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Food-derived exosomes: a revolutionary novel breakthrough in dietary nutrition and health

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ABSTRACT: Exosomes, small molecules with phospholipid bilayer structures derived from cell membranes, usually contain many biomacromolecules, such as proteins, mRNAs, and miRNAs. Exosomes have been verified to be among the most important mediators of material and information exchange within or between individuals. In recent decades, exosomes have attracted increasing attention from researchers. In this review, the structure, methods of separation and identification, and cell origination of exosomes are described in detail. The potential applications of exosomes, such as anti-inflammatory and immunomodulatory effects, tissue damage repair and regeneration, antioxidant function, drug delivery, and cancer therapy, are summarized. Food-derived exosomes from animals, plants and microorganisms have become a research hotspot. Exosomes carrying biomacromolecules are important mediators of signal transduction and regulation between cells from the same individual and between individuals of the same or different species. It is widely considered a promising intermediate for food nutrition and chronic disease prevention.

Keywords: Exosome; food source; isolation; identification; chronic disease prevention

1. Introduction

In 1987, Rose M. Johnstone harvested vesicles released from *in vitro* cultured sheep reticulocytes by centrifugation at 100,000 × g for 90 min, which has many of the characteristics of reticulocyte plasma membranes, and named these vesicles "exosomes" for the first time [1] . However, at the time, vesicle externalization was only thought to be a mechanism for reducing erythrocyte maturation; thus, exosomes have not received much attention, and in recent years, studies on exocytosis have demonstrated their potential for intercellular communication as well as for disease treatment [2]. Exosomes, which are extracellular vesicles with a diameter of 30–100 nm, consist of a lipid bilayer encompassing various components, such as nucleic acids, proteins, and lipids, that mediate intercellular communication and exchange by delivering these components to target cells [3]. Exosomes can transfer containing substances such as miRNAs, into recipient cells, leading to biological changes in the recipient cells that mediate communication between different species [4]. Plant-derived exosomes contribute to altering microbiome composition and host physiology; e.g.,

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ginger-derived exosomes in the gut, which contain microRNAs that target the *Lactobacillus rhamnosus* genes, are preferentially absorbed by *Lactobacillaceae* and regulate the host intestinal inflammatory response [5]. Exosomes can be secreted by almost all cells under either normal or pathological conditions and are widely and stably present in biological fluids, such as amniotic fluid, blood, breast milk, urine, and saliva. The stability of exosomes from cells cultured *in vitro* depends mainly on the membrane proteins they carry. Exosomes from food sources such as fruits, vegetables, and foods of animal origin have been successfully isolated, which include milk from animal-based food sources and fruits and vegetables from plant-based food sources, such as grapes, lemons, apples, and carrots. They are similar in size and morphology to those from mammals, yielding positive effects in the prevention and treatment of various chronic diseases—e.g., exosomes from yam sources have been used to prevent osteoporosis in mice [6]. Milk-derived exosomes play a regulatory role in inflammatory and immune responses, contributing positively to the mitigation of intestinal inflammation and the promotion of skin tissue repair. Furthermore, they serve as excellent delivery vehicles for anticancer drugs, demonstrating notable gastrointestinal stability and targeted delivery capabilities. Exosomes obtained from fruits and vegetables generally display strong anti-inflammatory properties. They exert therapeutic effects in various diseases, including colitis, through mechanisms such as downregulating inflammatory factors, suppressing inflammasome activation, and inducing macrophage polarization. Additionally, exosomes derived from strawberries, ginseng, and aloe vera exhibit antioxidant functions, which help counteract oxidative stress and other age-related physiological declines. Proteins carried by most exosomes include members of the transmembrane protein 4 superfamily (TM4SF, CD9, CD63, CD81, and CD82), the Ras-related protein GTPase Rab, heat shock proteins, and integrins, all of which can be used as reliable markers for exosome identification [2]. The substances carried by exosomes depend on the characteristics of the originating cells and the pathological state, and the identification of these specific components can be used to identify exosomes and markers for disease diagnosis. For example, by sequencing and mass spectrometry of exosome contents, tumor progression can be revealed at the molecular level [7].

2. Exosomes biogenesis

Exosomes are usually formed via invagination of the cell plasma membrane. First the plasma membrane invaginates to form early endosomes, and some early endosomes integrate into the surrounding layers to generate intraluminal vesicles (ILVs) that encapsulate exosomes in intracellular multivesicular bodies (MVBs), which subsequently fuse with the cytoplasmic membrane to secrete exosomes into the extracellular space [8]. The endosomal sorting complex required for transport (ESCRT) mechanism is the most widely described pathway for the biogenesis of MVBs [9]. ESCRT is divided into four complexes named ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III, which interact with intracellularly associated proteins to produce MVBs. The ESCRT-I complex is responsible for cargo sorting and induces germination through the deformed plasma membrane. ESCRT-I subsequently activates ESCRT-III, which is responsible for the concentration of MVB cargo molecules via the ESCRT-II complex, and the ESCRT-III complex triggers contraction and induces vesicle budding to divide during abscission [10]. The MVB pathway is shared by mammalian- or

plant-derived exosomes, and in plants there are also exocyst-positive organelles (EXPOs), which can fuse with the plasma membrane, leading to their release outside of membrane vesicles.

3. Classification of exosomes

Exosomes are generally divided into naturally derived, modified, and synthetic exosomes. Exosomes of natural origin include exosomes derived from animals and plants, which can be directly isolated from animal body fluids or fruits and vegetables without artificial modifications. Modified exosomes are artificial natural exosomes modified by surface or genetic engineering to increase the effectiveness of therapeutic targeted delivery, drug loading and other functions. Synthetic exosomes are synthesized via cell synthesis methods or lipid membrane construction methods to synthesize artificial exosomes with natural exosome characteristics, which overcomes the shortcomings of the low yield and slow production speed of natural exosomes [11].

3.1. Naturally derived exosomes

Naturally derived exosomes include animal-derived, plant-derived, and bacterial-derived, and the similarities and difference of exosomes from different sources are shown in Table 1.

Table 1 The similarities and differences of exosomes derived from different origins

Origin	Main structure	Signature membrane components	Contents
Animal-derived exosomes	Phospholipid bilayer membrane [22]	CD9, CD63, CD81 and cholesterol [22]	Animal miRNA, Cytokine [22]
Plant-derived exosomes	Phospholipid bilayer membrane [23]	phospholipid acid (PA), phytosterols [23]	Plant miRNA, Antigen [23]
Bacterial outer membrane vesicle	Phospholipid bilayer membrane (contains LPS) [24]	Lipopolysaccharide, Outer membrane protein (OMPS) [24]	Bacterial DNA, Toxins [24]

3.1.1 Animal-derived exosomes

Since researchers isolated exosomes from sheep reticulocytes in1987, the properties and biological activities of mammalian cell-derived exosomes have been explored. Exosomes of animal origin are derived primarily from biological fluids such as saliva, plasma, urine, and milk (Figure 1). Exosomes can inherit specific biomacromolecules from parental cells and exhibit heterogeneity [2]. Several types of cells including tumor cells, mesenchymal stem cells, dendritic cells, macrophages, epithelial cells, and many immune cells spontaneously produce exosomes [3]. Macrophages are monocytes widely distributed in the body that can polarize into M1 or M2 cells and play important roles in regulating immunity, inflammation, and wound healing. Exosomes derived from macrophages mediate communication between macrophages and other structural cells. Mesenchymal stem cell (MSC)-derived exosomes regulate various chronic diseases; for example, they can promote cell proliferation, migration and wound healing by mediating Wnt4 signaling [12]. In addition, MSC-derived exosomes increase intracellular ATP levels, reduce oxidative stress and activate the Akt pathway, which subsequently reduces local inflammation and infarct size in mice and plays a positive role in preventing myocardial ischemia [13]. In general, the production, content, and function of exosomes from different animal sources differ; therefore, they have multiple biological effects.

