoparticles (Antho-NPs) inhibited the proliferation, colony formation, and induced apoptosis of pancreatic CSCs and suppressed the self-renewal ability of CSCs by targeting the sonic hedgehog pathway and genes regulating cell survival and the cell cycle with no effect on human normal pancreatic ductal epithelial cells. Moreover, nimbolide-encapsulated PLGA nanoparticles (Nim NPs) are similar to Antho-NPs, both of which can induce the transition of pancreatic CSCs from mesenchyme to epithelium, thereby inhibiting their movement, migration, invasion, MDR, and self-renewal capacity[195,196] (Table 5).

Conclusions and Future Perspectives

Cancer remains a serious global health problem. With more in-depth research on cancer, the continuous emergence of new anticancer drugs and technical means, and the early screening of the disease, the treatment of cancer has made great progress, but serious treatment-related side effects, drug resistance, recurrence, and metastasis lead to high cancer mortality and a major social burden.[197] CSCs present in tumor tissues control the occurrence and development of tumors, chemotherapy resistance, recurrence, and metastasis due to their characteristics of high proliferation, self-renewal, multidirectional differentiation, high tumorigenicity, and multidrug resistance. CSCs are highly resistant to conventional chemotherapeutic drugs, and the application of chemotherapeutic drugs will greatly enrich CSCs.[40] Therefore, finding drugs that target and clear CSCs is a new strategy to improve the cure rate of cancer. A growing body of epidemiological and clinical research suggests that ingestion of natural plant compounds has health benefits, both in reducing cancer incidence and the risk of recurrence, and they exhibit synergistic effects with traditional anticancer drugs. More importantly, compared with most chemotherapeutic agents, plant compounds from abundant and safe sources directly or indirectly target key signaling pathways, self-renewal pathways, metabolism, epigenetic modifications, and the tumor microenvironment of CSCs, and this may become a new therapeutic strategy for targeting CSCs.[198,199] However, despite the tremendous health benefits of NP, their clinical use is severely limited by their poor water solubility, low absorption rate, low bioavailability, and nonspecific targeting. Nanocarriers, due to their superior storage stability, tissue permeability, and biocompatibility, target the delivery of biologically active compounds of natural origin to improve their bioavailability, prolong the drug circulation time in vivo, and enhance drug efficacy.[16] Therefore, the development of nanocarrier systems for targeted delivery and controlled drug release provides a possibility to overcome the toxic and side effects of traditional chemotherapeutic drugs and kill CSCs.

