


REVIEW

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# Formation of a traditional Chinese medicine self-assembly nanostrategy and its application in cancer: a promising treatment

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## Abstract

Traditional Chinese medicine (TCM) has been used for centuries to prevent and treat a variety of illnesses, and its popularity is increasing worldwide. However, the clinical applications of natural active components in TCM are hindered by the poor solubility and low bioavailability of these compounds. To address these issues, Chinese medicine self-assembly nanostrategy (CSAN) is being developed. Many active components of TCM possess self-assembly properties, allowing them to form nanoparticles (NPs) through various noncovalent forces. Self-assembled NPs (SANs) are also present in TCM decoctions, and they are closely linked to the therapeutic effects of these remedies. SAN is gaining popularity in the nano research field due to its simplicity, eco-friendliness, and enhanced biodegradability and biocompatibility compared to traditional nano preparation methods. The self-assembly of active ingredients from TCM that exhibit antitumour effects or are combined with other antitumour drugs has generated considerable interest in the field of cancer therapeutics. This paper provides a review of the principles and forms of CSAN, as well as an overview of recent reports on TCM that can be used for self-assembly. Additionally, the application of CSAN in various cancer diseases is summarized, and finally, a concluding summary and thoughts are proposed. We strongly believe that CSAN has the potential to offer fresh strategies and perspectives for the modernization of TCM.

**Keywords** Traditional Chinese medicine, Self-assembly nanostrategy, Cancer, Formation, Application, Combined chemotherapy

## Introduction

Traditional Chinese medicine (TCM) is used to prevent and cure a wide range of illnesses [1–4], and it includes a variety of plant-, animal-, and mineral-based medicinal substances. Since active components in TCM exhibits low bioavailability, novel formulations and administration methods are needed to enhance the efficiency and safety of drug delivery systems. Nanotechnology is used to reduce TCM-related issues such as poor solubility, lack of targeting, nonspecific distribution, high systemic toxicity, and a short half-life. Conventional nanomaterials, on the other hand, produce low yields, are expensive to prepare, accumulate in vivo, and are not degradable;

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thus, it is difficult to use conventional materials significantly in clinical applications [5–9].

Compared to traditional nanoformulations, self-assembled nanoformulations are easier to manufacture, more efficient and exhibit higher biodegradability and biocompatibility. Active components of TCM that possess self-assembly capabilities include alkaloids, organic acids, flavonoids, terpenoids, polysaccharides, and proteins derived from natural plants. By utilizing various types of noncovalent bonds, including intermolecular hydrogen bonds, van der Waals forces,  $\pi$ - $\pi$  stacking, electrostatic interactions, and coordination bonds, it is feasible to construct stable self-assembly systems with predetermined architectures [10, 11] (such as NPs, micelles, fibres, nanotubes, and vesicles). CSAN refers to a process that utilizes TCM to form self-assembled NPs (SAN) with particle sizes ranging from 10 to 1000 nm in this paper. CSAN can be prepared using single or combination TCM that can self-assemble to produce pure natural carrier-free nanoformulations. CSAN can improve the solubility and in vivo bioavailability of insoluble TCM active components. Since CSAN may increase the solubility and bioavailability of insoluble TCM active components, it may also be employed as a carrier-free nanodelivery system for drug delivery and therapeutic treatment. CSAN is effective, secure, straightforward, inexpensive, and does not require any specialized equipment. Additionally, it provides more benefits than conventional nanoformulations and is favourable for the clinical translation of nanomedicines.

CSAN has been shown to exert an antitumour impact through the active components found in TCM [12]. Furthermore, it has been found to exhibit a synergistic effect when used in conjunction with other antitumour drugs [13]. Moreover, CSAN shows potential as a natural nanocarrier for antitumour drugs [14]. It can also be utilized to construct nanopreparations with metal ions via coordination bonds for photothermal treatment or tumour imaging [15], which could be applied for the diagnosis and treatment of malignant tumours [16]. Therefore, we provide an overview of the self-assembly mechanism, composition, and use of CSAN in tumour disorders, and the integration of active components of TCM with self-assembly technology is expected to broaden the scope of TCM modernization.

### The mechanism of CSAN

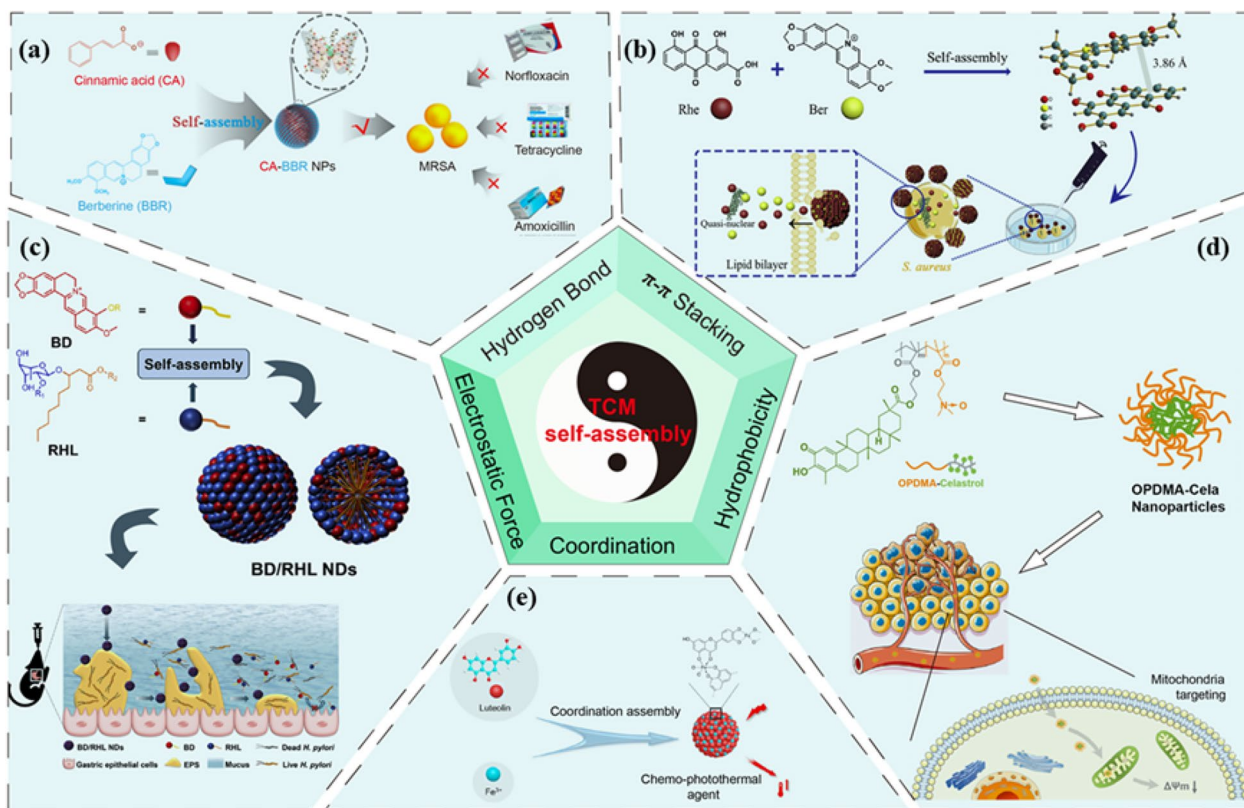
TCM is composed of a complex and diverse set of active components, such as alkaloids, organic acids, flavonoids, terpenoids, polysaccharides, and proteins. These components possess functional groups and multiple action sites, which make it easier for them to form noncovalent bonds. Additionally, their unique structure and

complicated physical and chemical characteristics facilitate self-assembly. The active components of TCM primarily self-assemble through noncovalent interactions, including hydrogen bonds [17], van der Waals forces,  $\pi$ - $\pi$  stacking [18], hydrophobic interactions [19], electrostatic interactions [20], and coordination interactions [15] (Fig. 1). The self-assembly process does not simply result from weak interactions between countless atoms, ions, and molecules. Rather, a diverse range of particles spontaneously come together to form a tightly organized structure, resulting in an overall complex synergy. In the process of self-assembly, it is uncommon for a single noncovalent bond to be the sole force. Rather, multiple noncovalent bonds often work together in tandem to aid the process. Therefore, determining the mechanism of CSAN is imperative. In this paper, we provide a detailed account of the key examples in CSAN (Table 1) and classify them according to the variations in their self-assembly driving force.

### Hydrogen bonding force

Hydrogen bonds are among the primarily weak electrostatic forces between atoms in nature and is responsible for the shape and structure of substances as well as their physical and chemical properties [21–23]. The bonds possess intermediate strength, directionality, and saturation and is an excellent driving factor for the formation and stabilization of supramolecular self-assembly systems. Hydrogen bonds, therefore, play an important role in the formation of CSAN. When molecules are joined together by hydrogen bonds, single and multiple hydrogen bonds are formed. The greater the strength of the multiple hydrogen bond, the greater the binding energy and stability between molecules. Since hydrogen bonds play such an important role in the process of self-assembly, most published research on the self-assembly of TCM is based on hydrogen bonds.

Berberine (BBR), a quaternary ammonium alkaloid extracted from the medicinal plant *Coptis chinensis* (Ranunculaceae), is widely used in TCM for its antibacterial and anti-inflammatory properties [24, 25]. It is easy to form nanoformulations due to its polyaromatic ring structure and quaternary ammonium ions. Many studies have found that BBR can self-assemble with various active components of TCM. Huang et al. [17] found that the combination of BBR and cinnamic acid (CA) can create a stable SAN through the interaction of hydrogen bonds. This interaction leads to the formation of butterfly shaped one-dimensional self-assembly units, as evidenced by single crystal X-ray diffraction. The  $\pi$ - $\pi$  stacking interaction promoted the formation of a layered three-dimensional crystal with a stacking spatial configuration and eventually completed the self-assembly

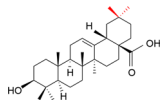
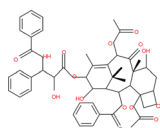
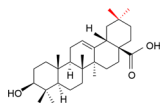
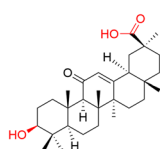
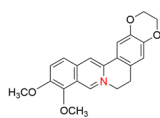
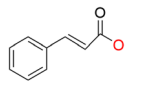
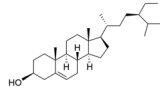
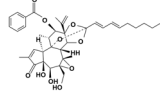
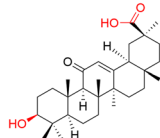
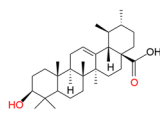
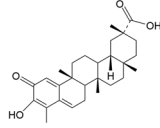
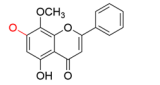
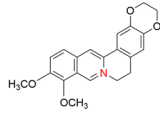


**Fig. 1** Different self-assembly forces in CSAN. **a** CA-BBR NPs formed by hydrogen bonding which as the main self-assembly force. Copyright 2020 American Chemical Society. **b** Rhe-BBR NPs formed by  $\pi$ - $\pi$  stacking which as the main self-assembly force. Copyright 2018 Elsevier. **c** BD/RHL NDs formed by electrostatic force which as the main self-assembly force. Copyright 2020 Elsevier. **d** OPDMA-Cela NPs formed by hydrophobic interaction which as the main self-assembly force. Copyright 2022 Elsevier. **e** Lut/Fe<sup>3+</sup> NPs formed by coordination which as the main self-assembly force. Copyright 2020 Elsevier

process. Among these, the carbonyl group of CA may form a hydrogen bond with the nitrogen atom of BBR, and aromatic ring association was a major source of the stacking structure. This self-assembly approach improved drug bioavailability and might be a viable way to combat bacterial resistance. Tian et al. [26] found the self-assembly mechanism of rhein (Rhe) and BBR by using nuclear magnetic resonance spectroscopy and X-ray single-crystal diffraction. Rhe, originating from TCM *Rheum palmatum* (Polygonaceae), serves as the layered stacked backbone of Rhe-BBR NPs, which are stabilized by hydrogen bonds. Additionally, BBR was embedded in the structure through  $\pi$ - $\pi$  stacking and electrostatic interactions, further enhancing the stability of the self-assembly. This self-assembly approach improved the bioavailability of the drugs and exhibited a better antibacterial effect than that of the single drug group. By hydrogen bonding and  $\pi$ - $\pi$  stacking, BBR and 3,4,5-methoxyic acid (3,4,5-Tca) self-assembled to create phytochemical NPs with high antibacterial activity [27]. B-Sitosterol (Sito), which is derived from *Arisaema heterophyllum Blume* (Araceae),

has the ability to self-assemble and form natural product gelators [28]. The self-assembly process was initiated by hydrogen bonds and was further strengthened by van der Waals forces. The resulting dimers were then organized longitudinally to create a secondary structure. The secondary structure continued to build up, resulting in fibrous network aggregates. This self-assembly approach improved drug stability and improved cancer cell inhibition and drug delivery. In another study, oleanolic acid (OA) and glycyrrhetic acid (GA) formed a self-assembly [29] through hydrogen bonding and hydrophobic interactions. Because the hydrophilic surface of OA tended to match that of GA (hydrogen bond donors and acceptors), the hydrophilic hydrogen-bond connectivity at the surface increased, and hydrogen-bond interactions developed. This self-assembly approach improved the biological solubility and stability of OA and GA, resulting in better antitumour effects. Both OA and irsolic acid (UA) are triterpenoids that can self-assemble with PTX to form NPs. According to Wang et al. [19], the major force of OA-PTX NPs was hydrogen bonding, whereas

**Table 1** Common self-assembly forces in CSAN

Self-assembly force	Self-assembly mechanism	Active ingredient	Primary source	Structure	Refs.
Hydrogen bond	Hydrogen bond	OA	Glossy privet fruit		[19]
		PTX	Taxus chinensis		
	Hydrogen bond and Hydrophobic interaction	OA	Glossy privet fruit		[29]
		GA	Licorice		
	Hydrogen bond and π-π stacking	BBR	Coptis chinensis		[17]
		CA	Cinnamon bark		
	Hydrogen bond and van der Waals forces	Sito	Arisaema heterophyllum Blume		[28]
Hydrophobic interaction	Hydrophobic interaction	GW	Daphne genkwa		[38]
		GA	Licorice		
	Hydrophobic interaction and hydrogen bond	UA	Loquat leaf		[12]
	Hydrophobic interaction and π-π stacking	Cela	Tripterygium wilfordii		[41]
	Hydrophobic interaction and electrostatic interaction	WOG	Baikal skullcap		[20]
		BBR	Coptis chinensis		

**Table 1** (continued)

Self-assembly force	Self-assembly mechanism	Active ingredient	Primary source	Structure	Refs.
Electrostatic interaction	Electrostatic interaction and hydrophobic interaction	BA	Baikal skullcap		[20]
		BBR	Coptis chinensis		
$\pi$ - $\pi$ stacking	$\pi$ - $\pi$ stacking and hydrogen bond	Rhe	Rheum officinale		[18]
	$\pi$ - $\pi$ stacking, van der Waals forces, and hydrogen bond	LDA	Liquidambar formosana		[14]
Coordination interaction	Coordination interaction	Lut	Lonicera japonica Thunb		[15]

the main force of UA-PTX NPs was hydrophobic interactions. In the molecular modelling process, OA-PTX NPs possessed more and stronger hydrogen bonds, which might explain why OA-PTX NPs were more stable. This self-assembly approach improved the solubility and anti-tumour activity of the three drugs.