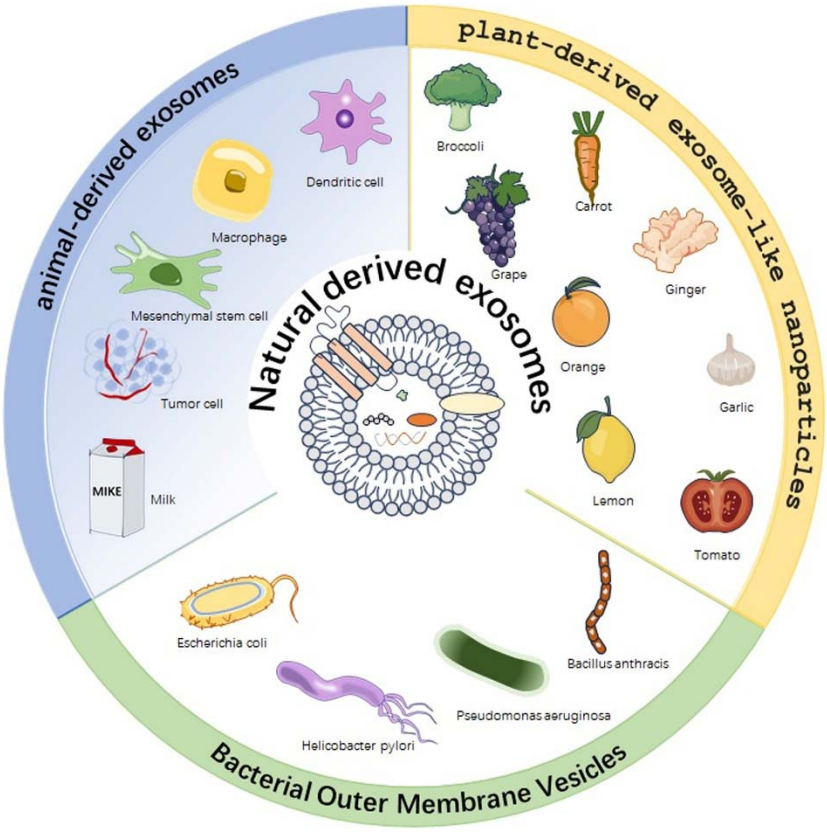

Figure 1 Schematic representation of natural derived exosomes
Natural derived exosomes categorized into animal-derived exosomes (including dendritic cell, macrophage, mesenchymal stem cell, tumor cell, and milk), plant-derived exosome-like nanoparticles (such as broccoli, carrot, grape, ginger, orange, garlic, lemon, and tomato), and bacterial outer membrane vesicles (including *Escherichia coli*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, and *Helicobacter pylori*).

3.1.2 Plant-derived exosomes

Exosomes derived from plants, including grapes, lemons, cauliflower, carrots, and apples, are similar to animal-derived exosomes in size, morphology and composition (Figure 1). Edible plant-derived exosome-like nanoparticles have bioactivity or pharmacological functions similar to those of the original plants. However, owing to their nanosize, they have increased bioavailability and barrier permeability and exert anti-inflammatory and immunomodulatory functions in various diseases, including colitis and cancer [14]. Plant-derived exosomes also allow interspecies communication with animal intestinal host cells [15]. Grape-derived exosomes target intestinal stem cells to protect mice from dextran sulfate (DSS)-induced colitis and induce the recovery of intestinal stem cells in a Wnt/β-catenin signaling pathway-dependent manner [16]. Ginger-derived exosome-like nanoparticles carrying shogaol can be targeted for delivery to hepatocytes and protect mice against alcohol-induced liver injury [17]. Owing to their excellent gastrointestinal stability, high cellular uptake, low immunogenicity, and targeting ability, plant-derived exosome-like nanoparticles are also promising delivery carriers for the functional ingredients of drugs and foods. The lipid bilayer of exosomes protects the encapsulated ingredients from being broken down by proteases and nucleases [18]. In summary, plant-derived exosome-like nanoparticles are rarely cytotoxic, do not carry pathogens, are mass produced, and thus have great potential in the biomedical field.

3.1.3 Bacterial outer membrane vesicle

Bacterial outer membrane vesicles (OMVs) are typically secreted by gram-negative bacteria and have structural features similar to those of exosomes (Figure 1), with a lipid bilayer structure containing bacterial antigens, proteins, and pathogen-associated molecular patterns (PAMPs). This specific structure with spherical, double-membrane nanostructures stimulates the body to generate an immune response, making it an excellent vehicle for drug delivery [19]. Studies have shown that virtually all gram-negative bacteria, some gram-positive bacteria, and several archaea, such as *Escherichia coli*, *Helicobacter pylori*, *Pseudomonas aeruginosa*, and *Bacillus anthracis*, can naturally secrete OMVs [19]. Escherichia coli-derived OMVs can aggravate liver cirrhosis in mice and humans by inducing inflammation and fibrosis and inhibiting albumin production [20]. Bacterial-derived OMVs carry antigens of parental bacterial origin and act on target cells to stimulate an antigen-specific immune response via the uptake of antigens by target cells and presentation to antigen-presenting cells (APCs) for further uptake [21]. Therefore, OMVs have emerged as crucial mediators of pathogen-host interactions.

3.2 Modified exosomes

Some naturally derived exosomes from mammalian cells or vegetables and fruits, can be surface modified to improve their drug load, targeted delivery, and biodistribution. In general, the modification of exosomes involvs two different pathways: internal modification (changing the composition of the exosome) and external modification (changing the surface of the exosome) [22]. Cell engineering technology is well used in modifying exosomes, as it introduces some unnatural substances into cells, which subsequently easily enter exosomes [23]. Genetic engineering is a very mature technology that involves loading recombinant protein and mRNA into exosomes, translating them into recipient cells in the ischemic region, and effectively reducing ischemic injury [24]. In addition, the targeting ability of exosomes can be improved by modification, which has great clinical value.

3.3 Synthetic exosomes

Synthetic exosomes are based on the bionic synthesis of exosome mimics that have natural key components, similar morphologies and functions to those of exosomes, but with higher yields and easier mass production [11]. Synthetic exosomes are based on two approaches. One approach is a top-down approach in which larger, more complex units are broken down into smaller parts to produce nanomaterials; that is, cultured cells are used as a source of membranes to produce vesicles. The other is a bottom-up approach that uses physical and chemical properties at the molecular level to create complex structures [25]. In a top-down approach, cultured drug-loaded cells are continuously extruded through a series of polycarbonate membranes with different pore sizes, which not only overcomes the drawbacks of low yields of mammalian exosomes and the complexity of purification, but also proves to be effective in delivering chemotherapeutic agents for the treatment of malignant tumors [26]. One study used polycarbonate membranes to make tiny filters through which live embryonic stem cells are passaged to generate exosome mimics to improve the ability of cells to proliferate [27]. A microfluidic system has been proposed to generate nanovesicles (NVs) by cutting living cell

membranes with micromachined 500-nm-thick silicon nitride (SixNy) blades, which can encapsulate exogenous substances and deliver them to recipient cells [28]. The bottom-up technique is based on the construction of liposomes, where specific lipids are doped into a lipid formulation and then specific proteins, antibodies, and peptides are selected to functionalize the liposomes. The bionic vesicles generated by incorporating proteins from the leukocyte plasma membrane into lipid nanoparticles efficiently delivered dexamethasone to inflamed tissues, reducing the incidence of local inflammation in the chemosarcoma [29].

