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Recognition on pharmacodynamic ingredients of natural products

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ABSTRACT

Natural products (NPs) play an irreplaceable role in the intervention of various diseases and have been considered a critical source of drug development. Many new pharmacodynamic compounds with potential clinical applications have recently been derived from NPs. These compounds range from small molecules to polysaccharides, polypeptides, proteins, self-assembled nanoparticles, and extracellular vesicles. This review summarizes various active substances found in NPs. The investigation of active substances in NPs can potentiate new drug development and promote the in-depth comprehension of the mechanism of action of NPs that can be beneficial in the prevention and treatment of human diseases.

1. Introduction

Natural products (NPs) play an essential role in the treatment of various diseases and have always been considered an important source of drug development (Newman, 2022). Plants, animals, minerals, and microorganisms are the major sources of NPs. In recent years, the chemical synthesis of drugs has advanced rapidly because of the development of combinatorial chemistry and high-throughput screening technology. However, developing drugs from NPs are still of great significance due to the novel structures, therapeutic capabilities, and certain unique pharmacological effects of the chemical molecules (Chopra and Dhingra, 2021; Rishton, 2008).

Generally, small molecular compounds (such as flavones, terpenes, alkaloids, anthraquinones and amino acids), polysaccharides, polypeptides, and proteins are considered the main active substances in NPs. Recently, novel structural molecules with significant pharmacological activities, such as SANs and EVs, have been derived from NPs and become the focus of research on the pharmacodynamic ingredients of NPs (Zhao et al., 2020; Colombo et al., 2014; Vader et al., 2016). The purpose of this review is to investigate the existing knowledge of active substances in NPs. We believe this review can help readers have a more in-depth understanding of the research on the active substances of NPs and provides new research direction for the readers who are studying the active substances of NPs.

2. Natural small molecules

Numerous NPs in nature contain a variety of effective and complex small molecules that play a key role in drug discovery (Atanasov et al., 2021; Coy-Barrera et al., 2023). These small molecules include alkaloids, phenylpropanoids, quinones, flavonoids, terpenoids, steroids, organic acids, amino acids, and microelements. These compounds have specific structures, enabling them to treat different diseases and provide a material basis for drug synthesis, structural modification, and other

Abbreviations: NPs, Natural products; TCM, Traditional Chinese medicines; SANs, Self-assembled nanoparticles; TCM-SANs, Self-assembled nanoparticles from traditional Chinese medicines; TCMD-SANs, Self-assembled nanoparticles from traditional Chinese medicines decoction; EVs, Extracellular vesicles; ELNs, Exosome-like nanoparticles; PDEVs, Plant-derived extracellular vesicles; ROS, Reactive oxygen species; HPLC, High performance liquid chromatography; LC-MS, Liquid chromatography-mass spectrometry; FTIR, Fourier transform infrared spectroscopy; NTA, Nanoparticle tracking analysis; PEG, Precipitation with polymers; PDI, Polydispersion index; SEM, Scanning electron microscope; SEC, Size exclusive chromatography; SDS-PAGE, Sodium dodecyl sulfate-polyacrylamide gel electrophoresis; TLC, Thin layer chromatography; TEM, Transmission electron microscope; PA, Phospholipic acid; HRED, Heparin-cRGD-EVs-DOX; SEC-MALLS, Size exclusive chromatography combined with multi-angle laser light scattering; siRNA-CD98 /GDLVs, Ginger-derived lipid vehicles loaded with siRNA-CD98; AFM, Atomic force microscope; DCR, Derived count rate; DOX, Doxorubicin; DLS, Dynamic light scattering; ATPS, Electrodialysis and aqueous two-phase systems.

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fields. For example, artemisinin is a sesquiterpene obtained from *Artemisia annua*. Its discovery breaks the idea that all antimalarial drugs have nitrogen-containing heterocyclic compounds because of their unique mechanism of action using peroxy groups (Eckstein-Ludwig et al., 2003; Tu, 2016). To improve its efficacy and solubility, a series of artemisinin derivatives were synthesized by structural modification: artemether has high oil solubility (useful for oil injections), arteannuinum succinate has good water solubility (useful for powders for injection), dihydroartemisinin has high antimalarial efficacy and low toxicity (Tu, 2016). In the field of antineoplastic drugs, the most eye-catching is paclitaxel from plants. Paclitaxel was isolated from the stem bark of the western yew (*Taxus brevifolia*) for the first time by Wall *et al.* (Wani et al., 1971). Horwitz *et al.* found that paclitaxel could promote tubulin polymerization and inhibit the proliferation of cancer cells, especially melanoma and ovarian cancer cells (Schiff et al., 1979; Horwitz, 2004). Through structural modification of paclitaxel, anticancer drugs such as docetaxel and cabazitaxel were developed. Today, paclitaxel is still one of the best natural anticancer drugs. Among the 1394 small molecular drugs approved from 1981 to 2019, NPs or their derivatives accounted for about 33.6 % (Newman and Cragg, 2020). This shows that natural small molecular compounds play an irreplaceable role in drug research and development. At present, many natural small molecules have entered clinical research for the treatment of diseases (Table. 1).

3. Polysaccharides

Polysaccharides are long-chain polymers composed of more than 10 identical or different monosaccharides linked by α- or β-glycosidic bonds and are found in animals, plants, and microorganisms (Shi, 2016). Active polysaccharides are polysaccharides involved in the physiological metabolism of the body, with several biological activities such as anti-inflammation, antitumor, anti-aging, anti-oxidation, liver protection, and immune regulation (Luo et al., 2024). The antitumor effect of polysaccharides is particularly evident in clinical studies (Table. 2). Polysaccharides derived from NPs are also used in drug carriers and vaccine adjuvants (Benalaya et al., 2024). Although polysaccharides derived from NPs have low toxicity, few side effects, and high activity, their clinical application is still limited due to their complex molecular structure, preparation procedure and action mechanism and the characteristics of un-directly-absorbed by intestinal epithelial cells.

4. Polypeptides

Peptides consist of α-amino acids linked together by peptide bonds and are intermediates of proteolysis. Most peptide drugs are hydrophilic polar macromolecules and substrates of proteases widely distributed in the human body. These drugs are clinically used as antibacterial, antitumor, antihypertensive, antioxidant, anti-inflammatory, and immunomodulatory treatments (Wang et al., 2022) (Table. 3). Compared with synthetic drugs, peptides derived from NPs have strong biological activity, high specificity, selectivity, and stability *in vivo*, with low side effects (Muttenthaler et al., 2021). Despite these advantages, these peptides have unstable physical and chemical properties, a short half-life, and limited permeability across the blood–brain barrier, and they cannot be administered orally.

Table 1
Small molecules from natural products (NPs) with clinical research.

