Edible plant-derived exosomes and their therapeutic applicatons.

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Abstract

Studies on exosomes -nano-sized vesicles containing nucleic acids, proteins and lipids- have increased over the past years due to their newly recognized role in cell-cell communication. While biogenesis and composition of exosomes from mammalian origin have been the focus of several studies, others demonstrated usage of these vesicles both as diagnostic and therapeutic tools. Recently, it has been shown that nanoparticles isolated from plant cells have very similar characteristics and secretion pattern with mammalian cells. These exosomes were isolated from different types of edible plants such as grapefruit, grape, ginger, lemon, and broccoli. Exosome-like nanoparticles from edible plants demonstrated to be the effective drug carrier which have role in decreasing liver damage and intestinal diseases. In this review, aspects of exosomes derived from edible plants, including their biogenesis and molecular composition as well as their therapeutic effects will be discussed in detail.

Keywords: Exosomes, Exosome like nanoparticles, Plant exosomes

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Introduction

First description of exosomes was made as exfoliations that play a role in secretion and export of waste materials out of the cell [1]. In general perspective, exosomes are defined as lipid membraned extracellular vesicles ranging from 30–100 nm in size [2]. They are secreted from various cell types, including dendritic cells, tumor cells, stem cells, and plant cells. Exosomes can be found in extracellular fluids such as saliva, urine and blood [3]. Specific cargo of exosomes may differ one cell type to another or from one organism to another, however in general they contain nucleic acid molecules such as DNA fragments, mRNA, proteins, and lipids. The surface of the lipid membrane contains surface receptors such as HSP70, which is useful for both transportation of the material to the recipient cells and also the identification of the exosomes [4]. In plants, the extracellular vesicles are referred as exosome-like, due to the similar morphology, content, and the release mechanism [5]. However, plant-derived exosomes are still a new area that needs further research.

Biogenesis of Exosomes

Exosome secretion is thought to be mediated by multivesicular bodies (MVBs). MVBs are formed by the inward budding of the endosomal membrane into the endosomal lumen. There are a number of nucleic acids, peptides, lipids and proteins in exosomes derived from multivesicular bodies (MVBs) from endosomal compartments [6]. These proteins come from the parent cell. Therefore, exosomes have a serious effect on physiological communication with other recipient cells. Such features have led to studies on important issues such as autoimmune disorders, neurodegenerative disorders, or cancer. Exosomes from an endosomal system, integrins, cytoskeleton, MHC class I and II molecules, and intercellular cell signaling agents are involved in the fusion and transport of membranes [7,8].

MVB's contain cargoes from the endosomes and then delivered to the lysosomes for degradation. Besides their role in the delivery of their cargo to lysosomes, MVBs also play an important role in secretion of the contents to the outside of the cell membrane by fusing with the plasma membrane [9]. In mammalian cells, once membrane fusion occurs, the exosomes found within the MVBs are secreted to the extracellular space and they are taken up by a recipient cell with three mechanisms: (i) fusion with the plasma membrane and releasing their contents inside the cytosol; (ii) through receptor-ligand binding; (iii) endocytosis [10]. Upon entry, exosomes can alter molecular pathways. There is evidence suggesting that exosome-like nanovesicles are secreted with similar characteristics from plant cells. For instance, MVB-mediated exosome release is thought to be the mechanism of secretion to the extracellular space [11]. According to the literature, plant derived extracellular vesicles have the same morphology with exosomes derived from MVBs. Abundance of MVB vesicles are found to be increased and upon various stimuli triggering events such as cellular stress or proliferation [11].