3.4. Comparison of exosomes from different sources

Exosomes derived from natural sources are biologically produced and contain native proteins, lipids, nucleic acids, and metabolites, endowing them with diverse and intricate biological functions [30]. Modified exosomes are engineered from natural exosomes by incorporating specific functional molecules such as targeting peptides or therapeutic RNAs [22]. In contrast, synthetic exosome mimics feature relatively simple compositions, typically comprising a limited set of designed polymers and functional moleculesb [31]. In targeted applications, the specificity of natural exosomes is inherently determined by their parent cells, which may result in limited targeting accuracy. To enhance precision, surface modifications can be applied to natural exosomes. Artificially synthesized exosomes, on the other hand, allow precise control through designed surface ligands. Regarding scalability, natural exosome production is often constrained by low cellular yield and complex extraction processes, posing challenges for large-scale manufacturing. However, certain plant-derived exosomes offer higher yields and are more amenable to mass production. Modified exosomes require additional engineering steps post-extraction, further complicating their production. Synthetic exosomes benefit from simpler, well-defined compositions, facilitating standardized and scalable fabrication.

Natural exosomes provide a valuable platform for basic research and serve as innate therapeutic agents, especially those derived from plants, which exhibit low immunogenicity and scalability. Modified exosomes combine the biological advantages of natural exosomes with the capacity for precise disease targeting and therapeutic modulation. Synthetic exosomes are particularly suitable for standardized large-scale production, overcoming the variability and yield limitations associated with natural sources.

4. Isolation and purification of exosomes

As exosomes are currently used in biomedicine on a large scale, there is an urgent need for an efficient, convenient and rapid extraction method to isolate and purify them, and the currently known exosome extraction methods have their own characteristics and limitations. Methods employed to isolate exosomes include centrifugation, size-based techniques (ultrafiltration and volumetric exclusion chromatography), capture-based techniques (magnetic beads and immunoaffinity), polymer-based techniques (commercial kits), and microfluidic-based techniques (microfluidic separations).

4.1. Centrifugation

Depending on the principle of separation of the mixture and mode of operation, centrifugation can be divided into density gradient centrifugation and differential centrifugation. Density gradient centrifugation is

considered the "gold standard" in the separation and extraction of exosomes [32]. By adjusting the centrifugal force and centrifugation time, exosomes are separated from other components of different densities and sizes. Density gradient centrifugation allows for the extraction of exosomes from various samples, such as plasma, urine, saliva and cell supernatants [33]. Differential centrifugation separates components with different densities by adjusting the rotational speed and is suitable for separating components with large density differences, whereas density gradient centrifugation is suitable for separating components with small density differences. When differential centrifugation is used to separate exosomes, more time and effort are needed during operation because of the sequential nature of the separation stages. For example, in separating milk-derived exosomes, low-speed and high-speed centrifugation need to be used sequentially, with floating fats and proteins being removed during low-speed centrifugation and with cellular debris and free proteins being removed during the high-speed stage, when the milk exosomes can be deposited at the bottom of the centrifuge tube [34]. For exosome extraction from plant sources, the plant fruits are usually cleaned and ground first, and the homogenate or juice is centrifuged at a series of different speeds. Differential centrifugation alone can contaminate residual proteins, and density gradient centrifugation is usually used after differential centrifugation to further purify the samples; e.g., tomato exosomes are extracted with a sequential sucrose gradient of 8–45%. The centrifugation conditions such as speed and time should be set and optimized according to different sample objectives [35]. The production of exosomes by centrifugation is simple, but the process is cumbersome and time-consuming and requires expensive centrifugation equipment, and some exosomes may be destroyed during high-speed centrifugation, which affects the final yield of exosomes.

4.2 Size-based technologies

The main size-based techniques for separating exosomes include ultrafiltration and size exclusion chromatography. In conventional membrane filtration, separating suspended particles or polymers are depends primarily on their size or molecular weights. Therefore, depending on the size of the exosomes, membrane filters with defined molecular weights or size exclusion limits can be used to separate the exosomes [36]. A filter with a pore size larger than the size of the exosomes is first used to remove impurities and large particles, such as cellular debris, from the filtrate, resulting in a relative enrichment of exosomes. A filter membrane with a pore size smaller than the size of the exosomes was subsequently used to remove small vesicles from the filtrate, and the purity of the resulting exosomes was further increased. Exosomes of the desired size range can be obtained after several filtrations [37]. Ultrafiltration techniques do not require complex and expensive equipment and are simple to perform. However, the yield and purity of the obtained exosomes were lower than those obtained via centrifugation, which may be due to the interaction between the vesicles and the membrane, which produces aggregates that block the pores of the membrane. Exosomes isolated from urine using ultrafiltration contain relatively small amounts of microRNA and mRNA, indicating that ultrafiltration is not as pure as other methods for isolating exosomes [38]. Size exclusion chromatography (SEC), also known as gel chromatography, uses molecular sieves to make molecules of different sizes and quantities, depending on the exclusion ability of each component, to separate the components. Compounds

with small molecular weight can enter gel pores and have long residence times, whereas compounds with large molecular weights cannot pass through pores and directly flow out with the mobile phase [39]. Therefore, separating exosomes by size and morphology is fast and reliable.

4.3 Capture-based technologies

Capture-based techniques usually use immunoaffinity chromatography, which is a method of separation that utilizes the highly specific affinity between antigens and antibodies present in the organism. In mammalian cell-derived exosomes, four transmembrane proteins, such as CD9, CD63, and CD81, are often considered protein markers on the surface of exosomes, and labeling antibodies to these specific proteins on magnetic beads allows the selective isolation of exosomes [40]. A magnetic bead-based ion exchange platform has been investigated, in which cationic polymers are coated on magnetic beads, which can attract negatively charged exosomes well and can be subsequently processed by steps such as elution, which can separate the exosomes well [41]. However, techniques based on highly specific capture have several limitations for exosome extraction from plant sources, as no clear surface markers have been established for exosomes from different sources; therefore, this method has not been applied on a large scale in plant exosome extraction.

4.4 Polymer-based technologies

Polymer precipitation technology is an effective method to separate exosomes from biological fluids by reducing their solubility. Polyethylene glycol (PEG) precipitation is based on the competitive binding of water molecules to separate exosomes from solution. PEG6000 is used to isolate exosome-like nanoparticles from ginger and is coat effective because it results in 60–90% more exosomes than centrifugation methods and dose not require expensive centrifugation equipment [42]. However, this precipitation method requires longer incubation times (usually 12 to 16 hours) and results in lower purity and quality when proteins and particles have similar solubilities to those of exosomes [43]. In addition, the polymer precipitation-based Exo Quick system can be employed to isolate ginseng-derived exosomes by mixing the Exo Quick solution with the crude ginseng extract, incubating overnight at 4°C, and centrifuging at 1,500 × g for 30 min at 4°C after incubation, followed by resuspension of the resulting exosome precipitate in 100 μL of PBS buffer [44].

4.5 Other methods

Microfluidics, also referred to as microfluidic chip technology or Lab-on-a-Chip, is a technology for the precise control and manipulation of microscale fluids and allows for the integration of exosome isolation and detection functionality into a single chip. It has the advantages of throughput isolation, high purity and recovery, as well as high speed, sensitivity, specificity, and low detection limits [45]. A microfluidic immunoaffinity method has been proposed that uses a small amount of sample to isolate exosomes from a small amount of serum in a blood sample, resulting in the extraction of high-quality RNA that provides a source of genetic information of a tumor as a biomarker for cancer diagnosis and prognosis [46]. In addition, many commercial kits are available for exosome isolation. A device called Exosome-Total-Isolation-Chip

(Exo TIC) is a size-based isolation device that provides higher yields and purities of exosomes than methods based on sedimentation and centrifugation.

