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REVIEW

Application of Pharmaceutical Nanotechnologies for Chinese Herbal Medicines in the Treatment of Pulmonary Diseases and Lung Cancer

Xiaoping Yang[1,2], Hongxin Niu[3,4], Wen Jiang[1], Wanpeng Yu[5], Wenqing Jiang[1]

[1]Qingdao Traditional Chinese Medicine Hospital, Qingdao Hiser Hospital Affiliated of Qingdao University, Qingdao, Shandong, People's Republic of China; [2]College of First Clinical Medical, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China; [3]Department of Intervention, Qilu Hospital (Qingdao), Qingdao, Shandong, People's Republic of China; [4]Cheeloo College of Medicine, Shandong University, Jinan, Shandong, People's Republic of China; [5]Qingdao Medical College, Qingdao University, Qingdao, Shandong, People's Republic of China

Correspondence: Wenqing Jiang; Wanpeng Yu, Email jiangwenqing126@126.com; yuwanpeng@qdu.edu.cn

Abstract: Chinese herbal medicines (CHMs) is the crystallization of wisdom accumulated by the Chinese nation over thousands of years. With the development and advancement of technology, extensive research has been conducted on the pharmacological activities of active components in CHMs. Natural constituents from medicinal plants exhibit rich scaffold diversity and structural complexity, playing crucial roles in the pharmacological effects of CHMs. However, many CHMs components have been found to suffer from poor water solubility, low stability, and limited bioavailability, which significantly restrict their clinical applications. In recent years, nanomedicine has been leveraging the power of nanotechnology to fully exploit its distinctive advantages. In the field of CHMs, the introduction of nanonization technology has enhanced the therapeutic efficacy of CHMs formulations. Especially the use of nano-modified CHMs solely derived from natural products has overcome several "bottlenecks" associated with chemical nanodelivery systems—such as insufficient drug loading, high production costs, potential systemic toxicity, and immunogenicity—emerging as an innovative and promising platform for disease treatment. Here, we review recent advancements in pharmaceutical nanotechnologies for CHMs in the treatment of pulmonary diseases and lung cancer. These nano-modified CHMs include nanoemulsions, self-assembled nanoparticles, nanocrystals, herbal-derived exosomes, and carbon dot-based nanozymes formulated from natural medicinal plants. They demonstrate unique advantages in enhancing the pharmacological effects of natural bioactive compounds and treating pulmonary disorders and lung cancer. This provides novel insights into the development of nano-modified CHMs in the treatment of pulmonary disease and lung cancer.

Keywords: Chinese herbal medicines, nanotechnologies, pulmonary disease, lung cancer

Introduction

Chinese herbal medicines (CHMs) is the crystallization of wisdom accumulated by the Chinese nation over thousands of years. With technological advancements, extensive research has been conducted on the extraction, isolation, identification, pharmacological activities, analysis, and formulation of active components in CHMs, leading to broader modern applications. The pharmacological effects of CHMs are determined by its active constituents, which have been extensively studied. The natural components of medicinal plants exhibit rich scaffold diversity and structural complexity, playing a crucial role in the pharmacological effects of CHMs. Based on structural characteristics, the active components of CHMs can be categorized into flavonoids, alkaloids, terpenoids, quinones, and polyphenols, among others. The discovery of natural lead compounds from plants has been and will continue to be at the forefront of biomedical research, representing a promising pathway for drug discovery and development. Natural plants are receiving increasing attention for disease treatment. However, challenges such as poor water solubility, low stability, limited bioavailability, and significant adverse reactions observed in many CHMs components have substantially constrained their clinical applications. These limitations also present new questions and challenges for the modernization of CHMs.

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In recent years, enhancing the therapeutic efficacy of CHMs has become a research hotspot. Nanomedicine is leveraging the power of nanotechnology to fully exploit its distinctive advantages. In the field of CHMs, the introduction of nanotechnology has strengthened the efficacy of herbal medicines. Nano-modified CHMs, a novel drug form, has emerged through the integration of CHMs with modern nanotechnology.[1]

Here, we review recent advances in nano-modified CHMs for the treatment of pulmonary diseases and lung cancer. These nano-modified CHMs include nanoemulsions, self-assembled nanoparticles (NPs), nanocrystals, extracellular vesicles derived from CHMs, and carbon dot-based nanozymes based on CHMs. They demonstrate unique advantages in enhancing the pharmacological effects of natural active compounds and treating pulmonary diseases and lung cancer. This provides new insights for the development of nano-modified CHMs in pulmonary disease and lung cancer therapy.

The Advantages of Nano-Modified CHMs in the Treatment of Pulmonary Diseases and Lung Cancer

Globally, lung diseases represented by acute respiratory infections, chronic obstructive pulmonary disease (COPD), bronchial asthma, and lung cancer are characterized by high incidence and mortality rates. There is an urgent need to discover new therapeutic approaches applicable to the physiology, pathology, and anatomy of the lungs to address the current challenges in preventing and treating pulmonary diseases.[2] The lungs are the foundational organs of the respiratory system and play a vital role in maintaining the physiological and biochemical pathways of the body's cells. Under normal conditions, various lung cells, including alveolar macrophages, T lymphocytes, mast cells, alveolar epithelial cells, neutrophils, and smooth muscle cells, produce interleukins to maintain lung health. These cells are responsible for secreting different types of interleukins in response to stimuli, which in turn regulate/initiate the immune system by recruiting inflammatory cells. Traditional drug delivery modes inevitably limit efficacy due to the degradation of active components in the gastrointestinal tract or first-pass metabolism in the liver. Moreover, this systemic administration increases non-specific toxicity due to high drug exposure to other organs. Therefore, the lungs present an attractive alternative route for drug delivery. They offer a large surface area for the deposition of therapeutic agents and are highly vascularized for the systemic delivery of various drugs. Pulmonary drug delivery via inhalation prevents the degradation of active ingredients in the gastrointestinal tract and avoids first-pass metabolism in the liver. However, pulmonary formulations are strictly constrained by the physiological characteristics of the lungs, such as their branching structure, mucociliary clearance, and macrophages, as well as certain properties of the drugs themselves, including particle size and solubility.[3]

Nanotechnology holds significant advantages for the pulmonary delivery of poorly soluble drugs. It can overcome numerous biological and physical barriers in the lungs, enhance drug solubility, prolong drug residence time in the lungs, and thereby improve the bioavailability of drugs in pulmonary tissues. As a non-invasive administration method, pulmonary drug delivery directly transports drugs to the lungs, achieving high local drug concentrations with relatively low doses, making it the preferred choice for treating pulmonary diseases and lung cancer. Compared to traditional administration routes, pulmonary delivery avoids the hepatic first-pass effect, reduces drug catabolism, and improves drug bioavailability. Designing rational nanodrug delivery systems to overcome these challenges and achieve efficient, precise pulmonary drug delivery represents an urgent problem to be solved in current lung disease treatment. Facing these challenges, researchers are continuously exploring novel nanotechnologies and materials to optimize pulmonary drug delivery systems, such as CHMs nanoformulations.[4] Nano-modified CHMs refers to active components, effective fractions, raw herbs, or compound formulations processed using nanotechnology with a particle size of less than 100 nm. When processed at the nanoscale, CHMs undergoes significant changes in physical properties, chemical characteristics, and biological behaviors, potentially leading to novel pharmacokinetic profiles. Notably, chemical carrier-free NPs composed solely of natural products achieve a 100% therapeutic component loading rate, overcoming several bottlenecks of chemical nanocarriers—such as insufficient drug loading, high production costs, potential systemic toxicity, and immunogenicity—thereby establishing a promising emerging platform for disease treatment.[5] Studies indicate that the onset time, potency, and duration of CHM's therapeutic effects in vivo are not only related to the chemical structure of the drug itself but also closely associated with its physical state. Modifying the unit size of the drug represents an

effective strategy to alter its physical properties. Compared to traditional drug delivery systems, nano-modified CHMs, owing to their unique size, shape, and other attributes, can significantly improve the pharmacokinetic and pharmacodynamic performance of natural active compounds. These enhancements include increased stability, improved solubility and bioavailability, reduced adverse effects, enhanced targeting capability, and prolonged circulation time in the bloodstream.[6] Through rational design of nano-modified CHMs, the stability and biocompatibility of drugs can be enhanced, extending pulmonary residence time and improving drug absorption efficiency in the lungs. This approach thus provides new opportunities for achieving precise treatment of pulmonary diseases and lung cancer.

Chinese Herbal Medicines (CHMs) Derived-Nanoemulsions

Nanoemulsions (NEs), formerly referred to as microemulsions, are biphasic dispersions of two immiscible liquids with particle sizes ranging from 10 to 100 nm. They exhibit exceptional stability, high dispersion capacity for solutes, and strong adsorption capabilities. Recognized as Generally Recognized as Safe (GRAS) by the US FDA, NEs serve as effective drug carriers capable of dissolving substantial amounts of hydrophobic drugs within their lipophilic core. They mitigate enzymatic degradation and hydrolysis of loaded drugs to achieve sustained drug release. Formulating CHMs extracts into NEs can enhance drug solubility, improve stability, and increase bioavailability. Drug encapsulation in NEs enables targeted delivery and toxicity reduction while facilitating pulmonary administration of poorly soluble molecules. For hydrolytically unstable drugs, water-in-oil NEs provide protective encapsulation.[7] Furthermore, the submicron size of NEs permits diffusion across cellular barriers, enabling prolonged retention and deposition in lung tissues. Therefore, NEs can serve as inhaled drug formulations for the treatment of pulmonary diseases and lung cancer, not only enabling controlled release of medications at lesion sites within the lungs but also protecting unstable biological agents from rapid degradation in the pulmonary microenvironment, demonstrating significant therapeutic potential for pulmonary disease and lung cancer.[8]

Current research on CHMs-derived NEs primarily focuses on the following components: tanshinone, norcantharidin, triptolide, 8-methoxypsoralen (8-MOP), quercetin, camptothecin, silymarin, andrographolide, puerarin, perilla seed oil, curcumin, Gynostemma pentaphyllum, Acanthopanax senticosus, paclitaxel, matrine, Coptis chinensis, and Scutellaria baicalensis. Generally, NEs are categorized into three types: water-in-oil (W/O) NEs, oil-in-water (O/W) NEs, and bicontinuous NEs (B.C).

Preparation Method of NEs

NEs are thermodynamically unstable systems that cannot form spontaneously, necessitating external energy input for their formation. Based on the energy source, preparation methods for NEs are categorized into high-energy and low-energy approaches.

High-energy methods, also termed mechanical methods, utilize mechanical devices such as high-pressure homogenizers, ultrasonic processors, or microfluidizers to impart energy to mixtures of oil phases, surfactants, and aqueous phases.[9] This energy input enables uniform droplet distribution in the dispersed phase, forming homogeneous and stable NEs. Among high-energy emulsification techniques, high-pressure homogenization is the most widely used. However, this method requires substantial energy consumption, is unsuitable for highly viscous systems, and may induce destructive effects on certain drugs. Thus, the viscosity characteristics of the drug must be carefully considered when employing this approach. Ultrasonic emulsification is highly effective for reducing droplet size, typically using probe-type ultrasonic processors, but is limited to small sample volumes.

Low-energy emulsification methods form NEs through the inherent chemical energy of the system itself, eliminating the need for additional specialized equipment and typically requiring only mild agitation.[10] This approach reduces physical damage to drugs during preparation and generates smaller emulsion droplets through spontaneous mechanisms. Low-energy emulsification encompasses two primary techniques: the Phase Inversion Temperature (PIT) method and the Phase Inversion Composition (PIC) method. The PIT method leverages the reduced interfacial tension of surfactant molecules at the phase inversion temperature to facilitate emulsification, making temperature the most critical influencing factor. Additionally, salt concentration and pH can also impact the emulsification process. In contrast, the Phase Inversion Composition (PIC) method maintains constant temperature while altering the composition of aqueous and oil phases

within the system to form NEs. For the PIC method, under appropriate temperature, stirring rate, and controlled addition speed, the particle size of the NEs primarily depends on the ratio of emulsifier to oil.

The Application of CHMs-Derived NEs in Pulmonary Diseases and Lung Cancer

The preparation of active ingredients from CHMs into NEs via emulsification methods can improve the bioavailability of CHMs preparations in vivo. As a novel drug delivery system, NEs can stabilize drug quality, enhance therapeutic efficacy, reduce toxic side effects, and improve targeted delivery. Studies have confirmed their effectiveness in therapeutic applications, including the treatment of pneumonia and lung cancer (Table 1).

