

How Traditional Chinese Medicine Can Play a Role In Nanomedicine? A Comprehensive Review of the Literature

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Abstract: Traditional Chinese medicine (TCM), a time-honored practice rooted in natural therapeutics, has served as a cornerstone in safeguarding human health across millennia, aiding in disease mitigation and life vitality preservation. However, many TCM active ingredients suffer from poor solubility, low bioavailability, uncertain toxicity and weak targeting ability. Nanomedicine represents a modern scientific frontier, emerging from the precise engineering of unique nanoscale characteristics, with extensive applications encompassing targeted therapeutic delivery and diverse biomedical fields. Although TCM and nanomedicine diverge fundamentally in historical origins and disciplinary foundations, growing investigations demonstrate their synergistic potential. In this review, nanosized TCM has been revealed as an innovative therapeutic strategy with significant clinical value. Based on the biological activities and structural characteristics of TCM active ingredients, we classify them into two categories: natural nanostructured formulations for TCM and nano-drug delivery systems for TCM. A systematic and comprehensive analysis of preparations specific and functions to two classes of TCM nanomedicines is highlighted. Insights into the advantage of TCM nanomedicines are also introduced. Subsequently, the applications of TCM nanomedicines in the biomedical treatment, including anti-cancer, anti-inflammation and anti-bacterial are summarized. Finally, challenges and future research directions are emphasized, aiming to offer guidance for the modernization of TCM nanomedicines.

Keywords: traditional Chinese medicine, active ingredients, drug delivery, biomedical treatment

Introduction

Traditional Chinese medicine (TCM), termed medicinal plants, has been of great importance in human health for thousands of years, serving as a complementary therapy for clinically treating diseases in China, South Korea, Japan, India and other countries. Specially, the World Health Organization has incorporated TCM into the supportive treatment system for cancer, allowing more countries in fully exploiting the therapeutic potential of TCM. A growing amount of research validates the diverse biological effects of TCM, such as anti-tumor,¹ anti-bacterial,² and anti-inflammatory³ properties. Furthermore, TCM extracts with unique structural skeleton and stereochemistry could effectively bind to drug targets, regulate physiological processes, and treat numerous diseases, providing extensive and valuable avenues for developing novel drugs.⁴ Many TCM-derived drugs are already in clinical use, including *artemisinin* extracted from sweet wormwood serves as a treatment for malaria,⁵ *curcumin* for anti-inflammation therapy,⁶ and *quercetin* as a tumor



chemotherapy drug.⁷ Regrettably, most TCM extracts have poor water solubility, restricted bioavailability, weak targeting ability and low stability, which impedes several novel drugs from entering clinical application.^{8–10} Thus, fully harnessing the biological activity of TCM, and developing innovative drug products with less side effects than the prevalent drugs, is a significant challenge in current scientific research.

The deep interdisciplinary convergence across biomedicine, chemistry, and materials has driven paradigm-shifting innovations, offering groundbreaking theoretical foundations for state-of-the-art technological advancements. In recent decades, emerging nanotechnology has brought about a revolutionary change in the domain of medicine and healthcare. Particularly, nanomedicines have been intensively investigated for the prevention and therapeutic interventions against diverse pathologies, such as cancer and infectious diseases. Nano-drug delivery systems (NDDS) as the specific application play a crucial role in driving the progress of advancing nanomedicine due to their multiple beneficial characteristics, including the high-efficiency encapsulation of hydrophobic pharmaceuticals within amphiphilic systems, the preservation of therapeutic payloads against metabolic clearance, the superior targeting capabilities on diseased tissue, and so on.^{11–13} Integrating the cutting-edge nanotechnology with TCM exhibiting polypharmacological activities is a strategically pivotal direction in the current biomedical innovation. So far, significant breakthroughs and progress have been achieved in the field of TCM through nanotechnology implementation, which primarily involves natural nanostructured formulations and NDDS. Nanosized TCM improves drug solubility and stability, enhancing therapeutic efficacy and reducing toxicity.¹⁴ Meanwhile, NDDS enables precise drug delivery and controlled release, maximizing efficacy and minimizing side effects through synergistic interactions with carriers.¹⁵

Herein, we summarize the nanostructured formulations of TCM active ingredients, including natural nanostructured formulations for TCM (such as the self-assembly of natural compounds, carbon dots and extracellular vesicles derived from TCM) and exogenous NDDS for TCM (such as inorganic nanocarriers, organic nanocarriers, and so on) (Figure 1). We elucidate their nanostructures, functions, as well as pharmacological activities, and categorically introduce the biomedical treatment applications of TCM nanomedicines. Moreover, we explore the advantages and challenges associated with TCM nanomedicines, thereby gaining a profound comprehension of how nanotechnology functions in TCM and driving the modernization process of TCM nanomedicines.

Where Do We Stand at TCM?

Plant resources and human medicine have evolved together throughout civilization, with their therapeutic practice extensively documented throughout human history. As a landmark treatise, the Compendium of Materia Medica (Bencao Gangmu) details rigorously the pharmacological properties of 1,892 medicinal plant species and their clinical indications. The bioactive potential of these TCM is originated from diverse components, encompassing leaves, flowers, buds, pollen, fruits, exocarps, seeds, roots, stems, bark, and entire plant organism, each endowing distinct therapeutic profiles. The advent of modern chemical methodologies enables the isolation and characterization of numerous bioactive natural products from TCM. German pharmacist Friedrich Serturmer first isolated morphine from *opium poppy*, which are now extensively employed in clinical practice as a potent analgesic and anesthetic, thus inaugurating a new era of natural ingredients of TCM research. Subsequent pharmacological investigations have elucidated the clinical efficacy of various TCM-derived ingredients, solidifying their role as indispensable sources of modern therapeutics. Prominent examples include: *artemisinin* from the leaves of *Artemisia annua* leaves with remarkable antimalarial properties;⁵ *baicalin* from the roots of *Scutellaria baicalensis* with anti-inflammatory activity;¹⁶ *camptothecin* from the stem bark of *camptotheca acuminata* with potent antitumor activity.¹⁷ These findings demonstrate the enduring value of TCM-derived natural ingredients in drug discovery and development. Given their structural diversity and biological relevance, natural ingredients from TCM will certainly remain a cornerstone of pharmacological innovation, contributing significantly to global therapeutic advancement. To further exploit the therapeutic potential of TCM active ingredients, advanced nanoformulation-based delivery strategies have emerged as a pivotal research focus. This direction not only impacts the clinical translation efficiency of TCM, but also may redefining the theoretical framework for natural products in intelligent drug development. Based on numerous recent studies, this review provides a systematic overview of current classifications of nanosized TCM, their corresponding constituent formulations, and preparation methodologies (Table 1).

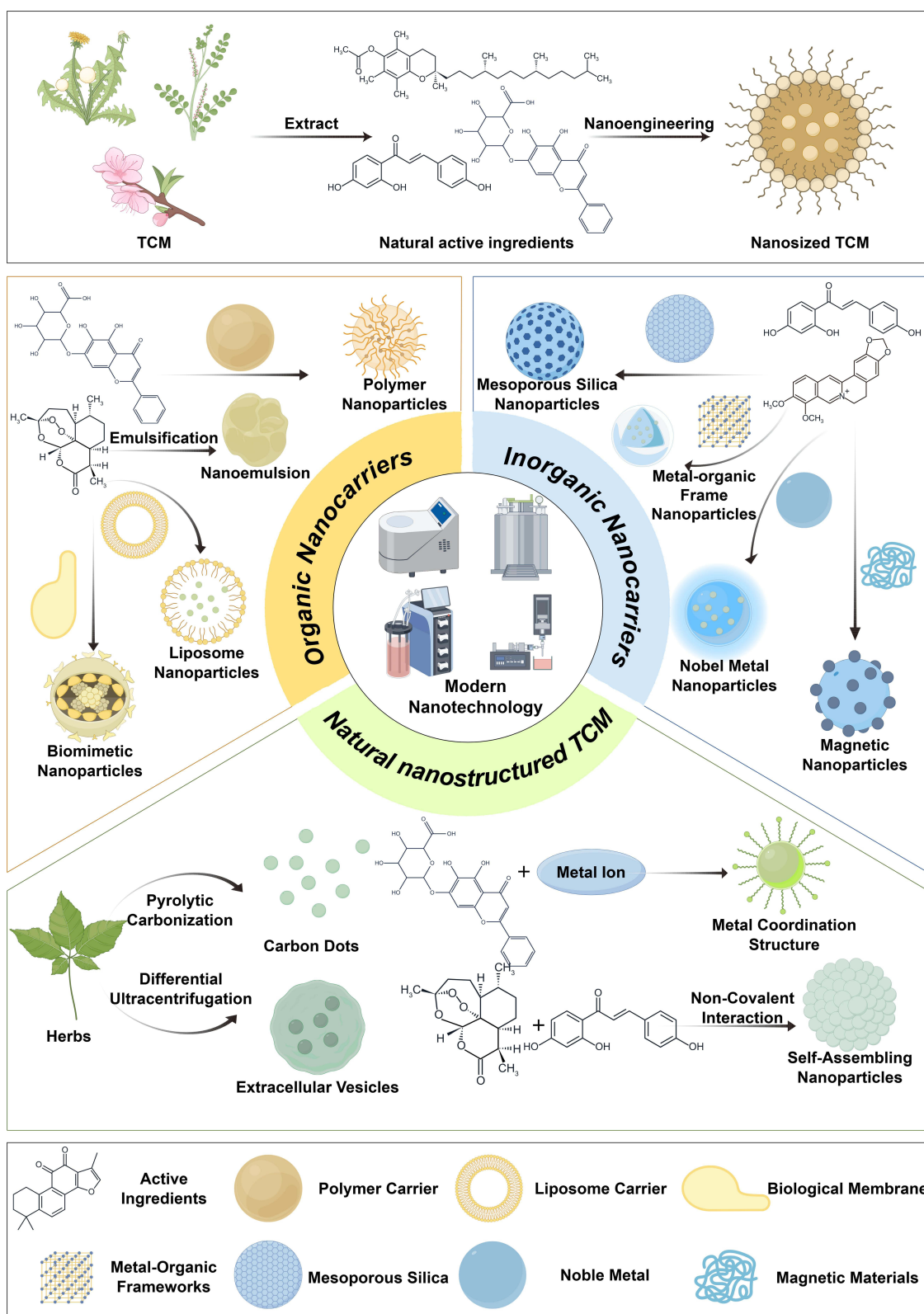


Figure 1 Engineering strategies for TCM nanomedicines. By Figdraw. <https://www.figdraw.com>.