5. Identification of exosomes

Exosomes obtained by isolation and purification can be identified based on morphology, size, marker protein content, liposomes and so on. It is usually necessary to test exosome morphology, particle size, surface markers, and comprehensive data to determine whether purified exosomes have been obtained.

5.1. Morphological evaluation

Exosomes have a circular morphological structure, and owing to their small average size, we can visualize them morphologically using electron microscopy. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), cryo-electron microscopy (cryo-EM) and atomic force microscopy (AFM) are usually employed to characterize the microstructure of exosomes. SEM uses a focused high-energy electron beam to irradiate a sample to produce various physical information and then magnifies the image to restore the sample morphology characteristics. SEM and confocal microscopy have been used to characterize exosome morphology, exosome uptake and translocation [47]. TEM is a commonly used method for morphological characterization in exosome studies [48]. The principle is to accelerate the electron beam transmitted to the sample to be observed, so that the electron collision with the sample of atoms generated scattering angle, different samples of different densities, and different thicknesses, resulting in different scattering angles, which can lead to different scenes of light and dark. Transmission electron microscopy has high resolution and can be used to identify the size and shape of exosomes. Cryo-EM is a method that uses sample freezing, low-dose electron tomography and three-dimensional reconstruction to resolve the electron microphase of macromolecular biological samples with improved resolution and quality, and it eliminates the dehydration and fixation steps of the sample. AFM, an advanced microscopy technique that detects the very weak interatomic interaction forces between the surface of a sample, is used to study the surface structure and properties of substances [49]. It can keep a sample in its natural state for measurement, which reduces the number of steps in the preparation of the sample and is well suited for observing the exosome morphology.

5.2 Size identification

Nanoparticle tracking analysis (NTA) and dynamic light scattering (DLS) are two common methods used for detecting particle distributions in suspensions. NTA has become a popular particle detection technique in recent years, and its detection accuracy is better than that of general dynamic light scattering, as well as its wide range of test characteristic. The methods can measure the average particle size, median size, particle concentration, particle Brownian trajectory, and so on. In the measurement of exosomes, NTA can be used to collect and analyze average particle size and distribution data [50]. Samples containing spherical particles usually act in solution in the form of Brownian motion, and DLS changes the wavelength of the light wave when the beam hits the particles. The wavelength of the particles changes differently depending on the size of the particles, and the size distribution of the particles and the motion process can be obtained through

correlation function calculations. The morphology and size of exosomes are usually well characterized and identified using transmission electron microscopy (TEM) and DLS.

5.3 Detection of surface markers

In addition to detecting the morphology and size of exosomes, detecting markers on the surface of exosomes can further characterize the isolated exosomes, including specific or nonspecific markers, such as lipids, proteins, or RNAs. Commonly used techniques for protein detection include Western blotting, flow cytometry, enzyme-linked immunosorbent assay (ELISA), and the BCA method.

Western blotting which is widely used in biological fields, enables qualitative and semiquantitative analysis of proteins. Cellular or tissue proteins are first separated by gel electrophoresis and stained with a specific antibody. By analyzing the markers coupled to the antibody, information such as the expression and molecular weight of proteins in the sample can be analyzed. It is a commonly used method for identifying protein markers for exosomes, such as CD9 and CD81.

Flow cytometry is a high-throughput technology with multiple parameters for rapid quantitative analysis and sorting of cells or biological particles. Analysis of *H. pylori*-infected macrophages by flow cytometry revealed increased expression of CD40, CD63, CD81 and MCH-1 in macrophages stimulated with exosomes + miR-155 compared with controls [51]. A solid-phase carrier coating with an antibody or antigen on the surface is usually used in ELISA. The specific binding of the antibody or antigen and the enzyme-labeled antibody are subsequently incubated, and the data are collected after the chromogenic reaction of a specific substrate is catalyzed. The BCA method is based on the principle of biuret, which detects the absorbance of the protein at 562 nm and calculates the protein concentration to be measured. A BCA kit is a common and convenient method for measuring protein concentrations in cell-derived and milk-derived exosomes [52].

6. Applications of food-derived exosomes

6.1. Anti-inflammatory and immunomodulatory effects

The inflammatory response is a defense mechanism employed by the immune system to combat infection, injury, or foreign invaders. However, sustained activation of this response can contribute to chronic inflammatory diseases, such as colitis [53]. NF-κB is a key transcription factor that plays a central role in regulating inflammatory processes. Under normal conditions, NF-κB is sequestered in the cytoplasm through binding to its inhibitory protein, IκB, which prevents its nuclear translocation. Upon reception of inflammatory signals via cell surface receptors, IκB kinase (IKK) is activated, leading to the phosphorylation and subsequent degradation of IκB. This process releases NF-κB, allowing it to translocate into the nucleus, where it promotes the transcription and expression of pro-inflammatory genes, thereby amplifying the inflammatory response [54]. The NF-κB family comprises five transcription factor subunits: p50 (NF-κB1), p52 (NF-κB2), p65 (RelA), c-Rel, and RelB. Its primary biological function involves binding to specific DNA sequences known as κB sites, thereby regulating the expression of inflammatory cytokines. In the context of

inflammatory diseases, inhibition of NF-κB overactivation and the subsequent downregulation of inflammatory mediators represents a common therapeutic strategy for mitigating inflammatory responses [55].

Exosomes derived from a wide range of foods are very important natural compounds that modulate cellular attack against pathogens, mediate the body's inflammatory response and maintain homeostasis of the immune system microenvironment [14]. Many exosomes are derived from food sources, and many studies have shown that exosomes are involved in inflammatory responses in the body, especially in the intestinal tract (Figure 2). Modulating the inflammatory response by regulating the dynamic balance between proinflammatory and anti-inflammatory cytokines plays an essential role in the host. Ultrafiltration and size-exclusion chromatography-extracted exosomes from cabbage downregulate IL-6 and IL-1β in human cells and exhibit anti-inflammatory activity [56]. Milk is essential in our lives and is rich in nutrients. Some researchers have extracted exosomes from commercial milk by centrifugation and demonstrated that exosomes can remain intact in the gastrointestinal tract and contain the immunomodulatory substance TGF-β [57]. In addition, milk exosomes play an active role in the scarless treatment of skin wounds by protecting cells from inflammatory responses and oxidative stress and by inhibiting the expression of the proinflammatory mediators IL-6 and TNF-α, as well as the chemokines COX-2 and iNOS. The results demonstrated that skin cell migration is significantly inhibited in a milk exosome dose-dependent manner [58]. There are also many functional active substances in plant food raw materials. We can explore whether these nanoparticles derived from food ingredients have relevant active functions. In a model of DSS-induced colitis, amaranth exosomes exhibited excellent safety and stability in the gastrointestinal tract and specifically targeted sites associated with mouse colitis [59]. Ginger-derived exosome treatment elevates the level of the anti-inflammatory cytokine IL-10 and suppresses the levels of proinflammatory cytokines IL-1β and IL-6 in the intestinal tract, providing a promising preventive and therapeutic approach for inflammatory bowel disease [60]. Edible pueraria mirifica-derived exosome-like nanovesicles may also effectively reduce colitis-associated lung injury by downregulating intestinal proinflammatory cytokines and increasing barrier function-related mRNA expression [61]. Ginseng-derived exosomes have been reported to ameliorate colitis by inactivating the NF-κB signaling pathway to reduce the levels of inflammatory cytokines such as TNF-α and IL-6 [62]. Broccoli-derived nanoparticles contribute to suppressing dendritic cell activation and monocyte recruitment in the intestine and activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway to inhibit colitis in mice with colitis [63]. In a rat model of intestinal ischaemia and reperfusion injury, human breast milk-derived exosomes downregulated the level of inflammatory cytokine TNF-α, alleviated intestinal inflammation, and triggered the proliferation of intestinal crypt cells to repair intestinal injury [64].