Hydrogen bonding plays a crucial role in the self-assembly of TCM. The self-assembly of TCM through hydrogen bonding offers several advantages, such as increased solubility, improved stability of TCM components, and enhanced absorption of medicine.

### Hydrophobic interaction

Hydrophobic interactions occur when hydrophobic groups in aqueous solution cluster close to each other to avoid water, which is common in nature [30–32]. In many instances of self-assembly, hydrophobic contact is the driving force, and hydrogen bonding is created simultaneously. There may be a fine balance between hydrophobic contacts and hydrogen bonding forces [33, 34].

Many triterpenoids have been reported to generate self-assembled NPs via hydrophobic interactions. UA is a pentacyclic triterpene produced from *Eriobotrya japonica* (Rosaceae), *Salvia officinalis* (Lamiaceae), *Fructus Chaenomelis Lagenariae* (Caricaceae), and other TCMs [35–37]. Hydrophobic interactions and hydrogen bonding between UA molecules resulted in the formation of UA NPs [12]. Furthermore, the intensity of hydrophobic interactions and hydrogen bonds can influence NP stability. The hydrophobic interaction was primarily

responsible for the self-assembly of UA- paclitaxel (PTX) NPs [19]. The benzene ring in the structures of UA and PTX had a strong hydrophobic interaction, which caused the two methyl groups in UA to generate a strong hydrophobic effect with the two benzene rings coupled with the amide bond in the structure of PTX. The mechanism of NPs prepared with yuanhuacine and glycyrrhizic acid that originate from *Genkwa Flos* (Thymelaeaceae) and *Glycyrrhiza glabra* (Fabaceae) has been investigated [38]. <sup>1</sup>H-NMR and NOESY 2D NMR spectra confirmed that H-14 and H-20 of Yuanhuacine and Glu groups of glycyrrhizic acid were self-assembly binding sites, and the self-assembly process was driven by hydrophobic interactions. The interaction was inwardly configured with hydrophobic pentacyclic triterpenoids from glycyrrhizic acid and yuanhuacine and outwards configured with hydrophilic glucuronic acid. BBR and PTX were linked by disulfide bonds. Cheng et al. [13] discovered that the conjugate molecule could self-assemble in an aqueous solution through hydrophobic interactions and  $\pi$ - $\pi$  stacking, resulting in the formation of PTX-ss-BBR NPs. This was determined using molecular dynamics simulations. PTX molecules with numerous phenyl groups were surrounded by BBR inside the nanostructure, eventually forming a stable nanostructure. Celastrol (Cela) is a triterpenoid metabolite derived from *Tripterygium wilfordii* (Celastraceae) [39, 40]. In an aqueous solution, Cela may self-assemble into NPs [41] with hydrophobic and  $\pi$ - $\pi$  stacking interactions. This was due to the amphiphilic character of Cela and the presence of a significant number of aromatic rings in the inner core.



### Electrostatic force

Electrostatic interactions are defined as an electrostatic attraction between charged groups, dipoles, and induced dipoles. A dipole distance occurs between polar molecules, and dipole molecules interact electrostatically. This intermolecular contact is known as electrostatic force, and it occurs during self-assembly [33, 42].

Baicalin (BA) and wogonoside (WOG) are flavonoids that are major components of *Scutellariae* radix (Lamiaceae) [43, 44]. In aqueous solution, BA and BBR self-assembled into NPs [20] via the electrostatic interaction generated between the carboxyl groups in BA and the quaternary ammonium ions in BBR. The electrostatic interaction promoted the formation of one-dimensional complex units, whereas the hydrophobic interaction facilitated further three-dimensional self-assembly, resulting in homogeneous spherical BA-BBR NPs. WOG and BA may self-assemble to produce nanofibers (NFs) in an aqueous solution, in which the major force is a strong hydrophobic effect. This was because WOG-BBR is not amphiphilic and hence cannot self-assemble into NPs but rather precipitates in aqueous solution due to its high hydrophobicity. As a result, type I planar hydrophobic molecules are more prone to form NFs. Importantly, there are significant differences in antibacterial effectiveness between the two, with the NPs significantly surpassing the NFs. BBR derivatives (BDS) self-assemble with rhamnolipids (RHL), an anionic surfactant secreted by *Pseudomonas aeruginosa*, to form stable nanodrugs (BD/RHL NDS) [45], and molecular dynamics modeling confirms that the formed self-assembly was due to electrostatic and hydrophobic interactions. Electrostatic interactions require attraction, repulsion, or directionality between particles and may occasionally affect the size and length of nanostructures [42].

### $\pi$ - $\pi$ stacking

$\pi$ - $\pi$  stacking is a spatial organization of aromatic compounds that involves a mild interaction between aromatic rings. It generally occurs between two molecules that are substantially electron-rich and electron-poor. It is a non-covalent bond interaction with equal importance as hydrogen bonding, and its mechanism is more complex than that of hydrogen bonding [46, 47].

Zheng et al. [18] used spectroscopy and single crystal X-ray diffraction to investigate the mechanism of direct self-assembly of hydrogels between Rhe molecules extracted from the TCM *Rheum palmatum* (Polygonaceae) and observed that certain Rhe molecules were deprotonated to form Rhe sodium when the pH was between 8.0 and 9.4. Through  $\pi$ - $\pi$  stacking and hydrogen bonding, the Rhe monomer and sodium

Rhe formed J-type aggregates, which then combined to create dimers. These dimers then assembled into trimers, tetramers, and other higher-order aggregates. Ultimately, this process resulted in the formation of a Rhe self-assembling gel. The study revealed that carboxyl groups played a crucial role in the gelation process, as emodin, chrysophanol, aloe-emodin, and emodin A failed to produce hydrogels. Additionally, liquidambaric acid (LDA) is a triterpenoid that originates from *Liquidambar formosana* (Altingiaceae). Its molecular structure can be divided into the following main parts: the alkane polycyclic skeleton (tricyclic, tetracyclic, and pentacyclic), the alkene (double bond), and the oxygen-containing moiety (such as hydroxyl). Zhi et al. [14] examined the potential interaction mechanism of these different parts through 2D NMR and 1D 1H NMR and found that LDA NPG initially developed one-dimensional fibres through the self-assembly of the following distinct noncovalent interactions:  $\pi$ - $\pi$  stacking, van der Waals forces, and hydrogen bonding. These fibres then interacted with the solvent, resulting in the formation of NPG with a three-dimensional network fibre structure over time. We observed that TCMs with aromatic ring conjugated structures tended to self-assemble directly under  $\pi$ - $\pi$  stacking or  $\pi$ - $\pi$  stacking coordination.

### Coordination

Coordination is a medium-strength intermolecular force that is weaker than covalent interactions and falls between hydrogen bonds and van der Waals interactions in terms of strength. The intensity of coordination is influenced by external factors [48, 49].

Luteolin (Lut) is a natural flavonoid that can be found in *Lonicera japonica* (Caprifoliaceae) [50, 51]. Recent research has shown that Lut can self-assemble with  $\text{Fe}^{3+}$  to form NPs [15]. This coordinated assembly with iron ions resulted in supramolecular photothermal action, enabling the NPs to act as chemotherapeutic or photothermal agents. It is worth mentioning that various catechol flavonoids, such as Lut, quercetin, kaferol, baicalin, and catechin, can combine with metal ions to self-assemble and form NPs. This coordination produced supramolecular photothermal action, allowing the NPs to function as chemotherapeutic or photothermal agents.

Many active components in TCM can self-assemble due to their unique structures. As a result, these components exhibit an ability to form nanoformulations with stable nanostructures, which is attributed to noncovalent processes, including hydrogen bonding,  $\pi$ - $\pi$  stacking, electrostatic interactions, hydrophobic interactions, and coordination.

### The self-assembly forms of CSAN

An increasing number of studies on the self-assembly of TCM [52–54] have been reported, and these studies range from the active components of TCM monomers to decoctions of single or compound TCM. In this paper, we classify and summarize CSAN based on its different forms of self-assembly.

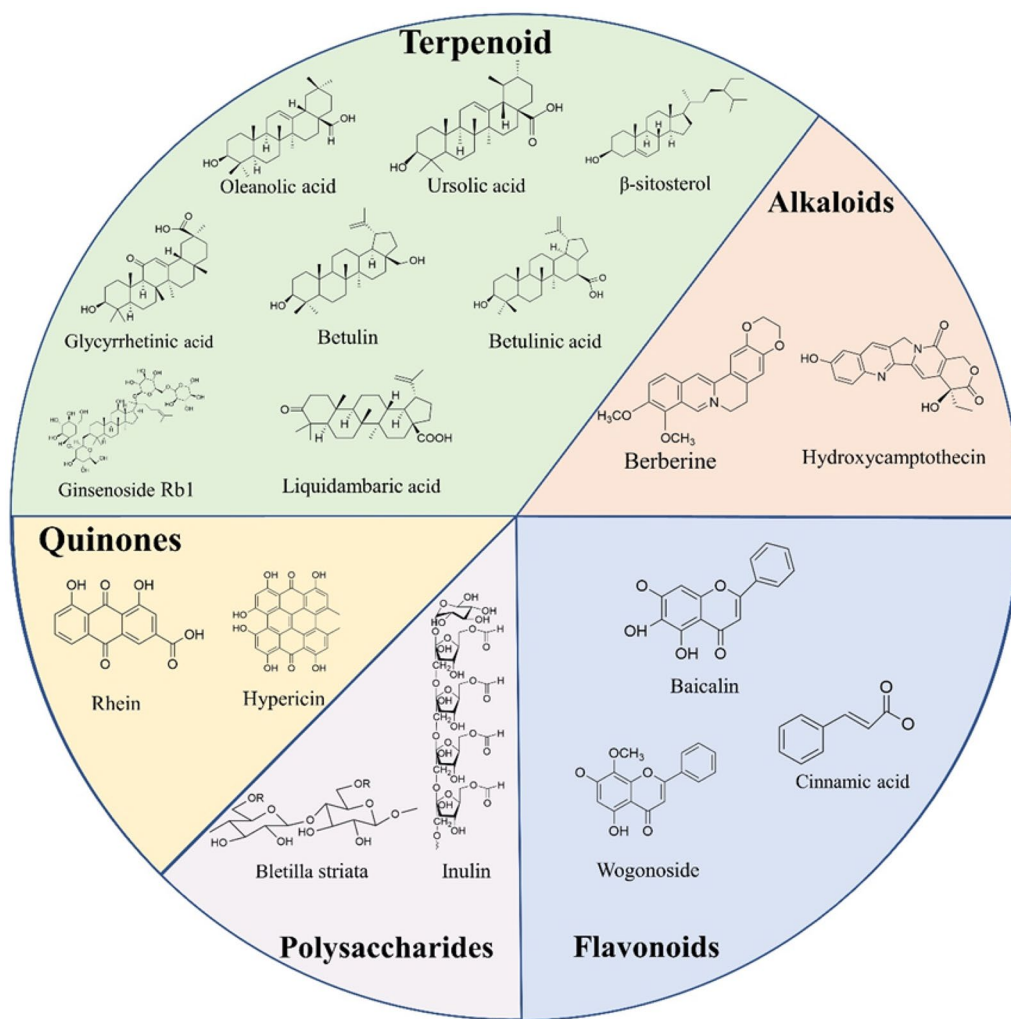
#### Pure natural nanoformulations formed by self-assembly of single or compound TCM components

Nanoformulations produced by the self-assembly of single or compound TCMs can increase the solubility and bioavailability of TCM active components and can be employed as natural nanodelivery carriers, which can play a coordinating role while exerting their own therapeutic effect. Due to the distinctive three-dimensional structure, multifunctional groups, and good biocompatibility of TCM, it is easy to build great nanostructures

(Fig. 2), amplifying the benefits of TCM. Furthermore, compared to the present nanopreparation procedure, this method is simpler, more ecologically friendly, and safer. Because of these properties, this technique has garnered widespread attention.

#### Self-assembly of TCM with the same components

**Terpenoids** Terpenoids, which utilize isoprene as a basic structural unit, are among the most abundant natural phytochemicals [55–57]. Terpenoids exhibit a distinct rigid skeleton, chiral centre, and many modification sites, as well as varied amounts of hydroxyl and carboxyl groups, and fold easily in diverse mediums to produce self-assembled NPs. Terpenoids are now the focus of nanoself-assembly research. UA is a pentacyclic triterpenoid found in a variety of TCMs. According to the findings of Braja Gopal Bag’s study [58], UA molecules self-assembled in most organic and aqueous organic solvents to form nano-



**Fig. 2** Chemical structure of TCM with self-assembly ability

structures, such as vesicles, tubes, fibres, flowers, and supramolecular gels, which were employed to entrap the anticancer drug doxorubicin (DOX). Fan et al. [12] prepared UA NPs by using the solvent exchange method, which was straightforward and efficient, and carriers or water-soluble medicines were not needed throughout the procedure; as a result, greater drug release ability and anticancer effects were obtained than those of free UA. GA, a pentacyclic triterpene, is among the most important active components in *Glycyrrhiza glabra* [59, 60]. GA may self-assemble in aqueous solution, form complexes with other drugs, improve the solubilization of poorly soluble drugs, and be utilized as DSS to deliver drugs and improve their solubility and bioavailability [61]. In in vivo studies, Yang et al. [62] applied GA micelles to deliver PTX in vivo, which enhanced oral bioavailability by nearly sixfold compared to that of free PTX. Wang et al. [63] used GA micelles to deliver podophyllotoxin (POD) transdermally, increasing POD distribution in the epidermis while decreasing skin inflammation. Paeoniflorin (Pae), a water-soluble monoterpene glycoside, exhibits high therapeutic value in autoimmune and inflammatory illnesses [64, 65]. Shen et al. [61] used GA micelles to enhance Pae oral absorption. Pae-loaded GA micelles increased Pae release and intestinal permeability compared to that of free Pae. LDA is a pentacyclic triterpene derivative extracted from the plant *Liquidambar formosana* (Altingiaceae). Zhi et al. [14] formed LDA natural product gels (NPGs) with good self-healing properties, controlled gelation, safety, and prolonged release through self-assembly of the solvent method. Sito is a tetracyclic triterpenoid derived from the plant *Arisaema heterophyllum* Blume (Araceae). He et al. [28] produced Sito NPG using heat-cool and ultrasonic technologies. In vitro, Sito NPG demonstrated equivalent or better carcinogenesis than that of Sito NPG and showed potential as a natural delivery vector. Braja Gopal Bag et al. [66] discovered self-assembly reactions for several triterpenoids in diverse liquids, including betulinic acid, OA, GA, gingerfruit acid, and its derivatives. These self-assembling reactions might be used to encapsulate fluorophores, DOX, and other molecules. Triterpenoids have been extensively explored in CSAN owing to their ease of self-assembly.

