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REVIEW

Unlocking the Medicinal Potential of Plant-Derived Extracellular Vesicles: current Progress and Future Perspectives

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Abstract: Botanical preparations for herbal medicine have received more and more attention from drug researchers, and the extraction of active ingredients and their successful clinical application have become an important direction of drug research in major pharmaceutical companies, but the complexity of extracts, multiple side effects, and significant individual differences have brought many difficulties to the clinical application of herbal preparations. It is noteworthy that extracellular vesicles as active biomolecules extracted from medicinal plants are believed to be useful for the treatment of a variety of diseases, including cancer, inflammation, regenerative-restorative and degenerative diseases, which may provide a new direction for the clinical utilization of herbal preparations. In this review, we sort out recent advances in medicinal plant extracellular vesicles and discuss their potential as disease therapeutics. Finally, future challenges and research directions for the clinical translation of medicinal plant extracellular vesicles are also discussed, and we expect that continued development based on medicinal plant extracellular vesicles will facilitate the clinical application of herbal preparations.

Keywords: plant-derived extracellular vesicles, Chinese medicine preparation, nanoparticle, drug delivery nanoplatforms, nanotherapeutics

Introduction

Herbal medicine has an interesting philosophical background and a long history of treating a variety of ailments, which has been questioned due to the lack of high-quality trials based on evidence of effectiveness. The abstract nature of traditional Chinese medicine (TCM) theories and the ambiguity of therapeutic mechanisms have, to some extent, severely hindered their popularity, as well as caused skepticism among Western scientists about their efficacy.[1] The biggest problem in the development of TCM is the inability to quantify therapeutic efficacy and the lack of uniformity in methodology and standards, which has resulted in the use of TCM to treat diseases with tremendous heterogeneity.[2] In terms of disease treatment modalities, the diversity of TCM components, multi-targets, and multi-pathways have made the study of drug targets also become extremely difficult to study.[3] Therefore, finding new alternatives is being progressively considered.

Over the past decades, extracellular vesicles (EVs) have emerged as important mediators of intercellular communication in lower and higher organisms, and play important roles in regulating a variety of physiopathological processes.[2,4,5] EVs from plant sources are also being focused on. Compared with animal EVs, plant-derived EVs exhibit the advantages of being widely available, cost-effective, and easy to obtain, etc. It has been found that plant-derived EVs can be used for the potential prevention or treatment of diseases, including cancer, inflammation, and degenerative diseases, which suggests that plant-derived EVs may be one of the promising drugs for the current research biopharmaceuticals. In addition, the potential of plant-derived EVs as natural or engineered drug carriers is also attractive, such as loading drugs with defined therapeutic effects for targeted

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introduction into damaged cells for the treatment of diseases. EVs of herbal origin are more homogeneous and less immunoreactive than the various mixtures in TCM formulations, and exploring the mechanism of disease treatment by defined biomolecules in a particular EV of herbal origin is also simpler than in TCM formulations, which creates the possibility of establishing a uniform evaluation index and efficacy of TCM.[6] Therefore, discussing the progress and value of research on EVs of herbal origin may give a new impetus to the use of TCM formulations and even to the new support for the international recognition of TCM.

Advantages and Dilemmas of Chinese Pharmaceutical Preparations

The use of Chinese herbs for the treatment of disease has a history and philosophical background of thousands of years in Asia, especially in developing countries such as China. In recent years, TCM has been gaining international acceptance as an alternative medicine.[7] TCM treatments focus on holistic balance, which is achieved by improving the body's condition and regulating hair-growing tissues, rather than directly supplementing with a particular hormone. For example, herbs can improve male fertility by supplementing micronutrients and vitamins, improving reproductive microcirculation, lowering serum anti-sperm antibody levels, and altering epigenetic markers.[6] In addition, active monomers and bioactive compounds extracted from TCM have been reported to have the potential to be new drugs for AD, and it was mentioned in the article that TCM may modulate AD by reducing β-amyloid production, cellular autophagy, apoptosis, inflammation, oxidative stress, and mitochondrial dysfunction.[8] Currently, the mechanisms of action of TCM are mainly involved in antiviral, anti-inflammatory, immunomodulatory, and organ protection.[9] And this may be one of the drug choices for the treatment of COVID-19, which is affecting human health globally.[10] A growing body of evidence supports that TCM has a definitive efficacy in alleviating the clinical symptoms of neocoronary arthritis.[11] Mechanistically, the TCM can inhibit the replication and transcription of SARS-CoV-2, prevent the entry of SARS-CoV-2 into host cells, and attenuate cytokine storm, immunodeficiency, and coagulation abnormalities caused by viral infection of the human body.[12] In addition, herbal formulas have a long history of treating chronic diseases of the gastrointestinal tract. Herbal formulas can improve chronic colitis by repairing the intestinal mucosal barrier. This may be related to the fact that herbal formulas increase intestinal epithelial cells, promote proliferation of intestinal stem cells, tight junction proteins and mucins, regulate the abundance of beneficial intestinal bacteria and improve intestinal innate and adaptive immunity.[13] Interestingly, the bi-directional effects of herbal medicines have also received much attention. For example, ginseng shows bidirectional regulation of immune function and the central nervous system; astragalus also has a bidirectional role in regulating blood pressure and immune function; in activating blood circulation and stopping bleeding, gastrointestinal peristalsis and immune function rhubarb also has a bidirectional role. Of course, this bidirectional effect is inextricably linked to the complexity of the herbal components, the difference in dosage, the processing and compounding of the herbs, the physiological condition of the patient, and the role of adaptogens.[14]

Initially, both TCM and Western medicine originated from plants. With the development of science and technology, Western medicines have evolved into active single compounds, while TCM is still at the stage of mixtures, ie, herbal formulations. Currently, Chinese medicine is mainly concerned with the regulation of the human body as a whole, whereas Western medicine acts directly on protein targets (targeted therapy) or holistic gene targets (radiotherapy). Specifically, Chinese medicine mainly regulates the activity of the whole set of genes in the human body, whereas Western medicine has a clear target that acts at the protein level. Therefore, TCM and Western medicine tend to complement each other well, and clinical combination therapy can achieve better therapeutic effects.[15] In the treatment of infectious diseases, the synergy of TCM and Western medicine has the advantages of improving efficacy, reducing drug resistance, and facilitating recovery in the later stages of the course of the disease.[16] However, the safety of the drugs involved has not yet been able to be adequately researched and understood in accordance with modern Western standards for pharmaceuticals, which has made the use of TCM in the treatment of infectious diseases highly suspect in the West. However, the safety of the drugs in question has not yet been adequately researched and understood according to modern Western pharmaceutical standards, making the treatment of infectious diseases with Chinese medicines highly skeptical in Western countries, as best represented by the Lianhua Qingdian capsule for the treatment of new coronaviruses. In terms of intervention in organ fibrosis, TCM has mostly shown holistic efficacy, and it is difficult to elucidate the detailed mechanism of herbal intervention in organ fibrosis because the composition and site of action of the herbs are not yet clear. This has led to similar treatment protocols for treating fibrosis in different organs, and the imprecision of the effects is highly suspected. Therefore, studies that visualize or contribute to the mechanism

of action and interaction process of herbal formulas would greatly promote the development of Chinese medicine. And the recent development on plant extracellular vesicles may help to accelerate this process, because, the plant cell extracellular.[17]