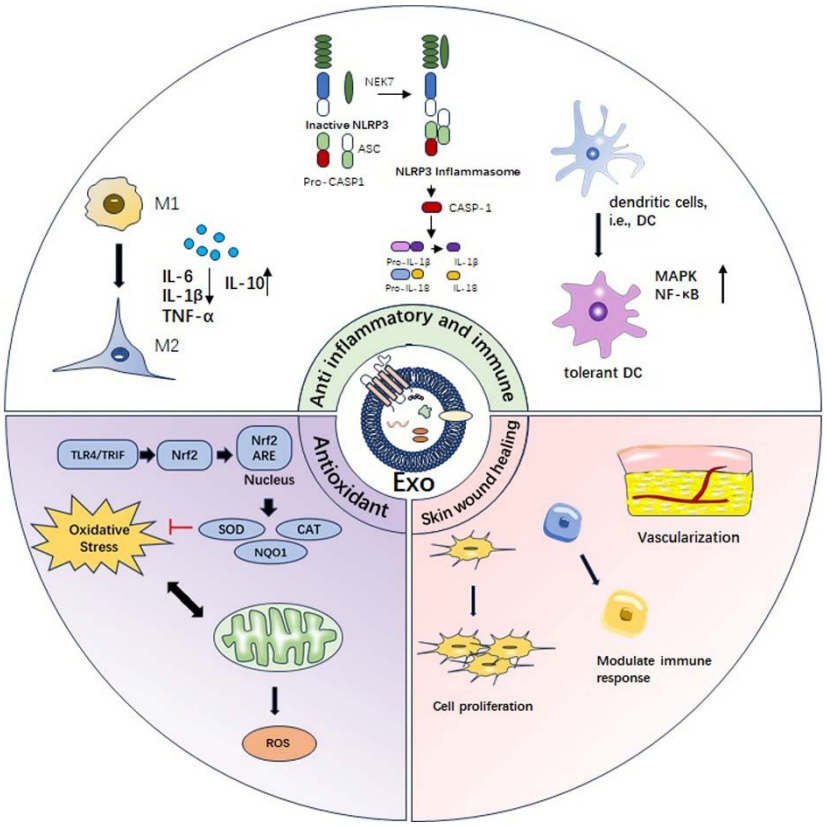

Figure 2 Natural food-derived exosomes play essential roles in regulation of inflammation, immunity, oxidative stress, and skin wound healing

First, exosomes regulate macrophage polarization to modulate inflammation-related cytokines (IL-6, IL-1β, TNF-α) expression, inhibit the downstream signaling pathways of NLRP3 inflammasome, and induce dendritic cell maturation (upregulating MAPK and NF-κB) to exert anti-inflammatory and immunomodulatory effects. Second, the TLR4/TRIF pathway leads to the activation and translocation of Nrf2 to the nucleus, where Nrf2 binds to ARE, thereby regulating the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and NQO1 to inhibit the production of reactive oxygen species (ROS) under oxidative stress. Exosomes can effectively prevent the progression of oxidative stress. Third, exosomes promote cell proliferation and angiogenesis as well as modulate the immune response to facilitate skin wound healing.

Macrophages are immune cells with plasticity and pluripotency that play important roles in the inflammatory response and tissue repair. They can be classified into M1 and M2 types according to their activation state and function, with M1 representing the classical proinflammatory phenotype and M2 associated with inflammatory abatement. Identifying macrophage types through phenotypes is important in studying macrophage function under different physiological and pathological conditions [65]. Milk-derived exosomes can influence macrophage proliferation under hypoxic conditions, thereby affecting the immunomodulatory effects of the organism [66]. Edible pueraria mirifica-derived exosomes promote changes in macrophage polarization and the translocation of M1 macrophages to M2 macrophages, thereby mediating the inflammatory response [67]. Low-degree chronic inflammation of adipose tissue and imbalanced liver lipid metabolism are the main driving factors for the development of obesity and related metabolic disorders. miR-396e in garlic-derived exosomes regulates the expression of the key glycolytic enzyme fructose-2,6-diphosphatase 3 (PFKFB3) to shape the metabolic reprogramming of macrophages induced by lipopolysaccharide (LPS) and alleviate the inflammatory response of adipocytes through macrophage-adipocyte crosstalk [68]. Acute liver failure is a potentially fatal clinical syndrome caused by viral

infection or drug abuse, with a high mortality rate and adverse prognosis typically caused by severe dysregulation of the systemic inflammatory response. Garlic-derived exosomes can inhibit macrophage migration and infiltration into the liver through CCR2/CCR5 blockade, prevent hepatocyte apoptosis and inflammasome activation, reduce the release of inflammatory cytokines, and protect the liver from damage through autophagy activation [69]. Grape-derived exosomes have a similar mechanism for improving acute liver failure and counteract oxidative stress induced by exogenous toxins in the liver by increasing Nrf2 nuclear translocation and upregulating HO-1 expression [70]. These results indicate that plant-derived exosomes have potential as novel liver-protective drugs. Exosomes derived from ginseng can promote the polarization of M2 to M1 macrophages, which rely on toll-like receptor-4- and myeloid differentiation antigen 88 (MyD88)-mediated signal transduction to produce total reactive oxygen species, thereby inhibiting the growth of mouse melanoma [71].

The NLRP3 inflammasome is a multiprotein complex that can be activated by various pathogens and danger signals, thus playing an important role in the immune system. However, improper activation of NLRP3 can induce many diseases, making inflammasomes important therapeutic targets for diseases. Exosomes extracted from garlic, chives, or other scallions have been shown to have anti-NLRP3 inflammasome activity. They inhibit downstream signaling pathways of NLRP3 activation, including caspase-1 self-cleavage, inflammatory cytokine release, and heat sink cell death in primary macrophages, reducing inflammation during acute liver injury and inflammatory responses in obesity metabolism [72]. The lipid components in the exosomes derived from ginger rhizomes can significantly inhibit the activity of the NLRP3 inflammasome, indicating that ginger exosomes are novel and effective ingredients that block the assembly and activation of the NLRP3 inflammasome [73]. Exosomes isolated from bitter gourd juice can inhibit the proliferation of oral squamous cell carcinoma cells. In addition, some RNAs derived from exosomes also exhibit anti-inflammatory activity, downregulating the activity of the NLRP3 inflammasome and reducing drug resistance in oral squamous cell carcinoma [74].

In the immune response, plant cell-derived exosomes can strongly induce dendritic cell maturation, which depends mainly on the MAPK and NF-κB signaling pathways [75]. After intraperitoneal injection, rose-derived exosomes can target immune organs via internalization by immune cells, strongly stimulating TNF-α secretion and activation of the NF-κB signaling pathway and increasing the expression of the hematopoietic function-related transcription factor PU.1 *in vitro* and *in vivo*. It subsequently alleviates the cyclophosphamide-induced cell cycle arrest associated with leukopenia and bone marrow in immunosuppressed mice [76]. Exosomes derived from the callus of *Aster sinensis* also inhibit T-cell proliferation and activity related to various inflammatory disease etiologies by transforming the phenotype and function of mature DCs into those of immature DCs and improving various symptoms of asthma [77].