Name	Source	Clinical application	References
Camptothecin	*Camptotheca acuminata*	Tumor	(Wang et al., 2023; Siena et al., 2021)
Puerarin	*Pueraria lobata*	Cardiac remodeling	(Lv et al., 2022)
Berberine	*Berberis vulgaris* L.	Diabetes and polycystic ovarian syndrome	(Imenshahidi and Hosseinzadeh, 2019)
Icaritin	Epimedium	Tumor	(Reyes-Hernández et al., 2024)
Norcantharidin	*Mylabris phalerata Pallas*	Tumor	(Zhai et al., 2022)
Ellagitannin	Pomegranate	Aging	(Singh et al., 2022; D'Amico et al., 2021)

5. Natural self-assembled nanoparticles (SANs)

The intermolecular interactions between chemical components in NPs, especially SANs, have attracted much attention (Zhao et al., 2020). These chemical components have several sources and unique structures, which can self-assemble into nanoparticles through intermolecular interactions (Zhao et al., 2020). Natural SANs are the molecular aggregation of organic compounds induced by non-covalent bonding such as hydrogen bonding, van der Waals forces, π-π stacking, molecular complexation, and electrostatic interactions (Qiao et al., 2022). Several natural SANs have been widely reported in traditional Chinese medicines (TCM) and are referred to as self-assembled nanoparticles from traditional Chinese medicines (TCM-SANs). TCM-SANs are mainly divided into self-assembled nanoparticles from traditional Chinese medicines decoction (TCMD-SANs) and those from the artificial assembly of TCM compounds. TCMD-SANs are nanoparticles formed by molecular recognition and self-assembly of chemical components during the decoction of TCMD. They include SANs from Ge-Gen-Qin-Lian-Tang decoction, Ma-Xing-Shi-Gan-Tang decoction, Bai-Hu-Tang decoction, *Coptis chinensis* decoction, Turkish galls decoction and Qi-Yin-San-Liang-San decoction (Ping et al., 2020; Lü et al., 2018; Wu et al., 2020; Lenaghan et al., 2013; Zhang et al., 2016; Lin et al., 2017; Zhou et al., 2014; Zhou et al., 2016; Zhou et al., 2019; Fan et al., 2023; Zhang et al., 2024). Conversely, SANs formed by artificial assembly of TCM compounds are generated when the chemical components of TCM have been manually assembled into nanoparticles. They include SANs from rhein, combined berberine and rhein, combined berberine and 3,4,5-methoxycinnamic acid, combined oleanolic and glycyrrhetinic acids, celastrol and galactose, and (−)-epigallocatechin-3-gallate (Weng et al., 2019; Ke et al., 2015; Tian et al., 2020; Han et al., 2021; Wang et al., 2015; Li et al., 2019; Guo et al., 2021; Wang et al., 2020; Huang et al., 2020; Zheng et al., 2019; Zhi et al., 2020; Hou et al., 2022; Wang et al., 2021; Zhang et al., 2024; Wu et al., 2024).

5.1. Preparation and characterization of self-assembled nanoparticles (SANs)

At present, related studies show that SANs are mainly separated from TCMD through filtration, dialysis, centrifugation, and particle size exclusion chromatography (Ping et al., 2020; Lü et al., 2018; Wu et al., 2020; Lenaghan et al., 2013; Zhang et al., 2016; Lin et al., 2017; Zhou et al., 2014; Zhou et al., 2016; Zhou et al., 2019; Fan et al., 2023; Zhang et al., 2024) (Table. 4). However, the separation and enrichment are not required for the manually-assembled SANs (Weng et al., 2019; Ke et al., 2015; Tian et al., 2020; Han et al., 2021; Wang et al., 2015; Li et al., 2019; Guo et al., 2021; Wang et al., 2020; Huang et al., 2020; Zheng et al., 2019; Zhi et al., 2020; Hou et al., 2022; Wang et al., 2021; Zhang et al., 2024; Wu et al., 2024).

The Characterization of SANs mainly involves morphological observation, particle size distribution analysis, zeta potential measurement, and composition analysis (Ping et al., 2020; Lü et al., 2018; Wu et al., 2020; Lenaghan et al., 2013; Zhang et al., 2016; Lin et al., 2017; Zhou et al., 2014; Zhou et al., 2016; Zhou et al., 2019; Fan et al., 2023; Zhang et al., 2024). However, analyzing the components of the manually-assembled SANs is unnecessary because their compositions are clear (Weng et al., 2019; Ke et al., 2015; Tian et al., 2020; Han et al., 2021; Wang et al., 2015; Li et al., 2019; Guo et al., 2021; Wang et al., 2020; Huang et al., 2020; Zheng et al., 2019; Zhi et al., 2020; Hou et al., 2022; Wang et al., 2021; Zhang et al., 2024; Wu et al., 2024). In addition to these methods, some studies also determined the polydispersion index (PDI) and derived count rate (DCR) to evaluate the distribution range

Table 2
Polysaccharides from natural products (NPs) with clinical research.

Name	Source	Clinical application	Mechanisms of action	References
Poria cocos polysaccharide	*Poria cocos*	Antitumor	Enhancing immunity, up-regulating the expression of apoptosis-related genes, and directly promoting the apoptosis of tumor cells	(Li et al., 2019; Li et al., 2021)
Astragalus polysaccharide	*Astragalus membranaceus*	Adjuvant therapy for lung cancer	Reducing the ratio of neutrophils to lymphocytes	(Li et al., 2021; Tsao et al., 2021)
Ganoderma lucidum polysaccharide	*Ganoderma lucidum*	Advanced-stage cancer	Boosting immunity	(Li et al., 2021; Chen et al., 2006; Gao et al., 2003)
Coriolus versicolor polysaccharide	*Coriolus versicolor*	Adjuvant therapy for liver disease	Reducing the expression of TLR4, MyD88, CD14, IL-1β and TNF-α	(Li et al., 2021; Wang et al., 2019)
Tremella Polysaccharide	*Tremella fuciformis*	Adjuvant therapy for chronic active hepatitis	Boosting immunity	(Li et al., 2021; Ma et al., 2021)
Lentinan	*Lentinula edodes*	Adjuvant therapy for non-small cell cancer and liver cancer	Boosting immunity	(Zhao et al., 2021; Zhang et al., 2018)
Ginseng polysaccharide	*Panax ginseng*	Adjuvant therapy for nasopharyngeal carcinoma	Reducing T-lymphocytes and lymphocyte transformation rate	(Xie et al., 2001; Zhang et al., 2023)
Grifola frondose polysaccharide	*Grifola frondosa*	Antitumor	Up-regulating TLR-4-mediated NO and TNF-α production	(Mao et al., 2015; Zhao et al., 2021)
Heparin	Bovine lung or porcine small intestine mucosa	Cardiovascular and cerebrovascular diseases, lung and kidney diseases, and cancer	Inhibiting thrombin and mediating heparin-antithrombin-thrombin complex formation	(Qiu et al., 2021)
Magnesium chondroitin sulfate	Extracellular matrix and cell surface of animal tissues	Anti-osteoarthritis	Reducing the joint swelling, pathological injury of the joints and the levels of IL-1, TNF-α, and PGE2 in synovial fluid.	(Li et al., 2019; Sun et al., 2018)
Seaweed polysaccharide	Seaweed	Antitumor	Promoting the production of TNF-α, NO, IL-2 and IFN-γ by activating macrophages, T lymphocytes and B lymphocytes. Inducing apoptosis of cancer cells by PI3K/AKT pathway, ROS-mediated mitochondrial apoptosis pathway, and JNK pathway.	(Minami et al., 2020; Liu et al., 2022)

Table 3
Peptides from natural products (NPs) with clinical research.