**Proteins** Proteins possess a distinctive structure that enables them to self-assemble via noncovalent interactions. Recently, there has been a growing interest in researching plant protein NPs obtained from TCM, such as licorice protein [67], almond protein [68], heterophylla protein [69], and several others. Protein self-assembly is a common occurrence in nature. Zhou et al. [67] identified glycosylated licorice protein (GLP) from licorice (*Glycyrrhiza uralensis* Fisch.). This protein is novel, plays an unknown

biological function and exhibits a molecular weight of 28 kDa. The team created GLP NPs through decocting, and these NPs demonstrated remarkable pH response properties. Furthermore, they were found to promote the growth of normal liver cells and dissolve insoluble astragaloside IV. Additionally, Radix Pseudostellariae (Caryophyllaceae, *Pseudostellaria heterophyll*) protein (RPP) displayed significant self-assembly properties and antioxidant activities. The combination of RPP with curcumin (Cur) has resulted in the development of RPP NPs loaded with Cur, forming nanocomplexes that exhibit enhanced photostability, antioxidant activity, and cell uptake efficiency [69]. This advancement should enable the delivery of more functional bioactive components. NPs were prepared using RPP-polysaccharide (CP3) conjugates through a heat treatment condensation technique [70], and these NPs can rapidly release DOX at an acidic pH. Additionally, protein NPs are present in the aqueous solution of *Coptis chinensis* extract [71], which can serve as a natural drug carrier to enhance the plasma exposure and biological activity of BBR. Apricot Kernels, commonly known as *Prunus armeniaca* Linne var. *ansu* Maximowicz, is widely used as a TCM [72, 73]. *Semen Armeniacae Amarum* Protein (SAP) found in the decoction can self-assemble to form SAP NPs [68]. SAP NPs are loaded with the anticancer drug PTX to form PTX-SAP-NPs, which compared to free PTX, were more effective against tumours. Huang et al. [74] discovered ivy NPs (INPs) from the adventitious roots of English ivy (Araliaceae; *Hedera helix*). These INPs can create INP-DOX nanoconjugates by encapsulating DOX through electrostatic and hydrophobic interactions and show promise in the treatment of tumours. Zhou et al. [75] isolated Ban-Lan-Gen (BLG) NPs from the decoction of *Isatis indigotica* Fort. They identified the main components of BLG NPs as two types of glycosylated proteins and found that they exhibit a tumour-inhibitory function. Protein NPs derived from TCM exhibit favourable pharmacological properties and exceptional bioavailability; thus, they are a highly promising avenue for developing therapeutic nanocarriers.

**Polysaccharides** Polysaccharides are natural macromolecules generated by the chemical polymerization of several monosaccharides [76, 77]. They are abundant in nature and exhibit antitumour [78], antioxidant [79], and other qualities [80]. The skeletal structure of polysaccharides is densely packed with hydrophilic groups. The balance between hydrophilic and hydrophobic groups can be achieved by introducing hydrophobic aromatic groups or alkyl chains to polysaccharide molecules, which promotes polysaccharide self-assembly. Stearic acid (SA)-modified *Bletilla striata* polysaccharides (BSPs-SA) isolated from the stem tubers of *Bletilla striata* (Orchidaceae) could



be self-assembled to form BSPs-SA NPs [81]. It displays an antitumour effect after loading with DOX. Angelica polysaccharide (ASP), a plant polysaccharide extracted from *Angelica sinensis* radix (Apiaceae), shows increased biocompatibility, is water soluble, and has the capacity to target the liver internally [82, 83]. When ASP is modified with a hydrophobic group (deoxycholic acid), it can self-assemble to generate ASP-DOCA NPs [84]. After ASP-DOCA NPs were encapsulated with DOX, they demonstrated a greater antitumour effect than that of free DOX. Inulin is a polysaccharide derived from *Cichorium intybus* radix (Asteraceae). Carboxymethyl-modified inulin may self-assemble into spherical NPs [85], which can be employed to treat spinal cord injury collaboratively. Inulin with a high molecular weight synthesized by enzymes can form stable spherical nanoparticles with an average diameter of  $112 \pm 5$  nm as a drug delivery system [86]. Therefore, polysaccharides are attracting the attention of researchers due to their excellent biocompatibility and self-assembly properties.

**Quinones** Quinones tend to form nanostructures due to their polycyclic rings and hydrogen bonds [87]. Rhe is a lipophilic anthraquinone molecule found in *Rheum palmatum* (Polygonaceae) that contains hydrophobic planar anthraquinone units as well as numerous hydroxyl and carboxyl groups that easily self-assemble. Rhe may self-assemble into Rhe hydrogel [18] without any structural alteration, providing long-lasting release as well as increased anti-neuroinflammatory effects by downregulating pro-inflammatory cytokines and neurotoxic factors. Hypericin, a dianthraquinone molecule, is extracted from *Hypericum perforatum* (Hypericaceae) and is among the strongest photosensitizers in nature [88, 89]. It specifically targets necrotic tumour lesion sites and may self-assemble with demyoglobin to produce nanostructures [90], which increase hypericin bioavailability, fluorescence, and bacterial photoactivation.

**Others** Ginger, the rhizome of *Zingiber officinale* (Zingiberaceae), is among the most widely used natural products [91]. Ginger NPs can be employed as natural nanocarriers, which offer benefits over conventionally manufactured nanocarriers. Zhang et al. [92] isolated a significant number of NPs from ginger, and these ginger-derived nanovectors (GDNVs) demonstrated good stability and drug release, making them suitable to deliver DOX. NPs derived from edible ginger (GDNPs 2) [93] contain a high concentration of lipids, a minor quantity of protein, ~125 microRNAs (miRNAs), and a high concentration of bioactive ginger components (6-gingerol and 6-gingerol). GDNPs 2 targets inflamed intestinal mucosa to prevent chronic colitis and colitis-related malignan-

cies. NPs composed of edible ginger-derived lipids, called ginger-derived lipid vectors (GDLVs) [94], were loaded with anti-CD98 siRNA to form siRNA-CD 98/GDLVs. At extremely low dosages, oral siRNA-CD 98/GDLVs suppressed colon CD98 gene expression specifically and efficiently. *Rabdosia rubescens* (Lamiaceae) is commonly used as an antithrombotic medicine. Peng et al. identified five nucleotides, four diterpenoids, and 21 phenolic acids from the aqueous extract of *Rabdosia rubescens* leaves (AERL), and AERL can form NPs in a concentration-dependent manner in water [95]. In addition, AERL concentration-dependently inhibited platelet aggregation in vitro and dose-dependently inhibited thrombosis in vivo, and it was predicted that frosamarinic acid may be its main antithrombotic active component.

#### **Self-assembly of TCM with different components**

**Alkaloids and flavonoids** BBR, an isoquinoline alkaloid, is the main active component of *Coptis chinensis* F. (Ranunculaceae) and is widely used in clinics. However, BBR exhibits a low water solubility and an unpleasant bitter flavour [25, 96]. These flaws can be effectively improved by CSAN. Simultaneously, the quaternary ammonium ion and benzene ring structure of BBR can be joined with other natural products, particularly flavonoids, to form NPs with suitable particle sizes. Because of its strong self-assembly ability and antibacterial potential, BBR has become among the most investigated drugs in TCM self-assembly. BA and WOG are flavonoids that are major components of *Scutellariae* radix (Lamiaceae). In an aqueous solution, BBR and BA self-assemble to generate stable BBR-BA NPs [20], which exhibit high biocompatibility and greatly increased antibacterial and biofilm removal properties. BBR and WOG can also self-assemble to form BBR-WOG NPs. Notably, BBR-WOG NPs exhibit much lower antibacterial activity than that of BBR-BA NPs. Alkaloid components easily interact with organic acid components to self-assemble. In aqueous solution, BBR and CA may self-assemble to generate CA-BBR NPs [17] without any carriers or additives during the self-assembly process. CA-BBR NPs are more effective than various first-line drugs at inhibiting multidrug-resistant *Staphylococcus aureus* (MRSA). BBR and 3,4,5-TCa could self-assemble in aqueous solution to create BCR-3,4,5-TCa NPs [27], which outperformed first-line amoxicillin, norfloxacin, and their self-assembled predecessors against MRSA.

**Alkaloids and quinones** In an aqueous solution, BBR and Rhe may self-assemble to form BBR-Rhe NPs [26]. that can bind to bacterial surfaces, increase antibacterial activity against *Staphylococcus aureus* and exhibit a higher biofilm clearance rate and synergistic antibacterial

ability than that of BBR or Rhe. Currently, the self-assembly technique of BBR-related TCM is mostly applied in antibacterial studies, and it has demonstrated strong antibacterial efficacy.

**Alkaloids and protein** In clinical practice, the combination of *Glycyrrhiza uralensis* with *Aconiti Kusnezoffii Radix* can effectively remove the toxicity of *Aconiti Kusnezoffii Radix* and improve the therapeutic effect [97]. CSAN offers a novel approach to study this phenomenon. Aconitine (AC) is an extremely poisonous alkaloid derived from several *Aconitum* plants [98]. Ke et al. [99] isolated a stable 31 kDa protein (GP) from *Radix glycyrrhizae*, and the GP-AC NPs produced by the solvent technique dramatically decreased AC toxicity.

**Alkaloids and organic acids** Aristolochic acid (AA) is present in *Asarum* and *Aristolochia* has been reported to cause acute kidney injury (AKI) [100]. However, AA-containing herbs are very safe in combination with BBR-containing herbs in TCM, and it has been found that the supramolecular self-assembly formed by BBR and AA significantly reduced the toxicity of AA and attenuated AA-induced acute kidney injury [101]. This self-assembly strategy guided by TCM compatibility theory not only provides a better curative effect but can also explain the TCM compatibility theory.

**Terpenoids** OA and GA are triterpenoids from natural Chinese medicine. The antitumour effect of OA-GA NPs [29] was much greater than that of free drugs, and OA-GA NPs may be employed as a drug carrier to deliver PTX, enhance antitumour activity and minimize liver damage caused by PTX. The coassembly of components with similar pharmacological activity can improve the pharmacological efficacy of drug carriers. The *Genkwa Flos*/GA self-assembled complex was prepared by combining Genkwanine (GW, one of main ingredients from *Genkwa Flos*) with GA in an aqueous solution [38], which exhibit stronger apoptosis than that of *Genkwa Flos*. In clinical practice, researchers believe that the combination of *Genkwa Flos* and *Glycyrrhiza glabra* will enhance their toxicity. Hence, this study explored the clinical incompatibility of these two drugs from another angle.

**Terpenoid and catechin** It has been claimed that epigallocatechin gallate (EGCG) from green functions as the "shell" of a multifunctional material coating. Zhang et al. [102] synthesized UA and EGCG. First, UA was simply self-assembled to create UA NPs, and then the surface was covered with EGCG to produce a core-shell structure. Finally, epithelial cell adhesion molecule (EpCAM) was introduced to modify UA@EGCG-Apt. The obtained

UA@EGCG-Apt NPs (UEA NPs) showed synergistic tumour therapy and induced immunotherapy effects. This self-assembly approach based on the structural properties of several active components of TCM yields positive results.

**Protein and diketones** Radix *Pseudostellariae* (Caryophyllaceae, *Pseudostellaria heterophyll*) and Curcuma longa (*Zingiberaceae*) are frequently utilized in illness treatment and health care. The RPP-Cur nanocomplexes exhibited better stability and reducing power than that of free Cur [103] and displayed an additive effect between Cur and RPP.

Self-assembly of TCM with different components can play a therapeutic role directly and act as a natural nanodelivery carrier, eliminating the adverse effects of loading chemotherapeutic chemicals and the added toxicity produced by long-term usage of nonbiologically active nanocarriers. The synthesis method is straightforward, efficient, and environmentally friendly, and it is being developed into a viable nanodrug delivery system.

#### **Self-assembly of TCM decoctions**

Decoction is among the most often utilized forms of TCM in clinical treatment [104–106]. TCM decoction is a complex dispersing system that contains solute, colloid, aggregate, emulsion, and precipitate, and many TCM decoctions can generate self-assembled NPs during decoction. The study of self-assembled NPs in TCM compound decoctions has biological significance and may provide a fresh viewpoint on the onset mechanism and safety of TCM decoctions and their active components.

Wu et al. [107] found that *Coptis chinensis* decoction (CCD) could form particle aggregates in CCD (CCD-Ps), which were primarily composed of polysaccharides, and BBR absorption in the intestinal tract could be improved by regulating tight junctions (TJs) between intestinal epithelial cells, active transport, and endocytosis. Nanometre aggregates (NAs) are present in Bai-Hu-Tang (BHT) water decoction [108], and BHT NAs are more likely to aggregate in the lung and brain and have a greater antipyretic effect than that of other BHT scattered phases. GDQ micro/nanoaggregates (MNA) included in Ge-Gen-Qin-LianTang decoction (GQD) [109] increase the absorption of BA and boost antidiabetic efficacy by dramatically decreasing the effect of oxidative damage on cell survival and function. The Ma-Xing-Shi-Gan-Tang (MXSGT) decoction is a traditional Chinese botanical drug preparation that contains ephedra as its major component. Zhou et al. [110] isolated and characterized colloidal nanoparticles (MXSGT NPs) from MXSGT and found that MXSGT NPs are associated with most ephedrine and pseudoephedrine compounds in decoctions and

can alter their biological activity. Elucidating the formation mechanism of SAN in TCM decoctions is helpful to promote research on TCM compounds.

The self-assembly of TCM decoctions is a self-assembly strategy that involves an easy preparation process and enhanced performance. Sometimes self-assembly is inspired by TCM theory's drug pairing experience, such as rhubarb (Polygonaceae; *Rheum rhabarbarum*)-*Coptis chinensis*, scutellarium-*Coptis chinensis*, *Coptis chinensis*-aconite, and other famous drug pairs, and exhibits positive effects. This widely accessible, versatile, and biocompatible self-assembly method offers a fresh perspective for comprehending TCM chemicals and is likely to aid in the development of novel effective nanopreparations inspired by TCM.