Plant-derived exosomes modulate intracellular inflammatory responses through multiple pathways, offering potential protection against chronic diseases driven by persistent inflammation. These exosomes contain bioactive components that suppress key inflammatory signaling pathways—particularly the NF-κB

and NLRP3 inflammasome pathways—thereby reducing the excessive production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Additionally, exosomes derived from milk and soybean promote macrophage polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype. M2 macrophages secrete anti-inflammatory cytokines, including IL-10, further contributing to the resolution of inflammation. Owing to their favorable properties-such as low toxicity, minimal immunogenicity, and high biocompatibility-plant-derived exosomes represent a promising oral therapeutic strategy for inflammatory bowel disease (IBD). The lipid bilayer structure of exosomes enhances their stability in the gastrointestinal environment, resisting degradation and ensuring high oral bioavailability. This structural feature also supports their intrinsic anti-inflammatory activity. Moreover, compared to conventional drug treatments, plant-derived exosomes exhibit superior targeting ability to intestinal lesion sites, thereby maximizing therapeutic efficacy [78]. Although numerous studies have confirmed the anti-inflammatory effects of plant-derived exosomes, the specific bioactive constituents, precise molecular targets, and detailed mechanisms of action remain to be fully elucidated.

6.2 Tissue damage repair and regeneration

Hyaluronic acid loaded on adipose stem cell-derived exosomes was observed in diabetic wounds, and the study revealed that the neoepidermal area, collagen density, fibroblast count, and expression of the TGF-β and VEGF genes were greater than those in the control group, suggesting the potential of hyaluronic acid to promote wound healing [79]. Food-derived exosomes are also therapeutic for chronic wounds, such as diabetic wounds (Figure 2). Exosomes extracted from *aloe vera* peel have antioxidant effects on skin wound healing and can decrease the level of intracellular reactive oxygen species (ROS). Scratch experiments have shown that exosomes enhance the migratory ability of HaCaT cells by activating Nrf2 and triggering antioxidant defense mechanisms [80]. Ginseng-derived exosomes play important roles in human skin aging and improving tissue conditions. They improve the aging-related pigment phenotype of human dermal fibroblasts or UV-induced human melanocytes by suppressing of aging-related molecules and melanin production-related proteins [81]. Exosomes extracted from *Beta vulgaris* juice have the potential to promote angiogenesis and prevent aging and scarring. They regulate the production of collagen I and III, as well as hyaluronic acid synthase by fibroblasts, and inhibit fibroblast migration [82]. A previous publication indicated that endothelial, epithelial, and dermal fibroblasts exhibited the greatest proliferation and migration behavior under treatment with wheat-derived exosomes at a concentration of 200 μg/mL [83]. In summary, exosomes are essential in regulating cell proliferation, migration, tissue repair and regeneration.

Plant-derived exosomes are highly biocompatible and are anticipated to cause minimal side effects. They facilitate skin wound healing through multiple mechanisms. Excessive or prolonged inflammation in the early stages of wound healing can impair the process; plant-derived exosomes counteract this by promoting macrophage polarization at the wound site, thereby reducing inflammation and creating a favorable foundation for accelerated healing. During the proliferative phase, certain plant exosomes, such as those derived from wheat, activate fibroblasts and enhance granulation tissue formation. Moreover, many plant

exosomes are rich in natural antioxidants, which help neutralize excess reactive oxygen species (ROS), shield cells from oxidative damage, and improve the wound microenvironment. In the context of diabetic wound therapy, exosomes exhibit superior tissue permeability compared to conventional treatments. They simultaneously modulate local inflammation, promote angiogenesis, and support extracellular matrix remodeling, thereby addressing multiple obstacles in diabetic wound healing. This multi-targeted action positions plant-derived exosomes as a promising alternative strategy to shorten treatment duration and reduce recurrence rates [84].

6.3 Antioxidants

The primary intracellular source of oxygen free radicals is the byproduct of mitochondrial oxygen metabolism. Under physiological conditions, these reactive species are effectively managed by the endogenous antioxidant system. However, in states such as disease, infection, or stress, the cellular redox balance is disrupted. Excessive generation of free radicals overwhelms the antioxidant capacity, leading to the accumulation of reactive oxygen species (ROS). This results in oxidative damage to various biomolecules-including nucleic acids, lipids, and proteins—ultimately contributing to aging and the development of age-related diseases [85]. Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a master regulator of the antioxidant response system. Under homeostatic conditions, Nrf2 is retained in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1), which facilitates its ubiquitination and proteasomal degradation. Upon oxidative or electrophilic stress, Nrf2 is released from Keap1, translocates into the nucleus, and binds to the antioxidant response element (ARE), thereby activating the transcription of downstream antioxidant genes. This process reduces intracellular ROS levels and alleviates oxidative stress [86]. Elevated mitochondrial ROS production, coupled with impaired ROS clearance mechanisms, leads to oxidative stress and lipid peroxidation. The excessive accumulation of ROS can activate NF-κB-mediated inflammatory pathways, stimulating the release of pro-inflammatory cytokines and chemokines. In turn, inflammatory cells generate additional ROS, creating a vicious cycle that amplifies both oxidative stress and inflammatory responses. Thus, oxidative stress is intimately linked with chronic inflammation, and their uncontrolled interplay forms the pathological basis of numerous chronic diseases [86]. Exosomes derived from food sources have many applications as antioxidants during oxidative stress [87] (Figure 2). Treating human mesenchymal stem cells (MSCs) with strawberries-derived exosomes prevents oxidative stress in a dose-dependent manner, possibly because of the presence of vitamin C in their vesicles [88]. In a model of UVB-induced HaCaT cells, exosomes derived from ginseng roots protect cells from death and reduce ROS production by downregulating the mRNA expression of proapoptotic genes, including Bax and caspase-1, -3, -6, -7, and -8, as well as the proportion of cleaved caspase-3, -8, and -9, in a dose-dependent manner. In addition, the mRNA expression of aging-related genes (*MMP* 2 and 3), proinflammatory genes (*IL-6* and *COX-2*), and the cell aging biomarker *p21* may be reduced by inhibiting the activation of protein-1 (AP-1) signaling [89]. Phenolic compounds extracted from *Aloe vera* are crucial for combating oxidative stress. The antioxidant capacity of *Aloe vera* exosomes was evaluated by measuring superoxide dismutase (SOD) activity and cellular antioxidant activity.

HaCaT cells treated with *Aloe vera* exosomes activate genes related to antioxidant defense, including Nrf2, HO1, CAT, and SOD, indicating that they activate antioxidant defense signals by activating the Nrf2 signaling pathway [80]. Pomegranates are regarded as a food of great medicinal value in folklore, and they contain many phenolic compounds, such as anthocyanins and tannins. These chemical components have positive effects, such as antioxidant, anti-inflammatory and hepatoprotective effects. In a study of nonalcoholic liver disease, pomegranate-derived exosomes ameliorated lipid accumulation and mitigated intracellular mitochondrial dysfunction in palmitic acid-induced HepG2 cells, which was further shown to restore the SIRT3/SOD2 signaling pathway and increase SOD2 activity in the liver tissues of high-fat-fed mice [90].

Plant-derived exosomes are rich in natural antioxidants, such as vitamin C from strawberries and ginsenosides from ginseng, which confer potent antioxidant capabilities and alleviate oxidative stress through multiple mechanisms. These exosomes can directly scavenge free radicals, thereby interrupting chain oxidation reactions, and also activate endogenous antioxidant systems, such as the Nrf2 pathway to sustain long-term antioxidant defense. As mitochondria represent the major source of reactive oxygen species (ROS) generation, oxidative stress can impair mitochondrial integrity and function, resulting in further ROS release. Plant-derived exosomes contribute to the preservation of mitochondrial health by helping to maintain membrane potential and reducing oxidative damage at its origin. In the context of cardiovascular diseases, the diverse miRNA cargo carried by plant-derived exosomes may help regulate oxidative homeostasis, thereby indirectly supporting cellular repair and regeneration. Rather than serving merely as passive delivery vehicles for antioxidants, plant-derived exosomes act as multifunctional systems that operate through synergistic regulation [91]. Owing to their natural biocompatibility and multifunctional properties, plant-derived exosomes show significant promise for applications in disease treatment and anti-aging therapies.