Name	Source	Clinical application	References
Insulin	Pancreas	Diabetes	(Sims et al., 2021)
Cyclosporin	*Tolypocladium inflatum*	Autoimmune diseases	(Jayaraman, 1988; Yu et al., 2023)
Eptifibatide	*Sistrurus miliarius barbourin*	Acute coronary syndromes	(Mohamed Abd El-Aziz et al., 2019; Tonin and Klen, 2023)
Exenatide	*Gila monster*	Type 2 diabetes	(Tamborlane et al., 2022)
Hirudin	*Leech*	Diabetic nephropathy	(Han et al., 2021)
Oxytocin	Posterior pituitary gland	Postpartum hemorrhage	(Adnan et al., 2018)
Glutathione	Yeast and wheat germ	Coronavirus disease (COVID-19)	(Guloyan et al., 2020)
Thymosin α1	Calf thymus	Hepatitis B virus-related acute-on-chronic liver failure	(Chen et al., 2022)
Lupinus angustifolius peptide	*Lupinus angustifolius* seed	Diabetes	(Cruz-Chamorro et al., 2023)

and physical stability of the particle size of SANs (Wang et al., 2015; Wang et al., 2020; Zheng et al., 2019; Zhang et al., 2024). The morphological characterizations of SANs are conducted by atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). However, the particle size distribution, zeta potential, PDI, and DCR of SANs are measured by a particle size analyzer based on the dynamic light scattering (DLS) principle. The composition of SANs is determined by high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS), Fourier transform infrared spectroscopy (FTIR) and sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). At present, several morphological characteristics of TCM-SANs have been reported. Most SANs are reportedly spherical (Fan et al., 2023; Guo et al., 2021; Han et al., 2021; Ke et al., 2015; Lenaghan et al., 2013; Li et al., 2019; Lü et al., 2018; Ping et al., 2020; Tian et al., 2020; Wang et al., 2015; Weng et al., 2019; Wu et al., 2024; Zhang et al., 2024; Zhang et al., 2024; Zhou et al., 2014; Zhou et al., 2016; Zhou et al., 2019), and a few are nanofibers or irregular nanoparticles (Hou et al., 2022; Li et al., 2019; Wang et al., 2021; Wu et al., 2020; Zheng et al., 2019; Zhi et al., 2020), such as irregular nanofibers from *Coptis chinensis* decoction, berberine and baicalin self-assembled nanofibers, and rhein self-assembled nanofibers. Others include poricoic acid A self-assembled nanofibers and dehydrotumulosic acid self-assembled nanofibers from *Poria cocos*, liquidambaric acid self-assembled nanofibers from *Liquidambar formosana*, pomolic acid self-assembled nanofibers, and aristolochic acid and berberine self-assembled nanofibers. Several particle sizes of TCM-SANs have also been reported, most of which are about 100 nm (Guo et al., 2021; Han et al., 2021; Huang et al., 2020; Lenaghan et al., 2013; Li et al., 2019; Lü et al., 2018; Ping et al., 2020; Tian et al., 2020; Wang et al., 2015; Wang et al., 2020; Weng et al., 2019; Wu et al., 2024; Zhang et al., 2024; Zhou et al., 2014; Zhou et al., 2016; Zhou et al., 2019), with a few being larger than 100 nm (Fan et al., 2023; Ke et al., 2015; Lin et al., 2017; Wu et al., 2020; Wu et al., 2024; Zhang et al., 2024). For example, the irregular nanoparticles from *Coptis chinensis* decoction are distributed from 200 nm to 500 nm, while those from Ge-Gen-Qin-Lian-Tang decoction are distributed from 300 nm to 1000 nm. Moreover, the 31 kDa protein SANs in licorice and the licorice protein SANs coated with aconitine are about 200 nm. The chemical composition of SANs may comprise proteins, polysaccharides, lipids, and small molecular active substances. The protein contents of SANs are determined using the quantitative method of Bradford assay (Wu et al., 2020) and the qualitative methods of SDS-PAGE and Edman degradation (Lenaghan et al., 2013; Zhou et al., 2016; Zhou et al., 2019). The polysaccharide content is mainly determined using the phenol–sulfuric acid method (Wu et al., 2020), while the analytical methods, including HPLC and LC-MS, are used to measure the small molecular active substances (Lenaghan et al., 2013; Lü et al., 2018; Ping et al., 2020; Wu et al., 2020; Zhang et al., 2016; Zhang et al., 2024; Zhou et al., 2014). Wu *et al.* demonstrated that the three SANs from *Coptis chinensis*

Table 4
Separation and characterization of natural self-assembled nanoparticles (SANs).

SAN sources	Separation methods	Characterization methods	References
Bai-Hu-Tang decoction	The residue in the decoction was removed by four layers of gauze filtration. The filtrate was then collected and separated by high-speed centrifugation coupled with dialysis.	Morphology was observed by TEM. Particle size distribution and zeta potential were determined by particle size analyzer, and the composition was analyzed by HPLC.	(Ping et al., 2020; Lü et al., 2018)
Licorice (*Glycyrrhiza uralensis* Fisch.) decoction	The residue in the decoction was removed by two layers of gauze filtration. The filtrate was then collected and separated by high-speed centrifugation, ethanol precipitation, anion exchange resin, and size-exclusive chromatography combined with multi-angle laser light scattering (SEC-MALLS).	Morphology was observed by SEM. Particle size distribution and zeta potential were determined by DLS, and the protein content was qualitatively analyzed by SDS-PAGE and Edman degradation.	(Zhou et al., 2019)
Ma-Xin-Shi-Gan-Tang decoction	The residue in the decoction was removed by high-speed centrifugation. The filtrate was then collected and separated by SEC-MALLS.	Morphology was observed by TEM and AFM, and the composition was analyzed by HPLC.	(Zhou et al., 2014)
English ivy (*Hedera helix* L.)	The residue in the decoction was removed by high-speed centrifugation. The filtrate was then collected and separated by dialysis and size-exclusion chromatography.	Morphology was observed by AFM. Particle size distribution and zeta potential were determined by DLS, and the protein content was qualitatively analyzed by SDS-PAGE.	(Lenaghan et al., 2013)
Isatis indigotica decoction	The residue in the decoction was removed by two layers of gauze filtration. The filtrate was then collected and separated by SEC-MALLS.	Morphology was observed by SEM. Particle size was analyzed by DLS, and the protein content was qualitatively analyzed by SDS-PAGE and Edman degradation.	(Zhou et al., 2016)
Coptis chinensis decoction	The residue in the decoction was removed by gauze filtration. The filtrate was then collected and separated by ultracentrifugation and anion exchange resin.	Morphology was observed by TEM. Particle size distribution and zeta potential were determined by laser particle analyzer. The composition was analyzed by HPLC, and polysaccharide and protein contents were determined by the phenol–sulfuric acid method and Bradford assay.	(Wu et al., 2020)
Ge-Gen-Qin-Lian-Tang decoction	The residue in the decoction was removed by two layers of gauze filtration. The filtrate was then collected and separated by high-speed centrifugation.	Particle size distribution was determined by a particle size analyzer.	(Lin et al., 2017)
Huang-Lian-Jie-Du-Tang decoction	The residue in the decoction was removed by non-woven bag packaging (equivalent to filtration). The filtrate was then collected and separated by high-speed centrifugation.	The composition was analyzed by LC-MS.	(Zhang et al., 2016)
Turkish galls extracts	The residue in the extracts was removed by sterile absorbent gauze filtration. The filtrate was then collected and separated by differential centrifugation.	Morphology was observed by SEM. Particle size distribution and zeta potential were determined by DLS.	(Fan et al., 2023)
Qi-Yin-San-Liang-San Decoction	The residue in the decoction was removed by gauze filtration. The filtrate was then collected and separated by gradient centrifugation and dialysis.	Morphology was observed by TEM and SEM. Particle size distribution and zeta potential were determined by DLS. The composition was analyzed by LC-MS.	(Zhang et al., 2024)
Radix Pseudostellariae protein		Morphology was observed by SEM. Particle size distribution, zeta potential, PDI, and DCR were determined by DLS.	(Weng et al., 2019)
Licorice protein and aconitine		Morphology was observed by SEM.	(Ke et al., 2015)
Berberine and rhein		Morphology was observed by SEM and TEM, and particle size distribution was determined by DLS.	(Tian et al., 2020)
Berberine and 3,4,5-methoxycinnamic acid		Morphology and particle size distribution were observed by SEM.	(Han et al., 2021)
Baicalein and paclitaxel		Morphology was observed by TEM, and particle size distribution, zeta potential, and PDI were determined by photon correlation spectroscopy.	(Wang et al., 2015)
Berberine and flavonoid		Morphology was observed by TEM	(Li et al., 2019)