#### **Combined self-assembly of active components of TCM and chemical drugs**

The active components extracted from TCM offer several benefits, including high efficiency, low toxicity, broad effects and various targets. However, many active components in TCM, such as chemical drugs, exhibit several drawbacks, including limited solubility and low bioavailability [111–113]. Many investigations have found that active components from TCM and chemical drugs self-assemble to generate nanopreparations [114]. This self-assembly technique increases the solubility and bioavailability of the two drugs, plays a synergistic function, and reduces the negative effects of chemical drugs. The technique is currently largely employed in antitumour research.

The strategy of self-assembling drugs that exhibit combined antitumour effects into nanopreparations is particularly successful, and the effects can be applied to several antitumour pathways. PTX is a regularly used anticancer drug in clinics; however, its drawbacks, such as water insolubility and multidrug resistance, severely restrict its therapeutic use [115–117]. The self-assembly of PTX with TCM active components can enhance its solubility and lessen adverse effects, allowing for greater PTX utilization in clinics. Zou et al. [118] discovered that the natural antiangiogenic agent tetramethylpyrazine (TMP) and PTX exert a synergistic effect to inhibit the growth of ovarian cancer, so they designed PTX-ss-TMP NPs with higher cytotoxicity and stronger antiangiogenesis than that of free drugs, as well as better antitumour activity and tumour-specific accumulation. Through hydrogen bonding and hydrophobic self-assembly, UA and PTX combine to generate UA-PTX NPs [19]. The synergistic action of UA and PTX can considerably increase tumour therapy efficacy and upregulate the major antioxidant system, lowering the risk of liver harm caused by chemotherapy drugs. These

self-contained bioactive nanocarriers have the potential to compensate for the inadequacies of standard nanocarriers, which offer no therapeutic or health advantages. According to research, BBR preferentially accumulates in the mitochondria of tumour cells and suppresses cancer cell growth via a different biological mechanism than that of PTX. The PTX-ss-BBR NPs [13] can target mitochondria and exhibits better antitumour effects. Gambogic acid (GBA) is the principal active ingredient in the traditional Chinese medication *Garcinia Cambogia* [119], and the DTX-GBA PLGA NPs [120] produced by the self-assembly approach may be used in tumour combination therapy and exhibit high potential for treating multidrug-resistant breast cancer. CSAN shows the potential to be an efficient and cost-effective drug delivery technology that improves the stability and safety of chemical drugs. For example, self-assembled glycyrrhizic acid-hydroxycamptothecin (GL-HCPT) micelles [121] greatly enhanced HCPT solubility and stability and demonstrated greater antitumour activity and biosafety than that of HCPT injection and HCPT/GL physical combination. By modifying the self-assembled nanopreparation, researchers may achieve the desired properties, such as the integrated function of tumour diagnostics and therapy. Gallic acid (GLA) is a polyphenolic chemical component found in plants, such as rhubarb, *Eucalyptus macrophylla* (Myrtaceae), and *Cornus officinalis* (Cornaceae) [122, 123]. An et al. [124, 125] demonstrated that GLA-Fe@BSA-PTX NPs exhibit excellent biological safety and can be utilized for both tumour diagnostics and therapy. The NPs might be utilized for tumour MRI comparison and chemical-photothermal combination therapy, which overcomes the limitations of single therapy and offers tremendous promise in tumour diagnosis and treatment. An irinotecan hydrochloride-curcumin nanosystem (SICN) [16] formed by Cur and irinotecan hydrochloride is a carrier-free SAN. These NPs can synergistically exert the antitumour effect of the two drugs. The NPs exhibit a self-monitor ability due to the fluorescent qualities of Cur. This type of multifunctional carrier-free NP offers a novel approach to tumour combination treatment.

In brief, active components of TCM can self-assemble with chemical drugs to generate nanoformulations. This method frequently outperforms single drug treatment or a simple combination of drugs. It may also be adapted to create a multifunctional nanodiagnostic and therapeutic platform with extensive cancer application potential.

#### **Other natural self-assembled nanocarriers that deliver active components of TCM**

Natural self-assembled nanocarriers (mostly chitosan, liposomes, and so on) can also be used to deliver active ingredients of TCM to CSAN. Given the importance of

green environmental preservation and biosafety, the distribution strategy of nonnatural materials is not covered in this study. Employing natural carriers to convey TCM active ingredients can increase TCM active ingredient solubility, bioavailability, and other qualities, as well as improve TCM active ingredient application.

Chitosan is a natural polymer that has been deacetylated from chitin. Chitosan and its derivatives are biocompatible, biodegradable, biologically active, and immunogenic. Hence, the use of chitosan to deliver active components of TCM shows great promise [126–128]. Cur is the primary polyphenolic component in *Curcuma longa*; however, its clinical use is restricted by its poor solubility and bioavailability [129, 130]. Lokesh Pathak et al. [131] employed an ionic gelation technique to prepare biodegradable, biocompatible anionic lipids (soya lecithin) and cationic biopolymers (chitosan) into lecithin/chitosan NPs and entrapped Cur to form Cur NPs, which exhibited antioxidant effects superior to those of free Cur. Artemisinin (AST) is currently the most extensively utilized artemisinin derivative. Renu Chadha et al. [132] loaded AST into lecithin/chitosan NPs composed of chitosan and lecithin to increase its antimalarial efficacy. In *P. berghei*-infected mice, oral administration of AST NPs resulted in higher antimalarial activity in vivo and a reduction in the parasitism rate. Eman M. El et al. [133] loaded ferulic acid with modified chitosan and conjugated glycyrrhizin to the surface of chitosan NPs. The prepared ferulic acid-conjugated MC NPs showed an excellent ability to target livers. The novel self-assembling bottlebrush polyethylene glycolpolynorbornene-thiocresol block copolymers (PEG-PNB-TC) [134]. Cur and PTX were successfully loaded to form PTX-CUR coloaded PEG-PNB-TC, which shows the potential to treat drug-resistant cervical cancer. Liposomes are bilayer-structured closed vesicles that can be employed as natural nanocarriers to carry TCM active ingredients. When nanoliposomes reach the human body, they are nontoxic, offer biocompatibility benefits, and may be modified to accomplish targeting. Psoralen-loaded nanosized liposomes increase psoralen skin deposition and exhibit high biocompatibility.

#### Self-assembled nanoformulations modified by active components of TCM

Some active components of TCM show considerable activity, and nanoformulations exhibit specific activity after CSAN is modified with active components of TCM. Therefore, self-assembled nanoformulations involving the active components of TCM are also included in this paper. Notably, this method coincides with the theory of TCM.

Borneol (Bor) is a monoterpene component derived from *Dryobalanops aromatica Gaertn f.* and *Blumea balsamifera DC.* Bor has been widely used in TCM [135, 136] as well as modern medicine; in particular, Bor stimulates the opening of the blood–brain barrier (BBB) and improve drug penetration and distribution in the brain in a reversible manner, which improve the delivery efficiency of nanomedicines. Guo et al. [137] self-assembled carmustine (CMS) into a micelle and prepared Pep-1/Bor/CMS-M by bifunctionally modifying Bor and Pep-1, which actively target brain glioma cells and hence enhance CMS accumulation in glioma. Lv et al. [138] designed Bor combined with CGKRK peptide-modified PTX prodrug self-assembled redox-responsive NPs (CGKRK-PSNPs), which provides a good effect on the treatment of glioblastoma multiforme (GBM). In TCM, Bor opens the body to awaken the mind and induces drug uptake. This may be related to the use of Bor-modified nanomedicine in CSAN to promote drugs to penetrate the BBB and improve the distribution of drugs in the brain. In clinical practice, Bor is often used as a channel ushering drug, such as in the classical formula compound Danshen dripping pill (CDDP). This is similar to the role of Bor in the modification of CSAN, and the strategy of using some TCM components with special activities for self-assembly is promising.

#### Application and advantages of CSAN in cancer

Cancer is a severe public health issue that endangers human life and health. Currently, the primary treatment methods include surgery, radiation, chemotherapy, immunotherapy, and other treatments, among which chemotherapy remains the most common treatment [139–141]. Many chemotherapy drugs, however, are known to induce a variety of adverse effects, and traditional single-agent chemotherapy is known to result in poor therapeutic effects, multidrug resistance, tumour recurrence, and metastasis. Combination chemotherapy combines two or more therapeutic drugs that target separate signalling pathways during tumour growth to achieve synergistic anticancer effects [142, 143].

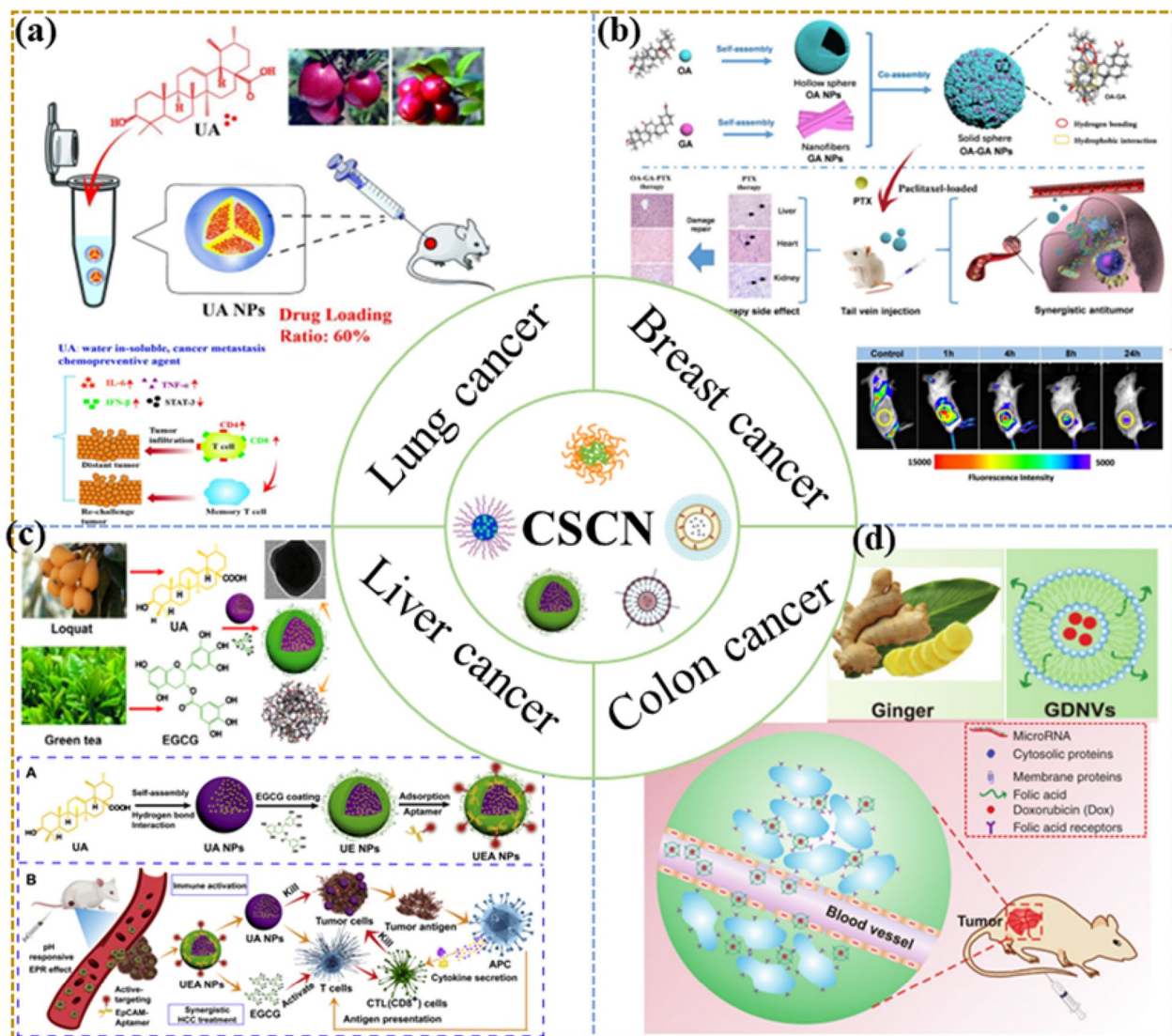
According to studies, many active components of TCM exhibit strong antitumour effects, high efficiency, low toxicity, multiple actions, various targets, and other benefits and can mitigate the side effects of chemotherapy to some extent [144–146]. In TCM, there are several active components that act on multiple targets simultaneously to produce additive or synergistic effects. TCM's antitumour effect includes increasing the activity of immune cells such as thymus-dependent lymphocytes and natural killer cells to kill tumour cells or directly acting on tumour cells to inhibit tumour growth and metastasis, as well as eliminating the side effects or complications of



chemotherapy, radiotherapy, or surgical resection [147, 148].

The combination of antitumour active components of TCM and chemotherapeutic drugs for antitumour treatment has attracted increasing attention. To date, combining the active components of TCM with first-line chemotherapy drugs has been shown to be effective at reversing tumour treatment resistance, making the treatment more effective and reducing adverse side effects. A variety of nanoformulations have been used in combination chemotherapy for malignancies to address the inadequacies of free drugs, but nanoformulations with targeting and high safety are still lacking.

Self-assembled nanoformulations based on CSAN can improve the solubility and bioavailability of TCM active components as well as tumour targeting. They can also be combined or loaded with chemical drugs with high side effects to play a combined therapeutic role, delay or inhibit the absorption of toxic components, and reduce side effects. The nanoformulations offer significant safety benefits and curative effects as a natural substance (Fig. 3). In vivo safety is critical in the clinical use of nanoformulations, and due to its excellent safety, CSAN will likely be applied in clinics. The application of CSAN in different tumours is summarized in Table 2.