6.4 Drug delivery

Exosomes are ideal drug delivery carriers with many advantages: 1) low immunogenicity, 2) good stability, and 3) localization ability [92]. The commonly used methods for loading therapeutic drugs into exosomes are incubation, saponin treatment, ultrasound treatment, and freeze-thaw cycles [93]. Compared with exosomes extracted from animal cells, food-derived exosomes have better biosafety and stability and function in disease prevention (Figure 3). They are excellent delivery carriers for the treatment of diseases such as cancer.

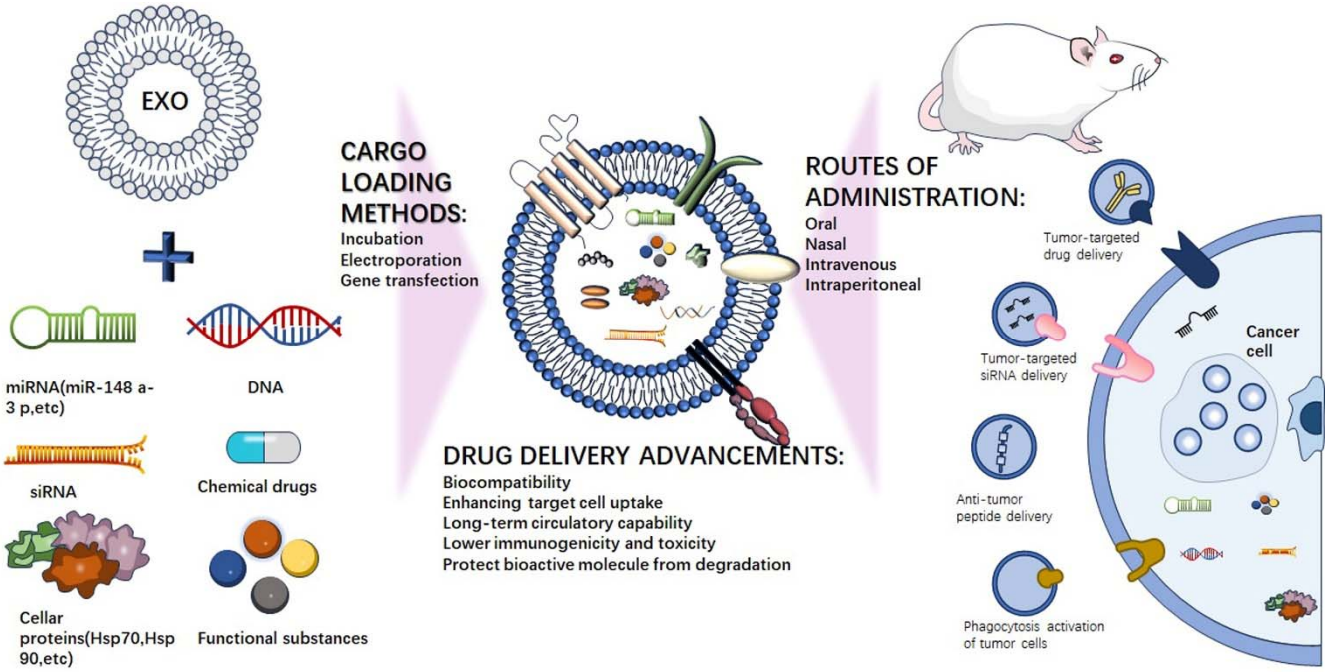

Figure 3 Schematic of exosome-based drug delivery system
Loading of miRNAs (e.g., miR-148a-3p, etc.), DNA, siRNAs, chemical drugs, cellular proteins (Hsp70, and Hsp 90, etc.), and functional substances into exosomes by incubation, electroporation, and gene transfection. Drug delivery from exosomes is tumor-targeted and biocompatible. Tumor-targeted drug delivery methods include tumor-targeted siRNA delivery, antitumor peptide delivery, and phagocytosis to activate tumor cells.

Milk-derived exosomes can be loaded with paclitaxel (PAC) for cancer therapy, ExoPAC is stable in a simulated gastrointestinal environment, and orally delivered drugs exhibit good tumor suppression and no observed toxicity to tissues or organs [94]. Giant grape-derived exosomes loaded with various drugs, such as metformin, doxorubicin, or tamoxifen, are used to treat breast tumors and have been found to target tumor cells and successfully induce cell death [95]. Lactogenic exosomes can also deliver miR-148a-3p for drug therapy, and the suitability of exosomes as RNA delivery vectors was demonstrated by testing their uptake in liver (HepG2) and intestinal (Caco-2) cell lines [96]. It can also be used to deliver some flower pigments, exhibiting anti-proliferative and anti-inflammatory effects on cancer cells [49]. Compared with free lignans, lignans are important bioactives, and the use of sesame leaf-derived exosomes for encapsulating lignans results in good water solubility and stability, as well as improved efficacy in attenuating oxidative stress and inflammatory responses [97]. Ultrasound treatment is used to load bioactive *Astragalus membranaceus* into exosomes derived from turmeric rhizomes, which are stable in simulated gastric and intestinal fluids. The survival rates of Caco-2 cells and HeLa cells treated with exosomes decreased, indicating their antitumor activity. The pharmacokinetic parameters of rat plasma revealed that exosomes derived from turmeric rhizomes can better promote the absorption of Astragalus membranaceus components and are potential delivery carriers [98].

Engineering the surface of exosomes can enhance the therapeutic targeting of the delivered drugs, such as conjugation peptide (RGDyK), to the surface of the exosomes, which successfully enables them to target areas of cerebral ischemic lesions [99]. Ligand modifications are usually added to the surface of exosomes to improve the targeting of the therapeutic site. Folic acid is displayed as a ligand on the surface of ginger-derived

exosomes, and therapeutic siRNA is targeted and delivered to the KB cancer cell model via intravenous administration, resulting in significant tumor inhibition [100]. The encapsulation of the chemotherapeutic drug doxorubicin in ginger-derived exosomes through electrostatic interactions has shown good targeting and tumor inhibition effects on colon cancer cells and excellent biocompatibility [60]. Exosomes derived from grapefruit can deliver therapeutic miR-17 to the brain to treat brain tumors. Exosomes coated with folic acid target GL-26 brain tumors that are positive for folic acid receptors. The polyethylene imines (FA pGNVs) encapsulated in these vesicles increase their ability to carry ribonucleic acids, and intranasal administration significantly delays the growth of mouse brain tumors [101]. Encapsulation of the anti-inflammatory drug methotrexate (MTX) into grapefruit-derived exosomes can reduce the toxicity of MTX in a DSS-induced colitis mouse model, which upregulates the expression of heme oxygenase-1 (HO-1) and inhibits the expression of IL-1β and TNF-α in intestinal macrophages [102]. It serves as an intestinal immune modulator to maintain the homeostasis of the intestinal system.

Plant-derived exosomes are regarded as promising drug delivery vehicles owing to their high biocompatibility and favorable safety profile. They are capable of encapsulating diverse therapeutic agents, including small-molecule drugs (e.g., doxorubicin) and natural bioactive compounds (e.g., lignin), through various loading strategies. To enhance site-specific delivery, the surface of exosomes can be functionally modified to target particular disease tissues. Whereas conventional oral drugs are often susceptible to degradation in the gastrointestinal tract, plant-derived exosomes effectively protect their cargo during gastric transit and facilitate efficient intestinal absorption. Doxorubicin (DOX), a widely used chemotherapeutic agent for colon cancer, is limited by its non-specific toxicity and poor water solubility. Ginger-derived exosomes loaded with DOX have been shown to be effectively internalized by colon cancer cells while demonstrating high biosafety [103]. For future clinical translation, however, it remains essential to establish standardized procedures for the extraction, purification, and drug loading of plant-derived exosomes to ensure batch-to-batch consistency and reproducibility.