Table 1 Classification and Fabrication Strategies of TCM Nanomedicines

Nanosized TCM categories	Active Ingredients	Nanocarrier	Synthesis Methods	Ref
Metal-Coordinated Nanoparticles	Curcumin	Fe ³⁺	Direct Blending Protocol	[18]
	Shikonin	Zn ²⁺ , PEG	Direct Blending Protocol	[19]
	Quercetin	Fe ³⁺	Interfacial Self-Assembly	[20]
	Tannic acid	Fe ³⁺ , Cu ²⁺	Sacrificial Template Method	[21]
	Procyanidin, Tannic acid	Fe ³⁺ , Gold nanorods	Layer-by-Layer Assembly	[22]
TCM Molecular Self-Assembly Nanoparticles	Morusin,	-	High-Temperature Processing	[23]
	Liquiritigenin	-	Nanoprecipitation Methodology	[24]
	Berberine,	-		
	Hesperetin	-	Sonication	[25]
	Resveratrol	-	pH Modulation Strategy	[26]
CDs	Berberine,	-		
	Chlorogenic Acid	-	Hydrothermal Method	[27]
	Rhein	-	Pyrolytic Carbonization	[28]
	Pollen Typhae	-	Solvothermal Method	[29]
EVs	Quercetin	-		
	Citrus peel	-	Microwave-Assisted Synthesis	[30]
	Ginseng	-	Density gradient ultracentrifugation	[31]
	Lonicera japonica	-	Density Gradient Ultracentrifugation	[32]
MSNs	Punica granatum	-	Size-Exclusion Chromatography	[33]
	Panax ginseng	-	Polymer Precipitation	[34]
	Allium cepa	-	Ultrafiltration	[35]
	Bufalin	Rod-shaped MSN	Template-Assisted Method	[36]
MOFs	Berberine	Gold nanoparticle and Folate-Modified MSN	Solvent Displacement Method	[37]
	Triptolide	TA-Iron Coordination Structure	Ultrasound-Mediated Synthesis	[38]
	Honokiol	CD-MOFs	Ultrasound-Mediated Synthesis	[39]
Nobel Metal Nanoparticles	Olive leaf	Silver nanoparticle	Solvothermal Synthesis	[40]
	Tannic acid	Platinum nanoparticle	Direct Blending Method	[41]
MNPs	Dihydroartemisinin	Magneto liposome	Film Dispersion-Ultrasonication Method	[42]
	6-gingerol	Magneto liposome	Film Dispersion-Ultrasonication Method	[43]
Polymeric nanoparticles	Quercetin	β-cyclodextrin	Nanoprecipitation	[44]
	Curcumin	Poly (methacryloyl beta-alanine)	Emulsification-solvent evaporation	[45]
	Artesunate	PLGA	Emulsification-solvent evaporation	[46]
Lipid nanoparticles	Curcumin	Solid Lipid Nanoparticle	Thin-Film Ultrasonic Method	[47]
	Camptothecin	Lipid Nanoparticle	Methanol/Ethanol Injection	[48]
Nanoemulsion	Scutellarin	-	Self-Emulsifying Drug Delivery System	[49]
	Tanshinone IIA	Rhamnolipids, Tea tree oil	Ultrasonication Emulsification Method	[50]
	Curcumin, Emodin	Egg yolk lecithin, Chitosan	Ultrasonication Emulsification Method	[51]
Biomimetic nanoparticles	Resveratrol	Erythrocyte membrane-coated PCL-PEG	Dialysis Method	[52]
	Curcumin	Milk-derived Exosomes	Passive Incubation, Sonication, and Electroporation.	[53]

Natural Nanoformulations for TCM Active Ingredients

Self-Assembly Nanoengineering of TCM Active Ingredients

Metal Coordination Strategy

Metal-coordinated self-assembled nanoparticles (MSANs), as an emerging paradigm in nanomedicine, leverage the synergistic interplay of coordination bonds between metal ions and organic ligands to construct metal-supramolecular

assemblies with precisely engineered topological architectures.⁵⁴ In recent years, a growing number of researchers have strategically employed bioactive components derived from TCM as organic ligands to construct MSANs for disease therapeutics.^{55,56} Typically, TCM active ingredients with strong coordination capacity, such as polyphenols and polysaccharides, are selected as organic ligands.^{57,58} Through coordination-driven assembly with transition metal ions (eg, Fe^{3+} , Zn^{2+} , Cu^{2+}) possessing multiple vacant electron orbitals, stable coordination bonds between metal ions and TCM active ingredients are formed, ultimately leading to the construction of corresponding nanoparticles.⁵⁹

Conventional synthesis strategies predominantly utilize a direct blending protocol, wherein TCM-derived ligands and metal ion solutions are mixed under precisely controlled conditions to induce nanostructural self-assembly via metal-ligand coordination interactions.⁶⁰ For instance, Yuan et al¹⁸ employed a direct blending method to synthesize *curcumin*-iron nanoparticles by coordinating *curcumin* with Fe^{3+} ions. Characterization results demonstrated the superior stability of the resulting nanosystem. Guo et al also fabricated Zn-Shik nanoparticles via this methodology using *shikonin* (Shik) and Zn^{2+} ions for anti-inflammatory therapy and reactive oxygen species (ROS) scavenging.¹⁹ Additionally, interfacial self-assembly also represents a critical methodology for fabricating TCM active ingredients-metal coordinated nanoparticles. Interfacial self-assembly refers to a nanostructural architecture strategy where molecules undergo self-organization at multiphase interfaces (eg, liquid-liquid, gas-liquid), demonstrating distinct advantages in the precise fabrication of complex nanostructures.⁶¹ Wang et al²⁰ innovatively leveraged the solid-liquid interface formed by a choline and geranic acid ionic liquid as a spatially confined reaction environment to construct MSANs through coordination-driven assembly between *quercetin* and Fe^{3+} , and systematically evaluating their antibacterial efficacy. In recent years, sacrificial template method (also referred to as the hard-particle directed self-assembly) has emerged as a novel strategy and has been successfully applied to the fabrication of TCM active ingredients-metal coordinated nanoparticles.^{62,63} The fundamental principle of this methodology involves the initial introduction of templating molecules to orchestrate coordination-driven assembly between TCM-derived ligands and metal ions. Following the completion of TCM active ingredients-metal coordination nanoparticle assembly, the templating agents are subsequently removed via selective separation and purification techniques.^{64,65} Qin et al²¹ successfully fabricated TA-Fe/Cu nanoparticles using zeolitic imidazolate framework-8 as a sacrificial template through coordination-driven assembly of *tannic acid* (TA) with Fe^{3+} and Cu^{2+} . Compared to conventional MSANs with solid structures, the hollow architecture of TA-Fe/Cu demonstrates superior photothermal conversion efficiency. In vitro and in vivo results confirm that TA-Fe/Cu exhibit remarkable wound-healing efficacy through synergistic photothermal effects and ROS scavenging capability.

Nanoengineered TCM active ingredients-metal complexes exhibit multifaceted advantages in disease therapeutics. First, their dynamic metal-ligand coordination networks significantly address the inherent limitations of TCM active ingredients, such as low bioavailability and poor chemical stability.⁶⁶ Second, the intrinsic functionalities of metal ions (eg, redox activity of Fe^{3+} and antimicrobial properties of Cu^{2+}) combined with the programmable loading capacity for functional molecules endow these nanoparticles with versatile functionalization capabilities. Zhang et al leveraged this characteristic to conjugate photothermally active gold nanorods with TCM active ingredients-metal complexes, successfully constructing a novel and highly efficient antibacterial nanosystem that synergistically integrates photothermal therapy with conventional chemotherapy.²² This coordination chemistry-guided precision nanoengineering strategy not only enhances the targeted delivery efficiency of TCM components but also enables synergistic therapeutic effects, thereby systematically expanding the mechanistic research dimensions of TCM in disease treatment.

TCM Molecular Self-Assembly Strategy

Beyond the aforementioned strategies, another prevalent approach in the self-assembly of TCM active components involves endogenous self-assembly, where amphiphilic-structured TCM molecules autonomously facilitate nanoparticle formation through intermolecular interactions.⁶⁷ The intermolecular interactions governing this self-assembly process are predominantly non-covalent, including electrostatic interactions, van der Waals forces, hydrogen bonding, hydrophobic interactions, and π - π stacking.⁶⁸ Current research in the field predominantly focuses on the self-assembly of TCM active components, including polysaccharides, saponins, polyphenols, terpenoids, and alkaloids, owing to their hydrogen bond-rich structures and amphiphilic nature (A molecule exhibits both hydrophilicity and hydrophobicity), which confer superior self-assembly capability compared to other TCM constituents.^{69–72}

The self-assembly process of TCM molecules encompasses multiple initiation strategies, including high-temperature heating, nano-coprecipitation, sonication treatment, and pH modulation methods. High temperature heating can promote non-covalent bonding processes between molecules and enhance the stability of reaction products.⁷³ For instance, Nie et al successfully constructed novel self-assembled nanoparticles through high-temperature processing at 120°C using *morusin* and *liquiritigenin*, and characterization results indicated that the nanoparticles displayed excellent stability.²³ The nanoprecipitation methodology, a classical approach in nanopharmaceutical fabrication, is primarily governed by two interrelated physicochemical processes: diffusion-controlled thermodynamic equilibration and aggregation-driven kinetic assembly.⁷⁴ Furthermore, Gao et al synthesized *berberine-hesperetin* nanoparticles via nano-coprecipitation mediated self-assembly for ulcerative colitis therapy, demonstrating a novel preclinical treatment strategy.²⁴ The underlying principle of sonication lies in its capacity to modulate molecular dimensions, thereby enhancing intermolecular interaction forces that facilitate molecular self-assembly.⁷⁵ Leveraging this mechanochemical mechanism, Chang et al engineered *resveratrol* nanoparticles through 100 hz sonication-induced supramolecular organization, establishing a bioengineered platform for developing targeted respiratory syncytial virus infection therapeutics.²⁵ The pH modulation strategy for optimizing the synthesis of self-assembled nanoparticles stems from the protonation-state-regulated mechanism under critical pH conditions, which substantially accelerates the reaction kinetics of molecular self-assembly processes.^{76,77} Therefore, Fu et al²⁶ successfully induced the self-assembly of *berberine* and *chlorogenic acid* by precisely adjusting the pH of the reaction system to 7.0–7.5 using NaOH. Characterization results demonstrated that the resulting self-assembled nanoparticles exhibited excellent structural stability.