Relative Advantages of Extracellular Vesicles in Drug-Derived Plants

EVs are vesicles with a membrane structure secreted by activated cells with diameters ranging from 40 ~ 1000 nm, including exosomes, microvesicles, and apoptotic vesicles.[18] Currently, virtually all living cells, including plants, animals, and microorganisms, are capable of secreting extracellular vesicles. In fact, the discovery of EVs in plants preceded the discovery of EVs in mammals by about 15 years. As early as the 1960s, it was first observed by transmission electron microscopy that multivesicular bodies in carrot cells fused with the plasma membrane and released secondary vesicles containing contents into the cell wall interstitials.[19] Plant-derived EVs have naturally attracted a great deal of attention due to the advantages of simple isolation, high yield, and good activity. Many similar reports have claimed that EVs isolated from freshly squeezed fruit and vegetable juices have activities similar to those of the original plants. In addition, EVs have been considered as a promising therapeutic drug and drug delivery vehicle, mainly because of their well-defined pharmacological activity, good biocompatibility, specific tissue targeting, and good drug-carrying capacity.[20] Therefore, it is clear that the extraction of extracellular vesicles from herbal medicines still retains the pharmacological activity of the drug, while its targeting ability may be more helpful for drug absorption to reduce the side effects of the drug.

Marker protein-based engineering of EVs has also been shown to be a drug delivery strategy with great potential.[21] The study of plant EVs compared to mammals has also been controversial, due to the fact that plants have a completely different structure (presence of cell wall) than animal cells. However, it has also been clearly reported that the structure and size of EVs derived from plants and animals do not differ much. For example, strawberry-derived nanovesicles have a similar size and structure to mammalian-derived exosomes, and strawberry-derived EVs taken up and internalized by human mesenchymal stromal cells did not show a toxic response to the cells. At the same time, plant-derived EVs do not require tightly controlled culture environments and have low production costs.[22] In addition, plant-derived EVs do not contain zoonotic or human pathogens. Therefore, plant-derived EVs have advantages over mammalian cell-derived EVs for clinical use.[23] This advantage of plant-derived EVs not being detected by the human immune system achieves longer circulation cycles and higher bioavailability, which are also optimal properties compared to synthetic nanoparticles (eg, liposomes).[24,25] The natural lipid bilayer structure of EVs provides a key benefit to plant-derived EVs critical protection, which allows plant-derived EVs to tolerate temperature changes, pH, simulated physiological environments, and sonication.[26] For example, the ability of freshly isolated ginger EVs stored at −80 °C to inhibit the activity of IL-1β was not significantly altered.[27] Nanovesicles derived from edible mulberry bark can inhibit the activity of IL-1β by promoting heat shock protein family A (Hsp70) member 8 (HSPA8)-mediated activation of the AhR signaling pathway, providing protection against colitis and shaping the function of the gut microbiota in a mouse model.[28] Plant-derived EVs can also penetrate the intestinal mucus barrier, which can then be taken up by mouse intestinal stem cells for repair of the intestinal mucosa. All of these studies suggest that plant-derived EVs are highly tolerant to gastrointestinal enzymes and bile. This implies that plant-derived EVs have relatively stable and beneficial processing properties and are particularly suitable as drug delivery vehicles.

Synthesizers of plant compounds are usually not as effective as mixed plant material (eg vitamins). This may imply the presence of multiple bioactive substances in plants as well as the presence of certain unrecognized bioactive components. Combined with the presence of cellular nanoparticles in both different plants and fruits, the ability of EVs to carry bioactive compounds and the presence of small RNAs, miRNAs, and high levels of vitamin C in plant EVs, etc.[29,30] It is not difficult to imagine that some of the unrecognized bioactive constituents are likely to be released by the plants.[31,32] Thus, the extracellular vesicles extracted from herbs are likely to have medicinal properties and potential new functions beyond those of the herbs (herbs that have been dried, extracted, boiled, etc.) themselves. At the plant level, the involvement of EVs in plant cell-to-cell communication modulates the plant's innate immunity by transporting mRNAs, miRNAs, bioactive lipids, and proteins to recipient cells in different environments.[33] At the animal level, plant-derived EVs have been the focus of numerous studies in recent years, which have revealed encouraging properties explaining their availability, biocompatibility, and biodegradability.[34] Unlike mammalian EVs, plant-derived EVs are not be detected by the human immune system and are highly biocompatible.[34] Plant-derived EVs have been found to activate cross-border regulation, transmitting molecular signals between plant cells, bacteria, parasites, fungi[35] and even animals.[36,37] Therefore, they have a promising application in the field of disease therapy.

Table 1 Advantages and Disadvantages of Extracellular Vesicles of Animal versus Plant Origin

Type	Vantage	Disadvantageous
Extracellular vesicles of plant origin	Low immunogenicity, low toxicity and side effects, wide range of sources, low price, easy to obtain and wide range of effects.	Diverse, difficult to extract, potential cross-species biohazard, unclear targeting.
Extracellular vesicles of animal origin	Relatively easy to extract, relatively clear targeting, good activity, high biocompatibility, no cross-species biohazards.	Potentially immunogenic, expensive, difficult to obtain, risk of tumor proliferation, difficult to store.