For example, tea tree oil (TTO) is a natural essential oil with broad pharmacological effects, including antibacterial, antifungal, anti-inflammatory, antioxidant, antitumor, and immunomodulatory activities. However, allergic reactions, instability, and hydrophobicity limit its clinical applications. Li et al developed inhalable nanoTTO through high-pressure homogenization of TTO/Cremophor EL/water, with an average particle size of 12.5 nm. In vitro experiments demonstrated that nanoTTO significantly inhibited *Escherichia coli, Acinetobacter baumannii, Klebsiella pneumoniae, Staphylococcus aureus*, and *Candida albicans*. In a rat model of fungal pneumonia, inhaled nanoTTO directly reached lung tissues with microbial infection, exhibiting superior antifungal activity compared to fluconazole, while suppressing leukocyte recruitment and pro-inflammatory mediators to alleviate lung injury. In a bacterial pneumonia rat model, although the efficacy of nanoTTO was slightly lower than penicillin, it required much lower doses and showed no significant adverse effects. Given the current prevalence of microbial antibiotic resistance, inhalable nanoTTO presents a promising alternative nanomedicine option for treating both bacterial and fungal pneumonia.[11]

Epigallocatechin-3-gallate (EGCG), the primary component of green tea, exhibits anti-proliferative, anti-inflammatory, anti-mutagenic, and antioxidant activities. Chen et al prepared EGCG NEs by mixing EGCG with lecithin, Tween 80, and water in appropriate proportions through stirring.[37] Experimental results demonstrated that the EGCG NEs showed enhanced stability and superior targeting capability towards human lung cancer cells compared to free EGCG. It significantly inhibited the proliferation, colony formation, migration, and invasion of lung cancer cells at lower doses than those required for EGCG. The anti-tumor efficacy of the EGCG NEs was found to be superior to that of EGCG alone against lung cancer cells.[12] Costunolide (CTD), a bioactive compound extracted from *Saussurea, Aucklandia*, and *Chrysanthemum* species, demonstrates potent anticancer effects, particularly against lung cancer and leukemia. Alhakamy et al developed CTD-green NEs (CTD-GNE) by combining CTD with the biocompatible surfactant α-cyclodextrin (α-CD), limonene oil, and water using high-pressure homogenization. The optimized CTD-GNE exhibited significantly enhanced inhibition of A549 cell proliferation. Compared to conventional formulations and raw CTD, CTD-GNE markedly upregulated mRNA expression of caspase-3, Bax, Bcl-2, and p53 while substantially suppressing TNF-α and NF-κB activities. These findings suggest that the CTD-GNE formulation represents a promising therapeutic strategy for lung cancer treatment.[13] Afshari et al prepared an anise essential oil (AGEO) NEs (AGEO-NE) using an ultrasonic method, which significantly enhanced its anticancer activity by improving its bio-solubility and biocompatibility. The results demonstrated that increased concentrations of AGEO-NE showed a significant correlation with reduced viability of cancer (A549) cells, while exhibiting no notable impact on normal human foreskin fibroblasts (HFF). Therefore, AGEO-NE may serve as a highly effective novel apoptosis inducer for lung cancer cells without adverse side effects.[14] Khan et al prepared a carvacrol NEs (CANE) using an ultrasonic method. Carvacrol, a monoterpenoid flavonoid, exhibits diverse biological activities, including antimicrobial, antioxidant, antiviral, and anticancer properties. However, its physicochemical instability and low aqueous solubility have limited its applications. The prepared CANE significantly enhanced its stability and bioavailability. In vitro experiments confirmed that CANE markedly increased the expression of apoptotic proteins such as Bax, cytochrome C, cleaved caspase-3, and cleaved caspase-9, while reducing the expression of cell cycle proteins, effectively inducing apoptosis in doxorubicin-resistant A549 lung cancer cells (A549DR). Additionally, CANE significantly suppressed autophagy. Further evaluation of CANE's anticancer efficacy was conducted using nude mice xenografted with A549DR cells. Results demonstrated that CANE effectively inhibited tumor growth by suppressing autophagy, modulating the cell cycle, and inducing apoptosis. The potential anticancer mechanism of CANE against drug-resistant cells, mediated through autophagy inhibition and apoptosis induction, highlights its promise as a candidate for lung cancer therapy.[15]

Table 1 The Characteristics of Nano-Modified CHMs and Their Applications in the Treatment of Pulmonary Diseases and Lung Cancer

Types	Active Ingredients	Preparation Method/Force	Bioactivity	Cellular Bioavailability	In-vivo Therapeutic Effect	Application	References
Nanoemulsions	Tea tree oil	High-pressure homogenization method	Antibacterial, anti-fungal, anti-inflammationorial activities and immune regulational effects	nanoTTOs are more readily deposited and and homogenous distributed in the lung after inhalation, facilitating delivery to the depth of the lung. The high water dispersion and penetration of nanoTTOs are favorable to their interaction with microorganisms.	The nanoTTOs (7 mg TTO/rat) showed a higher bacterial clearance rate compared with the control group in vivo.	Effectively treats bacterial andfungal pneumonia in rats in vivo, alleviates lung injury and reduces pro-inflammatory mediators.	[11]
	Epigallocatechin-3-gallate (EGCG)	Stirring method	Exhibits antiproliferative, and antimutagenic activities	The half-maximal inhibitory concentration (IC50) of nano-EGCG (4.71 μM) on H1299 lung cancer cells was significantly lower than that of EGCG (36.03 μM).	——	Significantly inhibit the proliferation, colony formation, migration and invasion abilities of lung cancer cells.	[12]
	Costunolide	High-pressure homogenization method	Antitumor activity	The optimized CTD (CTD-GNE, IC50 6.1±0.8μM) significantly reduced the IC50 values of A549 cells compared with CTD (IC50 ~24 μM).	——	Significantly inhibited the proliferation of A549 cells and significantly increased the expressions of caspase-3, Bax, Bcl-2 and p53 mRNA; significantly reduces the activities of TNF-α and NF-Kb.	[13]
	Anethum Graveolens Essential Oil	Ultrasound method	Antitumor activity	The lower IC50 concentrations of AGEO-NE impacted A549 cells compared with human foreskin fibroblast (HFF), indicating the cell-selective cytotoxicity of AGEO-NE.	——	Significantly inhibit the viability of A549 cells.	[14]
	Carvacrol	Ultrasound method	Antibacterial, antioxidant, antiviral and antitumor activities	CANE promotes dose-dependent cytotoxicity in $A549^{DR}$ cells.	——	Effectively induced apoptosis in doxorubicin-resistant A549 lung carcinoma cells (A549DR); elevated expression of apoptotic proteins; reduced cell cycle proteins.	[15]
	Tea tree oil+ Tanshinone IIA	Ultrasound method	Antioxidant and anti-inflammationorial activities	TSIIA loading into NE resulted in a significant 50% reduction in burst release ($p \leq 0.05$).	When compared to untreated rats, 1.4 and 1.9-fold increases in tidal volume and minute respiratory volume in-vivo, respectively, with 32% drop in wet/dry lung weight ratio and improved levels of arterial blood gases. TSIIA-NE-F8 significantdecrease in TNF-α and IL-17 with 63.3% and 52%, respectively, and ~ 2.7-folds increase in IL-10 when compared to the positive control.	Exhibit anti-inflammatory and antioxidant effects; improved the pulmonary ventilation dysfunction induced by LPS in rats.	[16]
	Palm oil ester/ ricinoleic acid +quercetin	High-pressure homogenization method	Antitumor activity	With high fine particle fraction (90.52 ± 0.10%), percent dispersed (83.12 ± 1.29%), and percent inhaled (81.26 ± 1.28%) for deposition in deep lung.	——	Significantly inhibit the growth of A549 lung cancer cells.	[17]

(*Continued*)

Table 1 (Continued).

Types	Active Ingredients	Preparation Method/Force	Bioactivity	Cellular Bioavailability	In-vivo Therapeutic Effect	Application	References
Self-Assembly	Ursolic acid (UA)	Solvent exchange method/hydrophobic interactions and hydrogen bond interactions	Antitumor activity	At the same concentration, UA NPs inhibited the growth of cancer cells in A549 cells and HeLa cells more effectively than UA; UA NPs are able to permeate by passive diffusion efficiently.	The deposition of UA NPs in the tumors was 0.96 ng/mL, which was higher than UA (0.37 ng/mL). Compared with UA, the inhibit tumor growth of UA NPs is more obvious.	Inhibit the proliferation of A549 lung cancer cells and induce their apoptosis; efficiently suppress the A549 tumor growth in vivo.	[18]
	P-NFs Nano-Filaments	Ultrasound method	Antitumor activity	The IC50 values of Ptx were 375.7 nM in A549and 359.3 nM in H460 cells, respectively, while the IC50 values of P-NFs nano-filaments in A549 and H460 cells were 244.0 nM and 210.7 nM, respectively.	——	Significant induced cell apoptosis; decreased A549 cells migration; significantly increased the expression of bax and reduce the expression of bcl-2.	[19]
	Glycyrrhizic acid (GA) and ephedrine (EPH)	Stirring method /hydrophobic interactions and hydrogen bond interactions	Antiviral and anti-inflammatory activities	The EC50 values changed from 310.83 μM for EPH and 262.88 μM for GA to 68.25 μM for the the self-assembled NPs EPH-GA. The area under the drug–time curve of EPH in EPH-GA was significantly increased, and it also maintained a high blood drug concentration in the later stage of the blood drug concentration reduction.	The EPH-GA group had the lowest viral load, and its viral inhibition rate reached 84.24% in vivo.	Significantly reduced viral load in the lungs of mice and improved lung lesions and tissue infiltration caused by RSV.	[20]
	Resveratrol	Sonication method/π–π and π-sigma interactions	Anti-inflammatory, antioxidant and antiviral activities	Res NPs have higher solubility (35-fold) and a faster dissolution rate (4-fold) compared to Res alone. Res NPs exhibit more potent pharmacological activities. The uptake of Res NPs increased 3.5-fold compared to free Res.	Res NPs were more effective in inhibiting viral load in lung lavage fluid (50%, $P < 0.001$) and reducing the expression of pro-inflammatory factors IL-6 and TNF-α compared to Res alone in vivo.	Reduce viral load, alleviate lung inflammation, and enhance lung function in RSV-induced pneumonia.	[21]
	Poly (epigallocatechin gallate)-baicalin	Hydrophobic interactions, hydrogen bond interactions and π–π interactions	Anti-inflammatory and antioxidant activities	HA-EBNPs significantly enhanced endocytosis efficiency in M1-type macrophages. HA-EBNPs showed efficient accumulation in the lungs of the ALI model.	Treatment with HA-EBNPs resulted in a marked reduction in both macrophage and neutrophil counts in LPS-induced ALI model; Effectively inhibited the excessive production of ROS. HA-EBNPs exhibits excellent hemocompatibility and do not induce organ toxicity.	Attenuate mitochondrial defects; promote the polarization of alveolar macrophages (AMs) towards the anti-inflammatory M2 phenotype; significantly inhibit lung inflammation, attenuate lung injury, improve lung histopathology.	[22]
	GP-682 micelles +Lev	Ultrasound method	Anti-inflammatory	The AUC_{0-t} of the GP-682 micelles combined with Lev group was 224.017 ± 34.494, and the AUC_{0-t} of the Lev group was 129.796 ± 16.161. Compared with the Lev group, the AUC_{0-t} of the GP-682 micelles combined Lev group was 1.8 times that of the Lev group. The C_{max} of Lev in the GP-682 micelles combined with Lev group was increased, and the clearance rate CLz/F was significantly decreased compared with the Lev group.	The combined use of levofloxacin (Lev) and GP-682 micelles significantly increased the survival rate compared with the corresponding Lev group ($p < 0.05$). GP-682 micelles enhanced the effect of Lev in the treatment of ALI in mice caused by *Pseudomonas aeruginosa* PA14.	Significantly inhibit lung inflammation, attenuate lung injury.	[23]

NANOCRYSTALS	Paclitaxel	High-pressure homogenization method	Antitumor activity	The IC50 value of HA-PTX/NC (0.64 mM) after 48 h was 2.1 fold lower than Taxol™ (1.35 mM) ($p < 0.05$) and 1.45 fold lower than HP-PTX/NC (0.93 mM) ($p < 0.05$). HA-PTX/NC showed 1.80 fold increased AUC in comparison to HP-PTX/NC.	At the end of 30 days tumor volume of Taxol™ (738.31± 118.15 mm^3) and HA-PTX/NC (228± 79.74 mm^3) treated group was 5.28 fold and 17.1 fold lower in comparison to control group (3900.5 ± 588.84 mm^3) respectively, though the later was more effective.	Exhibit higher antitumor efficacy, reduced lung metastasis and reduced toxicity in LA-7 tumor bearing rat model.	[24]
	Camtothecin	Antisolvent precipitation method	Antitumor activity	MDA-MB-231 cells displayed the highest sensitivity to HA-coated CPT nanocrystals (cellular uptake rate 30.8%). HA-coated CPT nanocrystals demonstrated the most potent in vitro anticancer efficacy among the three CPT formulations in the fact that they presented 4.1 −35.4-fold lower IC50 values in comparison with free CPT, while naked CPT nanocrystals were correspondingly 2.2−23.9-fold. HA-coated CPT nanocrystals showed excellent blood compatibility.	——	Significantly enhancing antitumor activity in vitro, inducing apoptosis, and inhibiting migration activity.	[25]
	Genistein	Wet ball milling technique	Antitumor activity	The C_{max} of Gen-NC formulations were 2.5-fold higher compared to free Gen. The area under the curve from time of administration to 24 h was 2.5 to 3-fold higher when compared with unprocessed drug.	——	Strong inhibitory effect on A549 lung cancer cells and L929 fibroblast cell.	[26]
	Paclitaxel	Antisolvent precipitation cum crystallization method and sonication method	Antitumor activity	The PTX-NCs, Lipo/PTX-NCs, BTB-NCs, and Lipo/BTB-NCs exhibited a lower IC50 value of 0.41, 0.22, 0.20, and 0.18 μg/mL, respectively, as compared to pure PTX and pure BTB. Lipid-coated nanocrystals exhibited higher interactions and internalization in cancer cells.	Lipo/PTXNCs (i.v). and Lipo/BTB-NCs (i.v.) had higher AUC, $t_{1/2}$, Cmax, and MRT as compared to PTX (i.v.) and BTB (i.v). Also, Lipo/PTXNCs (Inh.) and Lipo/BTB-NCs (Inh.) exhibited lower AUC in plasma but increased $t_{1/2}$ and MRT as compared to Lipo/PTXNCs (i.v.) and Lipo/BTB-NCs (i.v.), respectively.	Induce ROS generation and apoptosis, leading to cancer cell death; promote the prolonged retention time of drugs in the lungs.	[27]

(*Continued*)

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Table 1 (Continued).