TCM molecular self-assembled particles are endowed with inherent biocompatibility and broad-spectrum pharmacological activity profiles via nature-inspired architectural strategies, thereby demonstrating low-risk therapeutic potential with broad-spectrum efficacy in oncology,⁷⁸ inflammatory disorders,⁷⁹ and bacterial infection.⁸⁰ Furthermore, their intrinsic programmability enables precision functionalization modifications to achieve superior drug delivery performance through programmable supramolecular engineering.⁸¹

Carbon Dots Nanoengineering of TCM Active Ingredients

Carbon dots (CDs) are an emerging class of ultrasmall nanoparticles (with a size of less than 10 nm) that are primarily classified into four categories: graphene quantum dots (GQDs), carbon quantum dots (CQDs), carbon nanodots (CNDs), and carbon-based polymer dots (CPDs).⁸² Recently, with advancements in nanopharmaceutical preparation technologies and the deepening exploration of TCM, active ingredients derived from TCM have emerged as promising precursors for synthesizing novel CDs due to their unique natural architectures and biocompatibility.⁸³ These nanomaterials, fabricated using extracts or bioactive molecules from TCM as carbon sources, are collectively termed TCM-CDs.⁸⁴ Structurally, TCM-CDs can be categorized into two distinct classes: CQDs and CNDs.^{85,86}

The synthesis strategies of CDs are primarily categorized into two major classes: the “top-down” approach and the “bottom-up” approach. The so-called “top-down” synthesis of CDs fundamentally relies on physicochemical techniques to disintegrate bulk carbon materials into CDs, including electrochemical exfoliation, ultrasonication, laser ablation, and arc discharge methods.^{87–89} However, the “top-down” strategy exhibits intrinsic drawbacks such as broad size distribution, pronounced structural heterogeneity, inadequate control over processing parameters, and inevitable impurity/defect incorporation.⁹⁰ The “bottom-up” synthesis methodology relies on molecular-level assembly of precursors to enable the controlled fabrication of CDs,⁹¹ which demonstrates superior viability over the “top-down” approach for achieving large-scale and cost-effective production of CDs, primarily due to its inherent advantages in controllable molecular assembly and energy-efficient processing pathways.⁹² Consequently, the bottom-up approach has been established as the predominant methodology in CDs synthesis, particularly in the fabrication of TCM-CDs. The “bottom-up” synthesis strategy currently encompasses four principal methodologies for CDs fabrication: hydrothermal synthesis,⁹³ pyrolytic carbonization,⁹⁴ solvothermal synthesis,⁹⁵ and microwave-assisted processing.⁹⁶ The hydrothermal method represents an eco-friendly synthetic strategy, whose standardized protocol encompasses sequential steps including precursor dissolution, hydrothermal reaction under elevated temperature and pressure, controlled gradient cooling, centrifugal separation, membrane filtration purification, and terminal dialysis refinement, ultimately yielding CDs with well-defined structural characteristics.⁹⁷ Xia et al²⁷ engineered CDs with integrated fluorescence tracing and near-infrared

photothermal conversion capabilities via hydrothermal synthesis using *Rhein*, which effectively alleviated dextran sulfate sodium (DSS)-induced ulcerative colitis through ROS scavenging and suppression of NF- κ B-mediated inflammatory cascades. A representative pyrolytic carbonization strategy involves high-temperature carbonization of molecular precursors, followed by boiling and dialysis of the carbonized products to yield CDs.⁹⁸ Wang et al implemented this strategy in fabricating *Pollen Typhae* (PT)-derived carbon dots (PT-CDs). Specifically, PT was subjected to gradient pyrolysis treatment (250–400°C) in a crucible, followed by sequential boiling and dialysis purification of the carbonized products, ultimately yielding PT-CDs with remarkable therapeutic efficacy in ameliorating acute kidney injury.²⁸ The solvothermal method is fundamentally characterized by the employment of non-aqueous solvents (eg, ethanol, dimethylformamide) as reaction media, distinct from the hydrothermal approach that exclusively utilizes aqueous systems.^{99,100} This strategy achieves precise regulation of CDs synthesis through systematic modulation of solvent properties.¹⁰¹ Kasi and co-workers synthesized neuroregenerative CDs via a 180°C ethanol-mediated solvothermal strategy using *quercetin* as the carbon precursor. These CDs demonstrated significant enhancement of Schwann cell proliferative activity, thereby accelerating post-injury regeneration of peripheral nerve tissues.²⁹ Microwave-assisted synthesis facilitates CDs preparation through dielectric heating-induced bond dissociation in molecular precursors, which drives cascade physicochemical transformations. This approach demonstrates superior precursor activation kinetics and precise control over CDs morphology and surface chemistry compared to conventional thermal methods.¹⁰² Utilizing *citrus peel*-derived biomass as a carbon precursor, Hu et al³⁰ synthesized fluorescence-responsive functionalized CDs within 1 minute via a microwave-assisted approach. These CDs demonstrated sensitive detection of *Escherichia coli* in dairy matrices, highlighting the exceptional efficiency of microwave-driven synthesis in advancing green CD fabrication strategies.

The hallmark advantage of TCM-CDs lies in their environmentally benign synthesis, enabling energy-efficient fabrication under non-toxic reagent conditions.¹⁰³ Their sub-10 nm nanostructure facilitates rapid renal clearance via glomerular filtration, significantly mitigating bioaccumulation risks and demonstrating superior biocompatibility.¹⁰⁴ Furthermore, TCM-CDs inherently integrate fluorescence-based tracing capabilities with precise diagnostic functionalities, underscoring their versatility across diverse application scenarios.¹⁰⁵

Extracellular Vesicles Derived from TCM

Extracellular vesicles (EVs) are phospholipid bilayer-enclosed structures secreted by cells, characterized by their low immunogenicity and high biocompatibility, which have positioned them as an emerging therapeutic strategy in disease treatment.¹⁰⁶ TCM-EVs are naturally secreted nano-scale vesicles from herbal cells, encapsulating lipids, proteins, nucleic acids, and bioactive phytochemicals, demonstrating versatile therapeutic potential across multiple disease contexts.¹⁰⁷

Currently, the primary preparation methods for TCM-EVs include differential ultracentrifugation, density gradient centrifugation, size-exclusion chromatography, polymer-based precipitation, and ultrafiltration. Differential ultracentrifugation sequentially removes particulate impurities through gradient centrifugal forces, followed by ultracentrifugation pelleting to isolate EVs within a target size range. This standardized protocol employs multi-step centrifugation for precise preparation of EV products.¹⁰⁸ Density gradient ultracentrifugation represents a methodological refinement evolved from conventional differential ultracentrifugation protocols. Seo et al³¹ isolated *ginseng*-derived EVs utilizing a sucrose density gradient method. These EVs demonstrated efficacy in inhibiting osteoclast differentiation, positioning them as a potential therapeutic agent for osteoporosis. The core workflow comprises density gradient formation, isopycnic centrifugation, fractionation, and elution purification.¹⁰⁹ Li et al employed iodixanol density gradient construction coupled with fractionation-based isolation to prepare *Lonicera japonica*-derived EVs, which alleviated DSS-induced colitis.³² Size-exclusion chromatography achieves size-dependent separation of EVs through molecular sieving via porous matrices (eg, agarose/dextran gels). The standardized protocol involves chromatographic column elution of the sample mixture at a constant flow rate to achieve target EVs isolation.¹¹⁰ Sánchez-López et al isolated EVs from *punica granatum* using this methodology, demonstrating wound-healing promotion, anti-inflammatory, and antioxidant properties.³³ The principle of polymer precipitation involves competitive binding of hydrophilic polymer to water molecules in the hydration layer on the surface of EVs, disrupting their colloidal stability and thereby inducing precipitation for separation. The standardized protocol involves incubation of the sample with polymer solution followed by sequential centrifugation steps to achieve EVs isolation.¹¹¹ Zhang et al utilized ExoQuick solution to isolate *panax ginseng*-derived EVs via polymer-based precipitation.³⁴ Ultrafiltration achieves size-selective

separation of EVs through molecular sieving effects generated by porous membranes with defined pore size distributions.¹¹² Ham et al developed a novel molecular sieve membrane enabling high-efficiency isolation of *allium cepa*-derived EVs via ultrafiltration methodology.³⁵

Exogenous NDDS for TCM Active Ingredients

Inorganic Nanocarriers

Mesoporous Silica Nanoparticles

Mesoporous Silica Nanoparticles (MSNs) are silicon-based nanoparticles with a porous structure. MSN encompasses multiple categories, including ordered MSN, hollow MSN, core-shell MSN, dendrimer-like MSN, and biodegradable MSN, among others.¹¹³ Currently, the primary methods for synthesizing MSNs include the sol-gel process and template-assisted approaches.¹¹⁴ The sol-gel synthesis method of MSNs involves the condensation reaction of the precursor within the micelles confined by the emulsion, followed by template extraction to generate an ordered mesoporous structure.¹¹⁵ The template-assisted method entails selecting a suitable templating agent and mixing it with the precursor (or having it adsorbed onto a specific substrate), allowing the precursor to react and grow following the template, and then removing the template through methods such as calcination and extraction to obtain the material.¹¹⁶

Due to their high specific surface area, ease of modification, adjustable pore size, and good biosafety, MSN have been widely utilized as a sophisticated inorganic nano-carrier for drug delivery in various biomedical applications, including targeted therapy for cancer.¹¹⁷ MSN is frequently utilized for the delivery of active ingredients of TCM that possess anti-cancer properties. Fan and his colleagues employed rod-shaped MSN to encapsulate *bufalin* for targeted therapy of colorectal cancer. Thanks to the exceptional EPR effect exhibited by MSN, the efficacy of *bufalin* in treating colorectal cancer was significantly enhanced.³⁶ In recent years, functionalizing MSN to enhance its therapeutic effects has emerged as a new trend in research.¹¹⁸ Li and colleagues further utilized gold nanoparticles and folate-modified MSN for targeted delivery of *berberine* in the treatment of liver cancer. The gold nanoparticles endowed the nanoparticles with a photothermal effect, while the folate enabled active targeting and recognition of liver cancer cells by the nanoparticles. The high targeting efficiency, combined with the synergistic action of photothermal therapy (PTT) and chemotherapy, significantly enhanced the anticancer efficacy of *berberine*.³⁷

Metal-Organic Frameworks

Metal-Organic Frameworks (MOFs) are a novel type of porous materials assembled through the coordination bonding of metal ions or metal clusters with organic ligands.¹¹⁹ The synthetic methodologies for MOFs encompass hydrothermal/solvothermal synthesis, microwave-assisted synthesis, mechanochemical approaches, electrochemical methods, ultrasound-mediated synthesis, and diffusion techniques.¹²⁰

MOFs have been widely applied in the research and development of nanomedicines due to their adjustable porous structures, good biocompatibility, and ease of functionalization.¹²¹ Wang and his team have developed an iron-based MOFs nanocarrier for loading *triptolide*, targeting its application in the treatment of melanoma. This MOFs nanocarrier has undergone modifications with bovine serum albumin and folic acid, and possesses chemodynamic therapy (CDT) activity. These features not only enhance targeting efficacy but also achieve synergistic effects among multiple therapeutic approaches, thereby significantly improving the therapeutic efficacy of *triptolide* through various aspects.³⁸ In another study, He and colleagues developed a cyclodextrin-based MOFs system for loading *honokiol*, targeting its application in breast cancer treatment. This MOFs system was also loaded with indocyanine green and encapsulated with the cell membrane of MCF-7 cells (a type of breast cancer cell). This innovative approach not only enhanced the stability and targeting ability of *honokiol* but also synergized it with PTT, thereby significantly boosting the therapeutic efficacy of *honokiol*.³⁹

Noble Metal Nanoparticles

Noble metal nanoparticles refer to tiny particles with sizes typically not exceeding 100 nanometers, composed of precious metal elements such as gold, silver, platinum, and palladium. The synthetic methodologies for noble metal nanoparticles bear similarities to those employed in the fabrication of MOFs.