Interestingly, some EVs carried plant ceramides that were more effective than mammalian ceramides in stimulating the release of EVs. Regarding the sphingosine component of EVs, the plant-based fraction was also more effective than the mammalian-based component in stimulating the release of EVs, which may be due to the higher affinity of plant sphingosines for LAPTM4B compared to mammalian sphingosines and/or assisting in protein-protein interactions between LAPTM4B and other downstream signaling agents.[28] Overall, in comparison to man-made nanoparticles, the plant-derived EVs have the transport properties of natural molecules, lower immunogenicity and toxicity.[23] Not only are plant-derived EVs less potentially biohazardous compared to animal EVs, but their good biocompatibility, wide availability, low price, easy accessibility and wide range of actions (Table 1) make them more economically viable as drug nanocarriers. Therefore, plant-derived EVs are considered to be a biological nanodrug and transporter material with great research potential.[22]

Isolation and Extraction of Extracellular Vesicles from Plants of Pharmaceutical Origin

Since the understanding of plant-derived extracellular vesicles is still in the preliminary stage, the reliability of their isolation and extraction techniques still faces many challenges. In fact, only a few studies have reported the mechanism of nanovesicle formation in plants.[38] The pathway for the generation of plant-derived EVs is similar to that of animals due to the fact that the specific biomarkers PENETRATION1 and TETRASPANIN 8 are located in different positions, representing two different EVs.[34] In fact, plant-derived EVs are usually in a spherical structure when isolated that can pass through the cell wall. Specifically, MVB encapsulates plant-derived EVs, after which it binds to tetratransmembrane proteins and crosses the plasma membrane, ultimately releasing plant-derived EVs from the cell[34] (Figure 1). Tetratransmembrane

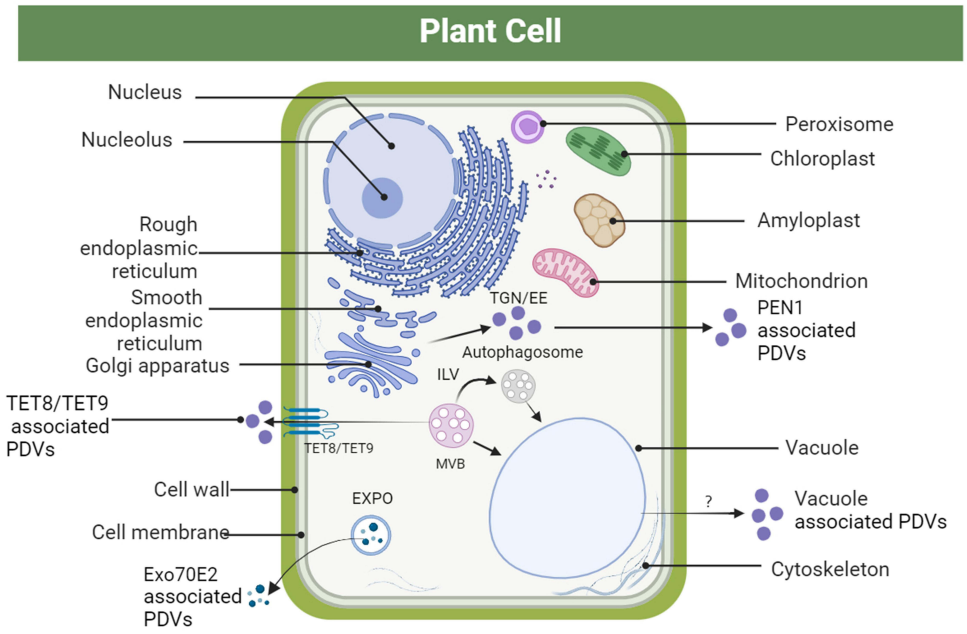

Figure 1 Formation of extracellular vesicles and secretory processes in plants. Data from Lian et al.[42] Created with Biorender.com.

proteins play a very important role in biosynthesis, especially for plant-derived EVs, eg, in cargo selection, membrane fusion, and nanovesicle uptake.[39] Interestingly, the proteins, small RNAs, and metabolites contained in a given class of plant-derived EVs can vary, depending on the type of plant selected and the plant cell.[40] For example, nanovesicles from different parts of the plant contain different substances and have different roles.[41,42]

How to obtain relatively pure plant-derived EVs is also a primary problem for researchers. Currently, differential ultracentrifugation, density gradient centrifugation, magnetic bead sorting[41] and size exclusion chromatography[43] have been used for the extraction of plant-derived EVs. However, these methods still face the problems of multiple residues of nonvesicular nanoparticles, low purification efficiency, high loss of plant-derived EVs, and damage to plant cellular structure due to improper separation.[44] Fortunately, a method that can produce relatively pure extracellular vesicles, ie, digesting the plant with cellulase and pectinase, and then gently separating the extracellular vesicles in body fluids without damaging the plant cellular structure, was proposed.[22] At the same, in order to be more efficient and effective, we need to develop a method for the extraction of EVs from plant sources. Meanwhile, in order to prepare plant-derived EVs more efficiently, they successfully constructed a plant cell culture technique, which provides the possibility of preparing plant-derived EVs rapidly and in large quantities.[22]

Medicinal Plant Extracellular Vesicles in Disease Therapy

Value in Cancer Treatment

Immunotherapeutic approaches based on plant extracellular vesicles have been demonstrated in cancer treatment. The use of plant extracellular vesicles in immunotherapy has not shown any qualitative or ethical difficulties.[45] As a result, plant extracellular vesicles of specific origin are regarded as substances capable of activating the immune response and destroying cancer cells. Based on the overall role of extracellular vesicles, the use of extracellular vesicles as an anticancer agent has become a new tool. For example, isolated lemon nanovesicles can inhibit the growth of chronic myeloid leukemia tumor cells in vivo by targeting to the tumor site and activating the TRAIL-mediated apoptosis process.[46] In short, they are able to inhibit the development of chronic granulocytic leukemia in vivo by targeting to the

Table 2 Studies on Extracellular Vesicles of Medicinal Plants

Source	Extraction Method	Methods of Medication	Type of Disease	Conclusion	References
Grapes	Sucrose Gradient Centrifugation	Oral gavage	Colitis	Stimulates intestinal stem cell proliferation and promotes intestinal tissue repair.	[30]
Grapefruit	Sucrose Gradient Centrifugation	Intravenous	Tumors	Enhances tumor chemotherapeutic agent delivery for improved tumor growth inhibition.	[51]
Lemon	Ultracentrifugation	Intravenous	Tumor	Induces TRAIL-mediated cell death to hinder cancer cell proliferation effectively.	[52]
Broccoli	Ultracentrifugation	Oral gavage	Colitis	Activates dendritic cells and AMP-activated protein kinase to inhibit colitis.	[53]
Ginger	Sucrose gradient centrifugation	Intravenous	Colon Cancer	Enhances chemotherapeutic inhibition of colon cancer growth by loading Adriamycin.	[54]
Ginger	Ultracentrifugation, Equilibrium Density Gradient Centrifugation	Intravenous	Tumors	Enables targeted delivery of siRNA for effective cancer inhibition.	[36]
Ginger	Sucrose Gradient Centrifugation	Oral tube feeding	Inflammatory Bowel Diseases	Maintains a healthy gut microbiota with ginger-derived microRNA in extracellular vesicles.	[55]
Ginger	Polymer precipitation	Oral gavage	Hereditary Haemochromatosis	Prevents iron overload in vivo with loaded Dmt1 siRNA.	[56]
Ginger	Sucrose Gradient Centrifugation	Oral gavage	Alcoholic Liver Injury	Reduces serum ALT and AST levels, as well as hepatocyte TG levels, to prevent alcoholic liver injury.	[57]

(*Continued*)

Table 2 (Continued).