Types	Active Ingredients	Preparation Method/Force	Bioactivity	Cellular Bioavailability	In-vivo Therapeutic Effect	Application	References
VCMH	Artemisia-derived nanovesicles (ADNVs)	Ultracentrifugation method	Anti-inflammatory, antioxidant, anticancer, and immune-modulatory properties	ADNVs rapidly trafficked to major tissues, livers and lungs particularly. ADNVs were efficiently taken by macrophages.	ADNVs protected mice from endotoxin-induced ALI by greatly increasing ratio of AMs and reducing the infiltration of MMs and neutrophils in lungs. ADNVs significantly elevated the survival rate of mice that were challenged with a lethal dose of IAV by reducing the expression of proinflammatory cytokines and decreasing infiltration of MMs and neutrophils. ADNVs protected mice from psSRAR-CoV-2 infection by significantly reducing the ratios of proinflammatory cell subsets, MMs and neutrophils.	Alleviated lung immunopathology and raised the survival rate of challenged mice induced by bacterial endotoxin, influenza A virus (IAV) and SARS-CoV-2 pseudovirus.	[28]
	Rhodiolae Crenulatae Radixet Rhizoma-derived nanovesicles	Bligh & Dyer method	Anti-fibrotic effects	——	HJT-sRNA-m7 significantly decreased the levels of hydroxyproline, α-SMA, fibronectin, and COL3A1 in the lung in a Bleomycin-induced fibrosis mouse model.	Targets fibrosis-related proteins, reduces fibrotic factor expression, and alleviates pulmonary fibrosis symptoms.	[29]
	Allium sativum nanovesicles	Differential centrifugation method	Anti-inflammatory and antifibrotic activity	——	100 μg of AS-NV decreases lung injury and attenuates BLM-induced lung fibrosis.	Reduced the mRNA levels of genes related to fibrosis, inflammation and ECM deposition induced by bleomycin; reduced lung fibrosis caused by bleomycin injury in mice.	[30]
	Cucumber sarcocarp-derived nanovesicles (CsDNVs)	Ultracentrifugation method	Antitumor activity	CsDNVs and CpDNVs caused significant cytotoxicity toward A549 cells with IC50 of 4.82 nM and 6.71 nM, respectively, while the IC50 value of CuB for A549 cells was 95.51 nM. CsDNVs showed excellent blood compatibility.	The tumor growth rate of mice in the CsDNVs group was significantly lower than that in the free CuB group. The expression level of p-STAT3 decreased in the tumor tissues of CsDNVs mice.	Enhance ROS generation, promote cell cycle arrest and increase caspase activity to inhibit cell proliferation; significantly reduce the growth rate of tumors in vivo.	[31]
	Artemisia-derived nanovesicles (ADNVs)	The combination of differential centrifugation method and sucrose density gradient supercentrifugation method	Antitumor activity	Treated mice with ADNVs at the dose up to 25 mg/ kg via intraperitoneal (i.p.) injection, and no apparent damages were observed in the heart, liver, spleen, lung, kidney, or intestines in mice upon ADNVs administration.	A murine lung cancer model by subcutaneously inoculating lewis lung carcinoma (LLC) cells into C57BL/6 mice. Compared with i.p. injection, the route of both i.t. and i.v. rendered ADNVs to efficiently reach the tumor site, while s.c. injection exhibited negligible effect. Moreover, ADNVs instillation via i.t. and i.v. had similar effects in tumor control compared to that via i.p. injection, while s.c. injection had much smaller effect.	Remodeling the tumor microenvironment and reprogramming tumor-associated macrophages (TAMs) to inhibit tumor growth and enhance anti-tumor immunity	[32]

TCM-CDs	Armeniacae Semen Amarum (ASA)- derived Carbon Dots	One-step calcination method	Antioxidant and anti-inflammatory activity	——	ASAC-CDs significantly ameliorated the infiltration state of inflammatory cells and red blood cells in the alveolar cavity and lung interstitium in dose-effect relationship; significantly reduced inflammatory cells; significantly reduced the levels of IL-6, IL-1β, and TNF-α in in serum and increased the levels of IL-10.	Significant antioxidant and anti-inflammatory effects; significantly alleviated the pulmonary inflammation in LPS-induced ALI rats.	[33]
	Honeysuckle-derived Carbon Dots	Carbonization method and hydrothermal method	Antioxidant and anti-inflammatory activity	Hy-CDs were predominantly aggregated in the lungs, liver, and kidneys. Continuous tail vein injection into mice for 7 days (5 mg/kg), no obvious tissue damage was observed, and there was no liver or kidney function damage. The blood compatibility was good.	Hy-CDs significantly down-regulated the levels of TNFα, IL-1β, and IL-6 that were overexpressed in the lung tissues of ALI mice and Lung ischemia-reperfusion injury (LIRI) mice. Hy-CDs significantly restored lung dysfunction.	Effectively alleviate cellular oxidative stress and inhibit the secretion of pro-inflammatory cytokines; effectively inhibit Caspase11/ GSDMD-dependent non-classical pyroptosis; significantly inhibit ALI and LIRI.	[34]
	Withania somnifera (L).- derived Carbon Dots	One-step hydrothermal method	Anti-inflammatory, antioxidant and antiviral activities	Surface passivated NCQDs to curb Covid-19 crises with around 85% inhibition of SARS-CoV pseudoviron cells, which is better in comparison to the non-doped NCQDs.	——	Significantly inhibit SARS-CoV pseudoviron cells.	[35]
	Dandelion, Violet, and Isatis root-derived Carbon Dots	One-pot hydrothermal method	Anti-inflammatory, antioxidant and antiviral activities	The inhibition rates of VIP-CDs against S. aureus and E. coli were 91.2% and 90.9% respectively. After complexing with copper ions, the inhibition rates increased to 96.3% and 98.4% respectively.	——	Effective against both Gram-positive and Gram-negative bacteria	[36]

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Furthermore, NEs can serve as pulmonary inhalation drug carriers, enabling targeted delivery of poorly soluble drugs to the lungs for therapeutic purposes. For instance, tanshinone IIA (TSIIA), a phenanthrenequinone derivative extracted from *Salvia miltiorrhiza*, is a widely used CHMs with diverse pharmacological functions, such as anti-inflammatory and antioxidant properties. However, its therapeutic activity is limited by low aqueous solubility, poor bioavailability, short half-life, and extensive metabolism. El-Moslemany et al developed a TSIIA-loaded NEs (TSIIA-NE) using ultrasonic technology, formulated with bioactive natural components, a rhamnolipid biosurfactant, and TTO as the oil phase. TSIIA-NE improved LPS-induced lung ventilation dysfunction and pathological changes through antioxidant effects (upregulation of superoxide dismutase (SOD) and glutathione peroxidase (GPxs), downregulation of malondialdehyde (MDA)), anti-inflammatory actions (upregulation of IL-10, downregulation of TNF-α and IL-17), and inhibition of glycocalyx degradation. This resulted in a 1.4-fold and 1.9-fold increase in tidal volume and minute ventilation, respectively, a 32% reduction in lung wet/dry weight ratio, and improved arterial blood gas levels.[16] Similarly, Arbain et al developed a quercetin-loaded NEs using palm oil esters/ricinoleic acid as the oil phase. This formulation exhibited a suitable mass median aerodynamic diameter (MMAD) of 3.09 ± 0.05 μm, a high fine particle fraction (FPF) of 90.52 ± 0.10%, and an inhalation efficiency of 81.26 ± 1.28%, meeting the physicochemical and aerosolization properties required for deep lung delivery applications.[17] The optimized NEs demonstrated potential cytotoxicity against A549 lung cancer cells without affecting normal cells.

However, NEs still face challenges in practical applications, such as low drug-loading capacity and poor stability. Therefore, developing novel natural emulsifiers with biocompatibility based on the characteristics of NEs represents a crucial direction for advancing this technology. The research and development of new excipients will serve as a breakthrough, not only enhancing the oral absorption rate of drugs but also ensuring their safety and operability—fundamental requirements for clinical translation. Additionally, research efforts into multi-component NEs drug delivery systems require further strengthening. Notably, CHMs, characterized by its multi-component nature, differs significantly from single-component Western medicine. Thus, particular emphasis should be placed on advancing research in multi-component NEs delivery systems for CHMs.

Self-Assembled NPs Based on Active Ingredients From CHMs

Studies have revealed that due to the structural diversity of components extracted from CHMs, certain active ingredients in CHMs formulas possess self-assembly properties, enabling them to spontaneously organize into ordered structures such as NPs, nanofibers, micelles, and vesicles. Self-assembly refers to the process by which molecules or molecular aggregates form stable, structurally defined systems through weak non-covalent interactions—including hydrogen bonds, van der Waals forces, π-π stacking, electrostatic interactions, and coordination bonds—driven by additive effects and synergistic interactions. Notably, intermolecular hydrogen bonds play a dominant role, with the stability and binding energy of the assembled system increasing with the multiplicity of hydrogen bonds (eg, single vs multiple hydrogen bonds). Nano-modified CHMs based on the self-assembly of CHMs-derived bioactive molecules can significantly enhance the solubility of poorly water-soluble components and improve their bioavailability in vivo.[38] Remarkably, these natural CHMs constituents not only act as nanocarriers but also exert synergistic therapeutic effects. Compared to conventional synthetic nanocarriers, the chemical carrier-free self-assembly strategy offers superior safety and minimal toxicity. Self-assembled NPs based on the self-assembly of CHMs-derived bioactive molecules can significantly enhance the solubility of poorly water-soluble components and improve their bioavailability in vivo. Natural active ingredients from CHMs can serve as nanocarriers while also exerting synergistic therapeutic effects themselves. Compared to commonly used nanocarriers, the carrier-free self-assembly strategy demonstrates higher safety with almost no toxicity. Self-assembled nano-modified CHMs feature simple preparation procedures and high drug loading capacity, while achieving highly stable drug delivery without requiring any carriers.[39]

Preparation Method of Self-Assembled NPs

According to the literature, there are two main categories of self-assembled NPs derived from CHMs: The first category consists of herbal decoction-based self-assembled NPs, namely, the nanoparticles formed through molecular recognition and self-assembly processes during the decoction preparation of herbal medicines, where active chemical components are extracted and subsequently self-organize. The second category is artificially assembled self-assembled NPs from CHMs,

which are inspired by the self-assembly phenomena of CHMs chemical components and involve the intentional assembly of relevant herbal constituents into nanoparticles. The latter can be further subdivided into two types: self-assembled NPs formed by CHMs active small molecules and those assembled from CHMs primary metabolites such as proteins, polysaccharides, and others. The preparation methods and formation conditions of CHMs-derived self-assembled NPs are relatively simple, requiring no complex processes. Self-assembled NPs derived from herbal components are typically formed by placing relevant constituents in water or buffer solutions, followed by assembly through methods such as heating and stirring, solvent exchange, or emulsion solvent evaporation. Self-assembly from CHMs decoctions is commonly achieved by extraction after boiling. Studies have revealed that active components of CHMs, such as small molecules (eg, terpenoids, flavonoids, alkaloids, quinones, and polyphenols) and macromolecular constituents (eg, polysaccharides and proteins), possess self-assembly capabilities. These components can undergo spontaneous self-assembly in various solutions (Figure 1).[38]