A distinct advantage of noble metal nanoparticles lies in their dual functionality: serving as nanocarriers for targeted delivery of TCM bioactive components while exerting therapeutic effects through their intrinsic physicochemical properties.^{122,123} For instance, gold nanoparticles (Au NPs) exhibit excellent photothermal effects. Taking advantage of this property, Zhang et al designed a functionalized Au NPs modified with AS1411 for targeted therapy of colorectal cancer. This nanoparticle demonstrates significant killing effects on colorectal cancer cells through the PTT effect.¹²⁴ In terms of serving as nanocarriers, noble metal nanoparticles can enhance the efficacy of active ingredients in TCM by increasing their stability, solubility, and other properties. It is reported that researchers utilized silver nanoparticles encapsulated with *olive leaf* extract for the treatment of colorectal cancer. In vitro experiments demonstrated the nanoparticles remarkable inhibitory effect on HCT-116 cells (a type of colorectal cancer cell), thereby showcasing their exceptional potential for anticancer therapy.⁴⁰ Furthermore, Xiang and his team have developed a metal-based nanoparticle system loaded with TA, utilizing platinum nanoparticles (Pt NPs) as the foundation. This system is designed to inhibit cancer progression by enhancing anti-cancer immune responses. As a nanocarrier, Pt NPs play a crucial role in significantly boosting the bioavailability and targeting efficiency of tannic acid, thereby prolonging its circulation time in the body and facilitating its accumulation at tumor sites. These improvements collectively enhance the anti-cancer activity of TA.⁴¹

Magnetic Nanoparticles

Mineral medicines are an important part of TCM in our country. Such as cinnabar, realgar, and magnetite, etc., they are known as “metal and stone medicines” and are widely used in traditional Chinese medicine. Some TCMs of inorganic mineral origin can be directly generated into nanomedicines through physical methods (mechanical crushing method, ball milling method) and chemical methods (precipitation method, sol-gel method, hydrothermal method). Similar to magnetite, magnetic nanoparticles (MNPs) are a type of nanoscale particles composed of magnetic elements (such as iron, nickel, cobalt) and their compounds, exhibiting unique properties including a high surface-to-volume ratio, magnetism, and high stability. These characteristics have led to their widespread application in the biomedical field.¹²⁵

When loaded with active ingredients of TCM for cancer treatment, MNPs can enhance the efficacy of these ingredients through two distinct properties. Firstly, the magnetic guidance effect of MNPs is utilized to achieve targeted delivery of the active ingredients of TCM. In previous research, MNPs have been shown to accumulate specifically at tumor sites under the guidance of an external magnetic field, thereby increasing the drug concentration at those sites and ultimately enhancing the therapeutic effect.¹²⁶ Li and his team have developed lipid-coated magnetic nanoparticles loaded with *dihydroartemisinin* (DHA), based on iron oxide, for the treatment of head and neck squamous cell carcinoma. Both in vitro and in vivo experiments have demonstrated that these nanoparticles can achieve targeted delivery of DHA under the influence of an external magnetic field, exhibiting significantly enhanced therapeutic efficacy compared to non-targeted DHA delivery.⁴² Furthermore, MNP can synergistically treat cancer along with the active ingredients of TCM through their magnetocaloric effect, thereby enhancing the therapeutic efficacy. Under the application of an external alternating magnetic field, MNPs can absorb magnetic energy to produce heat, thereby elevating the local temperature of tumor tissue to the point of eradicating tumor cells.¹²⁷ Li and his team have developed a targeted therapy for colorectal cancer based on magnetic mesoporous silicon nanoparticles (MMSNPs) encapsulating *6-gingerol*. Under the influence of an external alternating magnetic field, these MMSNPs synergistically induce colorectal cancer cell death through a combination of magneto-thermal effects, the stimulation of antitumor immunity, and oxidative stress. This approach has significantly enhanced the therapeutic efficacy of *6-gingerol* and demonstrated potent anticancer activity.⁴³

Organic Nanocarriers

Polymer Nanocarriers

Polymer nanocarriers are drug delivery systems constructed using one or more polymers, such as polyethylene glycol (PEG) and chitosan.^{128,129} In the preparation of polymeric nanocarriers, the most commonly employed methods are emulsification-solvent evaporation¹³⁰ and nanoprecipitation,¹³¹ which have emerged as predominant techniques due to their high efficiency, scalability, and broad applicability.

Polymeric nanocarriers are widely used in the field of targeted drug delivery, especially in the delivery of active ingredients of TCM for cancer treatment, due to their advantages such as high biocompatibility, high stability, adjustable surface properties, versatility, good drug loading and release capabilities, and low immunogenicity and renal filtration rate.¹³² Researchers developed a polymeric nanocarrier based on β -cyclodextrin that loads *quercetin* and doxorubicin. This nanocarrier not only enhances the bioavailability of *quercetin* but also reverses the resistance of MCF-7 cells to doxorubicin, achieving an improved anticancer effect through synergistic therapy.⁴⁴ In the treatment of cervical cancer, some researchers have developed a polymer nanoparticle based on poly (methacryloyl beta-alanine) for the targeted delivery of *curcumin*. This nanoparticle improves the targeting and therapeutic effect of *curcumin* by increasing the release rate of *curcumin* and guiding *curcumin* to act on the nucleus of HeLa cells (a type of cervical cancer cell), providing a new strategy for the clinical treatment of cervical cancer.⁴⁵ Leveraging the advantage of easy surface modification of polymer-based nanocarriers, some researchers have further conducted surface engineering to endow them with additional functionalities, thereby enhancing their drug delivery efficiency and amplifying the therapeutic effects of the administered drugs. For example, Peng et al constructed a biomimetic polymer nanocarrier by coating poly (lactic-co-glycolic acid) (PLGA) nanocarriers with mannose-modified red blood cell membranes, and utilized it to deliver *artemisinin* and chloroquine for targeted therapy of colorectal cancer. The mannose-modified red blood cell membranes enable the nanoparticles to have a longer circulation time in the body and to target and accumulate at tumor sites for effective action. In vitro and in vivo results indicate that this nanocarrier significantly enhances the anticancer therapeutic effects of *artemisinin* and chloroquine.⁴⁶

Lipid Nanoparticles

Lipid nanoparticles are vesicular nanostructures primarily composed of lipid molecules, encompassing various types such as liposomes, lipid nanoparticles (LNPs), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).¹³³ In the preparation of lipid-based nanocarriers, the most commonly used methods are Thin-Film Hydration¹³⁴ and Methanol/Ethanol Injection.¹³⁵ These two methods have become the preferred strategies for synthesis due to their well-established technology, ease of operation, and broad applicability.

Lipid nanoparticles have been extensively utilized in drug delivery,¹³⁶ biomedical imaging and diagnostics,¹³⁷ as well as gene therapy,¹³⁸ due to their advantages such as excellent controlled release properties, targeting capabilities, and enhanced drug bioavailability.¹³⁹ The utilization of lipid nanocarriers to load active ingredients of TCM for cancer treatment is also a new trend in the current development of nanomedicine. Zhang and his team have devised a functionalized SLN carrier for loading *curcumin*, specifically tailored for the treatment of liver cancer. By employing hyaluronic acid for surface modification, this nanoparticle carrier acquires the capability to specifically target liver cancer cells. Experimental results indicate that *curcumin* loaded onto this SLN carrier exhibits a higher degree of accumulation at the tumor site compared to free *curcumin*, resulting in a marked enhancement of its anticancer therapeutic efficacy.⁴⁷ In another study, Jing and colleagues utilized LNPs to encapsulate *camptothecin* for the treatment of liver cancer. These LNPs were also functionally modified, and innovatively co-delivered *camptothecin* along with a contrast agent. This enables these nanoparticles not only to possess targeted therapeutic capabilities against liver cancer but also to achieve synchronous in vitro MRI imaging, thereby integrating diagnosis and treatment. This not only broadens the application scenarios of active ingredients derived from TCM but also offers new insights into personalized cancer treatment.⁴⁸

Nanoemulsion

Nanoemulsions are nanoscale dispersion systems composed of oil phase, aqueous phase, and emulsifiers. Their nanoscale droplet size and exceptional stability demonstrate broad applicability in drug delivery.^{140,141} TCM-derived nanoemulsions represent an advanced drug delivery platform wherein active ingredients from TCM are encapsulated via nanotechnology within emulsion-based systems, aiming to enhance bioavailability, stability, and targeted delivery capabilities. The oil phase is predominantly constituted by lipophilic (*curcumin*, *paclitaxel*, *tanshinone*, etc) or oleaginous (*volatile oil of ligusticum chuanxiong*, *peppermint oil*, *zedoary oil*, etc) TCM active ingredients.

The currently prevalent preparation techniques for TCM nanoemulsions primarily include high-pressure homogenization,¹⁴² ultrasonication,¹⁴³ phase inversion temperature (PIT) method,¹⁴⁴ and self-emulsifying drug delivery

systems (SEDDS).¹⁴⁵ The former two methods fall into high-energy preparation techniques, while the latter two belong to low-energy fabrication approaches.