Source	Extraction Method	Methods of Medication	Type of Disease	Conclusion	References
Grapefruit	Sucrose gradient centrifugation	Oral	Colitis	Significantly enhances the anti-inflammatory effects of methotrexate (MTX) by loading it into extracellular vesicles.	[58]
Ginger	Sucrose gradient centrifugation	Oral	Colitis	Diminishes acute colitis, promotes intestinal repair, and prevents chronic colitis and associated cancers.	[48]
Ginger	Sucrose Gradient Centrifugation	Oral	Ulcerative colitis	Inhibits the inflammatory response in ulcerative colitis with negative carrier siRNA-CD98.	[59]
Asparagus	Sucrose Gradient Centrifugation	Intravenous	Hepatocellular carcinoma	Effectively inhibits hepatocellular carcinoma cell proliferation.	[60]
Grapefruit	Sucrose Gradient Centrifugation	Intravenous	Metastatic Liver Tumour	Induces M1 macrophages for colon cancer liver metastases treatment with loaded miR-18a.	[61]
Ginger	Sucrose Gradient Centrifugation	Oral	Chronic Periodontitis	Effectively inhibits Porphyromonas gingivalis pathogenicity.	[62]
Lemon	Ultracentrifugation	Oral	Clostridium difficile colitis	Protects mice from Clostridium difficile infection through probiotic regulation.	[63]
Honeysuckle	Ultracentrifugation	Oral	COVID-19	Inhibits SARS-CoV-2 replication with MIR2911 in extracellular vesicles from Porphyromonas gingivalis.	[64]
Grapefruit	Sucrose Gradient Centrifugation	Intranasal	Glioma	Inhibits mouse brain tumor cell growth with grapefruit-derived extracellular vesicles carrying miR17.	[65]
Orange	Ultracentrifugation	Oral gavage	Obesity Related Bowel Diseases	Reduces plasma lipids and inflammation in gastrointestinal diseases with orange juice-derived nanovesicles.	[66]
Rosewood Astragalus	Ultrafiltration	Subcutaneous injection	Diabetes	Lowers blood glucose levels and ameliorates diabetic complications with insulin-carrying rosewood astragalus nanoparticles.	[67]
Tea	Sucrose Gradient Centrifugation	Oral	Colon Diseases	Inhibits inflammatory bowel responses, restores damaged colonic barriers, and enhances gut microbiota diversity and abundance.	[68]

tumor and reducing the risk of cancer.[46] In another study, citrus lemon-derived nanovesicles have also been shown to inhibit the growth of p53-inactivated CRC cell line cancer cell growth effects.[47] In addition, ginger-derived nanovesicles have also been shown to reduce cell cycle protein D1 RNA levels in colorectal cancer mice thereby inhibiting colon cancer cell proliferation.[48] Plant-derived EVs did alleviate multiple indications of cyclophosphamide-induced immunosuppression, showing a restorative effect on myelosuppression after chemotherapy. For example, plant-derived EVs elevated macrophage phagocytosis, accelerated lymphocyte proliferation, and upregulated the expression of the hematopoiesis-related transcription factor PU.1. Targeted distribution of plant-derived EVs in immune organs after intraperitoneal injection is also possible, which can be taken up by immune organs and HSCs and ultimately exert proliferative and functional activation effects on immune cells.[22] Notably, plant-derived EVs have also been shown to inhibit tumor growth and enhance anti-tumor immunity in a mouse model of lung cancer, the mechanism of which may be that plant-derived EVs can remodel the tumor microenvironment and reprogramming tumor-associated macrophages. For example, artemisia-derived nanovesicles significantly enhanced the efficacy of PD-1 blockade in a mouse lung cancer model, revealing their antitumor potential. The mtDNA-induced cGAS-STING pathway in the nanovesicles is believed to be the main mechanism for the immunomodulatory effects of artemisinin-derived nanovesicles.[49] Thus, specific plant-derived EVs are expected to serve as a potential chemotherapeutic immune cofactor for improving hematopoietic function and

enhancing the immune response to tumors, and have shown excellent stability in a variety of brutal environments.[22] In conclusion, plant-derived EVs as an emerging platform that overcomes the limitations of low bioavailability, poor stability, and low safety associated with synthetic liposomes and animal extracellular vesicles of non-natural origin, offer new opportunities for cancer therapy from the perspective of delivering anticancer compounds (self and implanted).[50]

Value in the Treatment of Inflammatory Diseases

Plant-derived EVs do have unique immune-enhancing effects in vivo and in vitro and have shown excellent stability in a variety of brutal environments.[69,70] Indeed, it has also been found that plant-derived EVs can also inhibit inflammatory processes and attenuate inflammatory diseases. For example, a vector has been developed that can target plant-derived extracellular vesicles carrying ginger miRNA in the lungs to treat inflammation-related diseases in the lungs. This vector can be preferentially taken up by lung macrophages and lung epithelial cells, especially ACE2-positive lung cells. Ginger miRNAs were targeted for delivery to lung epithelial cells to inhibit Nsp12 expression, thereby preventing Nsp12+-mediated lung inflammation, possibly because targeting macrophages inhibits macrophage activation and alters the composition of Nsp12Nsp13-activated macrophage metabolites, thereby preventing lung inflammation.[12] EVs derived from edible mulberry bark have also demonstrated an ameliorative effect on colitis in animal models. In animal models, where EVs from mulberry bark provided effects directed at inhibiting the activation of the colitis signaling pathway, the rationale for which may be due to the promotion of AhR activation mediated by Heat Shock Protein Family A (Hsp70) member 8 (HSPA8).[28] Plant-derived EVs may also act as an antioxidant to mitigate inflammatory responses, for example, EVs from carrot sources contain glutathione that may prevent the oxidation of free radicals, an anti-inflammatory property that effectively alleviates rheumatic and arthritic symptoms.[71] In addition, these natural nanomedicines have been found to contain large amounts of lipids, some functional proteins, and many bioactive small molecules. Specifically, natural nanomedicines were able to reduce the production of reactive oxygen species, inhibit the expression of pro-inflammatory cytokines, and increase the secretion of anti-inflammatory IL-10. In vivo studies have found that oral administration of natural nanomedicines can also be effective in inhibiting inflammatory bowel responses, repairing the colonic barrier, and increasing the diversity and overall abundance of the intestinal microbiota, ultimately coming to the prevention or mitigation of inflammatory bowel disease. For example, saponins from ginseng are considered to be the main active components in ginseng.[72–74] It has been found that ginseng-derived saponin-containing EVs can exert anti-inflammatory effects by modulating the AMPK pathway and its downstream signaling pathways.[75] RNAs from ginger-derived EVs also ameliorate colitis in mice through an IL-22-dependent mechanism.[76] In summary, EVs from specific plant sources exhibit inhibition of inflammatory responses have shown significant therapeutic value for the treatment and prevention of long-term complex and difficult-to-heal chronic inflammatory diseases, such as chronic gastritis, chronic colitis, and Crohn's disease.