(*continued on next page*)

Table 4 (*continued*)

SAN sources	Separation methods	Characterization methods	References
		and SEM, and particle size distribution was determined by DLS.	
Camptothecin derivatives and curcuminoids		Morphology was observed by TEM.	(Guo et al., 2021)
Oleanolic acid and glycyrrhetinic acid		Morphology was observed by SEM and TEM, and particle size distribution, zeta potential, and PDI were determined by particle size analyzer.	(Wang et al., 2020)
Berberine and cinnamic acid		Morphology was observed by SEM, and particle size distribution and zeta potential were determined by DLS.	(Huang et al., 2020)
Rhein		Morphology was observed by SEM, AFM, and TEM.	(Zheng et al., 2019)
Triterpenoids from *Poria cocos* (Schw.) Wolf and *Liquidambar formosana*		Morphology was observed by SEM and TEM.	(Zhi et al., 2020)
Pomolic acid		Morphology was observed by SEM, TEM, and AFM, and zeta potential was analyzed by particle size analyzer.	(Hou et al., 2022)
Berberine and aristolochic acid		Morphology was observed by TEM and SEM, and particle size distribution and zeta potential were determined by DLS.	(Wang et al., 2021)
Celastrol and galactose		Morphology was observed by TEM. Particle size distribution, PDI and zeta potential were determined by DLS, and the composition was analyzed by FTIR.	(Zhang et al., 2024)
(−)-Epigallocatechin-3-gallate		Morphology was observed by SEM. Particle size distribution was determined by DLS. Absorption wavelength was determined by ultraviolet spectrophotometer.	(Wu et al., 2024)

decoction lacked the characteristic compounds of *Coptis chinensis* decoction following HPLC analysis. However, phenol–sulfuric acid analysis and Bradford assay showed that the SANs mainly contained polysaccharides and a few proteins (Wu et al., 2020). Zhou *et al.* isolated the protein SANs from licorice which was identified as a new protein by SDS-PAGE and Edman degradation analysis. Its relative molecular weight is 28 kDa, with the N-terminal amino acid sequence of NPDGLIACYCGQYCW (Zhou et al., 2019). Zhou *et al.* also analyzed the SANs separated from Ma-Xing-Shi-Gan-Tang decoction by HPLC and indicated that its main components were ephedrine and pseudoephedrine (Zhou et al., 2014). Furthermore, Zhang *et al.* analyzed precipitated compounds from Huang-Lian-Jie-Du-Tang decoction by LC-MS and indicated that their main components were baicalin and berberine (Zhang et al., 2016).

5.2. Applications and prospects of natural self-assembled nanoparticles (SANs)

The continuous study of natural SANs has revealed their novel compatibility mechanism with TCM. In addition, SANs can also be used as a natural nanocarrier, which undoubtedly provides a new research strategy for developing new drugs. This section describes the compatibility mechanism of natural SANs in TCM and their application as natural nanocarriers.

5.2.1. Study on compatibility mechanism of traditional Chinese medicines (TCM)

The discovery of TCM-SANs has revealed novel synergistic and toxicity-attenuating mechanisms of TCM prescriptions. TCM-SANs can load active ingredients, and enhance their solubilization and absorption, thus improving their curative effect. They can also load toxic components and delay or inhibit their absorption, thereby reducing their toxicity. SANs from Bai-Hu-Tang decoction are easily absorbed by cells and have better antipyretic with lung and brain targeting effects than the other components of Bai-Hu-Tang decoction. Moreover, it has been reported that nanoparticles can be formed only when rice is included in the decoction (Ping et al., 2020; Lü et al., 2018). The SANs from Ma-Xing-Shi-Gan-Tang decoction encapsulated ephedrine and pseudoephedrine, which have higher cell survival and proliferation rates on Caco-2, L-02, HepG2, and NR-8383 cells than synthetic ephedrine (Zhou et al., 2014). Furthermore, SANs from Ge-Gen-Qin-Lian-Tang decoction promoted the absorption and antioxidant activity of baicalin (Lin et al., 2017). Aconitine is the main toxic component of the aconite species, but its toxicity can be effectively eliminated by combining it with licorice, enhancing its curative effect. This synergistic detoxification mechanism can also be achieved by generating SANs from their active components. According to Ke *et al.*, *in vivo* toxicity tests showed that licorice-aconite decoction and aconitine encapsulated with licorice protein SANs had mild toxicity and resulted in no death. However, aconitine, particle-free licorice protein mixed with aconitine, and aconite decoction had serious toxicity, with a 100 % mortality rate (Ke et al., 2015). This indicated that generating SANs from licorice-aconite decoction stimulates the synergistic and attenuating effect of aconitine. Furthermore, the small molecular active components of TCM can form SANs and promote their absorption, thus showing stronger biological activity than monomer active components. Inspired by the phenomenon of self-precipitation in the decocting process of TCM (Ke et al., 2015), the antibacterial components (berberine and emodin) from *Coptis chinensis* were directly self-assembled into nanoparticles. Furthermore, an *in vitro* experiment demonstrated that SANs from by these two antibacterial components greatly enhanced their antibacterial activity (Tian et al., 2020). The neuroprotective effect of berberine and emodin SANs was reportedly similar to that of Huang-Lian-Jie-Du-Tang decoction, revealing the synergistic mechanism of Huang-Lian-Jie-Du-Tang decoction (Tian et al., 2020; Zhang et al., 2016).

5.2.2. Self-assembled nanoparticles (SANs) as a natural nanocarrier

Many compounds of NPs have various pharmacological activities and good biocompatibility. However, these compounds usually have poor stability, short half-life, serious adverse reactions and other problems, which greatly limit their development and application in diseases. The SANs study of compounds in NPs brings new hope for the application of active components with good pharmacological activity but various “defects”. The SANs formed by these compounds have the same drug entrapment ability as synthetic nanomaterials but with better biodegradability, biocompatibility, and safety than synthetic

nanomaterials. Therefore, these compounds can be used as natural nanocarriers to improve the bioavailability and efficacy of drugs (Qiao et al., 2022). Licorice protein SANs and *Radix Pseudostellariae* protein SANs have been successfully used to deliver curcumin and aconitine (Weng et al., 2019; Ke et al., 2015). Nanoparticles formed by self-assembling some natural small molecular compounds in TCM can also be used as nanocarriers. Poricoicacid A, dehydrotumulosic acid, and liquidambaric acid isolated from *Poria cocos* and *L. formosana* can be self-assembled into nanofibers for transporting doxorubicin (DOX) hydrochloride and paclitaxel (Zhi et al., 2020).