In practical applications, nanoemulsions are extensively employed in the construction of nanosized TCM formulations owing to their high stability, enhanced bioavailability, and superior safety profiles.¹⁴⁶ Liao et al developed a self-emulsifying nanodelivery system based on *scutellarin* to suppress excessive inflammatory responses. Characterization data demonstrated that the nanoemulsion exhibited excellent physical stability and achieved lymph node-specific accumulation in vivo, significantly mitigating LPS-induced systemic cytokine storms. This system markedly enhanced the anti-inflammatory efficacy of *scutellarin*. Biosafety evaluation further confirmed the absence of toxic effects on major organs (heart, liver, lungs, and kidneys) in experimental animals following administration of the nanoemulsion.⁴⁹ In addition, R. M. El-Moslemany et al prepared a *tanshinone IIA* nanoemulsion via the ultrasonication emulsification method. This nanoemulsion exhibited significant bioactivity and demonstrated remarkable therapeutic efficacy in mitigating acute lung injury in vivo.⁵⁰ Lei et al developed a pH-responsive sodium alginate hydrogel-encapsulated nanoemulsion co-loaded with *curcumin* and *emodin* via ultrasonication emulsification. This nanoemulsion demonstrated pH-triggered controlled drug release in the colon, effectively alleviating the inflammatory microenvironment through downregulation of pro-inflammatory cytokines (TNF- α , IL-6), upregulation of anti-inflammatory cytokine IL-10, scavenging of macrophage-derived ROS, and enhancement of intestinal mucosal tight junction protein expression.⁵¹

Biomimetic Nanoparticles

Biomimetic nanoparticles are a novel type of nanocarriers fabricated by coating the surfaces of traditional nanomaterials with cellular constituent (such as cell membranes, extracellular vesicles, etc.).^{147–149} The primary preparation strategies for membrane-coated biomimetic nanoparticles include membrane extrusion^{150,151} and electroporation.¹⁵² The detailed isolation and purification techniques for EVs (eg, differential centrifugation, size-exclusion chromatography, or ultracentrifugation) have been outlined above.

Compared with traditional nanocarriers, biomimetic nanocarriers exhibit better biocompatibility, higher targeting efficiency, and more superior abilities to penetrate biological membranes.¹⁵³ Based on these advantages, an increasing number of researchers are combining them with active ingredients of TCM that have anticancer effects to develop novel nanomedicines with even stronger anticancer properties. In the research conducted by Zhang and his team, they utilized red blood cell membranes to encapsulate a PCL-PEG polymer carrier, thereby creating a novel biomimetic nanocarrier loaded with *resveratrol* for targeted therapy of colorectal cancer. By leveraging the properties of the red blood cell membranes, this nanocarrier can effectively evade clearance by the body's immune system, leading to an extension of its circulation time within the body. This prolonged circulation enhances the chances of the drug reaching the disease site, ultimately boosting the therapeutic efficacy of *resveratrol*.⁵² Exosomes, a type of nanovesicles derived from cells, also serve as a type of biomimetic nanocarrier.¹⁵⁴ They are capable of encapsulating drugs and achieving targeted delivery without the need to bind with other nanoparticles. A group of researchers has successfully developed a delivery system based on milk-derived exosomes encapsulating *curcumin*. This system efficiently delivers *curcumin* to breast cancer cells, enhancing its anticancer activity and providing a promising strategy for the treatment of breast cancer.⁵³

Advantages of Nanosized TCM for Biomedical Applications

Compared with traditional TCM, nanosized TCMs exhibit a series of prominent advantages. They have better solubility, stronger permeability, more precise targeting, and can enable the combined application of multiple therapies. These advantages effectively enhance the pharmacological activity of nanosized TCMs, demonstrating greater potential in the treatment of disease.

Bioavailability

The bioavailability of active ingredients in TCM is generally not strong, primarily due to the intricate molecular architectures of these compounds, the high abundance of polar or hydrophobic functional groups, and hepatic first-pass metabolism. This poor bioavailability poses limitations on the clinical application of active ingredients in TCM. To address this issue, researchers have developed nanocarrier-based delivery systems for constructing nanosized TCM formulations to enhance their bioavailability¹⁵⁵ (Figure 2). The first strategy involves encapsulating TCM active

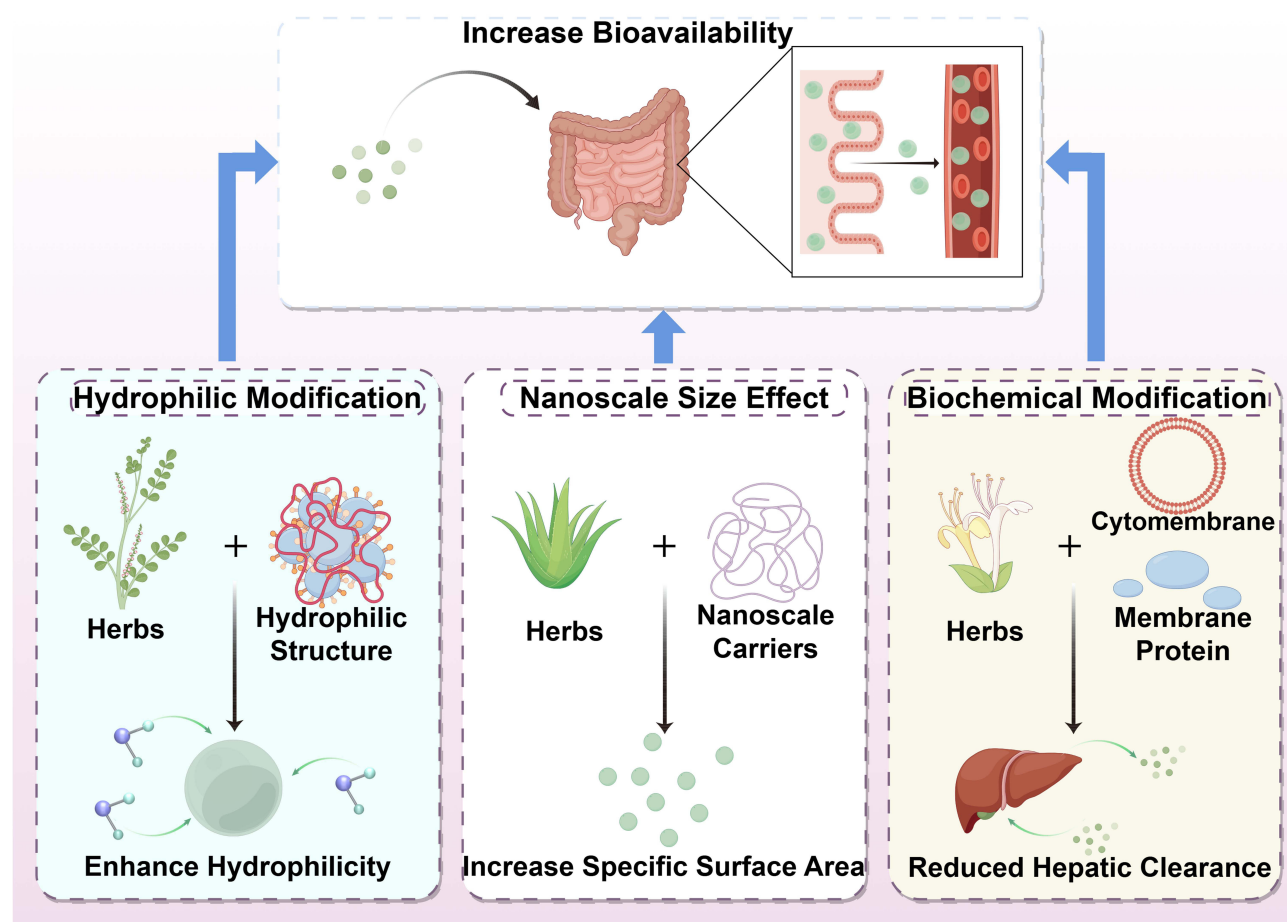


Figure 2 Strategies of nano-engineering for improving the bioavailability of active ingredients in TCM. By Figdraw. <https://www.figdraw.com>.

ingredients within amphiphilic nanocarriers to enhance hydrophilicity and solubility, thereby improving bioavailability. Yao et al developed an amphiphilic PEG-PLGA nanoparticle-based delivery system for encapsulating *isoliensinine* in hypertension treatment. Pharmacokinetic studies demonstrated that this nanocarrier significantly enhanced plasma drug concentration of *isoliensinine* and prolonged its systemic retention, thereby effectively improving bioavailability.¹⁵⁶ The second strategy leverages the nanoscale size effect by reducing drug particle size to increase specific surface area, thereby accelerating dissolution kinetics and markedly enhancing drug solubility and bioavailability. Ge et al group engineered an *ellagic acid-gallic acid-catechin* (EA-GA-CA) sandwich-like nanostructure for antibacterial therapy. Structural characterization revealed that this nanostructure exhibited a remarkably high specific surface area, which facilitated a substantial enhancement in aqueous solubility and ultimately optimized bioavailability.¹⁵⁷ Another strategy involves reducing hepatic clearance to prolong the systemic circulation time of the drug, thereby enhancing bioavailability. Zhou et al innovatively developed a biomimetic nanodelivery system utilizing erythrocyte membrane and PLGA for targeted shikonin delivery in colorectal cancer therapy. This bioinspired design, mimicking natural erythrocyte characteristics, effectively reduced hepatic metabolic clearance of the nanoparticles. Pharmacokinetic analysis demonstrated that the biomimetically engineered shikonin formulation significantly extended systemic circulation half-life compared to free drug, confirming the strategy's efficacy in enhancing bioavailability.¹⁵⁸

Targeting

Nanosized TCM active ingredients can increase the dosage of drugs accumulated at the lesion site, thereby improving drug delivery efficiency and therapeutic efficacy, and reduces adverse reactions caused by drug-induced damage to other

normal tissues in the body.¹⁵⁹ The mechanisms for enhancing drug targeting can be divided into passive targeting, active targeting, and physicochemical targeting (Figure 3).