Value in Regenerative Restoration

Regenerative medicine is considered to be one of the most effective methods for repairing the skin barrier, and nanovesicles are considered to be one of the most promising materials for regenerative medicine in the future.[77] In contrast to traditional chemosynthetic drugs, nanovesicle particles can easily fuse with skin cells and carry drugs across the stratum corneum barrier without altering the basic structure of the skin, and create drug storage sites on the surface of the skin as well as inside the skin, demonstrating a topical, long-term release of drugs for the treatment of diseases. The effect of topical long-term release of drugs for the treatment of diseases. Compared to conventional topical creams, nanoformulations have shown advantages in reducing the number of administrations, improving patient compliance, and penetrating biological barriers. For example, sugar beet-derived extracellular vesicles can have an effect on skin fibroblast migration and gene expression profiles.[28] The potential for neointimal formation in vascular endothelial cells and the ability of fibroblasts to produce collagen I, collagen III, and hyaluronan synthase were increased by the intervention of sugar beet-derived extracellular vesicles.[50] Ultimately, it was shown that sugar beet-derived extracellular vesicles have antioxidant and necrotic tissue scavenging properties, and their may offer potential for skin repair and slowing down aging. In addition, combinations containing EVs from ginseng, pine leaf, and Salvia divinorum sources penetrate the skin to exert antioxidant activity, provide nutrients to hair-growing cells and stimulate hair follicle regeneration, which ultimately promotes hair regrowth.[78] In terms of wound-healing promotion, ginger-sourced EVs have been shown to promote intestinal wound recovery by affecting the expression of mitochondrial and cytoplasmic proteins. This may be due to the fact that ginger-derived EVs contain growth factors and proteins essential for the tissue

regeneration process, and the growth factors therein can be selectively delivered to target cells through these vesicles to promote cell proliferation and differentiation.[79] In summary, the anti-aging and regenerative and repairing functions of herbal preparations can also be expressed through the extracellular vesicles released from them, and the advantages of plant-derived extracellular vesicles, such as biological barrier permeability, non-alteration of the original tissue structure, and targeted drug release may be the research direction to replace the traditional Chinese medicinal preparations. In addition, extracellular vesicles selectively carry potent biomolecules such as proteins and nucleic acids, which is convenient to explore the mechanism of treating related diseases.

Value in Degenerative Diseases

Plant-derived EVs not only have pro-active components, but can also be used to deliver biomolecules such as RNA, DNA, and proteins in quantities far superior to those of synthetic nanoparticles and mammalian nanovesicles.[80] Plant-derived extracellular vesicles containing these biomolecules also play a role in the prevention and repair of degenerative diseases. Strawberry-derived EVs can be taken up and internalized by human mesenchymal stromal cells without cytotoxic effects, and the presence of bioactive constituents, such as flavonoids, phenolic acids, and carotenoids, produces a role in decreasing the risk of chronic aging and degenerative diseases.33 Expectantly, strawberry-derived EVs have been found to be rich in vitamin C, which, due to its pronounced antioxidant activity, shows potential value for anti aging showed potential value.[29] In another study, carrot-derived EVs could be used as a novel biomaterial with antioxidant function in cardiomyoblastoma and neuroblastoma cells. It was found that in cardiomyocytes and neuroblastoma cells, carrot-derived EVs also possessed antioxidant and anti-apoptotic effects.[81] In bone-related degenerative diseases, ginseng-derived extracellular nanovesicles maintained high bone marrow-derived macrophage viability and proliferative capacity while hindering osteoclastogenesis. In a mouse model of lipopolysaccharide-induced bone resorption ginseng-derived extracellular nanovesicles showed inhibitory effects on osteoclast differentiation, and the higher ratios of Rb1 and Rg1 ginsenosides they contained were more potent than Rb1 and Rg1 ginsenosides alone or in combination in inhibiting osteoclast differentiation.[75] Thus, ginseng-derived extracellular nanovesicles have the potential to be used in the clinical prevention and treatment of bone-loss diseases such as osteoporosis.[75] Interestingly, ginseng is also frequently used in the treatment of neurodegenerative diseases. Extracellular nanovesicles of ginseng origin may exert neuroprotective effects by maintaining homeostasis in vivo and participating in anti-inflammatory, antioxidant, and anti-apoptotic cell death. Thus, it may show great potential in the treatment of brain disorders such as stroke and Parkinson's disease.[82] In summary, extracting extracellular vesicles of the parental plant from its pre-existing properties for the treatment of degenerative diseases may be more beneficial for the treatment of the disease, at least in terms of the specific abilities of the extracellular vesicles such as the ability to target cells, the high biophilicity, and the weak activation of the immune indeed.

Potential of Extracellular Vesicles of Drug-Derived Plants as Nanocarriers

Finding the most suitable nanodrug carriers is one of the current hotspots in nanoparticle research, and plant-derived EVs have been used as natural nanotherapeutic drugs and nanocarriers (Figure 2), which are mainly considered for their better bioavailability, targeting, recombination, reparability, and penetration advantages. Natural nanoplatforms, as a natural and stable nanoscale drug delivery system, enhance the bioavailability of the loaded active compounds because the encapsulated flavonoids, polyphenols, RNAs, and proteins are free to pass through the gastrointestinal tract without degradation and because of the naturally occurring targeting ligands on their surfaces, the nanocarriers mediate the targeted delivery of the drugs to immune or tumor cells.[50] For example, the ginseng-derived EVs are an efficient nanoplatform that has successfully transferred 20 intravesicular miRNAs into bone marrow mesenchymal stem cells in in vivo experiments. With the formation of new blood vessels and improved wound healing, ginseng-derived EVs have been shown to transfer functional plant miRNAs into stem cells and to promote neural differentiation, development, and restoration of sensory functions.[82] More interestingly, in addition to the fact that plant-derived EVs themselves can be biologically engineered to achieve therapeutic capabilities for specific diseases, the lipids in the plant-derived EVs can be reconstituted into novel nanocarriers. For example, EVs isolated from ginger can be extracted and reassembled into nanoparticles. The assembled nanoparticles can be effectively loaded with adriamycin, and the assembled nanoparticles modified with folic acid can target delivery of adriamycin into tumors, enhancing the inhibitory effect on tumor growth.[54] It is well known that the major physiological barriers in the human body include the skin, mucous membranes, and