The plasma membrane is where endocytosis occurs, and exosomes are often seen as a division between the lysosomes and the plasma membrane [12]. Exosomes are created in MVBs, another endosomal compartment called the endosomal sequencing complex (ESCRT), which is located inside the secretory cells and is often required for transplantation [13]. The ESCRT complex consists of 30 proteins, as well as four complexes called ESCRT-0, ESCRT-I, ESCRT-II and ESCRT-

III. Its main task is taken on the cytosolic side of the endosomal membrane to separate the target protein into the intraluminal vesicles (ILV) which is necessary for the ubiquitination of the cytosolic tail of endocytosis receptors [14,15]. ESCRT-0 detects and sequences trans-membrane proteins that are ubiquitic and in the endosomal membrane. ESCRT-I binds ubiquitized cargo proteins, resulting in the activation of the ESCRT-II complex. Therefore, ESCRT-I and ESCRT-II are among the proteins responsible for membrane deformation [16].

Exosome Secretion

Rab proteins are proteins involved in exosome secretion. These proteins are provided and regulated through MVB fusion with the plasma membrane, where they play a key role in intracellular and vesicle transport between different compartments [17]. Rab proteins belong to the GTPase family and consist of more than 60 members. It is characteristic of the Rab proteins that budding of vesicles, binding to the membrane of a receiving chamber or interacting by providing mobility with cytoskeletons [18]. A different combination of soluble N-ethylmaleimide-sensitive factor protein receptors (SNARE) can be seen in exosome secretion. SNAREs are localized in MVBs and interact with each other to create a membrane bridge responsible for membrane fusion. In addition, calcium flow has been found to induce exosome release in neurons in mast cells [19,20].

Intake of Exosomes into the Target Cell

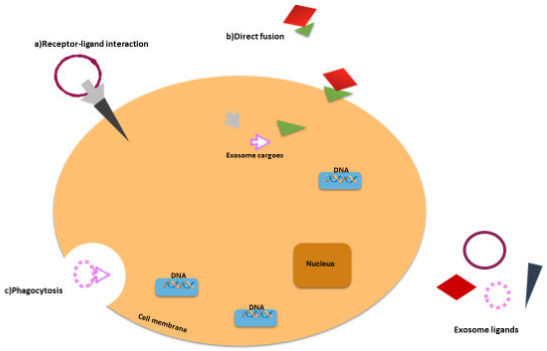

Figure 1. *Ways of intake of exosomes into the target cell: a) Receptor-ligand interaction; b) Direct intake of cargo by fusion of the exosome with the target cell membrane; c) Phagocytosis.*

As shown in the Figure 1, the exosomes are taken into the cell in three ways, but the mechanisms by which exosomes recognize the target cell are still not fully elucidated.

Proteases in the plasma membrane of the target cell combine with exosome membrane proteins by using receptor interaction and soluble ligands in the regions where the target receptors on the cell surface bind are released. The cargo in the exosome is taken into the lumen with selective permeable intracellular signals. Although they do not have specific receptors that mediate exosomes into cells, they have a large number of potential receptors, such as ICAM-1 for APCs (Antigen Presenting Cells) and Tim1/4 for B cells. Heparan sulfate proteoglycan (HSPGs) acts as effective receptors in the uptake of cancer cell-derived exosomes because enzymatic breakdown of HSPG on the cell surface has been shown to significantly reduce the uptake of the exosome into the cell [2].

Cytoskeletal proteins(tubulin, actin, kofilin, profiling) located in the cell membrane targeted by exosomes interact with the target cell membrane with their metabolic enzymes (pyruvate kinase and GAPDH) and membrane lipids (cholesterol, sphingolipid, ceramide) to carry out cargo delivery [21].

In direct fusion, the cargo within the exosome is taken into the cytoplasm by direct fusion of the membrane of the target cell and exosome membrane. Dendritic origin exosomes transfer the cargo they carry to the cytoplasm of the target cell by direct fusion with the target cell membrane via CD9 tetraspanins 5 [22]. In phagocytosis (internalisation), the exosome is taken into the cell as a whole with actin-cytoskeleton and phosphotidylinositol -3-kinase-dependent phagocytosis and the cargo carried by the exosome is distributed into the cytoplasm with the help of mechanisms within the cell [23].