The mechanism of passive targeting delivery by nanosized TCM primarily relies on the Enhanced Permeability and Retention (EPR) effect, which is closely related to the physicochemical properties of the nanocarriers, including particle size, morphology, molecular weight, charge properties, and charge amount.^{160,161} For example, Ji et al fabricated self-assembled nanoparticles based on *honokiol* via a hydrothermal method for colorectal cancer treatment. In vivo pharmacokinetic and biodistribution studies demonstrated that these nanoparticles could achieve targeted accumulation in tumor tissues through the EPR effect.¹⁶² Nanocarriers composed of PEG and PLGA can enhance drug stability and improve bioavailability.¹⁶³ Based on this advantage, researchers have utilized PEG-PLGA nanocarriers to encapsulate *honokiol* for the treatment of breast cancer. Through the EPR effect, the passive targeted delivery of *honokiol* can be achieved, thereby improving its therapeutic efficacy.¹⁶⁴ Specially, Zheng et al designed a self-assembling nanocarrier based on 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N- [maleimide (polyethylene glycol)-2000] (DSPE-PEG2000-Mal) and cholesterol for simultaneous targeted delivery of *curcumin* and *resveratrol* in the treatment of liver cancer. Both in vivo and in vitro experiments were conducted to verify its ability to enhance the anticancer efficacy of these drugs.¹⁶⁵

Active targeting refers to a drug targeting delivery strategy that nanoparticles modified with specific ligands can be precisely internalized by target cells to exert therapeutic effects. The core of this strategy lies in the specific binding between ligands and receptors.¹⁶⁶ This strategy not only specifically acts on target cells but can also bind to target organelles after cellular internalization, thereby improving the precision of treatment.¹⁶⁷ Currently, a popular strategy for achieving active targeting is to modify the surface of nanoparticles with ligands that can specifically recognize certain

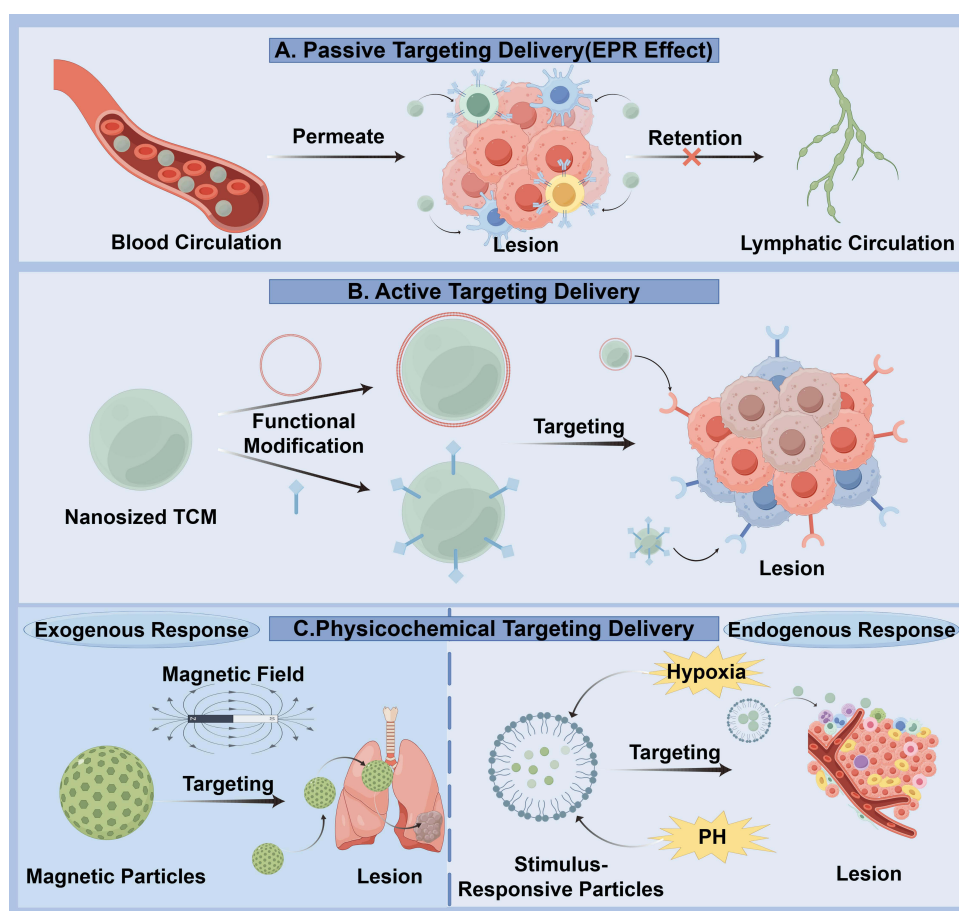


Figure 3 Schematic diagram of targeted delivery of nanosized TCM to pathological lesions. (A). Nanosized TCM achieves passive targeting to lesion sites via the EPR effect. (B). Nanosized TCM realizes active targeting to lesion sites through biomimetic modification or surface protein engineering. (C). Nanosized TCM enables physicochemical targeting to lesion sites by responding to endogenous or exogenous stimuli. By Figdraw. <https://www.figdraw.com>.

overexpressed receptors on the surface of cancer cells, thereby enabling the active targeted delivery of active ingredients in TCMs.¹⁶⁸ For instance, folate is a type of B vitamin, and its receptors are often overexpressed in cancer cells.¹⁶⁹ Therefore, targeting folate receptors has become one of the strategies for active targeted delivery. Guo et al utilized folate-modified star polyester nanocarriers for targeted delivery of *curcumin* to treat breast cancer. This nanocarrier exhibited good targeting ability for the *curcumin* and significantly enhanced its therapeutic efficacy.¹⁷⁰ Li et al also utilized folate-coated MSNs to load *tanshinone IIA*. This nanocarrier demonstrated good targeting toward promyelocytes both in vivo and in vitro, and exhibited superior therapeutic effects compared to MSNs carriers without folate coating.¹⁷¹ The asialoglycoprotein receptor is also one of the receptors that are overexpressed on the surface of cancer cells. Based on this, researchers have utilized galactose-modified PLGA nanocarriers to encapsulate *dalbergin* for the liver cancer treatment. This approach not only improves the bioavailability of *dalbergin* but also increases its distribution within liver cancer tissues, thereby achieving targeted therapy.¹⁷² Furthermore, Ling et al synthesized a polymer nanocarrier capable of targeted recognition of IL-13R α 2 (an IL-13 receptor that is highly expressed in glioblastoma multiforme, GBM), which was used to deliver *resveratrol*, thereby achieving precise treatment of GBM and enhancing the anticancer therapeutic effect of *resveratrol*.^{173,174} Guo et al engineered *curcumin*-derived extracellular vesicles with death receptor 5 (DR5) antibody functionalization. These nanoparticles achieved targeted delivery to tumor sites by specifically recognizing DR5 on senescent tumor cell surfaces, thereby overcoming the limited targeting capacity of *curcumin*. In vivo studies further demonstrated their potent tumor growth inhibitory efficacy.¹⁷⁵

Physicochemical targeting primarily achieves targeted delivery of drugs through the utilization of endogenous physicochemical stimuli within the disease microenvironment or the influence of certain external physicochemical factors.¹⁷⁶ For instance, hypoxia is a prominent characteristic of the tumor microenvironment.¹⁷⁷ Based on this characteristic, Liu et al developed a kind of micelle based on angelica polysaccharide for the delivery of *curcumin* in the treatment of liver cancer. This micelle was modified with azobenzene, which enables it to stimulate the release of *curcumin* under hypoxic conditions in liver cancer, achieving targeted therapy.¹⁷⁸ The pH value of tumor tissue is lower than that of normal tissue, exhibiting a weak acidity.¹⁷⁹ Therefore, the development of NDDSs with pH-responsive properties is also one of the current strategies for achieving active targeted drug delivery. Researchers have developed an MSN modified with folic acid and polyacrylic acid for the delivery of *chrysin* in the treatment of breast cancer. Experiments have demonstrated that this nanocarrier can efficiently release *chrysin* under the pH conditions specific to the tumor environment, achieving pH-responsive targeted drug delivery.¹⁸⁰ In addition to responding to internal stimuli within tumor tissues, researchers have also utilized strategies involving nano-carriers that respond to external stimuli to achieve physicochemical targeted delivery. S. Roy et al constructed a bioinspired magnetic nanocarrier system using *Lactobacillus rhamnosus* (Au-Lac)-derived biotemplates coupled with zinc ferrite, successfully achieving targeted delivery of *quercetin* – an anticancer bioactive compound from TCM. In vitro studies confirmed the nanoparticles' magnetically guided directional migration into cervical cancer cells under external magnetic field control, demonstrating remarkable magnetic targeting properties.¹⁸¹

Multimodal Therapy

Nanosized TCM can achieve combined therapy against disease through multiple mechanisms, thereby significantly enhancing treatment efficacy (Figure 4). PTT is an emerging and highly precise cancer treatment method. It primarily involves the targeted delivery of nanoparticles with photothermal conversion effects to the tumor site. Under the illumination of an external light source, these nanoparticles convert light energy into thermal energy, raising the local temperature of the tumor tissue to kill tumor cells, thereby achieving the goal of anticancer treatment.^{182,183} Polydopamine (PDA) is an excellent photothermal agent, Su and his team utilized polydopamine that possessing great photothermal conversion effect to load *camptothecin* for the treatment of lung cancer, which exhibits superior inhibitory effects on lung cancer cells under the dual mechanisms of chemotherapy and PTT, demonstrating more significant therapeutic effects compared to free *camptothecin*.¹⁸⁴ Molybdenum disulfide (MoS₂) is also a material with a photothermal conversion effect.¹⁸⁵ Chen et al utilized MoS₂ to construct a nanocarrier for targeted co-delivery of *curcumin* and erlotinib in the treatment of lung cancer. Under the synergistic treatment of combined chemotherapy and PTT, these nanoparticles demonstrated favorable therapeutic effects on lung cancer both in vitro and in vivo.¹⁸⁶

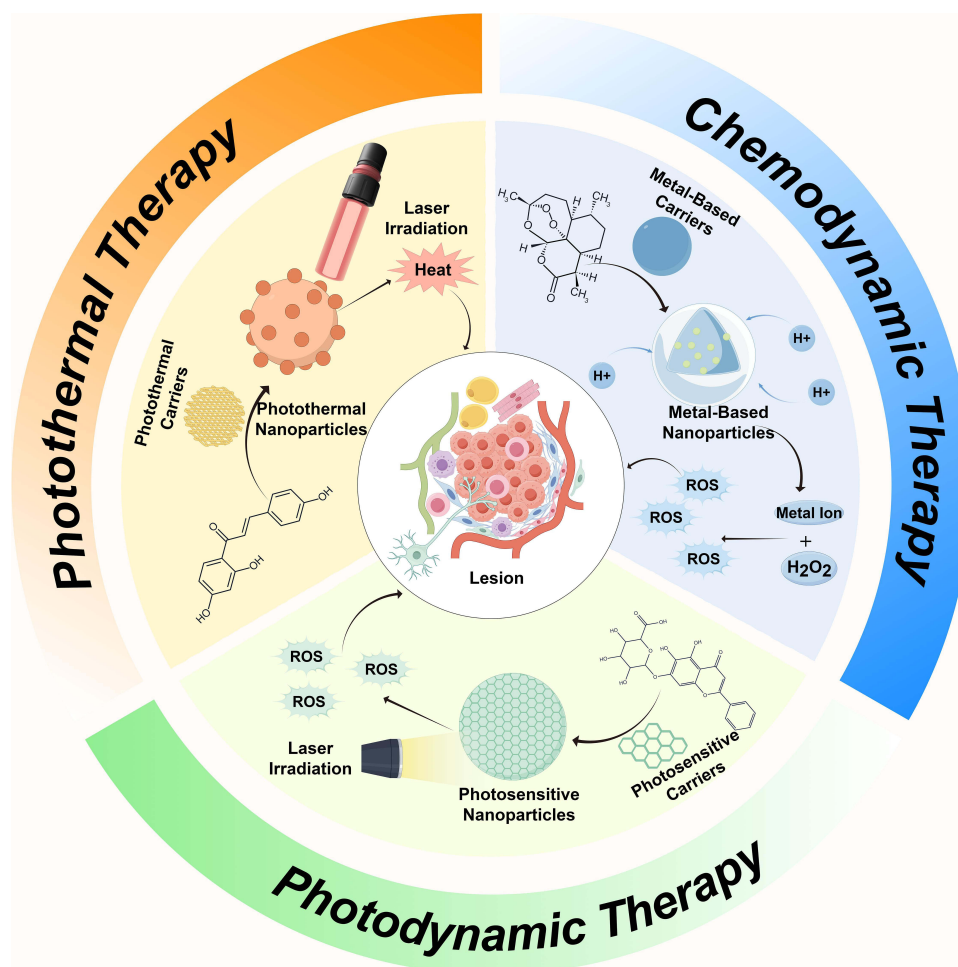


Figure 4 Phototherapy, chemodynamic therapy, and photodynamic therapy based on nanosized TCM. By Figdraw. <https://www.figdraw.com>.