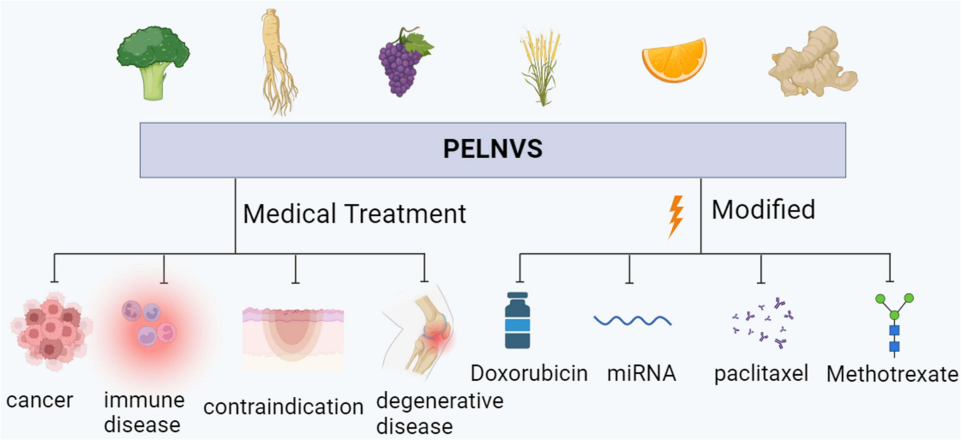

Figure 2 Plant-derived extracellular vesicles can be used to treat diseases directly or to treat specific diseases with modified modifications. Created with Biorender.com.

blood-brain barriers, which prevent most drugs from entering the diseased site thereby affecting the effectiveness of the drugs. Compared with traditional herbal compounds, these plant-derived nanocarriers can enhance biofilm drug transport via transcellular, paracellular, and carrier-mediated pathways, greatly improving the permeability of herbal medicines.[83] In conclusion, the carrier advantages exhibited by plant-derived nanovesicles may be one of the most promising targets for the selection of suitable nanocarriers at present, and it is foreseeable that in the future, the excellent carrier, the plant-derived extracellular vesicle, will be developed as a nano-delivery system with good stability, high transdermal permeation, and ease of use.

Challenges and Research Directions in the Clinical Use of Extracellular Vesicles from Drug-Derived Plants

Security Concerns

Currently, there is a lack of understanding of the target-specific mechanisms of applying vesicle surface drivers such as plant-derived EVs. The biosafety of plant extracellular vesicles remains a concern. Ideal drug delivery platforms should be guaranteed to be non-toxic, non-immunogenic and free of side effects both in vitro and in vivo.[57] Although some researchers have successfully used grapefruit-derived nanovesicles loaded with anticancer compounds[84] for targeting brain disorders, there are still reports that nanovesicle drug delivery strategies may cause potential biohazards such as stimulation of tumor proliferation.[85] In order to reduce the cost of nanomedicine drug delivery vectors and to make them more effective and safer in vivo and reduce accidental use, there is a clear need for new approaches and design principles in this field, especially to clarify the targeting mechanisms of nanovesicles. Compared to animal-derived nanoplatforms, plant-derived-based nanoplatforms exhibit the properties of being nontoxic, biocompatible, and able to be economically mass-produced. However, special attention needs to be paid to the fact that further studies on the immunogenicity or toxicity efficacy of plant extracellular vesicles are still crucial for their preclinical development. This is because in vitro and in vivo toxicity and safety assessments of plant EVs will help determine the dose for future clinical use. For example, in order to evaluate the toxicity of plant-derived EVs, some researchers used grapefruit-derived nanocarriers loaded with antitumor drugs to target tumor tissues, and observed whether significant damage occurred in vital organ tissues during the targeting process. It was found that less accumulation of carriers in the spleen and liver did not lead to large-scale vesicle lysis and release of antitumor drugs, which could minimize the systemic toxicity of antitumor drugs to normal tissues and also facilitate the blood diffusion of the drugs to reach the targeted targets. It was found that grapefruit-derived nanocarriers achieved antitumor effects and no significant damage was detected in the histological analysis of important human organs such as the heart, liver, spleen, lungs, or kidneys, and no long-term residuals were found in the experiments of individuals treated with phyto-nanovesicles.[86] In addition, no significant pathologic alterations were observed in histological samples of phytovesicles-treated livers, kidneys, spleens, and lungs.[86] This suggests that plant-

derived nanovesicles enhance drug efficacy and reduce the potential toxicity of the drugs.[79] Therefore, compared to animal-derived extracellular vesicles, plant extracellular vesicles may be more suitable as materials for the large-scale preparation of targeted nanocarriers.