6.5 Cancer therapy

Cancer is one of the leading causes of death worldwide, with high recurrence and mortality rates. Studies have shown that food-derived exosomes inhibit tumor cell proliferation (Figure 3). They induce cytotoxicity by increasing the content of ROS in tumor cells, thereby inhibiting cell proliferation, and have no significant side effects on normal cells. The nanocarrier from *camellia* can prevent the proliferation, migration and invasion of breast cancer cells and inhibits the lung metastasis of breast cancer cells, which may be related to its polyphenols and flavonoids [104]. Tea-derived exosomes can be internalized by breast tumor cells (4T1 cells), increasing the intracellular ROS content, and leading to mitochondrial damage, cell cycle arrest, and tumor cell apoptosis. Both intravenous and oral administration can achieve inhibitory effects on breast tumors in mice [105]. Exosomes derived from fingerroot exhibit selective uptake by colon cancer cells, and the levels of reactive oxygen species in cancer cells increase, indicating that they induce cell apoptosis by disrupting intracellular redox homeostasis but have no significant effect on normal colon cells [106].

Tumor necrosis factor-related apoptotic ligand (TRAIL) can induce tumor cell apoptosis, making it a promising approach for cancer treatment [107]. In a xenograft model of chronic myeloid leukemia (CML), *citrus lemon*-derived exosomes can be internalized and selectively trigger tumor cell apoptosis through the TRAIL pathway without affecting normal cells. Increased expression of proapoptotic genes (Bad and Bax) in cancer cell lines and reduced expression of antiapoptotic genes (Bcl-xl) are observed [108].

Tumor-associated macrophages play essential roles in the tumor microenvironment and are crucial components of tumor cell infiltration into immune cells. M2 macrophages account for a large proportion of the tumor environment, and inducing their transformation into M1 macrophages has become another strategy for cancer treatment [109]. Rhodiola polysaccharide can regulate tumor-related macrophages. By chemically modifying folic acid and stearic acid onto Rhodiola polysaccharide and encapsulating the hydrophobic drug DOX, the prepared nanoparticles can target breast cancer tumor cells, which induces tumor cell apoptosis by regulating the polarization of M2 macrophages into M1 macrophages, and enhances the chemical immune effect of triple-negative breast cancer [110]. In human kidney cancer, garlic-derived exosomes inhibit cell proliferation through endogenous pathways, increase activity by increasing Bcl-2 expression levels, reducing basal caspase 3 activity, and inducing cell apoptosis mediated by caspases, which exert anticancer effects [111].

Plant-derived exosomes exhibit intrinsic anti-tumor activities and can also be engineered into highly efficient targeted drug delivery systems. Rich in polyphenols and flavonoids, these exosomes can directly inhibit cancer cell proliferation by modulating cell cycle-related proteins and apoptosis signaling pathways. Furthermore, they contribute to reshaping the tumor immune microenvironment through macrophage polarization, thereby activating anti-tumor immune responses. In terms of engineered applications, plant-derived exosomes can be loaded with chemotherapeutic agents or nucleic acid-based therapeutics. Through surface modifications, they achieve precise targeting to tumor sites, demonstrating considerable potential as versatile anti-cancer platforms. For instance, in the treatment of colorectal cancer, ginger-derived exosomes have been employed to deliver doxorubicin. Their inherent therapeutic properties and delivery functions act synergistically to enhance treatment efficacy. Additionally, surface modification with folic acid (FA) further improves targeting specificity and promotes cellular uptake [112]. However, the detailed targeting mechanisms and *in vivo* metabolic pathways of these engineered exosomes remain to be fully elucidated and require further investigation.

6.6 Diagnosis of disease

Exosomes play a significant role in disease diagnosis due to several key characteristics. First, they carry biomarkers derived from their parent cells, and as diseases develop, the bioactive components within exosomes undergo corresponding changes. Second, the phospholipid bilayer structure of exosomes confers high stability, protecting their contents from degradation by extracellular proteases and other enzymes [113]. For instance, CD81 is a well-known exosomal membrane protein. In one study, exosomes isolated from human plasma via differential centrifugation showed elevated levels of soluble CD81 in patients with chronic hepatitis C compared to healthy controls [114]. Similarly, exosomes derived from the plasma of patients with

non-small cell lung cancer exhibited increased expression of CD151, CD171, and tetraspanin 8 (TSPAN8), suggesting the potential use of exosomal membrane proteins as biomarkers for cancer diagnosis [115]. Exosomal miRNAs also hold diagnostic value. While miRNAs are known to play complex roles in regulating cell proliferation and metastasis within the tumor microenvironment, the phospholipid bilayer of exosomes ensures the high stability of encapsulated miRNAs, making them suitable as diagnostic markers. For example, serum-derived exosomes from patients with esophageal squamous cell carcinoma (ESCC) showed significantly elevated levels of miR-1246, which exhibited a diagnostic specificity of 73.9% [116].

Exosomes are abundantly present in various body fluids, allowing non-invasive liquid biopsy-based diagnostics that avoid the trauma and discomfort associated with conventional tissue biopsies. The protective lipid membrane helps maintain the integrity of molecular cargo, enabling exosomes to faithfully reflect disease progression in a timely manner. These attributes position exosomes as promising tools for future applications in precision medicine and early disease detection.

7. Conclusion and prospects

Exosomes derived from mammalian cells have been widely studied, but some limitations exist. For example, exosomes derived from human body fluids may carry some potentially transferable toxic substances, which limits their use as therapeutic drug carriers. On the other hand, human exosomes are involved in certain functions of the body, which limits large-scale extraction and production, and their sources often involve ethical issues. Compared with those derived from humans, dietary source-derived exosomes have certain similarities in size, morphology, and certain properties and have certain advantages, such as wide sources, large-scale acquisition, noncytotoxicity, and easy absorption by the human body. However, research on exosomes from dietary sources is still in the early stages.

First, standardized large-scale GMP production methods for the separation and extraction of exosomes from dietary sources such as vegetables, fruits, and herbs are lacking. Although centrifugation is currently a relatively conventional extraction method for extraction, individual differences in exosomes due to their different sources often result in some deficiencies in the extraction process. Exosomes derived from mammalian cells have established surface marker proteins, such as CD9, CD63, and CD81, which have become good markers for recognition and characterization. However, the surface markers of exosomes derived from dietary sources have not been clearly explored, and further research should be conducted to help us better isolate and identify them. Second, the extracted exosomes usually need to be cryopreserved at low temperatures to ensure that their biological activity and functional stability are not compromised. Currently, there are cryoprotectants or freeze–drying processes used to extend the storage time of exosomes, but these all involve cost issues. Can we study the properties of exosomes themselves and modify them through various modification methods to avoid the need for cryopreservation and maintain their functional activity?

Exosomes from dietary sources are abundant, and vegetables, fruits, and other plants can be grown on a large scale. These foods themselves contain a very large amount of bioactive substances, which have great potential for disease treatment and prevention. However, there is currently limited research on the

development of exosomes from dietary sources, and exploration of their biological mechanisms and research applications is relatively limited. Therefore, efforts should be made to increase the development of new types of exosomes. Its bioavailability should be improved, its cross-species regulatory mechanisms should be explored in depth, its biological activity mechanisms should be fully understood, and its potential utilization value should be explored.

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Conflicts of interest

The authors declare no conflicts of interest.

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