Photodynamic therapy (PDT) refers to an anticancer treatment strategy where nanoparticles with photosensitizing properties are delivered to the tumor site, and under the action of exogenous light and the participation of molecular oxygen in the tissue, a reaction occurs to produce cytotoxic substances, thereby inducing tumor cell death.^{187,188} In recent years, researchers have employed nanotechnology to process the active ingredients of TCM, granting them additional photosensitizing effects. For example, researchers encapsulated *quercetin* and the photosensitizer zinc phthalocyanine within lipid nanocarriers to create anticancer nanoparticles that leverage both PDT and chemotherapy effects. Both in vitro and in vivo experiments demonstrated the nanoparticles' excellent anticancer efficacy.^{189,190} Fullerenes are nanoparticles capable of generating ROS under light illumination and are often utilized in PDT.¹⁹¹ Similarly, Zhang et al employed fullerene-based nanocarriers to deliver *artemisinin* for PDT and chemotherapy synergistic treatment.¹⁹² In addition, in the latest research, researchers have utilized nanotechnology to develop nanoparticles with two-photon excitation effects based on the inherently photosensitizing active ingredients of TCM, such as *curcumin* and *emodin*. Compared to traditional PDT, these nanoparticles exhibit more efficient ROS generation capabilities and demonstrate more significant therapeutic effects against cancer.^{193,194} In addition, Wen et al successfully engineered photodynamic *curcumin*-derived carbon dots via a chitosan-hyaluronic acid functionalization strategy. In vitro antibacterial assays revealed that 405 nm light irradiation markedly triggered ROS generation in the composite system, conferring robust antimicrobial activity.¹⁹⁵

CDT refers to a novel anticancer treatment approach that employs nanoparticles to catalyze the Fenton reaction within the tumor microenvironment, generating hydroxyl radicals which subsequently induce the death of tumor cells.¹⁹⁶ Metal particles (such as iron, copper, manganese, etc.) are commonly used as Fenton-like nanoparticles for CDT.¹⁹⁷ Zhang and

his colleagues developed a nano-hydrogel encapsulated with *artesanate*, utilizing Cu-Fe₃O₄ particles, for targeted therapy against osteosarcoma. Through the synergistic effects of CDT and chemotherapy, this nano-hydrogel demonstrated robust anticancer activity by inducing the generation of abundant radicals, triggering oxidative stress in tumor cells, and ultimately leading to cell death both in vitro and in vivo.¹⁹⁸ In another research endeavor, Chen and his team leveraged hollow mesoporous Prussian Blue (HMPB) nanoparticles for targeted delivery of *curcumin*. By reacting with endogenous hydrogen sulfide at the disease site to generate radicals, these nanoparticles elicit oxidative stress, thereby inducing autophagy in colorectal cancer cells and exerting an anticancer effect. Experiments further revealed that the combined use of *curcumin* and HMPB nanoparticles exhibited higher anticancer activity than either free *curcumin* or free HMPB nanoparticles alone. This underscores the complementary nature of CDT and chemotherapy, which together enhance therapeutic efficacy, achieving a synergistic effect where the whole is greater than the sum of its parts.¹⁹⁹

Therapeutic Applications of TCM Nanomedicines: From Mechanisms to Practice

Compared with conventional TCM formulations, TCM nanomedicines have demonstrated multifaceted therapeutic advantages and achieved broad clinical application across diverse pathological contexts. This review specifically elucidates the mechanistic foundations of TCM nanomedicines in three critical therapeutic domains – oncotherapy, inflammation modulation, and microbial eradication – through integrated analysis of nanostructured fabrication strategies and molecular targeting pathways (Figure 5).

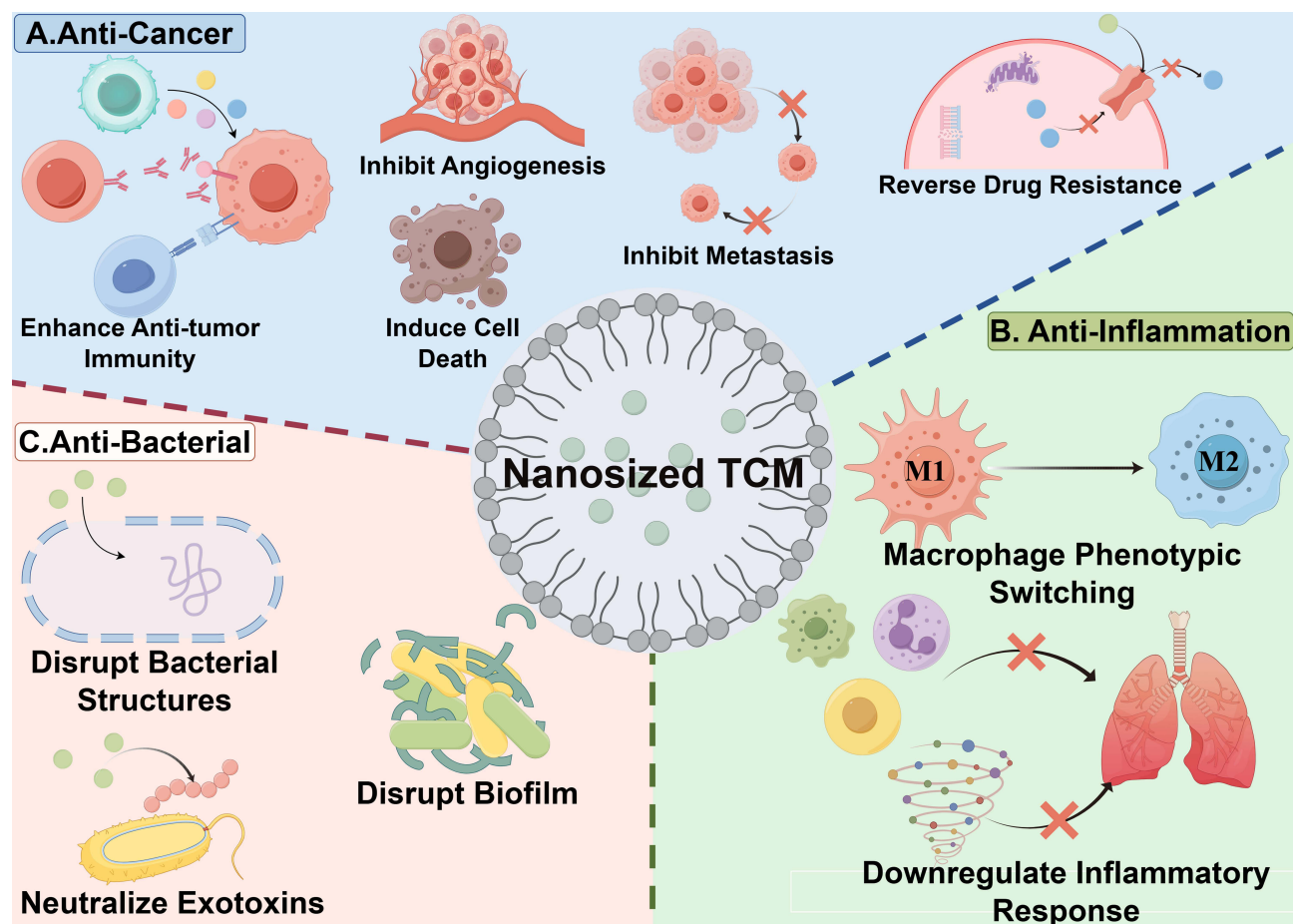


Figure 5 The applications of TCM nanomedicines in biomedical treatment field. (A). Anticancer mechanism mediated by nanosized TCM. (B). Anti-inflammation mechanisms exerted by nanosized TCM (C). Anti-bacterial mechanism of nanosized TCM. By Figdraw. <https://www.figdraw.com>.

Anti-Cancer

At present, cancer is a serious global public health problem. According to the International Agency for Research on Cancer (IARC), there were 20 million new cases of cancer worldwide in 2022, while 9.7 million people deaths from cancer.²⁰⁰ High morbidity and mortality rates of cancer make it one of the major threats to human health worldwide. The development of nanotechnology-based TCM has opened innovative intervention approaches for malignant tumor treatment. Through features such as precise drug delivery, multi-target regulation, and biological barrier penetration, it overcomes the inherent limitations of TCM components and provides nanoscale solutions with TCM characteristics for precision cancer therapy.