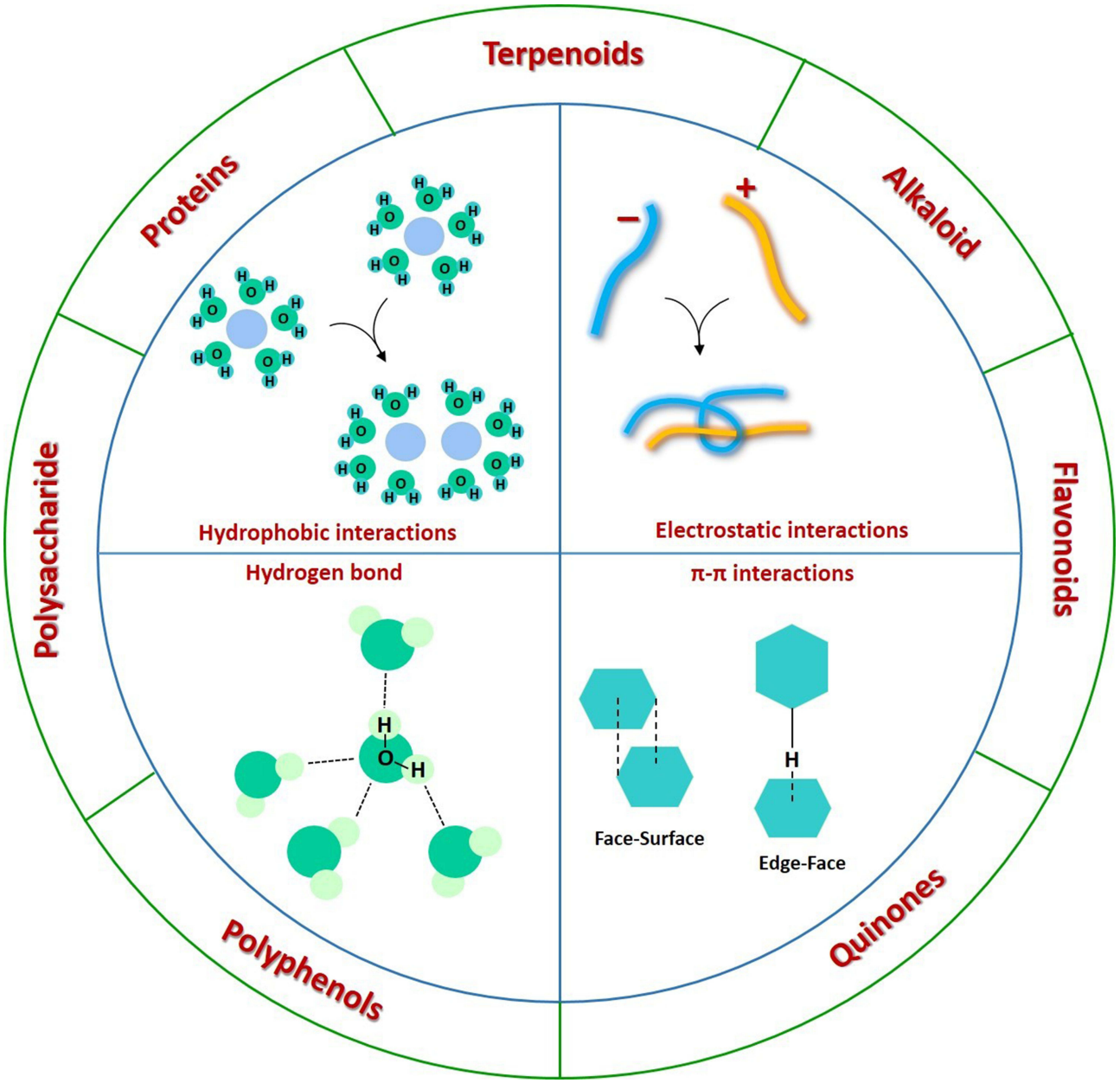

Figure 1 Molecules with self-assembly properties and the main types of interactions that drive the molecular self-assembly of natural products include hydrophobic interactions, electrostatic interactions, hydrogen bonds and π-π interactions.

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However, in CHMs, the self-assembly process of NPs often occurs simultaneously with the dissolution of herbal components. This "integrated extraction-assembly" mode restricts precise control over the assembly conditions, thereby limiting the optimization of self-assembled NPs in CHMs. To address these challenges, researchers in recent years have progressively proposed an improved "separated extraction-assembly" strategy. This approach decouples the extraction process of herbal components from the self-assembly process through technological separation, enabling independent control over parameters at each stage. Consequently, it significantly enhances the quality controllability and therapeutic application potential of self-assembled NPs in CHMs. Such refined construction strategies include microprecipitation, pH-driven methods, and heat-driven methods.

Microprecipitation is a self-assembly strategy for CHMs based on the solvent displacement principle, which has been widely applied in recent years for optimizing CHMs self-assembly processes. This method involves slowly adding a CHMs extract obtained using a good solvent (such as ethanol) into a poor solvent (such as a herbal decoction). Leveraging the polarity difference between the two solvents, it induces the self-assembly of CHMs molecules, ultimately forming stable NPs. Microprecipitation is particularly suitable for components in CHMs that exhibit significant hydrophilic-hydrophobic differences, such as molecules containing aromatic ring scaffolds, hydrophobic side chains, and polar functional groups.

The pH-driven method is a strategy that induces the self-assembly of CHMs compounds by adjusting the system's pH.[40] The key to this approach lies in leveraging the pH-responsive characteristics of both extraction and self-assembly stages, thereby optimizing the self-assembly process of CHMs in a stage-by-stage manner. This method is particularly suitable for CHMs compounds containing weakly acidic or weakly basic functional groups, as their self-assembly process is strongly influenced by the charge state and dissociation behavior of the constituents.

The thermally-driven method is a strategy that relies on temperature variations to induce the self-assembly of CHMs compounds into self-assembled NPs.[41] This approach first involves gradually heating the CHMs water decoction to enhance molecular thermal motion, thereby improving solubility and diffusion capacity in solution while inducing conformational rearrangement of molecules to promote self-assembly. Subsequently, by controlling the cooling rate or maintaining isothermal conditions, the nanostructure is further stabilized to precisely regulate particle size and morphological distribution, ultimately enhancing system homogeneity and stability. Through manipulation of key process parameters—including heating temperature, heating duration, and cooling rate—the thermally-driven method enables precise control over nanoparticle size, polydispersity index (PDI), and morphology of the self-assembled NPs.

Additionally, self-assembly methodologies encompass supporting techniques including supramolecular assembly, co-assembly techniques, microfluidic technology, and ultrasonication-assisted approaches.

The Application of Self-Assembled NPs in Pulmonary Diseases and Lung Cancer

Recent studies have reported a series of research achievements in nano-modified CHMs based on the self-assembly of CHMs-derived bioactive molecules. This self-assembly technology effectively addresses the limitations of CHMs extracts in practical applications. These carrier-free, self-assembled NPs, composed purely of natural products, reduce toxic side effects while enhancing the bioavailability of natural compounds and prolonging their retention time in vivo. The self-assembled nano-modified CHMs demonstrate multiple advantages in pulmonary diseases and lung cancer treatment, including simplified preparation processes, improved drug stability, and synergistic therapeutic effects inherent to CHMs components (Table 1).

Ursolic acid (UA), a natural product derived from edible plants, exhibits potent anticancer activity and low toxicity. However, its poor water solubility limits clinical applications. Fan et al employed a simple and green solvent exchange method to synthesize chemical carrier-free self-assembled NPs (UA NPs) through hydrophobic interactions and hydrogen bond interactions between UA molecular bases. UA NPs significantly inhibited COX-2/VEGFR2/VEGFA expression enhanced the immunostimulatory activity of TNF-α, IL-6, and IFN-β in cultured A549 cells, reduced STAT-3 activity, thereby suppressing proliferation and inducing apoptosis in human lung adenocarcinoma A549 cells. The half-maximal inhibitory concentrations (IC50) at 12 h and 24 h were both lower than those of free UA. In vivo experiments demonstrated that UA NPs outperformed free UA in reducing tumor volume and maintaining body weight in lung cancer-bearing mice. Additionally, UA NPs showed hepatoprotective effects and immunotherapeutic potential. These

chemical carrier-free self-assembled NPs of CHMs-derived components may represent a promising strategy to enhance the anticancer efficacy of herbal antitumor bioactive compounds.[18] He et al prepared self-assembling P-NFs nanofilaments by conjugating paclitaxel (Ptx) with succinic acid via ultrasonication.[19] Compared to free Ptx, P-NFs nanofilaments demonstrated enhanced antitumor efficacy against non-small cell lung cancer (NSCLC) cells. In vitro studies have shown that P-NFs nanofilaments can significantly induce apoptosis of A549 and H460 cells and inhibit the migration of A549 cells. P-NFs nano-filaments enhanced the expression of bax/bcl-2, protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), phospho-c-Jun N-terminal kinase (p-JNK), and C/EPB homologous protein (CHOP), which suggested that the strong antitumor effect of P-NFs nano-filaments may be partially attributed to the activation ER stress. Collectively, the results demonstrate that self-assembled P-NFs nanofilaments exhibit superior cytotoxicity toward lung cancer cells, highlighting their potential as a delivery strategy to enhance the therapeutic efficacy of Ptx in lung cancer treatment.[42]

Respiratory syncytial virus (RSV) is one of the most significant pathogenic infections in children, associated with high morbidity and mortality rates. Currently, there are no effective and safe drugs or vaccines available for RSV. Song et al proposed a dual-component carrier-free self-assembled nanogel based on glycyrrhizic acid (GA) and ephedrine (EPH), which forms an efficient nanomaterial with sustained drug-release capabilities (EPH-GA nanogel). This self-assembled nanogel primarily utilizes hydrogen bonding and hydrophobic interactions as the driving forces for self-assembly, enabling it to serve as an antiviral carrier-free nanomedicine with 100% drug-loading efficiency. More importantly, it enhances the bioavailability and targeting efficiency of glycyrrhizic acid (GA) and ephedrine (EPH). After oral administration, EPH-GA acts as a "physical barrier" in vivo, blocking 42.91% of RSV adsorption to host cells, significantly reducing viral load in mouse lungs, decreasing IL-6 expression induced by viral infection, and ameliorating RSV-induced pulmonary lesions and tissue infiltration. The in vivo process of EPH-GA demonstrates its advantage in delivering drugs at high concentrations to lesion sites, thereby enhancing its antiviral mechanisms at the cellular level. Therefore, this self-assembly phenomenon involving natural components holds promise as a new avenue for novel drug research, offering innovative strategies to address contemporary respiratory virus pandemics.[20] Chang et al employed an ultrasound-assisted antisolvent precipitation method to synthesize self-assembled resveratrol NPs (Res NPs) through π–π and π-sigma interactions, using resveratrol (Res) with low water solubility and bioavailability. The obtained Res NPs exhibited enhanced aqueous solubility and faster dissolution rates, which are more conducive to improving the therapeutic efficacy of Res against RSV-induced viral pneumonia. In vitro studies demonstrated that Res NPs exerted antiviral effects by inhibiting RSV replication and reducing the production of pro-inflammatory cytokines. Using an RSV-infected mouse model, it was confirmed that Res NPs achieved stronger pulmonary accumulation, thereby improving therapeutic outcomes for pneumonia. Res NPs demonstrated superior advantages in suppressing RSV viral load and ameliorating the pulmonary microenvironment in RSV-infected mice. Consequently, the self-assembled Res NPs could serve as a promising candidate for the treatment of RSV pneumonia (Figure 2).[21]

Pang et al prepared flavonoid-based nanomedicine (EBNPs) by driving the self-assembly of polyethyleneglycol-epigallocatechin gallate (pEGCG) and baicalin through intermolecular hydrogen bonding, hydrophobic interactions, and π-π stacking. The nanoparticles were further modified by conjugating hyaluronic acid (HA) with phenylboronic acid to design reactive oxygen species (ROS)-responsive NPs (HA-EBNPs). HA-EBNPs alleviated acute lung injury (ALI) by reprogramming the phenotype of alveolar macrophages (AMs). Results showed that HA-EBNPs attenuated mitochondrial defects by restoring mitochondrial membrane potential, oxidative phosphorylation activity, and ATP production via modulation of the AMPK/PGC-1α signaling pathway. HA-EBNPs selectively targeted M1-type AMs through CD44 receptor-mediated interaction, thereby polarizing AMs from pro-inflammatory M1 to anti-inflammatory M2 phenotypes, accompanied by reduced levels of inflammatory cytokines, ultimately exerting potent anti-inflammatory effects. In vivo experiments confirmed that nebulized HA-EBNPs effectively targeted lung inflammatory tissues, significantly suppressing pulmonary inflammation, mitigating lung injury, improving lung histopathology, and demonstrating favorable biocompatibility. These findings indicate that HA-EBNPs could serve as a promising nanomedicine for treating ALI.[22]

Moreover, self-assembling NPs can serve as a novel pulmonary drug delivery system (PDDS) to transport medications to the lungs, producing local or systemic therapeutic effects. Simultaneously, they enhance drug uptake and retention in pulmonary tissues while facilitating slow or controlled release of the drugs. For example, Zhang et al