**Fig. 3** Application of CSAN in different tumors. **a** UA NPs for lung cancer. Copyright 2018 Elsevier. **b** OA-GA-PTX NPs for breast cancer. Copyright 2020 American Chemical Society. **c** UEA NPs for liver cancer. Copyright 2020 Elsevier. **d** DOX-FA-GDNVs for colon cancer. Copyright 2018 The American Society of Gene Therapy

**Table 2** The application of CSAN in the field of antitumor

Tumor type	Nano preparation	Drug composition	Effects	Characteristic	Refs.
Lung cancer	UA NPs	UA	↓Tumor proliferation and growth ↑Cell apoptosis, ↑activation of CD4 <sup>+</sup> T cells	The ability of liver protection in vivo The potential for immunotherapy	[12]
Lung cancer	PTX-BBR NPs	BBR PTX	↑ROS levels, ↑Block the cell cycle and cell apoptosis ↓Tumor growth	Mitochondria-targeting delivery Synergistic enhancement	[13]
Lung cancer	Rb1/PPD NPs	Rb1 PPD	↑Accumulation at the tumor site, ↑Cytotoxicity ↑Blood circulation time, ↓Damage to normal tissues	Synergistic enhancement Simple, scalable, green economy process	[153]
Breast Cancer	OA-GA-PTX NPs	OA GA PTX	↑Drug releasing capacity and Cellular uptake ↑Tumor aggregation targeting and apoptosis ↓Tumor proliferation and growth, ↑Block the cell cycle ↓ALT、AST、LDH、CK、MDA, ↑SOD、GSH	Synergistic enhancement Reduce chemotherapy side-effects Different antitumor mechanisms Reduce damage caused by oxidative stress	[29]
Breast Cancer	UA-PTX NPs	UA PTX	↓Tumor growth ↑Block the cell cycle, ↑Cell apoptosis and cellular uptake ↑Tumor aggregation targeting, ↑SOD、GSH	Synergistic enhancement Different antitumor mechanisms Reduce chemotherapy side-effects	[19]
Breast Cancer	DTX/GBA-PLGA NPs	GA DTX	↑The expression of P-gp, ↑Cell apoptosis ↓Tumor growth	Synergistic enhancement Special in multidrug-resistant breast cancer	[81]
Liver cancer	UEA NPs	UA EGCG DOX	↑Drug releasing capacity and cellular uptake, ↓Tumor growth, ↑IL-12、IFN-γ、CD4 <sup>+</sup> 、CD8 <sup>+</sup> ↑Tumor aggregation targeting, ↑Cytotoxicity	Synergistic enhancement Improvement of Th1/Th2 imbalance	[102]
Liver cancer	GL-HCPT micelles	GL HCPT	↑Cytotoxicity, ↑Tumor aggregation targeting ↓Tumor growth	Improve the solubility and stability of HCPT Reducing the side effects of HCPT	[121]
Gastric cancer	SiCN	Cur Irinotecan hydrochloride	↑Drug releasing capacity and cellular uptake ↑Cytotoxicity, ↑Endocytosis	Synergistic enhancement Self-monitoring function	[16]
Colorectal cancer	DOX-FA-GDNVs	GDNV DOX	↓Tumor proliferation and growth, ↑Cell apoptosis ↑Drug releasing capacity and targeting ability	Loading Dox with high efficiency	[92]
Colorectal cancer	INP-DOX	INP DOX	↑Cytotoxicity, ↓Tumor growth	Synergistic enhancement PH-responsive	[74]
Ovarian cancer	PTX-ss-TMP NPs	TMP PTX	↑Cytotoxicity and cell apoptosis, ↑Block the cell cycle ↑Drug releasing capacity and cellular uptake ↑Tumor aggregation targeting, ↓p-VEGFR2/VEGFR2, p-AKT/AKT, p-mTOR/mTOR and p-p38/p38	Synergistic enhancement Redox-responsive drug release Anti-angiogenesis effect	[118]
Cervical cancer	PTX-Cur coloaded PEG-PNB-TC	Cur PTX	↑Endocytosis and cellular uptake, ↑Cytotoxicity	Circumvented the PTX resistance in the MDR cancer cells	[167]
Glioma	Pep-1/Bor/CMS-M	Bor CMS	↑Cytotoxicity and cell apoptosis, ↑Endocytosis and cellular uptake, ↓Tumor growth	Blood–brain barrier penetrating	[137]

**Table 2** (continued)

Tumor type	Nano preparation	Drug composition	Effects	Characteristic	Refs.
Neuroglioma	Lut-Fe <sup>3+</sup> NPs	Lut	↓Tumor proliferation, ↑Cyto-toxicity	High oxidation stability Chemotherapy combined with PPT	[15]
Melanoma	OPDMA-Cela NPs	Cela	↑Pharmacokinetics, ↑Mitochondria targeting capacity ↓Tumor growth	Mitochondria-targeted carrier for drug delivery	[41]

### Lung cancer

Lung cancer has been the most common type of malignant tumour in China over the last 30 years [149–151]. Many studies have found that numerous active components of TCM, such as UA, BBR, and ginsenoside, exhibit an intervention effect on lung cancer, and their stability and therapeutic efficacy were improved when they were self-assembled to form NPs.

UA NPs [12] can significantly inhibit proliferation and induce apoptosis in A549 human lung adenocarcinoma cells, reduce the expression of COX-2/VEGFR2/VEGFA, increase the immunostimulatory activities of TNF-, IL-6, and IFN-, and decrease STAT-3 activity, which can significantly improve CD4+ T-cell activation. UA NPs have the ability to suppress tumours, protect the liver, and provide immunotherapy. PTX-ss-BBR NPs [13] can actively target mitochondria, boost ROS levels in A549 cells, block A549 cells in the G2/M stage, induce apoptosis in A549 cells, and suppress tumour development. PTX-ss-BBR NPs were more effective against *Staphylococcus aureus*, which was linked to lung cancer incidence, indicating their potential for treating bacterially-induced lung cancer. The high hydrophobicity of PTX significantly reduced its bioavailability. This limitation might be addressed by self-assembled nanoformulations. Han et al. [152] synthesized PTX-ss-PTX and loaded it with 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide (DiR) to form DiR-loaded self-assembled NPs (DSNs). The disulfide bond in DSNs was exploited as a redox response bond to promote the rapid release of PTX in tumour cells. In in vivo and in vitro studies, DSNs demonstrated strong antitumour effects in chemotherapy and photothermal combination treatments. Protopanaxadiol (PPD-type) is the most important active component in *Panax ginseng* (Araliaceae). In in vivo and in vitro studies, Rb1/PPD NPs [153] exhibited the EPR effect of NPs and the synergistic effect of Rb1/PPD, resulting in a superior anti-lung cancer effect and adequate safety. Simultaneously, Rb1 NPs can be employed to distribute insoluble drugs, decrease adverse effects, and enhance anticancer benefits.

### Breast cancer

Breast cancer is among the most frequent malignant tumours in women, with the highest incidence rate among malignant tumours in females [154–156]. The active components of TCM in the treatment of breast cancer are continually being investigated. CSAN has the potential to boost the activity of TCM for the treatment of breast cancer, exert a synergistic effect in chemotherapy with the self-assembly of chemotherapy drugs, and lessen the side effects of chemotherapy drugs, such as PTX and DOX. It can also self-assemble with Fe<sup>3+</sup>, allowing nuclear magnetic resonance imaging as well as photothermal treatment to be performed with NPs.

Both in vivo and in vitro, OA-GA-PTX NPs [29] demonstrated powerful antitumour effects, achieving a maximum inhibitory rate of 82.6% for 4T1 breast cancer tumour-bearing mice. Additionally, the NPs may upregulate key antioxidant pathways to prevent PTX-induced liver damage. LDA exhibited an ability to self-assemble into LDA NPG and can be utilized to load DOX, resulting in DOX-LDA/NPG [14], which showed a synergistic anti-breast cancer effect and reduced DOX-induced cardiotoxicity. The UA-PTX NPs [19] preserved the antitumour and liver-protective properties of UA. Furthermore, these NPs demonstrated a synergistic effect in inhibiting tumours both in vivo and in vitro. Additionally, they had the ability to reduce liver damage caused by PTX. Another promising option is DTX-loaded BSP-SA NPs [81], which exhibit a strong drug release effect and are safe for use. Studies have shown that these NPs exhibit greater efficacy in combating cancer than that of free DTX while also minimizing the toxicity of DOX in the heart and kidneys. Wang et al. [157] developed 2-glucosamine-fluorescein-5(6)-isothiocyanate-glutamic acid-paclitaxel (2DA-FITC-PTX NPs) through self-assembly, which demonstrated a notable enhancement in tumour targeting and growth suppression in breast cancer cells. GLA-Fe@BSA-PTX NPs [125] were found to possess several desirable characteristics, including a moderate size, excellent water dispersibility and stability, low cytotoxicity, strong magnetic resonance imaging contrast, and the ability to provide combination chemo-photothermal

treatment for patients with breast cancer. DTX/GBA-PLGA NPs [120] were found to induce increased apoptosis of MCF-7/ADR cells by downregulating the expression level of P-gp. The most effective inhibition of tumour growth was observed in in vivo studies. The synergistic antitumour activity produced by GBA-PLGA NPs showed significant potential in the treatment of multidrug-resistant breast cancer.

### Liver cancer

Liver cancer is a highly common form of malignancy characterized by a low survival rate and high mortality rate among patients [158–160]. However, TCM has been found to contain active components that are effective in the treatment of liver cancer. CSAN exhibits a better therapeutic effect on liver cancer due to self-assembly of antitumour components of TCM or coassembly with chemotherapy drugs, and it can be actively or passively targeted to improve the drug delivery ability of nanoformulations.

UEA NPs [102] showed the ability to target EpCAM-positive liver cancer cells, exhibited strong cytotoxicity against HepG2 cancer cells, had higher tumour inhibition rates in vivo, and can provide large synergistic therapeutic benefits via immunotherapy that stimulates innate and acquired immunity. DOX/ASP-DOCA NPs [84] reduced cell growth by being preferentially internalized into HepG2 cells via ASPR recognition. DOX/ASP-DOCA NPs, on the other hand, can precisely target HepG2 solid tumours, leading to improved anticancer efficacy. HCPT, derived from *Camptotheca acuminata* (Nyssaceae), is a typical DNA topoisomerase I (Topo I) inhibitor with potent anticancer activity. However, HCPT is poorly soluble and unstable. GL-HCPT micelles [121] can greatly increase HCPT solubility and trigger apoptosis in HepG2 and Huh7 human hepatoma cells. In vivo studies revealed that compared to hydroxycamptothecin injection, GL-HCPT micelles achieved superior anticancer efficacy and safety. CP3-DOX NPs [70] can accelerate DOX release in the acidic pH of the tumour microenvironment, exhibit stronger cytotoxicity to HepG2 cells than that of free DOX, and promote early cell apoptosis.

### Other tumours

CSAN has also been used to study different types of cancer. Because of its superior stability and biocompatibility, stronger synergistic therapeutic impact, and improved safety, its research possibilities in the field of malignancies are promising.

Gastric cancer is among the most frequent types of cancer that endangers human health. The rate of early detection is low, and few tumour indicators are available [161, 162]. Through combination therapy, CSAN can

provide a greater anticancer impact. SiCN [16] exerted the synergistic therapeutic effect of irinotecan hydrochloride and Cur, had greater cytotoxicity, induced apoptosis and necrosis of HGC-27 human gastric cancer cells, arrested the cell cycle, and could monitor its uptake, absorption, and excretion in real time in vivo and in vitro.

Colorectal cancer is a common malignant tumour of the digestive tract [163, 164]. CSAN can deliver DOX through tumour targeting and provides a better anticancer effect. Ginger-derived GDNV [92] can be efficiently absorbed by colon cancer cells and loaded with DOS to treat colon cancer. Dox-FA-GDNVs can better cause apoptosis in colon-26 cells. In vitro and in vivo studies showed that compared to free Dox, they were more effective and safer. INP-DOX nanoconjugates [74] exhibited a much higher cytotoxic activity than that of free DOX on a variety of cancer cell lines. The tumour volume of resistant SW620/Ad-300 colon cancer cells was considerably lower in the INP-DOX group than in the free DOX group.

Ovarian cancer exhibits invasion and metastatic features with a very high fatality rate, and global morbidity and mortality are rising yearly [165, 166]. Several active components of TCM have been identified as having substantial anti-ovarian cancer action. CSAN combine the anti-ovarian cancer active components of TCM with PTX to create a therapeutic synergy. PTX-ss-TMP NPs [118] exhibited a good synergistic therapeutic effect on ovarian cancer. In vitro and in vivo studies revealed that PTX-ss-TMP NPs played a combined role in inhibiting the proliferation of ovarian cancer cells and angiogenesis and effectively inhibited the progression of tumours. TF-targeted PTX and CUR coloaded micelles [167] can better infiltrate NCI-ADR-RES ovarian cancer NCI-ADR-RES cell spheroids, and they have shown strong antiovarian cancer action in vivo.

Cervical cancer is the leading cause of cancer mortality among women in developing countries [168, 169]. Cisplatin (DDP) is the first-line treatment indicated for advanced, recurring, or metastatic cervical cancer. The molecular mechanism of Cur-induced cervical cancer cytotoxicity involves several targets, and the codelivery of DDP and Cur to tumour tissues is appealing. DDP and Cur-loaded lipid-polymer hybrid NPs (D/C/LPNs) [170] outperformed other preparations in terms of anti-cervical cancer tumour activity in vivo and in vitro. The synergistic anti-cervical cancer impact of PTX-Cur coloaded PEG-PNB-TC [134] was superior to that of the other treatment groups, and it could effectively overcome PTX resistance in MDR cancer cells.

Glioma is the most common primary intracranial malignancy and is usually invasive, has no apparent borders and is difficult to entirely resect with standard



surgery [171]. Poor BBB penetration and limited accumulation of therapeutic drugs at tumour locations are significant barriers to glioma therapy. Pep-1/Bor/CMS-M [137] may target gliomas with IL-13 receptor overexpression, cross the physiological barrier associated with brain microvascular endothelial cells, considerably boost human glioma BT325 cellular cytotoxicity, significantly improve internalization, and effectively induce cell apoptosis. In the treatment of orthotopic glioma-bearing nude mice, Pep-1/Bor/CMS-M showed the strongest tumour growth inhibition, the longest life duration, and the lowest systemic toxicity. CGKRK-PS NPs [138] can significantly improve anti-glioma activity and increase median survival time (39 days). LuT/Fe<sup>3+</sup> NPs [15] exhibited photothermal and chemotherapeutic effects. It can raise the temperature by more than 20 °C in less than 10 min and generate a photothermal conversion efficiency of 26.0%. LuT/Fe<sup>3+</sup> NPs exhibited greater cytotoxicity to U87MG glioma cells than that of Lut alone.

Cela, a natural triterpene component found in TCM, has been found to be useful in the treatment of melanoma [172], but its poor water solubility, short plasma half-life, and significant systemic toxicity have limited its clinical use. OPDMA-Cela NPs [41] exhibit better pharmacokinetics and mitochondrial targeting capacity and can cause considerable immunogenic cell death, improve Clea's therapeutic effect in vivo, and reduce systemic toxicity.