At the molecular mechanistic level, nanosized TCM exerts antitumor efficacy through multi-pathway and multi-target synergistic effects. The primary mechanism involves enhancing the host's antitumor immune response. Zhang et al developed a novel self-assembled TCM nanocomplex based on the molecular interaction characteristics of *ursolic acid* and *epigallocatechin gallate*, which was applied to precision therapy for Hepatocellular Carcinoma (HCC). Mechanistic studies revealed that this nanosystem could significantly enhance the anti-tumor response in the tumor immune microenvironment by stimulating anti-cancer cytokines (IL-12 and IFN- γ) and activating CD4⁺ T cells and CD8⁺ T cells.²⁰¹ Liu et al constructed a self-assembled nanodelivery system using *celastrol* as a precursor molecule. In vitro and in vivo results demonstrated that this nanotherapeutic agent could significantly suppress the growth of subcutaneously xenografted tumors by trigger death of tumor cells.²⁰² Furthermore, Zhou et al engineered erythrocyte membrane-coated biomimetic nanoparticles with *piceatannol* as the active pharmaceutical ingredient. Mechanistic studies confirmed their targeted inhibition of colorectal cancer metastasis through modulation of the Hippo/YAP1/SOX9 signaling axis.²⁰³ Additionally, it can effectively suppress tumor angiogenesis. Zhou et al engineered a coordination-driven metal-phenolic network architecture through *curcumin* complexation with Cu²⁺/Zn²⁺, subsequently integrating this system into a liposomal delivery platform for tumor-targeted delivery. In vitro validation confirmed that this nanotherapeutic potently suppressed tumor angiogenesis, thereby establishing a novel therapeutic strategy for clinical oncology.²⁰⁴ Moreover, nanosized TCM exerts therapeutic synergism by reversing tumor cell multidrug resistance, thereby significantly potentiating chemotherapeutic efficacy. Li et al engineered a hyaluronic acid-based nanodelivery system co-loaded with *capsaicin* and doxorubicin for combination chemotherapy in HCC. Experimental validation demonstrated that *capsaicin* reverses doxorubicin chemoresistance by modulating the Substance P/hepatic stellate cell axis.²⁰⁵

Anti-Inflammation

Inflammation is an evolutionarily conserved defense mechanism that orchestrates physiological responses to injury or infection by mediating pathogen eradication and tissue repair.²⁰⁶ However, pathological hyperactivation or chronic persistence of this process initiates autodestructive signaling cascades,²⁰⁶ culminating in irreversible organ dysfunction (eg, pulmonary fibrosis,²⁰⁷ hepatic cirrhosis,²⁰⁸ and renal failure²⁰⁹). Most active components of TCM possess excellent anti-inflammatory activity.²¹⁰ Therefore, developing novel anti-inflammatory nano-formulations based on the active components of TCM to precisely regulate inflammatory responses is of great clinical application value.

In terms of mechanistic dimensions, nanosized TCM exhibits multi-targeted modulation of inflammatory responses. Primarily, it attenuates inflammatory responses through immunomodulatory axis by precisely regulating immune cell populations. Gao et al prepared *curcumin*-derived EVs for the treatment of ulcerative colon cancer. Mechanistic studies demonstrated that these EVs could promote the phenotypic transformation of macrophages from M1 to M2, thereby down-regulating the inflammatory response.²¹¹ Secondly, it exerts anti-inflammatory effects by inhibiting inflammatory cell infiltration and downregulating inflammatory cytokines. Zheng et al constructed a pulmonary-targeted anti-inflammatory NDDS by co-loading *astragaloside IV* and *ligustrazine* into PEG-PLGA nanocarriers, which could inhibit bleomycin-induced pulmonary inflammation by suppressing inflammatory cell infiltration and downregulating the release of pro-inflammatory cytokines including IL-1 β , IL-6, and TNF- α .²¹²

Anti-Bacterial

Bacterial infections, a significant public health issue threatening human health for millennia, witnessed a historic turning point in prevention and control with the clinical application of antibiotics. Although the discovery of antibiotics provided

humanity with a temporary advantage in combating pathogenic bacteria, the evolution and spread of drug-resistant pathogens rapidly reversed this situation. WHO data reveal that global deaths caused by drug-resistant bacterial infections have surged to 1.27 million cases.²¹³ Against this backdrop, the development of innovative therapeutic strategies targeting resistant pathogenic bacteria has become a critical research area requiring urgent breakthroughs in global clinical medicine. TCM has been extensively applied in the anti-bacterial field with demonstrated remarkable efficacy.²¹⁴ With the continuous advancement of pharmaceutical technologies, researchers are integrating TCM with nanotechnology to develop novel anti-bacterial agents, providing innovative therapeutic strategies for the treatment of drug-resistant bacterial infections.

At the mechanistic level of antibacterial action, nanoscale TCM exerts bactericidal effects primarily through structural disruption of bacterial cell membranes. Ge et al engineered a self-assembled nanoparticle using *ellagic acid*, *gallic acid*, and *catechin*. Experimental studies demonstrated that this nanoparticle disrupts the cell membrane integrity of *Staphylococcus aureus*, inducing lytic rupture and exhibiting potent antibacterial efficacy.¹⁵⁷ Beyond bactericidal activity, nanoscale TCM exerts antibacterial effects through a key mechanistic strategy: suppression of bacterial biofilm formation. Zhang et al engineered a *quercetin*-based nanomicelle system. Experimental validation demonstrated that this nanomicelle potently suppresses biofilm formation in *Staphylococcus aureus*.²¹⁵ Another antibacterial therapeutic mechanism involves neutralizing bacterial exotoxins to mitigate pathogen-induced pathological damage at the infection site. Tan et al synthesized *dandelion*-derived EVs, which promoted infected wound healing through specific neutralization of *Staphylococcus aureus* exotoxins.²¹⁶

The Future Perspectives

The emergence of nano-TCM has written a new chapter in the modern nanomedicine field. This convergence of traditional medicine and cutting-edge science has reignited the millennia-old herbal medicine heritage with renewed radiance. In recent years, with the extensive integration of nanotechnology into TCM, the biosafety evaluation and elucidation of pharmacological mechanisms of nano-engineered TCM formulations have emerged as critical scientific challenges impeding their clinical translation. Current research demonstrates that while nanoscale modifications can significantly enhance the bioavailability and targeted delivery efficiency of TCM, with preliminary validation of their biosafety in experimental animal models, their potential cytotoxicity in humans, alterations in metabolic pathways, and long-term biological effects still require further clinical validation through rigorous trials. Additionally, scalable production and cost-effective manufacturing of nano-engineered TCM is also a considerable problem. Established preparation techniques,

Table 2 Clinical Translation Status of TCM Nanomedicines

Active ingredient	Herb	Nanocarrier	Name	Status	Ref
Elemene	Wen Yujin	Emulsion	<i>Elemene Injection</i>	Approved in China (1993)	[220]
		Liposome	<i>Elemene Liposome</i>	Approved in China (2011)	[221]
Coix seed oil	<i>Coix lacryma-jobi</i>	Emulsion	<i>Kanglaite</i>	Approved in China (1997)	[222]
Vincristine	<i>Catharanthus roseus</i>	Liposome	<i>Marqibo</i>	Approved in the US (2012)	[223]
Crocin	<i>Crocus sativus</i> L.	Nanoparticle	<i>Crocin-Selenium Nanoparticle</i>	Clinic trial	[224]
Aloe extract	<i>Aloe vera</i>	Nanoparticle	<i>Aloe Vera Nanoparticle</i>	Clinic trial	[225]
Curcumin	<i>Curcuma longa</i> L.	Nanoparticle	<i>Nanocurcumin/ Curcumin nanoparticle</i>	Clinic trial	[226,227]
Capsaicinoids	<i>Bhut Jolokia</i>	Nanolipid Vesicle	<i>Nanolipid Vesicles Formulation of Capsaicinoids</i>	Clinic trial	[228]
Camptothecin	<i>Camptotheca acuminata</i> Decne	Nanoparticle	<i>Camptothecin nanoparticle</i>	Clinic trial	[229,230]
<i>Melaleuca alternifolia</i> extract	<i>Melaleuca alternifolia</i>	Nanoparticle	<i>Melaleuca alternifolia nanoparticle</i>	Clinic trial	[231]
Rutin	<i>Sophora japonica</i> L.	Nanoparticle	<i>Rutin nanoparticle</i>	Clinic trial	[232]

including nano-co-precipitation and ultrasonic fragmentation, face significant industrialization barriers due to limitations in process complexity and equipment costs. The development of green and sustainable preparation processes represents a critical pathway to overcoming translational bottlenecks from laboratory-scale research to clinical applications.

Generally, TCM compound prescriptions serve as the primary modality and means in clinical TCM practice. As a modernized TCM form of TCM formulations, component-based Chinese medicine is systematically developed by combining bioactive constituents in accordance with the fundamental “monarch (Jun), minister (Chen), assistant (Zuo), and envoy (Shi)” compatibility principle of herbal prescription. Rooted in TCM theory while incorporating contemporary pharmacological evidence, these multi-component systems demonstrate characteristic polypharmacological synergism through precisely designed component interactions. However, current nanosized TCM research is predominantly focused on single-active compounds (Table 2). Developing advanced nanosized TCM technologies for multi-component TCM formulations necessitates immediate breakthroughs. Building on supramolecular assembly principles and natural drug compatibility theory, Qian et al developed a novel strategy to elucidate the anti-inflammatory mechanism of the classical Huanglian Wumei decoction, which features the *rhizoma coptidis-fructus mume* (RC-FM) pair as its signature combination. Self-assembled natural phytochemicals were obtained during the decoction process of HLWMD, then infrared/ultraviolet-visible spectroscopy revealed that *berberine* (BBR) and *chlorogenic acid* (CGA) are two main active constituents of RC-FM pair. Subsequently, BBR and CGA self-assemble into an amphiphilic spheroid macromolecule (BCS) with an average size of about 98.3 nm through electrostatic interactions, π - π stacking and hydrophobic interactions. In vitro results demonstrated that the stacking pattern and amphiphilic molecular structure of BCS significantly augmented the anti-inflammatory performance compared with that of BBR and CGA alone. This findings explained the scientific connotations of TCM compatibility from the perspective of self-assembly and synergistic effects, providing a novel insight and strategy for elucidating the mechanism of multi-component combinations of TCM.²¹⁷ Emerging studies have reported that the presence of naturally occurring nanoparticles in certain TCM decoctions, where these nanoscale components exhibit enhanced therapeutic efficacy through their stabilized morphological characteristics.²¹⁸ Zhang et al assessed the pharmacodynamic basis of the TCM formula T-QY305, which consists of five herbs: *astragalus membranaceus*, *Lonicera japonica*, *angelica sinensis*, *licorice*, and *centipede*. The study demonstrated that the T-QY305 spontaneously forms self-assembled nanostructures (N-QY305) during decoction. Through comprehensive characterization and animal experiments, N-QY305 was identified as the crucial bioactive component underlying the formula’s pharmacological effects.²¹⁹ From this study, TCM research may further be considered as significantly related to nanomedicine, opening new avenues for nanotechnology-driven exploration. Collectively, developing compound-based nano-formulations aligned with the holistic principles of TCM and systematically establishing multi-component targeted co-delivery systems will emerge as a pivotal research direction for enhancing the clinical efficacy of nano-engineered TCM.

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Disclosure

The authors declare no conflict of interest.

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