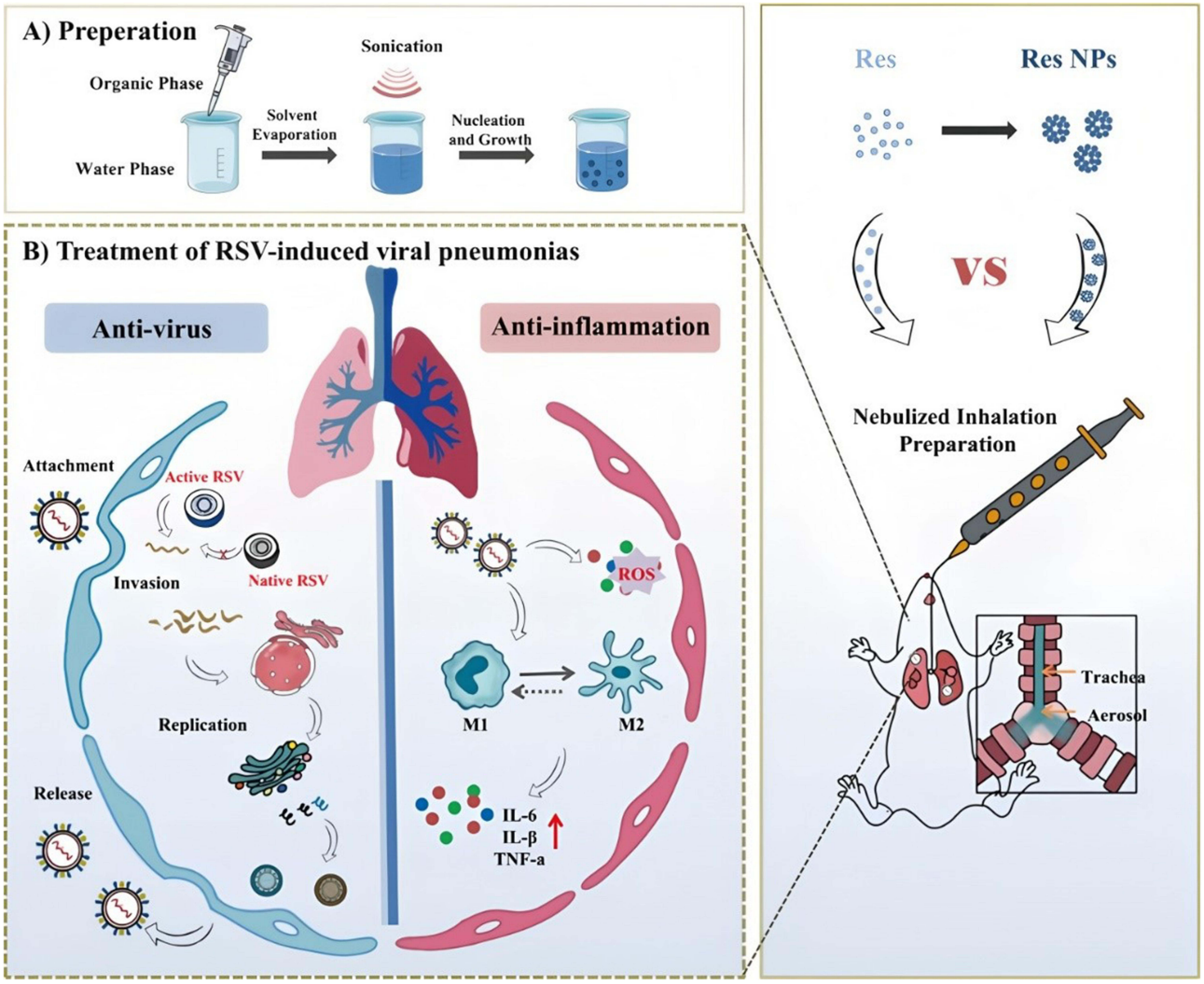

Figure 2 Schematic diagrams of Res NPs nebulized inhalation preparations and their therapeutic mechanism for RSV-Induced Viral Pneumonia. (**A**) The preparation process of the self-assembled Res NPs. (**B**) The therapeutic mechanism of the self-assembled Res NPs for RSV-Induced Viral Pneumonia. The red upward arrow represents the expression levels increasing. Adapted with permission from Chang C, Lu C, Zheng Y, et al. Sonication-assisted self-assembled resveratrol nanoparticles with enhanced antiviral and anti-inflammatory activity against respiratory syncytial virus-induced pneumonia. *ACS Appl Mater Interfaces*. 2024;16:50442–50458,[21] copyright 2024, American Chemical Society.

designed and constructed a universal lung-targeting NPs. Utilizing the amphiphilic structural properties of platycodon secondary saponin 3-O-β-d-glucopyranosyl platycodigenin 682 (GP-682), they self-assembled GP-682 nanomicelles to enhance the efficacy of levofloxacin (Lev) in treating *Pseudomonas aeruginosa* PA14-induced acute lung injury in mice. Studies demonstrate that GP-682 nanomicelles significantly improved GP-682's cell membrane permeability and in vitro cellular uptake, facilitating drug absorption. In murine models of *P. aeruginosa* PA14-induced acute lung injury of mice, pre-administration of GP-682 micelles before antibiotic treatment improved survival rates and anti-infective outcomes. Compared to Lev monotherapy, the micelles reduced lung injury, bacterial invasion, and cytokine expression. GP-682 micelles enhanced Lev distribution in murine lung tissues while decreasing antibiotic overexposure. Although GP-682 micelles alone exhibited no antimicrobial activity, their combination with Lev achieved therapeutic effects comparable to high-dose Lev treatment. These results confirm that GP-682 micelles improve Lev distribution in murine lungs by increasing pulmonary permeability, thereby exerting novel protective antibacterial effects. This study verifies that GP-682 nanomicelles combined with Lev (and potentially other drugs) provide a more flexible pulmonary drug delivery pathway.[23]

Self-assembled NPs of active CHMs molecules overcome the limitations of carrier materials, featuring simple and eco-friendly preparation processes. Moreover, owing to the diverse therapeutic effects of natural medicinal components,

self-assembled NPs of different drug molecules can exert synergistic actions against multiple diseases. However, current self-assembly interactions among active CHMs molecules primarily rely on non-covalent forces, resulting in inherent physicochemical instability. Enhancing the stability of these nanoformulations represents a key challenge for advancing their clinical translation. Therefore, it is imperative to establish molecular structure-based databases and AI prediction tools to reduce the difficulty in identifying small molecules with suitable self-assembly properties. Furthermore, exploring optimized preparation methods is crucial for improving the characteristics of self-assembled NPs derived from CHMs, while additional research is needed to investigate and enhance their stability. More critically, chemical carrier-free nanoformulations based on self-assembled modified active CHMs components may lack specific targeting in disease treatment. The passive targeting effect fails to achieve effective accumulation at lesion sites and remains constrained by biological barriers, necessitating further improvements in nanoformulation delivery efficiency.

Nanocrystal

Nanocrystal are nanoscale crystals of active pharmaceutical ingredients (APIs) directly obtained through high-intensity mechanical forces, requiring no carrier materials and easily meeting clinical needs. These drugs typically consist of pure drug particles with a particle size ranging from 1 to 1000 nm, which can be stabilized using surfactants or stabilizing agents without the need for carrier materials.

Nanocrystal, with their enormous specific surface area, can enhance adhesion to biofilms while improving the drug's saturated solubility and dissolution rate, thereby increasing bioavailability.[43] These nanocrystalline drugs primarily enhance biological activity by reducing particle size and increasing specific surface area. Due to their small particle size, nanocrystals significantly reduce the likelihood of macrophage clearance. When administered via pulmonary inhalation, drug nanocrystals leverage their nanoscale properties to minimize pulmonary macrophage clearance, promote deep lung deposition and enhanced airway penetration, achieve more uniform drug distribution, higher deposition rates, and more precise therapeutic targeting. Consequently, nanocrystal-based pulmonary delivery serves as an effective non-invasive method to transport anticancer drugs to lung cancer cells. Nanocrystals can passively accumulate in cancer cells via the enhanced permeability and retention (EPR) effect. Absorbed through deep lung tissues into the lymphatic circulation, these drugs can specifically target lymph node metastases in advanced lung cancer.

The Preparation Methods of Nanocrystal

There are three main methods for preparing nanocrystal: "Top-down" technology, "Bottom-up" technology, and combination techniques (Figure 3). The Bottom-up approach, also known as the "precipitation method", involves dissolving the drug in a good solvent first, followed by adding it to a poor solvent. By altering the solvent, the drug precipitates to form uniform, fine crystals. Specific methods include micro-precipitation and supercritical fluid techniques. The key to this technology lies in controlling the crystallization structure to prevent drug aggregation and ensure particle sizes remain within the nanoscale range. This method offers advantages such as simple operation, low cost, single-step completion, and ease of industrial-scale production. However, its drawbacks include challenges in scaling up, poor reproducibility, the necessity of organic solvents (leading to residual solvent concerns), and unsuitability for drugs insoluble in both aqueous and non-aqueous solvents.

The Top-down technology, also known as the "dispersion method", refers to techniques that use mechanical forces to reduce larger drug particles into nanoparticles. These include media milling and high-pressure homogenization. Top-down processes demonstrate good reproducibility and industrial scalability, making them the most widely applied preparation technology for nanocrystals. Currently, the majority of nanocrystal drugs available are produced using Top-down methods. However, drawbacks of this technology include the requirement for extensive processing cycles to achieve the desired particle size, as well as potential particle aggregation over time, leading to poor physical stability.

The Application of Nanocrystal in Lung Cancer

Sharma et al utilized a "Top-down" method, employing Pluronic grafted chitosan (Pl-g-CH) as a stabilizer, and optimized the preparation of oral paclitaxel (PTX) cationic nanocrystals (PTX/NC) using a high-pressure homogenizer. This approach addressed side effects such as erythrocyte aggregation, neutropenia, and hyperlipidemia-related allergic

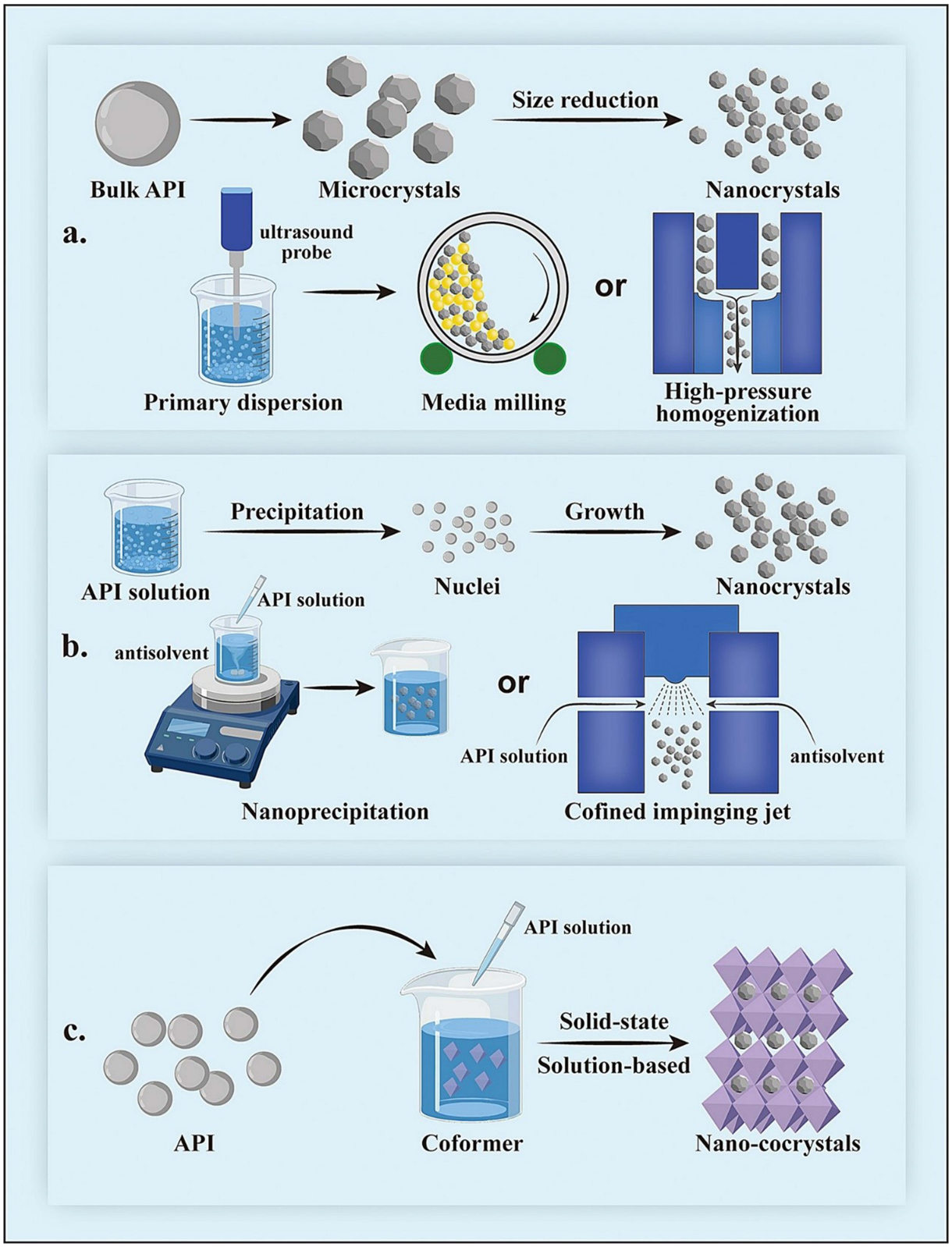

Figure 3 Nanocrystals preparation techniques. (**a**) "Top-down technology". (**b**) "Bottom-up" technology. (**c**) Strategies for the formation of nanococrystals. Reproduced with permission from Yao Y, Xu Z, Ding H, et al. Carrier-free nanoparticles-new strategy of improving druggability of natural products. *J Nanobiotechnol*. 2025;23:108.[6] Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license.