By using the EPR effect of NPs and the active targeting that can be achieved through modification, CSAN may overcome the problems of poor solubility and low bioavailability of antitumour active ingredients and better target tumour cells. Self-assembly exert the active component's antitumour effect and be combined with other antitumour drugs to exert a combined chemotherapeutic effect, as well as reduce toxic and side effects. Nanoformulations can be become photothermal or magnetic by modification, allowing for the integration of tumour diagnostics and therapy. Due to the advantages of advantages self-assembled nanopreparations of TCM, including high efficiency, plasticity, and safety, these nanopreparations show great potential in tumour diagnosis and treatment.

## Conclusions

CSAN employs the self-assembly properties of TCM's natural activity to self-assemble a drug or combine it with other drugs to generate nanopreparations. The preparation process is straightforward and ecologically friendly, which can increase drug solubility and bioavailability while also increasing delivery efficiency via NP targeting. At the same time, CSAN is very safe and can lessen the side effects of chemotherapy drugs. The research conducted by CSAN holds great significance in enhancing

the potential application of TCM, studying TCM theory, developing new TCM medications, and promoting the clinical transformation of nanoformulations. This research is expected to play a crucial role in modernizing TCM.

## Exploiting the application potential of TCM

TCM has a lengthy history of usage and significantly contributed to the health of people in Asian. TCM's natural active components are secondary metabolites with low molecular weights that are derived naturally from plants, animals, or minerals and display a variety of pharmacological effects, high biocompatibility, and regulated degradation [173]. These active components involve drawbacks, such as poor stability, a short half-life in vivo, a rapid clearance rate, a modest curative impact, and poor water solubility; however, they can be self-assembled into stable and beneficial nanoformulations. Simultaneously, due to its outstanding absorptivity, biodegradability, biocompatibility, and safety, SAN is a novel form of natural drug delivery nanocarrier that can replace artificially manufactured nanomaterials; in addition, SAN may be utilized to transport drugs to improve efficacy and decrease side effects. The construction of self-assembled nanosystems of natural TCM active components can fully exploit their self-assembly capabilities and enable the development of novel TCM active component applications.

## Studying TCM theory from a new perspective

In clinical practice, it is essential to use medicine under the guidance of TCM theory. The development of CSAN is closely linked to TCM theory and offers a fresh perspective for its study. TCM's compatibility theory suggests that certain drug pairs can have a synergistic effect, such as Rhubarb and Coptis, Scutellaria and Coptis. This theory can also reduce the toxicity of drug pairs. For example, AA-containing herbs and BBR-containing herbs can reduce toxicity when used in combination, which is also similar in the self-assembly products between them. Research on CSAN may provide a new perspective for revealing the synergistic and attenuating effect of TCM compatibility theory [101]. The CSAN, which is guided by TCM theory, has the potential to expand the clinical use of many Chinese medicinal plants. At the same time, it has been found that the SAN present in the decoction is closely linked to its curative effect. This approach of exploring the onset mechanism of TCM decoction through the perspective of SAN is innovative. However, research on CSAN is currently not extensive enough. Therefore, CSAN needs to be further investigated under the guidance of TCM theory, and this direction requires more effort in the future.

### Developing novel TCM medicines

TCM is a fantastic treasure trove. Many freshly licenced small molecule novel drugs are now generated from natural phytochemicals [174]. In clinical practice, TCM compound decoction is a frequent medicinal dosing type. However, the constituents of TCM compounds are intricate, their mechanisms of action are often unknown, and performing quality control is challenging. Effective isolated during separation and purification cannot adequately reflect the components present in the compounds and explain the onset mechanism of the components. SAN may exhibit greater biological activity than that of extracted active components or simple combinations of active ingredients. SAN might be the true form of the material basis for the effectiveness of TCM and compound prescriptions. Some SANs have been shown to improve the absorption of active ingredients in TCM. Investigating the causes behind SAN's increased efficacy can aid in the development of new and improved Chinese medicines. SAN might be a new research strategy for developing novel TCM medications.

### Promoting the clinical transformation of nanoformulations

Nanoformulations have tremendous benefits over traditional drug preparations and are frequently employed to deliver insoluble drugs, antitumour drugs, gene drugs, and drugs that must cross the blood–brain barrier. Basic research on nanoformulations is active, but few breakthroughs have been achieved in clinical transformation. Safety concerns and problems in the preparation process are the primary reasons that restrict the clinical transformation of nanoformulations. The Food and Drug Administration (FDA) has now authorized a few nanoformulations and demands that nanotherapeutic preparations are totally removed in the body within a reasonable period. In terms of safety, CSAN provides benefits that traditional nanomedicines lack, such as the ability to cooperate with pharmaceuticals in addition to exhibiting particular biological properties. Simultaneously, the preparation method is often easy to perform, ecologically benign, and requires no expensive equipment or precious ingredients. CSAN is predicted to contribute to the clinical transformation of nanoformulations due to these properties.

There are certain issues with current CSAN research. The constituents of self-assembled drugs restrict the therapeutic efficacy of SAN, and present research is primarily limited to single-drug research or two-drug combinations. There have been a few reports of three-drug or even multidrug self-assembly, whereas multidrug use is common in clinics. Nanostructure construction is strongly reliant on molecular configuration,

intermolecular forces, and spatial molecular organization, making its study reliant upon chance. The formation force of CSAN is mostly the weak interaction of molecules, which exhibits low physical and chemical stability. Improving SAN stability will be a critical challenge in the future. To date, only a few studies have been conducted to investigate the effectiveness mechanism and safety of SAN. SAN is more effective than active components or their basic mixture. However, the precise method through which SAN promotes the absorption of active components and exerts more biological activity is unknown. Biotransport characteristics such as SAN absorption, distribution, and degradation in vivo, as well as cellular uptake and transport mechanisms, must be investigated further. Furthermore, the toxicity of several active substances in TCM should be evaluated more comprehensively and thoroughly. SAN research is now applied to only a few kinds of illness, and this area must be extended in the future.

The self-assembly of TCM natural products is a key step in the development of TCM natural products, and the potential of CSAN will be further explored as research progresses. The modernization of TCM necessitates cross-disciplinary collaboration and innovation, encouraging the integration of TCM with modern scientific and technological methods. While preserving the fundamental principles of TCM theory, it is crucial to remain innovative and progressive to revitalize the practice. Self-assembly technology utilized by the CSAN presents an opportunity to explore the application of TCM, and the integration of TCM and self-assembly nanotechnology can offer innovative strategies and viewpoints to advance the modernization of TCM. In conclusion, CSAN shows significant research value and potential and should be further studied and explored. The anticipated role of CSAN in modernizing TCM and contributing to human health is important and promising.

### Abbreviations

TCM	Traditional Chinese Medicine
CSAN	Chinese medicine self-assembly nanostrategy
NPs	Nanoparticles
SAN	Self-assembly NPs
BBR	Berberine
CA	Cinnamic acid
Rhe	Rhein
3,4, 5-Tca	3,4, 5-Methoxyic acid
Sito	B-sitosterol
OA	Oleanolic acid
GA	Glycyrrhetic acid
UA	Ursolic acid
PTX	Paclitaxel
Cela	Celastrol
BA	Baicalin
WOG	Wogonoside
NFs	Nanofibers
BDS	BBR derivatives

RHL	Rhamnolipids
LDA	Liquidambaric acid
Lut	Luteolin
DOX	Doxorubicin
POD	Podophyllotoxin
Pae	Paeoniflorin
NPG	Natural product gels
GLP	Glycated Licorice Protein
RPP	Radix Pseudostellariae Protein
Cur	Curcumin
SAP	Semen Armeniacae Amarum Protein
BLG	Ban-Lan-Gen decoction
SA	Stearic acid
ASP	Angelica polysaccharide
GDNVs	Ginger-derived nanovectors
GDLVs	Ginger derived lipid vectors
MRSA	Multidrug-resistant <i>Staphylococcus aureus</i>
AC	Aconitine
AA	Aristolochic acid
AKI	Acute kidney injury
GW	Genkwanine
EGCG	Epigallocatechin gallate
EpCAM	Epithelial cell adhesion molecule
UEA NPs	UA@EGCG-Apt NPs
CCD	Coptis chinensis decoction
TJs	Tight junctions
GQD	Ge-Gen-Qin-LianTang decoction
MXSGT	Ma-XingShi-Gan-Tang decoction
TMP	Tetramethylpyrazine
GBA	Gambogic acid
GLA	Gallic acid
AST	Artemisinin
Bor	Borneol
BBB	Blood-brain barrier
CMS	Carmustine
GBM	Glioblastoma multiforme
CDDP	Compound Danshen dripping pill
DiR	1,1-Dioctadecyl-3,3,3-tetramethylindotricarbocyanine iodide
Topo I	Typical DNA topoisomerase I
FDA	Food and Drug Administration

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#### Author contributions

JH contributed to the preparation of the figures and tables, and writing of the manuscript. YZ and HX contributed to data collection and preparation of Figures and Tables. JL, SL and QZ reviewed the manuscript. JT and XM contributed to the establishment of the structure of this manuscript and acted as the main supervisor. All authors read and approved the final manuscript.

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#### Declarations

#### Ethics approval and consent to participate

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#### References

- Hassan A. Traditional Chinese herbal medication for corona-virus 2019. *Travel Med Infect Dis.* 2020;36: 101810.
- Liu YX, Zhou YH, Jiang CH, et al. Prevention, treatment and potential mechanism of herbal medicine for corona viruses: a review. *Bioengineered.* 2022;13(3):5480–508.
- Lyu M, Fan G, Xiao G, et al. Traditional Chinese medicine in COVID-19. *Acta Pharm Sin B.* 2021;11(11):3337–63.
- Qiao L, Huang W, Zhang X, et al. Evaluation of the immunomodulatory effects of anti-COVID-19 TCM formulae by multiple virus-related pathways. *Signal Transduct Target Ther.* 2021;6(1):50.
- Kopeček J, Yang J. Polymer nanomedicines. *Adv Drug Deliv Rev.* 2020;156:40–64.
- Perciani CT, Liu LY, Wood L, et al. Enhancing immunity with nanomedicine: employing nanoparticles to harness the immune system. *ACS Nano.* 2021;15(1):7–20.
- Tan YF, Lao LL, Xiong GM, et al. Controlled-release nanotherapeutics: state of translation. *J Control Release.* 2018;284:39–48.
- Xu XX, Chen SY, Yi NB, et al. Research progress on tumor hypoxia-associative nanomedicine. *J Control Release.* 2022. <https://doi.org/10.1016/j.jconrel.2022.09.003>.
- Zhang Y, He J. Tumor vasculature-targeting nanomedicines. *Acta Biomater.* 2021;134:1–12.
- Zhao Q, Luan X, Zheng M, et al. Synergistic mechanisms of constituents in herbal extracts during intestinal absorption: focus on natural occurring nanoparticles. *Pharmaceutics.* 2020;12(2):128.
- Mao Q, Min J, Zeng R, et al. Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. *Theranostics.* 2022;12(14):6088–105.
- Fan L, Zhang B, Xu A, et al. Carrier-free, pure nanodrug formed by the self-assembly of an anticancer drug for cancer immune therapy. *Mol Pharm.* 2018;15(6):2466–78.
- Cheng Y, Ji Y. Mitochondria-targeting nanomedicine self-assembled from GSH-responsive paclitaxel-ss-berberine conjugate for synergetic cancer treatment with enhanced cytotoxicity. *J Control Release.* 2020;318:38–49.
- Zhi K, Wang J, Zhao H, et al. Self-assembled small molecule natural product gel for drug delivery: a breakthrough in new application of small molecule natural products. *Acta Pharm Sin B.* 2020;10(5):913–27.
- Liu Y, Zhao L, Shen G, et al. Coordination self-assembly of natural flavonoids into robust nanoparticles for enhanced in vitro chemo and photothermal cancer therapy. *Colloids Surf A: Physicochem Eng Asp.* 2020;598:124805.
- Liu H, Yuan M, Liu Y, et al. Self-monitoring and self-delivery of self-assembled fluorescent nanoparticles in cancer therapy. *Int J Nanomedicine.* 2021;16:2487–99.
- Huang X, Wang P, Li T, et al. Self-assemblies based on traditional medicine Berberine and Cinnamic acid for adhesion-induced inhibition multidrug-resistant *Staphylococcus aureus*. *ACS Appl Mater Interfaces.* 2020;12(1):227–37.
- Zheng J, Fan R, Wu H, et al. Directed self-assembly of herbal small molecules into sustained release hydrogels for treating neural inflammation. *Nat Commun.* 2019;10(1):1604.
- Wang J, Zhao H, Zhi K, et al. Exploration of the natural active small-molecule drug-loading process and highly efficient synergistic antitumor efficacy. *ACS Appl Mater Interfaces.* 2020;12(6):6827–39.
- Li T, Wang P, Guo W, et al. Natural berberine-based Chinese herb medicine assembled nanostructures with modified antibacterial application. *ACS Nano.* 2019;13(6):6770–81.
- Shokri A, Schmidt J, Wang XB, et al. Hydrogen bonded arrays: the power of multiple hydrogen bonds. *J Am Chem Soc.* 2012;134(4):2094–9.