6. Extracellular vesicles (EVs)

Back in the 1960 s, a new era in the study of EVs began when scientists first observed plant-derived extracellular vesicles (PDEVs) using TEM (Fig. 1). EVs are membrane-contained vesicles released in an evolutionally conserved manner by prokaryotic and eukaryotic cells (Yáñez-Mó et al., 2015). They are delimited by a lipidbilayer and contain components of the cells releasing them (Cocozza et al., 2020). EVs are mainly divided into exosomes (50–110 nm), microvesicles (100–300 nm), and apoptotic bodies (300–2000 nm) and are secreted through conventional and unconventional pathways (Wang et al., 2017). Microvesicles and exosomes are mainly released through the unconventional pathway (Fig. 2). The apoptotic bodies are larger vesicles formed by the rupture of the skeleton and protrusion of the cell membrane caused by apoptosis (Rome, 2019; U Stotz et al., 2022) (Fig. 2). Components of EVs have gradually emerged recently with the development of research, including proteins, lipids, nucleic acids, and even the related special chemical components. These components enable quick and efficient identification of EVs.

6.1. Isolation and identification of extracellular vesicles (EVs)

Exploring the EVs of NPs has gained more attention, with many researchers continuously exploring their properties. However, there is no standardized and unique separation scheme for evaluating the EVs of NPs so far. At present, the methods of separating the EVs of NPs mainly include ultracentrifugation, density gradient centrifugation, ultrafiltration, size exclusive chromatography (SEC), precipitation with polymers (PEG), electrodialysis, and aqueous two-phase systems (ATPS) (Konoshenko et al., 2018; Suharta et al., 2021; Yang et al., 2020; You et al., 2021; Perut et al., 2021; Baldini et al., 2018; Ito et al., 2021; Pocsfalvi et al., 2018; Xiao et al., 2018; De Robertis et al., 2020; Kim et al., 2021; Schuh et al., 2019; Chen et al., 2022; Pérez-Bermúdez et al., 2016; Han et al., 2021; Garaeva et al., 2021; Timms et al., 2019; Liu et al., 2020; Regente et al., 2009; Logozzi et al., 2021; Umezu et al., 2021; Yuana et al., 2014; Zu et al., 2021; Liu et al., 2021; Raimondo et al., 2015; Chen et al., 2022; Zhang et al., 2016; Wang et al., 2022; Cui et al., 2022; Chen et al., 2019; Lei et al., 2020; Lei et al., 2021; Xiao et al., 2022; Ju et al., 2013; Wang et al., 2013; Cao et al., 2019; Cho et al., 2021; Xu et al., 2021; Zhuang et al., 2015; Zhang et al., 2021; Xu et al., 2021; Deng et al., 2017; Li et al., 2018; Wang et al., 2016; Mu et al., 2014; Sundaram et al., 2019; Teng et al., 2018; Teng et al., 2021; Bruno et al., 2021; Lee et al., 2019; Kim et al., 2020; Kim and Rhee, 2021; Abraham et al., 2022; Bokka et al., 2020; Meng et al., 2017; Yang et al., 2021; Yang et al., 2020; Rider et al., 2016; Yin et al., 2022; Özkan et al., 2021; Kırbaş et al., 2019). Super-centrifugation is still the most commonly used separation method for EVs; however, it is being gradually replaced by other methods, such as electrodialysis (Table. 5), due to its effects on the concentration, size, and morphology of EVs.

EVs contain various components, such as proteins, lipids, plant metabolites, and genetic material [such as microRNAs (miRNAs)], and each component has its own biologically active functions. For example, proteins are related to the uptake mechanism, and lipids are essential for cells, while miRNAs regulate gene expression (Suharta et al., 2021; Xiao et al., 2018). Due to their different sources; content complexity, and heterogeneity, it is important to identify and analyze EVs components (Kırbaş et al., 2019; Urzì et al., 2021). At present, the characterization of EVs mainly involves particle size distribution, surface charge, morphology, and composition analysis. EVs from different plant sources vary in particle size, surface charge, morphology, and composition. The particle size and surface charge are measured by DLS and nanoparticle tracking analysis (NTA). The morphological characteristics are determined by TEM, while lipids, proteins, and RNA are characterized by thin layer chromatography (TLC), western blot, and SDS-PAGE, respectively. Furthermore, the composition of EVs can be analyzed by proteomics, lipidomics, and RNA transcriptomics to identify proteins or lipids that may be used as markers and determine the specific molecular profile of EVs from NPs. This provides a basis for improving the rigor and standardization of the research on external vesicles derived from NPs (Urzì et al., 2021; Pinedo et al., 2021; Alfieri et al., 2021). Zhuang *et al.* analyzed the lipid components of ginger-derived nanoparticles and found that the components mainly comprised phospholipic acid (PA), digalactose diacylglycerol, monogalactose diacylglycerol, and monogalactose monacylglycerol. It was also reported that the principal components of lipids in EVs with different sucrose density layers were slightly different (Zhang et al., 2016; Zhuang et al., 2015). PA is reportedly involved in various biological functions, including cell

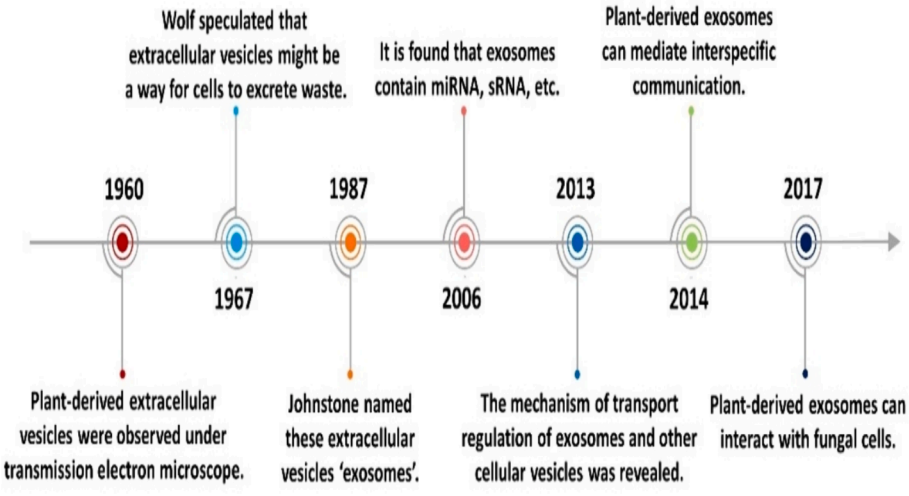

Fig. 1. The past and present lives of extracellular vesicles (EVs).