reactions observed in the clinical application of PTX for antitumor therapy. Further, by electrostatically adsorbing hyaluronic acid (HA) onto PTX/NC, they developed anionic nanocrystals (HA-PTX/NC) for tumor targeting. The interaction of HA-PTX/NC with CD44 receptors significantly enhanced cancer cell uptake of PTX and prolonged its blood circulation time. In LA-7 tumor-bearing rat models, HA-PTX/NC exhibited superior antitumor efficacy, reduced pulmonary metastasis, and lower toxicity compared to Taxol® (TM). Thus, this targeted nanocrystal system may serve as a promising anticancer therapeutic strategy.[24]

Wang et al successfully prepared camptothecin (CPT) nanocrystals using the antisolvent precipitation method, a classic "Bottom-up" technique, significantly improving CPT's water solubility and bioavailability. Furthermore, they coated the CPT nanocrystals with hyaluronic acid (HA), leveraging HA's unique CD44-binding ability to enable specific targeting of CD44-positive cancer cells. Compared to crude CPT and uncoated CPT nanocrystals, the HA-coated CPT nanocrystals (HA-CPT) exhibited markedly enhanced in vitro anticancer activity and apoptosis-inducing capacity against CD44-overexpressing cancer cells, while showing lower toxicity toward normal cells. Importantly, HA-CPT induced apoptosis in MDA-MB-231 cells by mediating the mitochondrial intrinsic apoptotic pathway, achieved through an increased Bax/Bcl-2 ratio and upregulated P53 expression. By combining nanocrystal preparation with HA coating, this study established a potential drug delivery platform for hydrophobic agents targeting CD44-positive cancer cells, aiming to enhance anticancer efficacy and reduce side effects.[25]

Iqbal et al employed the wet milling technique to prepare genistein (Gen), a flavonoid with anticancer properties, into genistein nanocrystals (NCs), overcoming clinical limitations such as poor solubility and low bioavailability. To further enhance the targeting capability of the nanocrystals, they surface-modified the NCs with transferrin (Tf), creating Tf-conjugated Gen-NCs (Tf-Gen-NCs). In tumor cells, overexpression of Tf receptors increased receptor-mediated endocytosis, thereby improving the selectivity and cytotoxicity of Tf-Gen-NCs toward cancer cells. Results demonstrated that Tf-Gen-NCs and Gen-NCs released 96% and 80% of the drug content within 20 minutes at 37°C, respectively, while unprocessed genistein released only 18%. Additionally, Tf-Gen-NCs exhibited strong inhibitory effects on lung adenocarcinoma epithelial cells (A549) and fibroblast cells (L929), with minimal toxicity to normal cells. Pharmacokinetic studies in mice following intraperitoneal administration revealed that the formation of NCs significantly enhanced the absorption and bioavailability of Gen after intraperitoneal injection (Figure 4).[26]

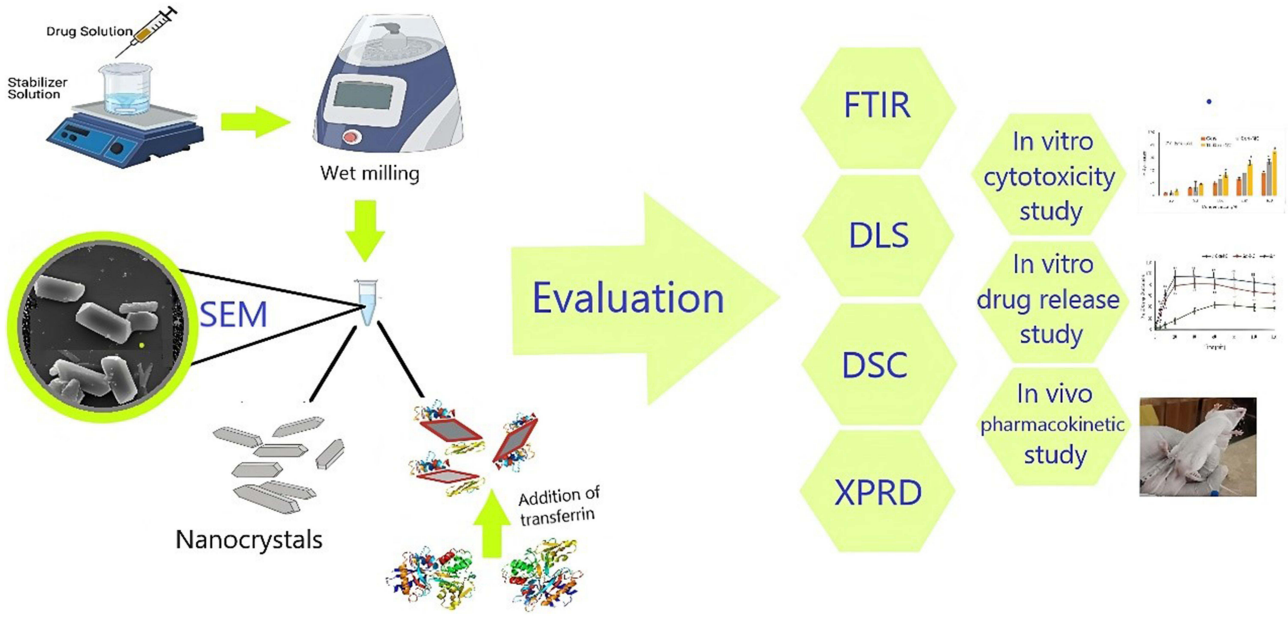

Figure 4 Schematic Diagrams of transferrin-modified genistein nanocrystals preparations and their anti-cancer assessment and pharmacokinetic evaluation. Reproduced with permission from, Iqbal FM, Rodríguez-Nogales C, Boulens N, Delie F. Formulation and optimization of transferrin-modified genistein nanocrystals: in vitro anticancer assessment and pharmacokinetic evaluation. *Int J Pharm*. 2024;667:124863.[26] Creative Commons Attribution 4.0 International license.

The nanocrystal preparation strategy also enables the crystallization of chemotherapeutic drugs, addressing limitations such as poor solubility and low bioavailability, thereby enabling synergistic cancer treatment. Kumar et al prepared paclitaxel (PTX) and bosutinib (BTB) nanocrystals using antisolvent precipitation crystallization and ultrasonication methods, respectively. These nanocrystals were further coated with liposomes to create Lipo/PTX-NCs. Compared to standalone drugs, these nanocrystals enhanced cellular internalization levels in cancer cells, inducing higher ROS generation and cancer cell apoptosis. Additionally, lipid-modified nanocrystals demonstrated improved translocational efficiency compared to unmodified nanocrystals. Intratracheally administered nanocrystals exhibited reduced drug distribution in other organs and prolonged drug retention in the lungs, indicating that the developed nanocrystals could facilitate preferential pulmonary accumulation for sustained drug efficacy, thereby enhancing anticancer activity against lung cancer. In conclusion, lipid-modified nanocrystals delivered via the pulmonary route offer a novel therapeutic approach for lung cancer.[27]

Research on pulmonary inhalation of nanocrystal particles represents a hotspot in nanocrystal technology, offering unique advantages for pulmonary delivery of personalized medications and poorly soluble drugs. However, the potential pulmonary toxicity of nanocrystal formulations hinders their development for inhalation applications. Additionally, major constraints impeding the therapeutic advancement of pulmonary nanocrystal delivery systems include: insufficient evidence regarding nanocrystal dissolution in pulmonary regions, absence of animal models for evaluating in vivo nanocrystal performance, and lack of effective methods to determine formulation aerodynamic properties. Consequently, more focused and extensive research is imperative to elucidate the fate of nanocrystals in pulmonary delivery systems. Investigating the in vivo safety assessment of drug nanocrystals holds significant importance for advancing nanocrystal-based pharmaceuticals.

CHMs-Derived Nanovesicles

Nanovesicles derived from CHMs (VCMH) are ubiquitous vesicular microstructures in herbal plants, characterized by a specific phospholipid bilayer structure. These nanovesicles are rich in bioactive lipids, proteins, RNA, and other pharmacologically active molecules, playing crucial roles in intercellular communication, signal transduction, and maintaining organismal homeostasis. With excellent biocompatibility, high stability in vivo, and intrinsic bioactive components derived from their source plants, VCMH also demonstrate superior drug-loading capabilities. Their unique properties have garnered significant attention for their broad application potential in biomedicine and nanotechnology.

VCMH exhibit excellent biocompatibility and low toxicity, along with anti-inflammatory, antioxidant, antitumor, and antifibrotic effects. In the preparation of VCMH from herbal materials, unprocessed medicinal herbs or fresh plants are utilized, preserving the multi-component complex system characteristic of CHMs, which offers significant advantages over single active ingredients. As nanoscale particles, VCMH demonstrate enhanced absorption in vivo, positioning them as novel bioactive substances in CHMs research. VCMH inherently combine bioactivity and targeting capabilities. Their vesicular cavity structure effectively protects encapsulated drugs by forming a protective barrier, significantly improving drug delivery efficiency, stability both in vivo and in vitro, and enabling precise targeted transport. Furthermore, applying appropriate physical or chemical modifications to their cavity structures can create more stable and precisely engineered drug carriers.[44]

The Preparation Method of VCMH-Derived Nanovesicles

VCMH can be extracted from both fresh herbal materials and dried medicinal plants. Fresh plants can be directly juiced or soaked after minimal processing to obtain extracts, while dried herbs require decoction to yield extract solutions. The resulting extracts can then undergo appropriate methods for further separation and enrichment of VCMH. Common isolation and purification techniques for VCMH include ultracentrifugation, density gradient centrifugation, size-exclusion chromatography, ultrafiltration, and polymer-based precipitation. Most studies combine two or more methods to improve extraction efficiency and purity. A widely used combined approach involves initial low-speed centrifugation of the extract to remove impurities, followed by ultracentrifugation to collect vesicles, and further enrichment via density gradient centrifugation.[45] Sucrose solutions are commonly employed to establish density gradients, enabling high-concentration vesicle isolation. VCMH typically distribute within the 30–45% sucrose layer, though this method cannot

fully eliminate protein contamination. Alternatively, iodixanol-based gradients are utilized.[46] Different methods yield varying results. For instance, ultracentrifugation produces Astragalus-derived VCMH with more intact morphology and higher yields compared to size-exclusion chromatography. Polyethylene glycol (PEG) precipitation achieves double the yield of ultracentrifugation, but retains substantial proteins due to PEG's high water solubility.[47,48] To address this, You et al combined size-exclusion chromatography with ultrafiltration, achieving high vesicle concentrations while minimizing protein interference, outperforming both ultracentrifugation and PEG precipitation.[49] Additionally, the ultra-pure solid film technology integrates sequential ultracentrifugation and multiple ultrafiltration steps. This method processes crude extracts from fresh plant juices through ultracentrifugation and repeated ultrafiltration, followed by solid film component addition, maximizing structural integrity and activity preservation. The resulting VCMH exhibit more uniform particle sizes and higher purity than those obtained via sucrose density gradient ultracentrifugation (SDGUC).

The Application of VCMH in Pulmonary Diseases and Lung Cancer

VCMH, containing numerous natural bioactive components, exhibit anti-inflammatory, antioxidant, anticancer, and immune-modulatory properties, and have attracted widespread attention in the treatment of pulmonary diseases (Table 1).