22. Shokri A, Wang Y, O'Doherty GA, et al. Hydrogen-bond networks: strengths of different types of hydrogen bonds and an alternative to the low barrier hydrogen-bond proposal. *J Am Chem Soc.* 2013;135(47):17919–24.
23. Belkova NV, Epstein LM, Filippov OA, et al. Hydrogen and dihydrogen bonds in the reactions of metal hydrides. *Chem Rev.* 2016;116(15):8545–87.
24. Liu Y, Wang B, Shu S, et al. Analysis of the *Coptis chinensis* genome reveals the diversification of protoberberine-type alkaloids. *Nat Commun.* 2021;12(1):3276.
25. Imenshahidi M, Hosseinzadeh H. Berberine and barberry (*Berberis vulgaris*): a clinical review. *Phytother Res.* 2019;33(3):504–23.
26. Tian X, Wang P, Li T, et al. Self-assembled natural phytochemicals for synergistically antibacterial application from the enlightenment of traditional Chinese medicine combination. *Acta Pharm Sin B.* 2020;10(9):1784–95.
27. Han N, Huang X, Tian X, et al. Self-assembled nanoparticles of natural phytochemicals (Berberine and 3,4,5-methoxycinnamic Acid) originated from traditional Chinese medicine for inhibiting multidrug-resistant *Staphylococcus aureus*. *Curr Drug Deliv.* 2021;18(7):914–21.
28. He N, Zhi K, Yang X, et al. Self-assembled fibrillar networks induced by two methods: a new unmodified natural product gel. *New J Chem.* 2018;42(17):14170–8.
29. Wang J, Zhao H, Qiao W, et al. Nanomedicine-cum-carrier by Co-assembly of natural small products for synergistic enhanced antitumor with tissues protective actions. *ACS Appl Mater Interfaces.* 2020;12(38):42537–50.
30. Lindman B, Medronho B, Alves L, et al. Hydrophobic interactions control the self-assembly of DNA and cellulose. *Q Rev Biophys.* 2021;54: e3.
31. Water-Mediated B-A, Interactions H. Water-mediated hydrophobic interactions. *Annu Rev Phys Chem.* 2016;67:617–38.
32. Garde S. Physical chemistry: Hydrophobic interactions in context. *Nature.* 2015;517(7534):277–9.
33. Song S, Zheng Q, Song A, et al. Self-assembled aggregates originated from the balance of hydrogen-bonding, electrostatic, and hydrophobic interactions. *Langmuir.* 2012;28(1):219–26.
34. Leenders CM, Baker MB, Pijpers IA, et al. Supramolecular polymerisation in water; elucidating the role of hydrophobic and hydrogen-bond interactions. *Soft Matter.* 2016;12(11):2887–93.
35. López-Hortas L, Pérez-Larrán P, González-Muñoz MJ, et al. Recent developments on the extraction and application of ursolic acid. A review. *Food Res Int.* 2018;103:130–49.
36. Wang L, Yin Q, Liu C, et al. Nanoformulations of ursolic acid: a modern natural anticancer molecule. *Front Pharmacol.* 2021;12: 706121.
37. Loesche A, Köwitsch A, Lucas SD, et al. Ursolic and oleanolic acid derivatives with cholinesterase inhibiting potential. *Bioorg Chem.* 2019;85:23–32.
38. Yang Y, Li F, Yan M, et al. Revealing the toxicity-enhancing essence of *Glycyrrhiza* on *Genkwa* flos based on ultra-high-performance liquid chromatography coupled with quadrupole-orbitrap high-resolution mass spectrometry and self-assembled supramolecular technology. *Front Chem.* 2021;9: 740952.
39. Chen SR, Dai Y, Zhao J, et al. A mechanistic overview of Triptolide and Celastrol, natural products from *Tripterygium wilfordii* hook F. *Front Pharmacol.* 2018;9:104.
40. Park JM, Lee TH, Kang TH. Roles of Tristetraprolin in Tumorigenesis. *Int J Mol Sci.* 2018. <https://doi.org/10.3390/ijms19113384>.
41. Geng Y, Xiang J, Shao S, et al. Mitochondria-targeted polymer-celastrol conjugate with enhanced anticancer efficacy. *J Control Release.* 2022;342:122–33.
42. Bishop KJ, Wilmer CE, Soh S, et al. Nanoscale forces and their uses in self-assembly. *Small.* 2009;5(14):1600–30.
43. Huang Y, Cui LJ, Wang JM, et al. Comparative studies on interactions of baicalin, baicalin and scutellarin with lysozyme. *Eur J Med Chem.* 2011;46(12):6039–45.
44. Wang C, Sun W, Wang X, et al. Large-scale separation of baicalin and wogonoside from *Scutellaria baicalensis* Georgi by the combination of pH-zone-refining and conventional counter-current chromatography. *J Chromatogr A.* 2019;1601:266–73.
45. Shen Y, Zou Y, Chen X, et al. Antibacterial self-assembled nanodrugs composed of berberine derivatives and rhamnolipids against *Helicobacter pylori*. *J Control Release.* 2020;328:575–86.
46. Carter-Fenk K, Herbert JM. Reinterpreting  $\pi$ -stacking. *Phys Chem Chem Phys.* 2020;22(43):24870–86.
47. Yang D, Gao S, Fang Y, et al. The  $\pi$ - $\pi$  stacking-guided supramolecular self-assembly of nanomedicine for effective delivery of antineoplastic therapies. *Nanomedicine (Lond).* 2018;13(24):3159–77.
48. Pal VK, Roy S. Cooperative metal ion coordination to the short self-assembling peptide promotes hydrogelation and cellular proliferation. *Macromol Biosci.* 2022;22(5):e2100462.
49. Hu Y, Xu W, Li G, et al. Self-assembled peptide nanofibers encapsulated with superfine silver nanoparticles via  $\text{Ag}^+$  coordination. *Langmuir.* 2015;31(31):8599–605.
50. Theoharides TC. Luteolin: the wonder flavonoid. *BioFactors.* 2021;47(2):139–40.
51. Tesio AY, Robledo SN. Analytical determinations of luteolin. *BioFactors.* 2021;47(2):141–64.
52. Zhu J, Zhang Z, Wang R, et al. Review of natural phytochemical-based self-assembled nanostructures for applications in medicine. *ACS Applied Nano Materials.* 2022;5(3):3146–69.
53. Wei D, Yang H, Zhang Y, et al. Nano-traditional Chinese medicine: a promising strategy and its recent advances. *J Mater Chem B.* 2022;10(16):2973–94.
54. Liao W, Li Y, Wang J, et al. Natural products-based nanoformulations: a new approach targeting CSCs to Cancer therapy. *Int J Nanomed.* 2022;17:4163–93.
55. Zhuo Y, Li M, Jiang Q, et al. Evolving roles of natural terpenoids from traditional Chinese Medicine in the treatment of Osteoporosis. *Front Endocrinol (Lausanne).* 2022;13: 901545.
56. Penuelas J, Llusia J, Estiarte M. Terpenoids: a plant language. *Trends Ecol Evol.* 1995;10(7):289.
57. Wang L, Yang B, Lin XP, et al. Sesterterpenoids. *Nat Prod Rep.* 2013;30(3):455–73.
58. Bag BG, Das S, Hasan SN, et al. Nanoarchitectures by hierarchical self-assembly of ursolic acid: entrapment and release of fluorophores including anticancer drug doxorubicin. *RSC Adv.* 2017;7(29):18136–43.
59. Zhu Y, Chen X, Wang S, et al. Simultaneous measurement of contents of liquiritin and glycyrrhizic acid in liquorice based on near infrared spectroscopy. *Spectrochim Acta A Mol Biomol Spectrosc.* 2018;196:209–14.
60. Huan C, Xu Y, Zhang W, et al. Research progress on the antiviral activity of glycyrrhizin and its derivatives in liquorice. *Front Pharmacol.* 2021;12: 680674.
61. Selyutina OY, Polyakov NE. Glycyrrhizic acid as a multifunctional drug carrier - from physicochemical properties to biomedical applications: a modern insight on the ancient drug. *Int J Pharm.* 2019;559:271–9.
62. Yang FH, Zhang Q, Liang QY, et al. Bioavailability enhancement of paclitaxel via a novel oral drug delivery system: paclitaxel-loaded glycyrrhizic acid micelles. *Molecules.* 2015;20(3):4337–56.
63. Wang Y, Zhao B, Wang S, et al. Formulation and evaluation of novel glycyrrhizic acid micelles for transdermal delivery of podophyllotoxin. *Drug Deliv.* 2016;23(5):1623–35.
64. Hong H, Lu X, Wu C, et al. A review for the pharmacological effects of paeoniflorin in the nervous system. *Front Pharmacol.* 2022;13: 898955.
65. Tu J, Guo Y, Hong W, et al. The regulatory effects of paeoniflorin and its derivative paeoniflorin-6'-O-benzene sulfonate CP-25 on inflammation and immune diseases. *Front Pharmacol.* 2019;10:57.
66. Bag BG, Majumdar R. Self-assembly of renewable nano-sized triterpenoids. *Chem Rec.* 2017;17(9):841–73.
67. Zhou J, Zhang J, Gao G, et al. Boiling licorice produces self-assembled protein nanoparticles: a novel source of bioactive nanomaterials. *J Agric Food Chem.* 2019;67(33):9354–61.
68. Lin D, Lin W, Gao G, et al. Purification and characterization of the major protein isolated from *Semen Armeniacae Amarum* and the properties of its thermally induced nanoparticles. *Int J Biol Macromol.* 2020;159:850–8.
69. Cai X, Yang Q, Weng Q, et al. pH sensitive doxorubicin-loaded nanoparticle based on *Radix pseudostellariae* protein-polysaccharide conjugate and its improvement on HepG2 cellular uptake of doxorubicin. *Food Chem Toxicol.* 2020;136: 111099.



70. Cai X, Weng Q, Lin J, et al. Radix Pseudostellariae protein-curcumin nanocomplex: Improvement on the stability, cellular uptake and anti-oxidant activity of curcumin. *Food Chem Toxicol.* 2021;151: 112110.
71. Ma BL, Yin C, Zhang BK, et al. Naturally occurring proteinaceous nanoparticles in *Coptidis Rhizoma* extract act as concentration-dependent carriers that facilitate berberine absorption. *Sci Rep.* 2016;6:20110.
72. Xiong X, Wang P, Su K, et al. Chinese herbal medicine for coronavirus disease 2019: a systematic review and meta-analysis. *Pharmacol Res.* 2020;160: 105056.
73. Song S, Ma Q, Tang Q, et al. Stereoselective metabolism of amygdalin-based study of detoxification of Semen *Armeniaca* Amarum in the Herba *Ephedrae-Semen Armeniaca* Amarum herb pair. *J Ethnopharmacol.* 2016;179:356–66.
74. Huang Y, Wang YJ, Wang Y, et al. Exploring naturally occurring ivy nanoparticles as an alternative biomaterial. *Acta Biomater.* 2015;25:268–83.
75. Zhou J, Liu J, Lin D, et al. Boiling-induced nanoparticles and their constitutive proteins from *Isatis indigotica* Fort. root decoction: purification and identification. *J Tradit Complement Med.* 2017;7(2):178–87.
76. Guo M, Shao S, Wang D, et al. Recent progress in polysaccharides from *Panax ginseng* C. A Meyer Food Funct. 2021;12(2):494–518.
77. Mei X, Yang W, Huang G, et al. The antioxidant activities of balsam pear polysaccharide. *Int J Biol Macromol.* 2020;142:232–6.
78. Khan T, Date A, Chawda H, et al. Polysaccharides as potential anticancer agents-A review of their progress. *Carbohydr Polym.* 2019;210:412–28.
79. Chen F, Huang G, Yang Z, et al. Antioxidant activity of *Momordica charantia* polysaccharide and its derivatives. *Int J Biol Macromol.* 2019;138:673–80.
80. Zheng Y, Bai L, Zhou Y, et al. Polysaccharides from Chinese herbal medicine for anti-diabetes recent advances. *Int J Biol Macromol.* 2019;121:1240–53.
81. Zhang G, Qiao J, Liu X, et al. Interactions of self-assembled *Bletilla Striata* polysaccharide nanoparticles with bovine serum albumin and biodistribution of its docetaxel-loaded nanoparticles. *Pharmaceutics.* 2019. <https://doi.org/10.3390/pharmaceutics11010043>.
82. Wang Y, Li X, Zhao P, et al. Physicochemical characterizations of polysaccharides from *Angelica Sinensis* Radix under different drying methods for various applications. *Int J Biol Macromol.* 2019;121:381–9.
83. Wang K, Xu J, Liu Y, et al. Self-assembled *Angelica sinensis* polysaccharide nanoparticles with an instinctive liver-targeting ability as a drug carrier for acute alcoholic liver damage protection. *Int J Pharm.* 2020;577: 118996.
84. Zhang Y, Cui Z, Mei H, et al. *Angelica sinensis* polysaccharide nanoparticles as a targeted drug delivery system for enhanced therapy of liver cancer. *Carbohydr Polym.* 2019;219:143–54.
85. Zhang L, Li Y, Wang C, et al. Synthesis of methylprednisolone loaded ibuprofen modified inulin based nanoparticles and their application for drug delivery. *Mater Sci Eng C Mater Biol Appl.* 2014;42:111–5.
86. Jimenez-Sanchez M, Perez-Morales R, Goycoolea FM, et al. Self-assembled high molecular weight inulin nanoparticles: enzymatic synthesis, physicochemical and biological properties. *Carbohydr Polym.* 2019;215:160–9.
87. Sunoqrot S, Alfaraj M, Hammad AM, et al. Development of a thymoquinone polymeric anticancer nanomedicine through optimization of polymer molecular weight and nanoparticle architecture. *Pharmaceutics.* 2020. <https://doi.org/10.3390/pharmaceutics12090811>.
88. Jendželovský R, Jendželovská Z, Kuchárová B, et al. Breast cancer resistance protein is the enemy of hypericin accumulation and toxicity of hypericin-mediated photodynamic therapy. *Biomed Pharmacother.* 2019;109:2173–81.
89. Gattuso H, Marazzi M, Dehez F, et al. Deciphering the photosensitization mechanisms of hypericin towards biological membranes. *Phys Chem Chem Phys.* 2017;19(34):23187–93.
90. Delcanale P, Pennacchietti F, Maestrini G, et al. Subdiffraction localization of a nanostructured photosensitizer in bacterial cells. *Sci Rep.* 2015;5:15564.
91. Sang S, Snook HD, Tareq FS, et al. Precision research on ginger: the type of ginger matters. *J Agric Food Chem.* 2020;68(32):8517–23.
92. Zhang M, Xiao B, Wang H, et al. Edible ginger-derived nano-lipids loaded with doxorubicin as a novel drug-delivery approach for colon cancer therapy. *Mol Ther.* 2016;24(10):1783–96.
93. Zhang M, Viennois E, Prasad M, et al. Edible ginger-derived nanoparticles: a novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials.* 2016;101:321–40.
94. Zhang M, Wang X, Han MK, et al. Oral administration of ginger-derived nanolipids loaded with siRNA as a novel approach for efficient siRNA drug delivery to treat ulcerative colitis. *Nanomedicine (Lond).* 2017;12(16):1927–43.
95. Wang Y, Tang J, Zhu H, et al. Aqueous extract of *Rabdosia rubescens* leaves: forming nanoparticles, targeting P-selectin, and inhibiting thrombosis. *Int J Nanomedicine.* 2015;10:6905–18.
96. Yu Y, Hao G, Zhang Q, et al. Berberine induces GLP-1 secretion through activation of bitter taste receptor pathways. *Biochem Pharmacol.* 2015;97(2):173–7.
97. Zhou B, Zhang J, Wu S, et al. The influence of compatibility of processed radix *Aconiti Kusnezoffii* on the pharmacokinetic of four components in *Glycyrrhiza uralensis* Fisch. *J Ethnopharmacol.* 2015;169:1–7.
98. Gao X, Hu J, Zhang X, et al. Research progress of aconitine toxicity and forensic analysis of aconitine poisoning. *Forensic Sci Res.* 2020;5(1):25–31.
99. Ke LJ, Gao GZ, Shen Y, et al. Encapsulation of Aconitine in Self-Assembled Licorice Protein Nanoparticles Reduces the Toxicity In Vivo. *Nanoscale Res Lett.* 2015;10(1):449.
100. Overstreet JM, Gifford CC, Tang J, et al. Emerging role of tumor suppressor p53 in acute and chronic kidney diseases. *Cell Mol Life Sci.* 2022;79(9):474.
101. Wang P, Guo W, Huang G, et al. Berberine-based heterogeneous linear supramolecules neutralized the acute nephrotoxicity of aristolochic acid by the self-assembly strategy. *ACS Appl Mater Interfaces.* 2021;13(28):32729–42.
102. Zhang B, Jiang J, Wu P, et al. A smart dual-drug nanosystem based on co-assembly of plant and food-derived natural products for synergistic HCC immunotherapy. *Acta Pharm Sin B.* 2021;11(1):246–57.
103. Weng Q, Cai X, Zhang F, et al. Fabrication of self-assembled Radix *Pseudostellariae* protein nanoparticles and the entrapment of curcumin. *Food Chem.* 2019;274:796–802.
104. Gao Y, Dong Y, Guo Q, et al. Study on Supramolecules in Traditional Chinese Medicine Decoction. *Molecules.* 2022. <https://doi.org/10.3390/molecules27103268>.
105. Wang Z, Li W, Lu J, et al. Revealing the active ingredients of the traditional Chinese medicine decoction by the supramolecular strategies and multitechnologies. *J Ethnopharmacol.* 2022;300:115704.
106. Liu JX, Zhang Y, Yuan HY, et al. The treatment of asthma using the Chinese Materia Medica. *J Ethnopharmacol.* 2021;269: 113558.
107. Wu J, Yang Y, Yuan X, et al. Role of particle aggregates in herbal medicine decoction showing they are not useless: considering *Coptis chinensis* decoction as an example. *Food Funct.* 2020;11(12):10480–92.
108. Lu S, Su H, Sun S, et al. Isolation and characterization of nanometre aggregates from a Bai-Hu-Tang decoction and their antipyretic effect. *Sci Rep.* 2018;8(1):12209.
109. Lin D, Du Q, Wang H, et al. Antidiabetic Micro-/Nanoaggregates from Ge-Gen-Qin-Lian-Tang decoction increase absorption of Baicalin and cellular antioxidant activity in vitro. *Biomed Res Int.* 2017;2017:9217912.
110. Zhou J, Gao G, Chu Q, et al. Chromatographic isolation of nanoparticles from Ma-Xing-Shi-Gan-Tang decoction and their characterization. *J Ethnopharmacol.* 2014;151(3):1116–23.
111. Ren JL, Yang L, Qiu S, et al. Efficacy evaluation, active ingredients, and multitarget exploration of herbal medicine. *Trends Endocrinol Metab.* 2023. <https://doi.org/10.1016/j.tem.2023.01.005>.
112. Qiao L, Chen W. Atheroprotective effects and molecular targets of bioactive compounds from traditional Chinese medicine. *Pharmacol Res.* 2018;135:212–29.
113. Gong X, Li X, Bo A, et al. The interactions between gut microbiota and bioactive ingredients of traditional Chinese medicines: a review. *Pharmacol Res.* 2020;157: 104824.
114. Li Q, Xiong Y, Ji C, et al. The application of nanotechnology in the codelivery of active constituents of plants and chemotherapeutics for overcoming physiological barriers during antitumor treatment. *Biomed Res Int.* 2019;2019:9083068.
115. Zhu L, Chen L. Progress in research on paclitaxel and tumor immunotherapy. *Cell Mol Biol Lett.* 2019;24:40.