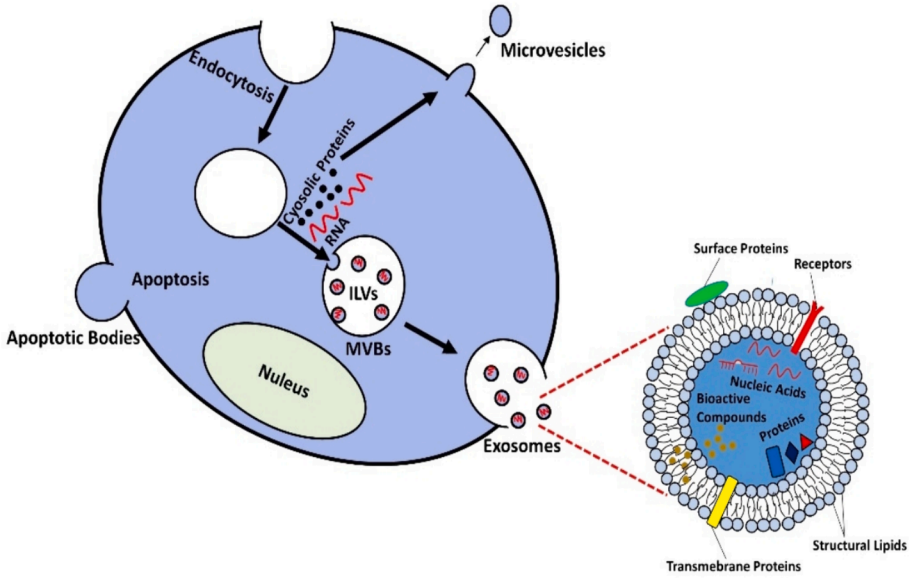

Fig. 2. The production of extracellular vesicles (EVs) in plants. Cells release various vesicle types into the extracellular environment (including exosomes released by the fusion of multivesicular bodies and plasma membrane, particles released by the budding plasma membrane, and apoptotic bodies released by apoptosis). ILVs, intraluminal vesicles; MVBs, multivesicular bodies.

proliferation and differentiation. Moreover, galactose has been shown to be a key ligand for macrophage-targeted drug delivery (Rome, 2019; Xiao et al., 2018). Raimondo *et al.* performed proteomic analysis of *Citrus limon* L.-derived nanovesicles and found that many of the proteins in the vesicles were identical to exosomes of the mammalian tissues and cells and functioned similarly to exosomes from different cell sources (Raimondo et al., 2015). Furthermore, Kim *et al.* isolated EVs from *Dendropanax morbifera* and *Pinus densiflora*, and identified their peroxidase and cell wall deposition proteins by proteomic analysis (Kim et al., 2020). Peroxidase mitigates cellular oxidative stress in many diseases (Liguori et al., 2018), while cell wall protein deposits resist pathogen invasion (Miedes et al., 2014). Teng *et al.* demonstrated that EVs from plants are preferentially taken up by intestinal flora in a lipid-dependent manner and that RNAs in EVs regulate the composition and localization of intestinal microbiota and host physiology (Teng et al., 2018). Xiao *et al.* analyzed the highly expressed miRNAs from 11 plant-derived EVs and found that these miRNAs may regulate the expression of genes related to inflammatory cytokines and tumor responses and may mediate intercellular communication between species (Xiao et al., 2018).

With the increasing understanding of EVs, attention has shifted from animal to plant EVs. Although many plant EVs with significant pharmacological effects have been identified, the individual components responsible for these effects remain unknown. In recent years, researchers have evaluated whether proteins, lipids, RNA, or secondary metabolites of the natural product-derived EVs exhibit therapeutic roles. Among them, RNA (especially miRNAs) has received extensive attention in therapeutic applications. Several studies have reported that miRNAs of natural product-derived EVs may be key regulators of human gene expression, suggesting that they could be a new class of transboundary regulators (Urzì et al., 2021; Urzì et al., 2022; Woith et al., 2019).

6.2. Biological activity and application of extracellular vesicles (EVs)

EVs mainly serve as a protection chamber for material transportation between cells and play an important role in plant growth and development, plant defense response, and symbiosis between plants and microorganisms (Cui et al., 2019). The possible involvement of PDEVs in cross-kingdom communication has recently attracted the attention of many researchers. Several studies reported the interactions between PDEVs and mammalian cells, indicating potential applications of PDEVs in human health. Additionally, PDEVs can cross biological barriers and resist the harsh gastrointestinal environment, making them ideal candidates for exogenous drug delivery. Many synthetic and natural biomolecules have good pharmacological activities but are limited by low solubility and poor stability. Therefore, PDEVs have a broad development prospect as drug carriers for transporting these biomolecules. In this section, we discuss the antitumor and antimicrobial activities of PDEVs, the involvement of PDEVs in gastrointestinal diseases, liver diseases, and other diseases, and their application as natural nanocarriers (Fig. 3).

6.2.1. Antitumor activities of plant-derived extracellular vesicles (PDEVs)

Many studies have shown that some PDEVs can affect the development of cancer. Raimondo *et al.* isolated exosome-like nanoparticles (ELNs) from *Citrus limon* and found that the ELNs inhibited the proliferation of different tumor cells by tumor targeting and activating TRAIL-mediated apoptosis *in vitro*. The ELNs also inhibited chronic myeloid leukemia tumor growth, and this study represents the first cancer treatment using PDEVs (Raimondo et al., 2015). Chen *et al.* isolated ELNs from edible tea flowers (*Camellia sinensis*) and confirmed that these ELNs amplified the production of reactive oxygen species (ROS). This caused mitochondrial damage in breast cancer cells, thereby promoting apoptosis of the breast cancer cells and inhibiting their lung metastasis (Chen et al., 2022). Furthermore, Wang *et al.* reported that the ELNs isolated from charantia gourd inhibited proliferation, migration, and invasion of glioma cells by regulating the PI3K/AKT signaling pathway but did not significantly promote apoptosis(Wang et al., 2022). Cao *et al.* also demonstrated that ELNs isolated from *Panax ginseng* inhibited melanoma growth by inducing macrophage polarization from M2 to M1 macrophages, a process mainly dependent on TLR4 and MyD88 signaling (Cao et al., 2019). Moreover, several studies also showed that PDEVs inhibit the growth, proliferation, and metastasis of tumor cells in various ways. Furthermore, which have almost no side effects and makes PDEVs are expected to provide a strong development basis for a new generation of chemotherapy drugs with minimal side effects.

6.2.2. Antimicrobial activities of plant-derived extracellular vesicles (PDEVs)

The interaction between PDEVs and pathogenic fungi has been

Table 5
Advantages and limitations of current separation methods for plant-derived extracellular vesicles (PDEVs).