Acute Lung Injury (ALI), often triggered by severe respiratory infections, is characterized by excessive inflammatory responses and inefficient pathogen suppression, ultimately leading to extensive lung tissue damage and progression to Acute Respiratory Distress Syndrome (ARDS). Various pathogens, such as Gram-negative bacteria, Influenza A Virus (IAV), or SARS-CoV-2, have been shown to induce severe pulmonary inflammation and injury, resulting in high morbidity and mortality in critical cases. Recent studies highlight the role of VCMH in modulating pulmonary macrophages and promoting recovery from lung diseases, particularly ALI and ARDS. Ye et al developed Artemisia-derived nanovesicles (ADNVs) using an optimized ultracentrifugation method. Studies indicate that Artemisia and its extracts possess diverse pharmacological effects, including anti-inflammatory, antiviral, immunomodulatory, antifibrotic, and antitumor activities, with notable therapeutic potential against severe respiratory conditions such as COVID-19.[50,51] The findings from Ye et al demonstrated that ADNVs are effectively internalized by pulmonary macrophages, reprogramming them toward the anti-inflammatory M2 phenotype. GABA within ADNVs acts on lung macrophages via GABA receptors, promoting mitochondrial gene reprogramming and bioenergy production, while reducing oxidative stress and inflammatory signaling, thereby enhancing alveolar macrophage (AM)-mediated inflammation resolution. In mouse models of ALI induced by LPS, IAV, and SARS-CoV-2 pseudovirus, ADNVs significantly alleviated immunopathology and improved survival rates. This study underscores ADNVs' potential in mitigating lung pathology and accelerating recovery, offering a novel therapeutic avenue for respiratory diseases.[28]

Furthermore, studies suggest that VCMH also hold potential in treating pulmonary fibrosis, a progressive, chronic disease with high mortality rates and limited current therapeutic options. Du et al isolated VCMH from the CHMs *Rhodiola rosea* and demonstrated that its derived sRNA (HJT-sRNA-m7) targets fibrosis-related proteins, reduces fibrotic factor expression, and alleviates pulmonary fibrosis symptoms. Notably, most lipid components in *Rhodiola* decoctions are shared with other herbs such as *Andrographis paniculata, Taraxacum officinale* (dandelion), and *Lonicera japonica* (honeysuckle). Their study confirmed that lipid-formed vesicles enhance sRNA absorption into the bloodstream, highlighting the therapeutic promise of plant-derived vesicles in pulmonary fibrosis management.[29] Allium sativum is recognized for its anti-inflammatory, antioxidant, chemopreventive, and anti-cancer cell proliferation properties, making it applicable in the treatment of various diseases. Santos-Álvarez et al utilized differential centrifugation to isolate Allium sativum nanovesicles (AS-NV). Results demonstrated that AS-NV reduced NLRP3 inflammasome activation in primary macrophages. In a bleomycin-induced idiopathic pulmonary fibrosis (IPF) mouse model, AS-NV treatment lowered mRNA levels of genes associated with fibrosis, inflammation, and extracellular matrix (ECM) deposition in bleomycin-induced IPF, confirming AS-NV's ability to mitigate BLM-induced damage in pulmonary fibrosis models. These findings suggest AS-NV holds promise for developing novel nanovesicle-based therapeutic strategies against pulmonary fibrosis.[30]

VCMH also holds significant potential in lung cancer treatment (Table 1). The active components contained in VCMH can not only directly act on cancer cells to induce their apoptosis but also exert indirect anti-cancer effects through immunomodulation. Chen et al employed ultracentrifugation to prepare cucumber sarcocarp-derived

nanovesicles (CsDNVs) and cucumber pericarp-derived nanovesicles (CpDNVs). The results demonstrated that CsDNVs could be internalized by A549 cells, suppressing proliferation through inhibiting STAT3 phosphorylation, enhancing ROS generation, promoting cell cycle arrest, and increasing caspase activity. Compared to free CuB, CsDNVs exhibited stronger anticancer activity both in vitro and in vivo, reducing tumor growth rates without significant toxicity to murine visceral organs. This confirms that bioactive molecules within CsDNVs contribute to tumor growth inhibition.[31] Liu et al employed a combination of differential centrifugation and sucrose density gradient ultracentrifugation to isolate artemisia-derived nanovesicles (ADNVs). Artemisia species are recognized as antimalarial agents with broad biological activities, including immunomodulatory and antitumor properties. Results revealed that ADNVs specifically induced activation of the STING pathway, thereby promoting the transition of tumor-associated macrophages (TAMs) from the M2 to M1 phenotype, which enhanced antitumor immunity. Further studies demonstrated that TAMs internalized Artemisia-derived mtDNA via vesicle uptake, triggering cGAS-STING pathway activation to reprogram macrophages, thereby boosting cytotoxic T-cell responses and facilitating tumor regression. In a mouse lung cancer model established by subcutaneous inoculation of Lewis lung carcinoma (LLC) cells, ADNVs treatment was shown to inhibit tumor growth and enhance antitumor immunity by remodeling the tumor microenvironment and reprogramming TAMs. These findings confirm that nanovesicles derived from medicinal plants may be utilized to develop novel therapeutic approaches for cancer treatment.[32]

These studies have validated the use of VCMH in developing cancer therapeutics, while offering a novel perspective for isolating therapeutic agents from medicinal plants.

Despite its multiple advantages, the research and application of VCMH still face significant challenges. Substantial experimental validation remains necessary to further enhance the stability and drug-loading capacity of herbal vesicles, as well as to deepen our understanding of their in vivo metabolic mechanisms and immunomodulatory effects. Additionally, yield and purity continue to be critical research priorities for achieving clinical translation of VCMH. Crucially, substantial variations exist in VCMH derived from plants—organisms phylogenetically distant from animals and humans. Investigating the structural and functional uniqueness of VCMH thus represents a key area requiring in-depth exploration in future research.

Carbon Dot-Based Nanozymes Derived From CHMs

Carbon dots (CDs), a class of photoluminescent nanomaterials, have attracted significant research attention over the past decade due to their unique properties. C-dots exhibit advantages such as small size, ease of synthesis, and low cost. Their surfaces are rich in oxygen-containing functional groups (eg, carbonyl, carboxyl, and hydroxyl groups), endowing them with excellent water solubility and facile functionalization. CHMs-derived carbon dots (TCM-CDs) are synthesized using bioactive components and chemical substances from CHMs, such as polysaccharides, phenolic compounds, and alkaloids. Precursors for synthesizing TCM-CDs primarily include medicinal plants (rhizomes, leaves, flowers and pollen, fruits and pericarps, seeds), mineral-based medicines, and animal-derived medicines. Chinese herbal medicines contain abundant bioactive components, and TCM-CDs retain partial bioactivity from their carbon sources, thereby exhibiting diverse pharmacological effects. Different plant parts contain distinct bioactive constituents, which critically influence the properties and applications of TCM-CDs.[52]

CDs-based nanozymes are nanomaterials with enzymatic activity synthesized from carbon nanomaterials, typically smaller than 10 nm in size, consisting of a carbon core and surface functional groups. The carbon core acts as a framework composed of either sp^2-hybridized graphitic microcrystalline carbon or sp^3-hybridized amorphous carbon. The structure of surface groups primarily depends on the synthesis method of the CDs and the type of passivating agents selected. The covalent bonding between surface functional groups and the carbon core influences their physicochemical properties. An increasing number of CDs-based materials have been found to exhibit enzyme-like activities, including peroxidase-like, oxidase-like, catalase-like, and superoxide dismutase-like activities. These nanozymes regulate the production or elimination of ROS to treat diseases associated with redox imbalance.[53] TCM-derived CDs-based nanozymes exhibit high stability, biocompatibility, and enhanced pharmacological activity inherited from herbal sources, such as antibacterial, antioxidant, and antitumor effects, making them promising candidates for drug development and therapeutic applications.

Preparation Methods of CHMs-Derived CDs

The synthesis of CDs can be categorized into two strategies: top-down and bottom-up. Top-down synthesis involves breaking down larger particles into smaller ones at the nanoscale, primarily through methods such as laser ablation, arc discharge, and electrochemical oxidation. These approaches can produce monodisperse CDs with precisely defined molecular structures and sizes. However, they require expensive materials and setups, harsh and labor-intensive reaction conditions, and typically yield low quantities. In contrast, bottom-up approaches offer advantages such as eco-friendliness, low-temperature operation, simplicity, cost-effectiveness, and scalability, aligning with green chemistry and sustainable production principles.[54] Bottom-up methods involve pyrolyzing or carbonizing small molecules into nanoparticles within a desired size range, including hydrothermal synthesis, high-temperature pyrolysis, microwave-assisted methods, and solvothermal synthesis.[55,56] CDs synthesized via different methods exhibit distinct properties in terms of particle size, quantum yield, and pharmacological activity. Additionally, bottom-up approaches enable better control over size, morphology, and surface chemistry, making them the predominant method for preparing TCM-CDs.[57] Therefore, here we introduce several bottom-up methods for synthesizing CDs.

Hydrothermal Method

The hydrothermal method involves dissolving or dispersing pretreated starting materials in water, followed by ultrasonication. The reaction solution is then placed in a high-pressure autoclave and heated at specific reaction temperatures and durations to achieve effective homogeneous nucleation and growth of CHMs-CDs.[58] To further purify the CHMs-CDs, the suspension is filtered through a cellulose membrane and dialyzed using a dialysis bag for a designated period. CHMs contains abundant hydroxyl, carboxyl, or epoxy groups. During the hydrothermal synthesis of CHMs-CDs, these functional groups, derived from raw materials or partially carbonized organic carbohydrates such as oligosaccharides and fatty chains, condense onto the surface of the CHMs-CDs. As a result, the synthesized CHMs-CDs typically exhibit excellent water solubility, high purity, and distinct pharmacological activities.[52,59]

High-Temperature Pyrolysis Method

High-temperature pyrolysis refers to the direct thermal degradation of biomass under oxygen-free conditions, offering advantages such as easy reaction control, simple operation, and straightforward experimental setup. The process involves placing herbal materials in a crucible first, then heating the crucible at specific temperatures until carbonization occurs. During the entire synthesis, organic substances in the herbal medicine precursor can be gradually converted into herbal-derived CDs through sequential processes of heating, dehydration, degradation, and high-temperature carbonization under vacuum or inert atmospheres.[55]

Microwave-Assisted Method

The microwave-assisted method involves directly carbonizing the herbal medicine matrix into herbal-derived CDs under microwave irradiation. This approach offers a faster way to prepare CDs from CHMs. By combining microwave technology with chemical synthesis, these techniques provide efficient and uniform energy to the precursor solution. Consequently, the microwave-assisted method enables rapid and even heating of the reaction medium, significantly reducing reaction time while enhancing product yield and purity.

Solvothermal Method

Unlike the hydrothermal method, the solvothermal method employs various solvents other than water, yet it retains similar advantages such as low cost and simple operation, akin to the hydrothermal approach. A wide range of CHMs precursors can be utilized in the synthesis of herbal-derived CDs via the solvothermal method.[60]

The Application of CDs-Based Nanozymes in Pulmonary Diseases

Studies have shown that many biogenic carbon dots possess nanozyme efficacy, effectively scavenging intracellular ROS, inhibiting oxidative stress, and alleviating various diseases caused by oxidative damage. Since Zhao et al developed bifunctional fluorescent CDs using garlic as a natural precursor, which first demonstrated scavenging activity against DPPH radicals (DPPH•), various biomass CDs with free radical scavenging activity have subsequently been successfully

isolated from natural plants.[61] Deng et al utilized broccoli aqueous extract as a precursor to prepare biomass-derived carbon dots (BWE-CDs) with strong antioxidant activity through an optimized hydrothermal method. These BWE-CDs exhibited remarkable antioxidant properties due to their surface abundance of C=C bonds, carbonyl groups, and amino groups, while demonstrating lower cytotoxicity and superior biocompatibility. In both cellular models and zebrafish, BWE-CDs effectively scavenged ROS and inhibited LPS-induced inflammatory responses by modulating NO levels and upregulating the expression of superoxide dismutase (SOD) and the enzyme glutathione peroxidase 4 (GPX-4). The results indicate that these biologically derived CDs possess excellent antioxidant activity and favorable biocompatibility, suggesting their potential as promising antioxidant nanodrugs for inflammation treatment.[62]

Therefore, the antioxidant and anti-inflammatory activities of biologically derived CDs can be leveraged for the treatment of pulmonary inflammatory diseases, including acute lung injury (ALI) and other related conditions (Table 1). The carbonized product of *Armeniacae Semen Amarum* (ASA), ASAC Carbonisata (ASAC), has been widely used for its anti-inflammatory effects. Zhao et al employed ASAC as a carbon source and developed novel carbon dots (ASAC-CDs) using a green one-step calcination strategy. In an LPS-induced rat acute lung injury (ALI) model, ASAC-CDs alleviated LPS-induced inflammatory responses by reducing serum levels of IL-6, IL-1β, and TNF-α while increasing IL-10 levels. Notably, ASAC-CDs decreased MDA and MPO levels, enhanced SOD activity, and elevated GSH content, demonstrating their antioxidant activity. These results highlight the significant antioxidative and anti-inflammatory effects of ASAC-CDs against LPS-induced ALI, providing critical evidence for the clinical application of bio-derived CDs in anti-pneumonia therapies.[33] Deng et al developed CDs named Hy-CDs with both catalytic properties and pharmacological activity using the Chinese herbal medicine Lonicera japonica (honeysuckle) as a precursor, and applied them to the treatment of pulmonary inflammation including ALI and pulmonary ischemia-reperfusion injury. In this work, researchers employed carbonization and hydrothermal methods to prepare two distinct types of honeysuckle-derived CDs with SOD-like enzymatic activity, designated as Ca-CDs and Hy-CDs respectively. The study revealed that Hy-CDs exhibited stronger antioxidant properties compared to Ca-CDs, with differences in catalytic activity potentially originating from variations in surface functional groups. In vitro experiments demonstrated that Hy-CDs effectively alleviated cellular oxidative stress and inhibited the secretion of pro-inflammatory cytokines. Furthermore, they established an acute lung injury model and conducted intravenous injection therapy. Results showed that Hy-CDs displayed significant therapeutic effects, markedly suppressing inflammation caused by acute lung injury. The mechanism may involve Hy-CDs down-regulating GBP2 protein expression to effectively inhibit Caspase11/GSDMD-dependent non-canonical pyroptosis, thereby mitigating pulmonary inflammation. This work confirms that CDs derived from CHMs can possess enzymatic activity and favorable bioactivity, demonstrating potential as novel therapeutic agents for disease treatment (Figure 5).[34]