Choice of Route of Administration

The first aspect of plant-derived nanomaterials used in the clinic that needs to be faced is the selection of the nano-delivery route, and the selection of the appropriate route will likely provide significant nanocarrier properties and disease therapeutic efficacy. It has been found that plant-derived extracellular vesicles, when applied to the skin, can achieve drug delivery directly by penetrating the hair follicle-rich fat layer.[87] In addition, the trans-annexal route is also a good route, whereby plant-derived extracellular vesicles are absorbed through the hair follicles, sebaceous glands, and sweat glands.[88] Both modalities allow the drug to reach the hair shaft.[89] In contrast to other transdermal agents, plant-derived extracellular vesicles are cost-effective, stable, permeable, and immunogenic, advantages of low cost, high stability, good permeability and low immunogenicity. In particular, plant-derived extracellular vesicles can be used as effective carriers for transdermal drugs, providing an effective solution for transdermal delivery of drugs.[80] Therefore, the clinical use of plant-derived extracellular vesicles can be realized by transdermal drug delivery. Currently, plant-derived extracellular vesicles are also well studied as an excellent drug carrier for oral drug delivery and intravenous targeted delivery. In vivo experiments have shown that plant-derived extracellular vesicles have achieved good therapeutic effects on breast tumors whether administered intravenously or orally. However, it should be noted that intravenous administration still produced more pronounced liver and kidney toxicity and immune activation effects.[90] In contrast, oral administration of plant-derived extracellular vesicles caused no detectable toxicity to healthy organs, and this treatment did not induce activation of the immune system. Overall, the oral route is better adapted to plant-derived nanovesicle drug carriers for the treatment of breast cancer. Intraperitoneal titration of plant-derived extracellular vesicles can also be efficiently transported to tumor tissues and preferentially taken up by intra-tumor macrophages, leading to an immunocidal effect on tumor cells without exhibiting significant organ toxicity.[49,58,91] In addition, a number of studies on liposomal routes of drug delivery are also informative, such as the aerosolization route of liposomes to protect their volatile and unstable components (eg, volatile oils), it is difficult to avoid the non-volatilization of plant nanovesicles into the air due to their nanoscale size, whereas nebulized sprays with the help of nasal and pulmonary mucosal interstitiality may be more conducive to nanomedicine uptake and blood spreading. Liposomal nanoemulsions are also a good way of drug delivery, and nanoemulsions of plant-derived extracellular vesicles will have good surface activity and thermodynamic stability, which can reduce the probability of adverse reactions and improve skin permeability and patient compliance through transdermal systems.[92–94] In summary, exploring the in vivo routes of administration of plant-derived extracellular vesicles and selecting modalities with high bioavailability and low biohazard still requires sufficient research. Of course, this may be closely related to different plant-derived vesicles and disease types.

Dilemma of Separation and Extraction Methods

Since the biological mechanism of extracellular vesicle formation in most plant sources remains unknown. How to obtain relatively pure and stable extracellular vesicles has been a primary problem for researchers. Currently, extraction methods such as differential ultracentrifugation, density gradient centrifugation, ultrafiltration, magnetic bead sorting (immunoaffinity method), polymer precipitation, and size exclusion chromatography have been used for the extraction of plant-derived extracellular vesicles. However, these methods still face problems such as high content of non-vesicular nanoparticles, low extraction efficiency and inability to properly separate vesicles.[44] For example, ultracentrifugation of plant sap is still the main method to isolate plant extracellular vesicles, but its extraction efficiency is low.[44] Sucrose density gradient centrifugation of plant exosomes can be used to separate exosomes by taking advantage of the difference in size and density of vesicles and other species. Although the method is well established and inexpensive and can be used for high volume production. However, it is cumbersome and time consuming and the vesicles can be damaged in large numbers. Ultrafiltration uses an ultrafiltration membrane to separate vesicles from biomolecules. This method is simple and does not require special equipment or reagents. However, the ultrafiltration process is prone to the loss of small-sized vesicles, clogging of the membrane, and damage to vesicles caused by extrusion.[95] Magnetic bead sorting (immunoaffinity) is based on the affinity between antibodies and membrane proteins on the surface of the vesicles to separate specific vesicle subtypes, and has a high degree of specificity and purity for the extraction of specific vesicles,

but this method is also facing the problem of high cost, harsh conditions, and the loss of targeting properties (loss of targeting proteins) of the exocysts separated. However, this method also faces the problems of high cost, harsh conditions, loss of targeting of isolated exosomes (loss of targeting proteins), and low extraction quantities.[96] Polymer precipitation refers to the use of highly hydrophilic polymers, such as polyethylene glycol, to reduce vesicle solubility or dispersion, which is the main method used in most commercial kits. This method is simple and suitable for extraction of large samples, but there are potential contaminants such as the presence of highly hydrophilic polymers and vesicle-like impurities leading to a decrease in the purity of the extraction.[97] Size exclusion chromatography is a technique that separates vesicles based on the varying sizes and molecular weights of the particles. This method is simple, economical, has high separation purity, and largely preserves the biological function and structure of the vesicles, but it is not inexpensive (separation injection and addition of separating solution), and there is the possibility of membrane protein contamination.[98] In recent years, microfluidics has been gaining attention for the separation of vesicles with high sensitivity and speed based on differences in the biochemical and physical properties of the vesicles, but the method is still faced with low throughput and is only suitable for diagnostics where the characteristics are not yet well characterized. However, the current method still faces the problems of low yield and is only applicable to diagnostic properties and cannot be applied to extract plant vesicles on a large scale.[99] Therefore, optimizing the extraction process to improve the efficiency of vesicle acquisition is urgent. In addition, an intact plant contains a large number of nanovesicle subpopulations in different parts of the plant with different structures and functions, and extracellular vesicles originating from different species have even more diverse compositions.[53] This high degree of heterogeneity makes it difficult to obtain homogeneous plant extracellular vesicles, which also severely limits the industrialized production of plant extracellular vesicles. Therefore, it is necessary to conduct a comprehensive and systematic study of the membrane composition, stability, and biocompatibility of specific plant-derived extracellular vesicles, as well as the biodistribution characteristics of the contained biomolecules and other parameters. Currently, plant-derived extracellular vesicles have demonstrated excellent biosafety and therapeutic efficacy in disease treatment, but the medical translation of vesicles is still limited by low yields and difficult storage. Therefore, the development of new technologies to produce and store them on a large scale remains the greatest resistance to the use of plant vesicles in the clinic.[50]

The Challenge of Increasing Drug Loading and Targeting Capabilities

Although the study of plant-derived extracellular vesicles is not comprehensive enough, their good biocompatibility as well as the advantages of being widely available, inexpensive, and easy to obtain are considered to be a bio-nanomaterial with great potential for development.[22] This will require large-scale, multicenter, randomized controlled trials to validate the application of herbal nanomedicines in clinical practice. Of course, the first thing that needs to be considered is the drug loading capacity and targeting ability of plant-derived extracellular vesicles. Excellent loading capacity is more helpful to reduce the biohazardousness as well as the cost of vesicles, while targeting ability is the most important indicator to be concerned about in selecting suitable plant-derived vesicles. Since different plants or even different parts or tissues of the same plant bring about different types of vesicles, their targeting ability is likely to be different as well, and it is very important to study the types of surface targeting proteins and their targeting mechanism of a specific plant's extracellular vesicles before they are used in the clinic. It is essential to study the types of surface targeting proteins of specific plant extracellular vesicles and their targeting mechanisms before their use in the clinic. In addition, the efficacy of nanoparticles relying on passive targeting strategies on infarcted myocardial tissues may be limited in elderly patients with poor hemodynamics or cardiovascular disease, where blood supply is poor due to slowing of vesicle entry and other factors. Future studies should focus on exploring the mechanisms of active targeting strategies to identify new targets and ligands that can enhance drug targeting and therapeutic effects.[100] Due to the synergistic effect of co-administration of different herbal components with a lower single dose and safer treatment, this is similar to the compound prescription of traditional Chinese medicine. Therefore, whether plant-derived nanovesicles can achieve the therapeutic effect of Chinese medicine prescription by loading different drugs or the combined action of multiple plant vesicles is awaiting further investigation.