Table 5 Characteristics of NP-Based Nanoformulations with Other Natural Products

Natural Products	Nanomaterials	Co-loaded	Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Loading (%)	Target CSCs	Mechanism	Refs
Sulforaphane	Mineralized hyaluronic acid-SS-tetradecyl nano-carrier	-	85.90 ± 3.49	0.13 ± 0.01	-13.81 ± 0.36	92.36 ± 2.17	33.64 ± 1.33	Breast cancer	↓ Invasion, self-renewal of CSC ↓ Tumor growth	[180]
	Self-Assembled Poly(D, L-lactide-co-glycolide)/Hyaluronic Acid Block Copolymer-Based Nanoparticles	Doxorubicin	179.3 ± 2.8	0.113 ± 0.023	-26.3 ± 1.5	-	5.7 ± 1.0	Breast cancer	↓ Wnt/β-catenin signaling pathway ↓ Self-renewal of breast CSCs	[181]
Wedelolactone	PLGA nanoparticles	Doxorubicin	95 ± 0.34	0.77 ± 0.065	-8.5 ± 2.35	83.3 ± 2.15	-	Breast cancer	↓ Self-renewal, pluripotency, invasiveness ↑ Sensitivity to paclitaxel	[185]
Thymoquinone	Cockle Shell-derived aragonite CaCO3 nanoparticles	-	-	-	-	-	-	Breast cancer	↓ALDH, CD44 and CD24 ↓ Migration, invasion and sphere formation	[186]
Citral	Polymeric micelles	Paclitaxel	26.51	0.1	-13.87	99.73	9.95	Breast cancer	↓ Self-renewal, differentiation and migration, aldehyde dehydrogenase family (ALDH1A1)	[187]
	Nanoparticle	Paclitaxel	-	-	-	-	-	Breast cancer	↓ Colony forming, aldehyde dehydrogenase family(ALDH1A3)	[188]
Realgar	Realgar nanoparticles	-	131	-	-	-	-	Multiple myeloma	↓ Clonogenic capacity	[192]
	Nano-realgar particles	-	72.79	-	-	-	-	Lung cancer	↓ Glucose metabolism, CSCs viability and tumor growth	[193]
Ginsenoside Rg3	Graphene Oxide Nanoparticle	-	-	-	-	-	-	Osteosarcoma	↓ Sphere formation ↑ Photodynamic therapy	[194]
Anthothecol	PLGA-nanoparticles	-	275	0.3	-20	-	-	Pancreatic cancer	↓ Epithelial-mesenchymal transition; ↓ AKT and mTOR	[195]
	PLGA-nanoparticles	-	190.52 ± 5.39	0.02 ± 0.01	-	45.25 ± 3.55	-	Pancreatic cancer	↓ Proliferation, colony formation, self-renewal, sonic hedgehog pathway, epithelial-mesenchymal transition ↑ Apoptosis	[196]

Notes: PDI, polydispersity index;↑, increase or promote;↓, decrease or inhibit; -, no data available.

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Furthermore, non-CSCs can be spontaneously and randomly transformed into CSCs.[31,200] Therefore, better therapeutic outcomes can be achieved using a combination of conventional chemotherapy and antitumor stem cell agents to simultaneously remove cancer cells and CSCs. Currently, clinical combination therapies are mainly based on the combined administration of conventional agents, which may have synergistic, additive, or even antagonistic effects. Nanoformulations are powerful tools whose pharmacokinetics and distribution in vivo depend on the nanocarriers themselves, independent of the characteristics of the drug.[201] Currently, coadministration regimens for nanoformulations are divided into the combined use of two single-drug delivery systems and the combination of two drugs in a single-drug delivery system. The use of two separate nanoformulations allows the flexibility to administer drugs at different doses and times, but it is difficult to achieve synchronization of their pharmacokinetics and biodistribution to maintain a synergistic ratio of drugs at the tumor site. In contrast, drug delivery systems that coload NP (killing CSCs) and conventional chemotherapeutic agents (killing cancer cells) can deliver them simultaneously to the tumor site in synergistic ratios, thus synchronizing tumor treatment in time and space and ensuring the elimination of different cancer cell subpopulations to achieve synergistic therapeutic effects.[202–204] However, maintaining synergistic drug ratios in the same nanodelivery system is not easy because each drug exhibits different release rates according to its properties, which also poses new challenges for the design of nanodelivery systems.

In this review, we summarize the great potential of nanocarrier-delivered natural product agents in targeting CSCs to overcome cancer recurrence, metastasis, and drug resistance. Nanocarriers improve the bioavailability of natural active compounds such as curcumin, PTX, doxorubicin, cyclopamine, and all-trans retinoic acid, which are passively or actively targeted by ligand modification for delivery to CSCs to inhibit their stemness and they show excellent synergistic effects in combination with chemotherapeutic agents, providing more options for the development of novel, safe, and effective antitumor drugs. Although breakthroughs have been made in the experimental research of nanomedicines in the preclinical stage, they are still far from the core goal of achieving clinical therapeutic effects. Currently, moving from basic laboratory research to clinical applications is a key issue in the development of the nanomedicine field. With significant advances in nanotechnology, targeted drug delivery, and cancer biology, this work is expected to achieve a breakthrough soon.

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Disclosure

The authors report no conflicts of interest in this work.

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