116. Twine CP, Dosluoglu HH. Paclitaxel and mortality: where are we now? *Eur J Vasc Endovasc Surg.* 2020;60(2):230.
117. Chen Q, Xu S, Liu S, et al. Emerging nanomedicines of paclitaxel for cancer treatment. *J Control Release.* 2022;342:280–94.
118. Zou L, Liu X, Li J, et al. Redox-sensitive carrier-free nanoparticles self-assembled by disulfide-linked paclitaxel-tetramethylpyrazine conjugate for combination cancer chemotherapy. *Theranostics.* 2021;11(9):4171–86.
119. Li M, Chen Y, Wang L, et al. Investigations into the antibacterial effects and potential mechanism of gambogic acid and neogambogic acid. *Front Microbiol.* 2022;13:1045291.
120. Xu Y, Wang C, Ding Y, et al. Nanoparticles with optimal ratiometric Co-delivery of docetaxel with gambogic acid for treatment of multidrug-resistant breast cancer. *J Biomed Nanotechnol.* 2016;12(9):1774–81.
121. Cai J, Luo S, Lv X, et al. Formulation of injectable glycyrrhizic acid-hydroxycamptothecin micelles as new generation of DNA topoisomerase I inhibitor for enhanced antitumor activity. *Int J Pharm.* 2019;571:118693.
122. Giordani B, Basnet P, Mishchenko E, et al. Utilizing liposomal quercetin and Gallic acid in localized treatment of vaginal candida infections. *Pharmaceutics.* 2019. <https://doi.org/10.3390/pharmaceutics12010009>.
123. Tanaka Y, Tsuneoka M. Gallic acid derivatives propyl gallate and epigallocatechin gallate reduce rRNA transcription via induction of KDM2A activation. *Biomolecules.* 2021. <https://doi.org/10.3390/biom12010030>.
124. An L, Yan C, Mu X, et al. Paclitaxel-induced ultrasmall gallic acid-Fe@BSA self-assembly with enhanced MRI performance and tumor accumulation for cancer theranostics. *ACS Appl Mater Interfaces.* 2018;10(34):28483–93.
125. Mu X, Yan C, Tian Q, et al. BSA-assisted synthesis of ultrasmall gallic acid-Fe(III) coordination polymer nanoparticles for cancer theranostics. *Int J Nanomedicine.* 2017;12:7207–23.
126. Adhikari HS, Yadav PN. Anticancer activity of chitosan, chitosan derivatives, and their mechanism of action. *Int J Biomater.* 2018;2018:2952085.
127. Shariatnia Z. Pharmaceutical applications of chitosan. *Adv Colloid Interface Sci.* 2019;263:131–94.
128. Sivanesan I, Gopal J, Muthu M, et al. Green synthesized chitosan/chitosan nanofibers/nanocomposites for drug delivery applications. *Polymers (Basel).* 2021. <https://doi.org/10.3390/polym13142256>.
129. Di Martino RM, Luppi B, Bisi A, et al. Recent progress on curcumin-based therapeutics: a patent review (2012–2016). Part I: Curcumin. *Expert Opin Ther Pat.* 2017;27(5):579–90.
130. Kocaadam B, Şanlıer N. Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. *Crit Rev Food Sci Nutr.* 2017;57(13):2889–95.
131. Pathak L, Kanwal A, Agrawal Y. Curcumin loaded self assembled lipid-biopolymer nanoparticles for functional food applications. *J Food Sci Technol.* 2015;52(10):6143–56.
132. Chadha R, Gupta S, Pathak N. Artesunate-loaded chitosan/lecithin nanoparticles: preparation, characterization, and in vivo studies. *Drug Dev Ind Pharm.* 2012;38(12):1538–46.
133. El-Marakby EM, Hathout RM, Taha I, et al. A novel serum-stable liver targeted cytotoxic system using valerate-conjugated chitosan nanoparticles surface decorated with glycyrrhizin. *Int J Pharm.* 2017;525(1):123–38.
134. Yao Q, Gutierrez DC, Hoang NH, et al. Efficient codelivery of paclitaxel and curcumin by novel bottlebrush copolymer-based micelles. *Mol Pharm.* 2017;14(7):2378–89.
135. Cheng C, Liu XW, Du FF, et al. Sensitive assay for measurement of volatile borneol, isoborneol, and the metabolite camphor in rat pharmacokinetic study of Borneolum (Bingpian) and Borneolum syntheticum (synthetic Bingpian). *Acta Pharmacol Sin.* 2013;34(10):1337–48.
136. Dong T, Chen N, Ma X, et al. The protective roles of L-borneolum, D-borneolum and synthetic borneol in cerebral ischaemia via modulation of the neurovascular unit. *Biomed Pharmacother.* 2018;102:874–83.
137. Guo X, Wu G, Wang H, et al. Pep-1&borneol-bifunctionalized curcumin-loaded micelles enhance anti-glioma efficacy through tumor-targeting and BBB-penetrating. *J Pharm Sci.* 2019;108(5):1726–35.
138. Lv L, Li X, Qian W, et al. Enhanced anti-glioma efficacy by borneol combined with CGKRK-modified paclitaxel self-assembled redox-sensitive nanoparticles. *Front Pharmacol.* 2020;11:558.
139. Sancar A, Van Gelder RN. Clocks, cancer, and chronochemotherapy. *Science.* 2021. <https://doi.org/10.1126/science.abb0738>.
140. Phillips AJK, Lawther AJ, Walker AK. Clocking onto chemotherapy to enhance cancer treatment. *Brain Behav Immun.* 2022;100:172–3.
141. Wei G, Wang Y, Yang G, et al. Recent progress in nanomedicine for enhanced cancer chemotherapy. *Theranostics.* 2021;11(13):6370–92.
142. Aibani N, Nesbitt H, Marino N, et al. Electroneutral polymersomes for combined cancer chemotherapy. *Acta Biomater.* 2018;80:327–40.
143. Pomeroy AE, Schmidt EV, Sorger PK, et al. Drug independence and the curability of cancer by combination chemotherapy. *Trends Cancer.* 2022. <https://doi.org/10.1016/j.trecan.2022.06.009>.
144. Yao CL, Zhang JQ, Li JY, et al. Traditional Chinese medicine (TCM) as a source of new anticancer drugs. *Nat Prod Rep.* 2021;38(9):1618–33.
145. Sheng J, Zou X, Cheng Z, et al. Recent advances in herbal medicines for digestive system malignancies. *Front Pharmacol.* 2018;9:1249.
146. Huang MY, Zhang LL, Ding J, et al. Anticancer drug discovery from Chinese medicinal herbs. *Chin Med.* 2018;13:35.
147. Wang S, Long S, Wu W. Application of traditional Chinese medicines as personalized therapy in human cancers. *Am J Chin Med.* 2018;46(5):953–70.
148. Liu Y, Yang S, Wang K, et al. Cellular senescence and cancer: focusing on traditional Chinese medicine and natural products. *Cell Prolif.* 2020;53(10):e12894.
149. Slatore C, Lareau SC, Fahy B. Staging of lung cancer. *Am J Respir Crit Care Med.* 2022;205(9):p17-p19.
150. Deb D, Moore AC, Roy UB. The 2021 Global Lung Cancer Therapy Landscape. *J Thorac Oncol.* 2022;17(7):931–6.
151. Geraldes FO. Lung Cancer. IASLC 2022 World Conference on Lung Cancer. 2022;23(9):1128.
152. Han X, Chen J, Jiang M, et al. Paclitaxel-paclitaxel prodrug nanoassembly as a versatile nanopatform for combinational cancer therapy. *ACS Appl Mater Interfaces.* 2016;8(49):33506–13.
153. Dai L, Zhu W, Si C, et al. "Nano-ginseng" for enhanced cytotoxicity against cancer cells. *Int J Mol Sci.* 2018. <https://doi.org/10.3390/ijms19020627>.
154. Giaquinto AN, Sung H, Miller KD, et al. Breast cancer statistics, 2022. *CA Cancer J Clin.* 2022. <https://doi.org/10.3322/caac.21754>.
155. Thomas A, Parsons HA, Smith KL. Late recurrence following early breast cancer. *J Clin Oncol.* 2022;40(13):1400–6.
156. Crunkhorn S. Blocking breast cancer metastasis. *Nat Rev Drug Discov.* 2022;21(3):180.
157. Wang W, Fan J, Zhu G, et al. Targeted prodrug-based self-assembled nanoparticles for cancer therapy. *Int J Nanomedicine.* 2020;15:2921–33.
158. Paradis V, Zucman-Rossi J. Pathogenesis of primary liver carcinomas. *J Hepatol.* 2022. <https://doi.org/10.1016/j.jhep.2022.05.037>.
159. Ladd AD, Duarte S, Sahin I, et al. Mechanisms of drug resistance in HCC. *Hepatology.* 2023. <https://doi.org/10.1097/HEP.0000000000000237>.
160. Huang DQ, Singal AG, Kono Y, et al. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. *Cell Metab.* 2022;34(7):969–977.e962.
161. Ruge M, Genta RM, Malfertheiner P, et al. Steps forward in understanding gastric cancer risk. *Gut.* 2022. <https://doi.org/10.1136/gutjnl-2022-328514>.
162. Lei ZN, Teng QX, Tian Q, et al. Signaling pathways and therapeutic interventions in gastric cancer. *Signal Transduct Target Ther.* 2022;7(1):358.
163. Saltz LB. Top advances of the year in colorectal cancer. *Cancer.* 2022;128(12):2236–9.
164. Qu R, Ma Y, Zhang Z, et al. Increasing burden of colorectal cancer in China. *Lancet Gastroenterol Hepatol.* 2022;7(8):700.
165. Hurwitz LM, Pinsky PF, Trabert B. General population screening for ovarian cancer. *Lancet.* 2021;397(10290):2128–30.
166. Lee JM, Minasian L, Kohn EC. New strategies in ovarian cancer treatment. *Cancer.* 2019;125(24):4623–9.
167. Sarisozen C, Abouzeid AH, Torchilin VP. The effect of co-delivery of paclitaxel and curcumin by transferrin-targeted PEG-PE-based mixed micelles on resistant ovarian cancer in 3-D spheroids and in vivo tumors. *Eur J Pharm Biopharm.* 2014;88(2):539–50.
168. The L. Eliminating cervical cancer. *Lancet.* 2020;395(10221):312.
169. Screening for cervical cancer. *CA Cancer J Clin.* 2020. 70(5): 347–348. <https://doi.org/10.3322/caac.21629>.

170. Li C, Ge X, Wang L. Construction and comparison of different nanocarriers for co-delivery of cisplatin and curcumin: a synergistic combination nanotherapy for cervical cancer. *Biomed Pharmacother.* 2017;86:628–36.
171. Wang H, Xu T, Huang Q, et al. Immunotherapy for malignant glioma: current status and future directions. *Trends Pharmacol Sci.* 2020;41(2):123–38.
172. Li J, Jia Y, Zhang P, et al. Celastrol self-stabilized nanoparticles for effective treatment of melanoma. *Int J Nanomedicine.* 2020;15:1205–14.
173. Wang K, Chen Q, Shao Y, et al. Anticancer activities of TCM and their active components against tumor metastasis. *Biomed Pharmacother.* 2021;133: 111044.
174. Liang X, Wu P, Yang Q, et al. An update of new small-molecule anti-cancer drugs approved from 2015 to 2020. *Eur J Med Chem.* 2021;220: 113473.

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