Methods	Separation principle	Advantages	Limitations	Examples of application	References
Ultracentrifugation	Particles of different densities and sizes exhibit different deposition rates under centrifugal force.	The most common method of EVs extraction; allows for large-scale extraction of EVs.	Expensive equipment; tedious and time-consuming operation; low purity (such as protein); morphology of EVs may be impaired; EVs may be aggregated.	Cabbage, strawberry, lemon, pineapple, grape, grapefruit, pepper, orange, coconut, ginger, cantaloupe, blueberry, kiwi, pea, soybean, pear, tomato, Aloe vera, bee pollen, honey, royal jelly, arabidopsis, watermelon, shiitake mushroom, sunflower, papaya, and mango.	(Konoshenko et al., 2018; Suharta et al., 2021; Yang et al., 2020; You et al., 2021; Perut et al., 2021; Baldini et al., 2018; Ito et al., 2021; Pocsfalvi et al., 2018; Xiao et al., 2018; De Robertis et al., 2020; Kim et al., 2021; Schuh et al., 2019; Chen et al., 2022; Pérez-Bermúdez et al., 2016; Han et al., 2021; Garaeva et al., 2021; Timms et al., 2019; Liu et al., 2020; Regente et al., 2009; Logozzi et al., 2021; Umezu et al., 2021)
Density gradient ultracentrifugation	After centrifuging sucrose solution with different concentrations, EVs could be retained in sucrose solution of similar density.	Large-scale extraction of EVs; Compared with the ultra-centrifugal method, several impurities (such as protein and RNAs) can be removed, and the purity of EVs is improved.	Expensive equipment; tedious and time-consuming operation; bubbles of similar density (sedimentation rate) cannot be separated; morphology of EVs may be impaired.	*Panax ginseng*, *Asparagus cochinchinensis*, lemon, grape, grapefruit, aloe vera, tea, tea flower (*Camellia sinensis*), carrot, ginger, bitter melon, oat, broccoli, coriander, garlic, onion, scallion, and lavender.	(Konoshenko et al., 2018; Suharta et al., 2021; Yang et al., 2020; Yuana et al., 2014; Zu et al., 2021; Liu et al., 2021; Raimondo et al., 2015; Chen et al., 2022; Zhang et al., 2016; Wang et al., 2022; Cui et al., 2022; Chen et al., 2019; Lei et al., 2020; Lei et al., 2021; Xiao et al., 2022; Ju et al., 2013; Wang et al., 2013; Cao et al., 2019; Cho et al., 2021; Xu et al., 2021; Zhuang et al., 2015; Zhang et al., 2021; Xu et al., 2021; Deng et al., 2017; Li et al., 2018; Wang et al., 2016; Mu et al., 2014; Sundaram et al., 2019; Teng et al., 2018; Teng et al., 2021)
Ultrafiltration	EV particles are separated according to their size or molecular weight.	Simple and fast operation; multiple samples can be processed simultaneously; no expensive equipment is required.	Possible loss due to filter blockage; low purity (such as non-vesicular impurities of the same size as EVs).	Orange, *Aloe vera*, *Dendropanax morbifera*, *Pinus densiflora*, *Thuja occidentalis* and *Chamaecyparis obtuse*.	(Konoshenko et al., 2018; Suharta et al., 2021; Yang et al., 2020; You et al., 2021; Kim et al., 2021; Bruno et al., 2021; Lee et al., 2019; Kim et al., 2020)
Size-exclusive chromatography (SEC)	The separation is conducted based on the size of EV particles.	Simple and fast operation; The integral morphology of EVs can be maintained with high purity and yield; suitable for small-volume samples.	High cost; the samples treated by SEC need to be concentrated.	Cabbage, carrot, cucumber, and tomato.	(Konoshenko et al., 2018; Suharta et al., 2021; Yang et al., 2020; You et al., 2021; Kim and Rhee, 2021; Abraham et al., 2022; Bokka et al., 2020)
Electrodialysis	Based on the electric vehicle size, the EVs are separated under the condition that a certain current is applied to the sample in the dialysis bag.	Simple and low-cost operation; the integral morphology of EVs can be maintained with high purity.	Time-consuming.	Bitter melon and lemon.	(Meng et al., 2017; Yang et al., 2021; Yang et al., 2020)
Precipitation with polymers (PEG)	Separation is based on the reduced solubility of EVs in superhydrophilic polymer solution.	Low cost, non-usage of overspeed centrifugation; suitable for all sample types; Simple and fast operation; the integral morphology of EVs can be maintained.	Low purity (such as protein).	Cabbage and ginger.	(Konoshenko et al., 2018; Suharta et al., 2021; Yang et al., 2020; You et al., 2021; Rider et al., 2016; Yin et al., 2022)
Aqueous two-phase systems (ATPS)	Separation is based on specific physicochemical characteristics of interactions between EVs and polymer molecules.	Low cost; simple and fast operation; the integral morphology of EVs can be maintained with high purity.	The concentration of polyethylene glycol and dextran should be strictly controlled; the introduction of new impurities (dextran).	Garlic.	(Konoshenko et al., 2018; Özkan et al., 2021; Kırbaş et al., 2019)

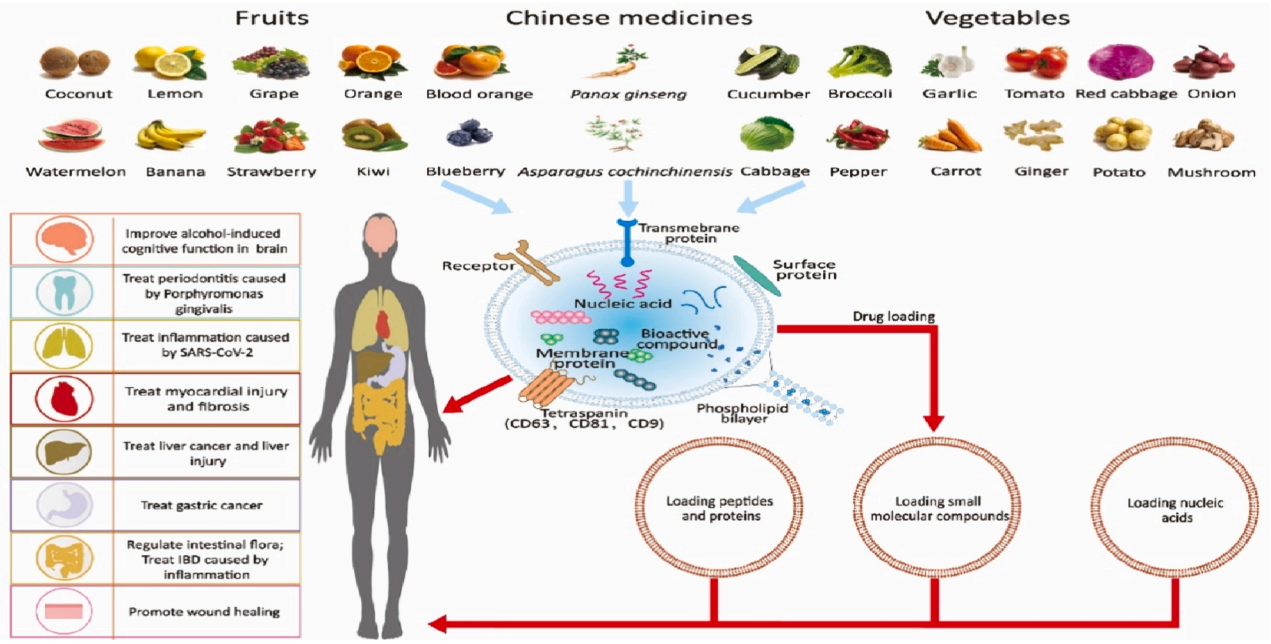

Fig. 3. Applications of plant-derived extracellular vesicles (EVs).

widely explored. For example, the EVs produced by *Arabidopsis thaliana* can silence the virulence genes of various pathogenic fungi, thus inhibiting their virulence (Cai et al., 2018). Although PDEVs can protect plants from pathogenic bacteria, it is unclear whether they can also protect mammals. It has been reported that ELNs produced by bee pollen, honey, and royal jelly have antibacterial activity and biofilm-inhibiting effects on *Staphylococcus aureus* (Chen et al., 2022). ELNs from lemons stimulated probiotics to inhibit the growth of *Clostridium difficile* (Lei et al., 2020). Furthermore, ginger-derived ELNs significantly reduced periodontitis by interacting with the hemin-binding protein 35 on the surface of *Porphyromonas gingivalis*, and this effect was closely related to PA unsaturation and miRNA (Sundaram et al., 2019). These findings suggest that PDEVs can prevent plant and mammalian diseases caused by cross-kingdom pathogenic bacteria.