Conclusion and Future Directions

Components of Chinese medicines are complex, and research on active ingredients of Chinese medicines and their mechanisms of action should be strengthened to achieve rational use of medicines and to enrich the theoretical basis for the clinical use of Chinese medicines. In order to promote the use of Chinese medicines, we should first focus on practice and mechanism research, truly study the mechanism of action of Chinese medicines from a biological perspective, and establish a unified quantitative system before the science of Chinese medicines can usher in a new situation.[15] There is no doubt that Chinese medicines have been successfully applied to the prevention and treatment of a wide range of diseases, and they have an irreplaceable role in rehabilitation and health care. However, the shortcomings of traditional Chinese medicine, such as poor single drug delivery, low water solubility, low bioavailability, and weak targeting, have greatly limited the clinical application of traditional Chinese medicine, and the extraction of plant extracellular vesicles from traditional Chinese medicine to generate medicinal value not only in the activity, bioavailability, and targeting to fully change the current shortcomings of traditional Chinese medicine, but also its easy to molecular mechanism research and potential new therapeutic effects and other characteristics will greatly change the current status quo of traditional Chinese medicine.

In recent years, nanovesicles have been widely used to address drug bioavailability barriers due to their large surface area, strong targeting ability, and slow release. This is because of their ability to cross biological barriers, enhance drug metabolism and utilization, and reduce the biotoxic side effects of artificial liposomes. In addition, plant-derived extracellular vesicles can be chemically modified to incorporate implanted targeting ligands to achieve targeted drug delivery with precision. Certainly, their ability to transport medicinal plant-derived biomolecules (ie, proteins, lipids, and nucleic acids) into animal cells would make them a favorable tool for disease recovery and healthcare. However, there is still a need to consider issues such as extraction and storage techniques for plant vesicles, practical efficacy in disease treatment, and biosafety.[101,102] A variety of measures have been considered to minimize factors affecting the utilization of vesicles, including the selection of the source of the vesicles, the method of vesicle extraction and purification, and the routes of storage and administration.[102] Currently, in particular, the selection of the vesicles and the biomolecules within the vesicles, the vesicle-generating process, the specific functions, and uptake modes are still unknown due to the fact that there are few specifically labeled proteins for plant-derived extracellular vesicles, the biological characterization of vesicles still requires sufficient complementary studies as surface markers and other characteristic elements of plant vesicles are still uncertain, and the use of high fluorescence microscopy may improve the understanding of the biogenesis, uptake, and surface protein composition of plant-derived extracellular vesicles.[103] In terms of isolation, the results of vesicles obtained in various studies are usually confounded by a number of factors, such as the type of plant, the site, the physiological state, and the isolation technique varies.

A variety of disease therapeutic drugs can be made more bioavailable by loading them into modifiable plant vesicles.[104] It has been found that one way in which plants defend themselves against pathogenic microorganisms is that anti-microbial active secondary metabolites are included in plant nanovesicles, resulting in a substantial increase in the bioavailability of the secondary and metabolic molecules.[105] It is reasonable to imagine that a number of pests predominantly infect specific plants or families of plants, and that those plants not being infected plants exhibit insect resistance, not only the cargo of the vesicles is actively modified, but also the envelope of the vesicle surface is altered to be as effective as possible against these pests in preventing infection.[105] Obviously, current research suggests that plant nanovesicles do not yet exhibit any toxicity or immunogenic effects.[105] This is the greatest advantage of the current use of plant extracellular vesicles in in vivo drug research; however, for the human drug use of plant nanovesicles, there is little information about their toxicity and immunogenicity, or about their bioavailability in humans. However, not enough is known about the properties of plant nanovesicles for human drug use. The production of adequate, stable, and safe plant nanovesicles for drug delivery, either by themselves or for drug delivery, still requires further enhancement of nanotechnology. In addition, understanding the metabolic pathways of plant vesicles in vivo is crucial for their safe use, and challenges remain to reduce the risk of systemic toxicity of vesicles, remove excess vesicles efficiently and rapidly, and stabilize the vesicular drug carrier system.[100] Just as single drugs in TCM formulas are ineffective, the therapeutic effect of nanoparticles loaded with single TCM actives is limited, and the combined use of vesicular particles with TCM actives may accelerate their interaction with each other applied in combination may accelerate their interactions and increase drug toxicity. Further studies should focus on the implantation of

multiple TCM active substances into a particular nanovesicle system to provide new avenues for the development of nano-pathways for TCM formulations.

As a result, we can consider the following aspects for the further study of extracellular vesicles extracted from Chinese herbs: 1) The efficacy of the extracted extracellular vesicles varies due to the different parts of the plant, which may need to be fixed to the part of the extracted vesicles and to find the most efficacious part to be investigated. 2) As the value of the precious Chinese herbs is gradually rising due to their unique efficacy, it may help to change the current situation of difficulties in obtaining precious Chinese herbs, if the molecules inside the vesicle are probed and implanted into the cheap plant vesicles and targeted to the organs. 3) There exists obvious sameness in the anti-cancer of Chinese medicines resulting in different efficacy from person to person, and most of the current Chinese medicines exist to improve the complications of anti-cancer drugs. If the anti-cancer mechanism can be elucidated from the extracellular vesicles of Chinese medicines, it will help to discover new anti-cancer molecules and improve the cancer cure rate.4) In fact, Chinese herbal medicine is a product of herbal processing, and it is still unknown whether the extracellular vesicles extracted from active plants can reproduce their therapeutic effects. 5) Whether the combined use of plant extracellular vesicles can achieve the efficacy of Chinese herbal medicine still needs to be proved, and it is still unknown whether the combined use of plant extracellular vesicles will lead to immune storms or aggravate the damage to the organs of Chinese herbal medicine. 6) Whether orally administered plant extracellular vesicles can achieve the efficacy of orally administered herbal medicines remains to be confirmed. 7) The current extraction and purification technology of plant extracellular vesicles is very complicated and expensive, while some Chinese herbal medicines are taken from the whole plant. Therefore, it may be interesting to see whether the extracellular vesicles of specific herbal sources can be extracted in a crude way to reduce the cost. In conclusion, the extraction of plant extracellular vesicles from herbal medicines will likely change the status quo of TCM in the global healthcare industry, which will also make it possible for TCM to fight cancer and be accepted internationally.

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