The antibacterial activity of CDs primarily involves cell wall damage and disruption of the infectious biofilm matrix through ROS generation, thereby curbing the spread of infectious pathogens and enhancing their susceptibility to antibiotics. Consequently, bio-derived CDs can effectively combat lung injury caused by pathogenic infections. Nair et al prepared three types of *Withania somnifera (L)*. (ASH)-derived NCQDs using a simple one-step hydrothermal method (bottom-up approach), designated as HASHP (undoped), nitrogen-doped HASHNH3 (ammonia surface passivation), and HASHEDA (ethylenediamine surface passivation). The ammonia-passivated HASHNH3 and ethylenediamine-passivated HASHEDA demonstrated more significant antiviral activity compared to the undoped NCQDs (HASHP), particularly showing an inhibition rate of approximately 85% against SARS-CoV-2 pseudovirus. This provides a promising pathway for addressing critical pathogenic diseases such as COVID-19.[35] Deng et al developed a composite nanozyme, DVI-CDs-Cu, by complexing DVI-CDs (derived from *dandelion, violet*, and *Isatis indigotica*) with Cu^{2+} ions, which exhibits exceptional antioxidant and antibacterial properties. The DVI-CDs, featuring abundant surface functional groups, not only form stable complexes with copper ions but also demonstrate remarkable SOD-like activity. The attached Cu^{2+} ions further exhibit peroxidase (POD)-like functionality, forming a cascade effect that significantly enhances the antioxidant capacity of DVI-CDs-Cu and amplifies its antibacterial performance. This nanozyme achieves comprehensive scavenging of 90% ROS while eliminating approximately 98% of bacteria. This work provides novel insights into the application of bio-derived CDs with nanozyme activity for therapeutic strategies against lung injury caused by pathogenic infections.[36]

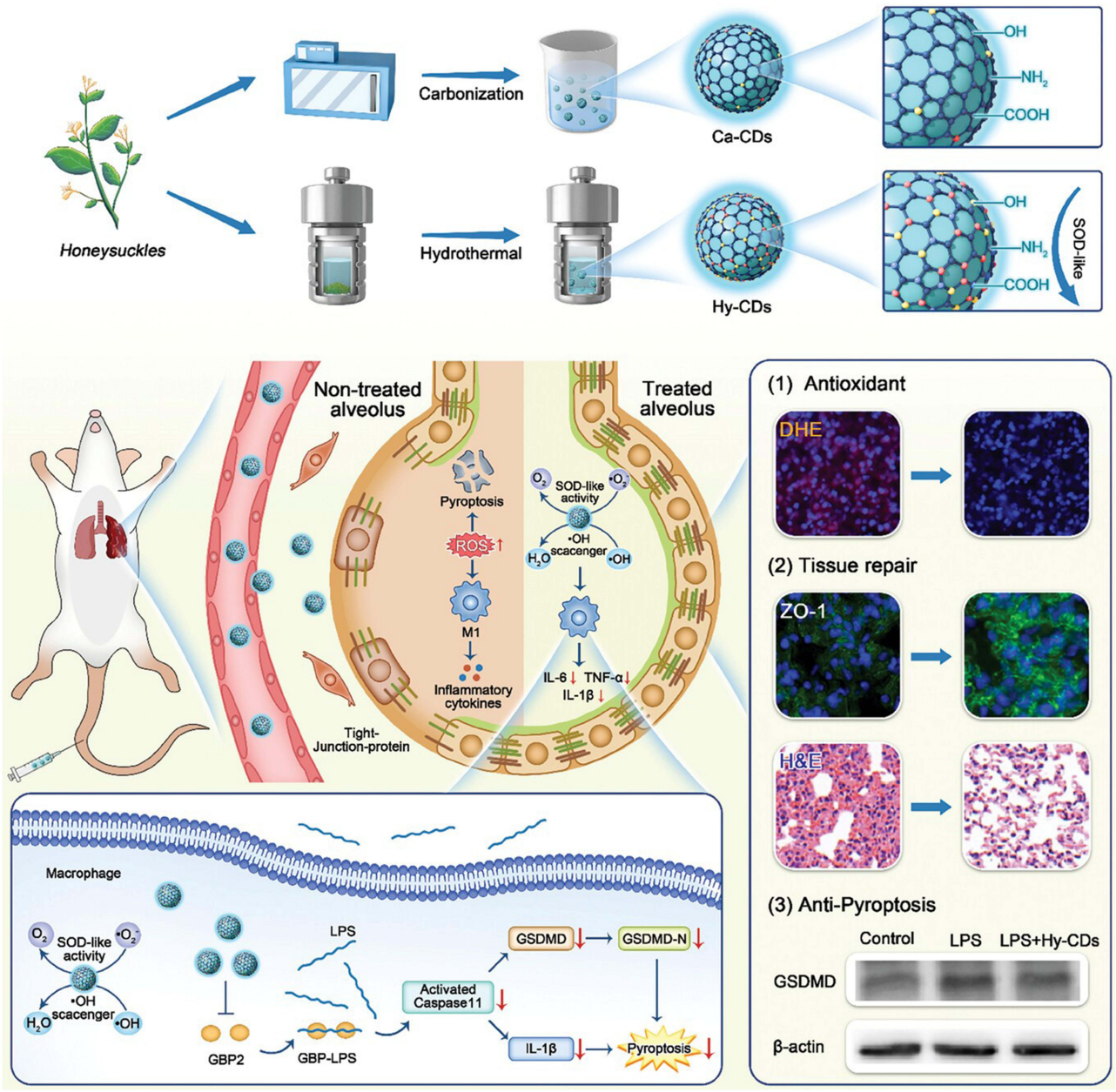

Figure 5 The process of synthesizing honeysuckle-derived CDs and their mechanism of action in alleviating lung inflammation. Hy-CDs exhibited enhanced enzymatic catalytic activity. In the context of mitigating oxidative stress injury in the lungs, Hy-CDs demonstrated the capability to scavenge excessive ROS and concurrently inhibited Caspase11/GSDMD-mediated non-classical pyroptosis by downregulating the expression of GBP2 protein. The red upward arrow represents the expression levels increasing. The red downward arrow represents the expression levels increasing decreasing. Reproduced with permission from, Deng Z, Zhang Y, Li R, et al. Honeysuckle-derived carbon dots with robust catalytic and pharmacological activities for mitigating lung inflammation by inhibition of Caspase11/GSDMD-dependent pyroptosis,[34] © 2025 Wiley-VCH GmbH.

CHM-CDs exhibit tremendous potential in pharmacotherapy and clinical translation due to their remarkable intrinsic bioactivity and underlying pharmacological effects. Despite promising applications across multiple fields, current research on CHM-CDs still faces limitations, particularly insufficient investigation into drug delivery and targeting capabilities. Therefore, future efforts will focus on developing smart CHM-CDs engineered according to disease microenvironment characteristics. Through surface modifications incorporating targeting ligands (eg, antibodies, peptides), these nanostructures will achieve precise recognition of disease-specific biomarkers at lesion sites. Utilizing stimulus-responsive strategies (pH-, temperature-, or enzyme-triggered mechanisms), CHM-CDs will enable targeted drug release within specific pathological microenvironments—enhancing delivery efficiency and therapeutic efficacy while minimizing off-target effects in healthy tissues. Key approaches to improve in vivo stability include: implementing

rational surface modifications, exploring novel stabilizers and coating materials, and strengthening long-term stability assessments of CHM-CDs in biological systems.

Discussions and Prospects

Introducing nanotechnology into the theory of CHMs can address many bottleneck issues that constrain conventional herbal medicine, such as low efficacy, slow therapeutic effects, poor solubility, limited bioavailability, and restricted dosage forms. Therefore, the nano-scale transformation of CHMs is destined to become a critical breakthrough in the modernization of CHMs applications. The application of nanotechnology in herbal medicine alleviates the limitations of compounds, including low water solubility, short half-life, and poor bioavailability, thereby accelerating the development of CHMs remedies. The research on nano-modified CHMs involves the molecular-level design and modification of CHMs, representing a pivotal trend and direction for the future development of medical science. By integrating nanotechnology with natural medicinal plants, new possibilities emerge for natural product development. This approach helps mitigate potential toxicity and metabolic issues caused by traditional carriers while enhancing solubility, targeting precision, and safety. It holds significant potential for amplifying the medicinal properties of CHMs and creating innovative formulations.[63,64]

This review summarizes recent advances in chemical carrier-free NPs derived from natural CHMs for treating pulmonary diseases and lung cancer. These nano-modified CHMs include NEs, self-assembled NPs, nanocrystals, herbal-derived extracellular vesicles, and CDs-based nanozymes formulated from CHMs components. The preparation methods and mechanisms of action of these nano-modified CHMs are elaborated, highlighting their unique advantages in enhancing the pharmacological effects of natural bioactive compounds and treating lung disorders. The nanostructures of these formulations determine the therapeutic efficacy of herbal active ingredients in pulmonary disease management.[65–67] For instance, nanoemulsified herbal components can be administered via inhalation for targeted lung therapy, prolonging pulmonary retention, avoiding rapid clearance, reducing systemic drug distribution, and minimizing adverse systemic effects. Self-assembled NPs and VCMH derived from natural products not only exhibit drug encapsulation capabilities comparable to synthetic nanomaterials but also demonstrate superior biodegradability, biocompatibility, and safety. This dual functionality allows herbal bioactive components to act both as nanocarriers and synergistic therapeutic agents. Herbal nanocrystals, leveraging their large surface area, passively accumulate in cancer cells through the enhanced permeability and retention (EPR) effect. These nano-modified CHMs can penetrate deep lung tissues to access the lymphatic system, enabling targeted treatment of lymph node metastases in advanced lung cancer, thus broadening their application in anti-cancer therapies. CDs-based nanozymes derived from CHMs exhibit enzymatic activity, demonstrating potent antioxidant and anti-inflammatory effects, with significant potential in treating inflammation and pathogen-induced lung injuries. Notably, nano-engineered natural products and extracts can be directly formulated into diverse dosage forms, such as nanopowder injections, or delivered via NPs as carriers. This innovation fundamentally transforms traditional drug delivery approaches, overcoming the limitations of conventional formulations, such as delayed onset of action.[68,69]

Although chemical carrier-free nano-platforms derived from natural CHMs have demonstrated potential therapeutic activity, there remain numerous challenges to be resolved for their successful clinical application. While the nano-modified CHMs derived from fresh plants were discovered relatively early, research in this field remains insufficiently comprehensive, particularly in biomedical applications where most studies remain at the laboratory investigation stage. Notably, when nano-modified CHMs are employed as therapeutic agents or drug carriers in biomedical fields, their safety, efficacy, stability, and quality standards require rigorous regulation. Furthermore, modulating the ratios of multiple compounds within a single nano-platform to enhance synergistic efficiency continues to present significant challenges. Finally, improving the active targeting capabilities of nano-modified CHMs through surface modifications remains a critical consideration requiring further investigation.

During the application process, the optimal nanodrug delivery system (NDDS) must be selected based on the characteristics of the active ingredients in CHMs and the practical requirements. However, the challenges involved still require continuous breakthroughs and refinement. Only then can we provide more new directions for the subsequent design and development of CHMs-based nanoformulations that are more stable, controllable, safe, and effective. In the

future, advanced technological means such as multi-omics technologies and molecular imaging need to be utilized to elucidate the targets and mechanisms of action. This will provide theoretical support for clinical applications and new drug development. Furthermore, although studies on the safety and efficacy of most CHMs nanoformulations have been validated in various cell lines and animal models, human biological responses may differ. This necessitates more comprehensive in vivo safety evaluations and preclinical application studies to clarify the therapeutic effects of CHMs nanomedicines. Research into the in vivo distribution, targeted accumulation, pharmacokinetics, pharmacodynamics, and long-term in vivo toxicity of nanoformulations remains to be explored by more researchers.

In summary, nano-modified CHMs significantly enhance the therapeutic efficacy for pulmonary diseases and lung cancer through targeted delivery, multi-mechanism synergy, and high-efficiency penetration capabilities, while reducing side effects. They demonstrate promising prospects in the treatment of acute lung injury, pneumonia, pulmonary fibrosis, and lung cancer. Future efforts should focus on optimizing preparation techniques and advancing clinical translation research to validate their long-term safety.

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Disclosure

The authors declare that they have no competing interests in this work.

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