6.2.3. Application of plant-derived extracellular vesicles (PDEVs) in treating gastrointestinal diseases

PDEVs have also been reported as the treatment of gastrointestinal diseases. For example, the miRNA of the ginger-derived ELNs stimulates IL-22 production from *Lactobacillus rhamnosus* in the gastrointestinal tract to regulate the intestinal barrier function, thereby preventing colitis (Teng et al., 2018). PDEVs can also act on intestinal stem cells, intestinal epithelial cells, and macrophages to treat colitis. For instance, grape-derived ELNs could target and promote the proliferation of intestinal stem cells in glucan sodium sulfate-induced colitis to regulate the regeneration process of the intestinal tissues. Grape-derived ELNs were reportedly involved in remodeling the intestinal tissues (Ju et al., 2013). In a different study, ginger-derived ELNs were mainly taken up by intestinal epithelial cells and macrophages. These ELNs could increase the survival and proliferation of intestinal endothelial cells, reduce proinflammatory cytokines (TNF-α, IL-6, and IL-1β), and increase anti-inflammatory cytokines (IL-10, and IL-22) in different colitis models to effectively treat colitis (Zhang et al., 2016). The galactose group on the surface of tea-derived ELNs can increase the secretion of anti-inflammatory cytokines (IL-10) by macrophages, reduce the production of ROS, and inhibit the expression of proinflammatory cytokines (TNF-α, IL-6, and IL-12), to prevent or alleviate colitis-related diseases (Zu et al., 2021). Additionally, lemon-derived EVs have been used in treating gastric cancer through ROS production-related mechanisms. ROS can up-regulate GADD45a, resulting in S-phase arrest of the gastric cancer cell cycle and apoptosis (Yang et al., 2020).

6.2.4. Application of plant-derived extracellular vesicles (PDEVs) in treating liver diseases

PDEVs also have good therapeutic effects on various liver diseases. For example, Shiitake mushroom-derived ELNs could significantly inhibit NLRP3-mediated inflammasome activation of primary macrophages and proinflammatory cytokines (IL-6, IL-1β, and IL-18), thus preventing acute liver injury induced by d-galactosamine and lipopolysaccharide (Liu et al., 2020). Ginger-derived ELNs prevented alcohol-induced liver injury by mediating Nrf2-induced expression of hepatic detoxification/antioxidant genes and inhibiting ROS production (Zhuang et al., 2015). Furthermore, *Asparagus cochinchinensis*-derived ELNs inhibited the proliferation of hepatocellular carcinoma cells by inducing apoptosis (Zhang et al., 2021).

6.2.5. Application of plant-derived extracellular vesicles (PDEVs) in treating other diseases

Aloe vera-derived EVs exerted their antioxidant activity by activating Nrf2 in HaCaT cells. These EVs also promoted the migration of HaCaT and human dermal fibroblasts, which is essential for wound healing (Kim et al., 2021). Moreover, ginger-derived ELNs inhibited the expression of SARS-CoV-2 Nsp12 and spike genes through Aly-miR396a-5p and rlcv-miR-RL1-28-3p to alleviate SARS-CoV-2 Nsp12-induced pulmonary inflammation (Teng et al., 2021). Oat-derived ELNs reportedly suppressed brain and liver inflammation. These ELNs are preferentially taken up by microglia when β-glucan binds the hippocalcin. The oat-derived ELNs could also inhibit the activation of alcohol-induced brain inflammation signaling pathways by interacting with Rab11a to increase the exportation of dectin-1 into exosomes in a Rab11a-dependent manner, thus improving brain memory function (Xu et al., 2021). Furthermore, *Momordica charantia*-derived EVs promoted the proliferation of myocardial H9C2 cells after 16 Gy X-ray irradiation, thus inhibiting apoptosis and reducing DNA damage and mitochondrial ROS production in H9C2 cells after radiation. These effects might be related to the ability of EVs to scavenge free radicals. It was also confirmed that ELNs could reduce chest irradiation-induced myocardial injury and fibrosis in mice (Cui et al., 2022).

6.2.6. Extracellular vesicles (EVs) as natural nanocarriers

EVs have been widely used in nanocarriers, and like liposomes and other commonly used drug carriers, EVs can enhance the stability of drugs while reducing their toxicity. However, compared with these liposomes and other commonly used drug carriers, EVs have inherent biocompatibility, appropriate particle size distribution, high modification flexibility and biological barrier permeability, low immunogenicity, and intrinsic targeting (Song et al., 2022).

Wang *et al.* prepared nanoparticles from the lipid components of grapefruit-derived EVs to export chemotherapeutic drugs, siRNAs, DNA expression vectors, and proteins to different cell types. These grapefruit-derived nanocarriers were also used to deliver therapeutic agents and folic acid into pregnant mice. The results showed that these nanocarriers enhanced the chemotherapy inhibitory effect on tumor growth in the CT26 and SW620 cell-derived mice. The study also showed that grapefruit-derived nanocarriers are less toxic than those from synthetic lipids (Wang et al., 2016). Furthermore, Xiao *et al.* engineered heparin-cRGD onto the surface of lemon-derived EVs and fabricated it with DOX to generate a biomimetic drug delivery system for heparin-cRGD-EVs-DOX (HRED). HRED could efficiently enter the drug-resistant ovarian cancer cells through caveolin-mediated endocytosis, micropinocytosis, or clathrin-mediated endocytosis. These endocytosis techniques could effectively dissipate intracellular energy while reducing the downstream production of adenosine triphosphate. This significantly reduced drug effusion and enhanced the anti-proliferation ability of HRED to effectively overcome the multidrug resistance of ovarian cancer cells *in vivo* (Xiao et al., 2022). In addition to peptides and small molecule compounds, PDEVs can also carry genetic material. Zhang *et al.* developed a novel siRNA delivery system, the ginger-derived lipid vehicles loaded with siRNA-CD98 (siRNA-CD98 /GDLVs). Oral siRNA-CD98/GDLVs could effectively target colon tissues and reduce CD98 expression in the colon (Zhang et al., 2017). These findings indicated that EVs have more advantages, especially targeting, as natural nanocarriers than synthetic drug carriers. EVs also have simple sources, low toxicity, and can be mass-produced, making them suitable nanocarriers.

7. Conclusion

Various active components of NPs have been confirmed, such as small molecular compounds, polysaccharides, polypeptides, proteins, SANs, and EVs. These components promote the discovery of lead compounds and the development of new drugs while enhancing our understanding of the substance-based efficacy of NPs, which is important for preventing and treating human diseases. However, many natural active substances are yet to be applied to prevent and treat clinical diseases. Thus, the druggability evaluation of these active substances should be accelerated to promote the application of more active substances in treating clinical diseases. Some natural active monomers have good efficacy, but their applications are limited by low bioavailability and high toxicity. Modifying the structure and structure–activity relationship of these molecules could be beneficial in developing new drugs with clinical significance. Although several newly-discovered active substances, such as SANs and EVs, have good pharmacological activities and application prospects, their pharmacological mechanisms are still unclear. Moreover, the druggability evaluation and clinical trials of these substances have not been conducted. Therefore, there is a need to conduct druggability evaluation and clinical trials of these substances. With the development of science and technology, several natural substances with novel structures, high activity, and low toxicity can be identified and developed for clinical usage to aid in preventing and treating human diseases.

CRediT authorship contribution statement

Tao Wang: Writing – original draft, Writing – review & editing. **Zhong-Yu Fu:** Writing – original draft, Writing – review & editing. **Yan-Juan Li:** Data curation, Investigation. **Lei Zi:** Data curation, Investigation. **Cheng-Zhu Song:** Data curation, Investigation. **Yu-Xuan Tao:** Data curation, Investigation. **Mei Zhang:** Data curation, Investigation. **Wen Gu:** Data curation, Investigation. **Jie Yu:** Project administration, Resources, Supervision, Validation. **Xing-Xin Yang:** Project administration, Resources, Supervision, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

Publication of the manuscript has been approved by all co-authors.

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