Molecular Composition of Exosomes

Exosomes contain lipids, proteins, and nucleic acids and the properties of these components may differ from one cell to another. The surface of the exosomes has tetraspanins including CD63, CD81, CD9, heat shock proteins such as HSP70, and various other proteins involved in cell-cell communication [24]. Tetraspanin family is commonly used as one of the main biomarkers for the characterization of exosomes. Both mammalian and plant exosomes contain nucleic acids, mRNA, and miRNAs in varying amounts. It is known that around 100-300 miRNAs are contained within the mammalian exosomes whereas this number is less than 100 in plant-derived vesicles [2]. Lipid composition of the exosomes from mammalian origin is rich in cholesterol, but the abundance of phospholipids is relatively less. It is shown that plant-derived vesicles contain up to 98% phospholipids and some plant lipids such as galactolipids [2].

Most plant exosomes has spherical structure and essential lipid bilayers [25]. Exosomes can be used to deliver moleculaes such as drugs, chemothreapeutic agents, proteins or siRNA to other cells by nature and size of exosomes [26]. According to research conducted especially in recent years S. Wang et al showed that nanoparticules obtained from grapefruit are able to deliver to cell with special molecules. Nanovesicles, which are natural like plant exosomes, have an important role in distribution of drugs. With a few chemical changes are made so that such molecules can go to the target tissue and have no biological distribution to non-target locations.

Thus the immunogenicity of these substances is increased. Also there are a lot of research and cytotoxity assays about toxicity of exosomes from edible plants in another study, *in vivo* and in vitro studies have been carried out to indicate exosomes obtained from ginger do not show toxic properties. This type of work has also been performed for exosomes from wheat and grapefruit. According to researchers from Q. Wang et al, grapefruit nanoparticles were found to be more stable

than cationic liposomes. In another study, M. Zhang et al observed that nanoparticles from ginger maintain their stability in areas such as gut or stomach [27,28].

Chemical properties of Plant derived exosomes

Chemical profiles of plant derived exosomes have different profiles than mammalian derived exosomes. Although the lipid layer of exosomes obtained from the mammalian cell is rich in cholesterol, glycosphinolipids and fostatidylserine, there is no cholesterol in plant-derived exosomes [29].

Exosomes are structures that contain RNA and protein for this reason, they can be functionally produced by extracellular vesicles and transferred to recipient cells and additionally, plant-derived exosomes carry a large number of miRNAs to provide this intercellular communication. In the study with plant exosomes from ginger, it has been shown that each of the nanoparticles that are produced contain at least 125 different miRNAs containing 15-27 nucleotides. It has also been shown that plant-derived exosomes have the potential to establish communication between species by binding to 30 untrasnlated regions in the human gene [30].

In addition, mammalian exosomes have higher amounts of protein than plant exosomes, and have been found to be different in protein compositions between these two types of nanovesicles [29]. When the exosome studies obtained from ginger and lemon were examined, it was seen that the two groups had an opposite approach to each other. It has been found that the proteins of plant exosomes derived from ginger tend to be more cytosolic, and in this study, they found that membrane carriers/channels (such as aquaporin and chloride channels), which are thought to contribute to the infrastructure of exosomes derived from plants. In contrast, plant exosomes from lemon juice were found to have a high protein concentration and approximately 57% of these proteins overlapped with proteins from exosomes from mammalian cells regardless of cell origin [30,31].

When studies are examined, it is believed that plants are generally less developed than animals and therefore do not need complex surface associated proteins to communicate with different parts/organs. Therefore, it seems logical that the chemical profiles of plant-derived exosomes may be simpler and have less protein than mammalian exosomes, but data of studies are very limited now for this reason it may be early to make meaningful outcomes in this regard [32].

Therapeutic Applications of Edible Plant Derived Exosomes

Over the past few years, different edible plants are aimed to use for the exosome isolation and used in different research areas. One common reason for using edible plant derive exosomes in therapy is that food, passing through the organs, have role in homeostasis of the body. Investigated plants so far include grapefruit, grape, ginger, lemon, and broccoli:

Grape

In 2013, grape exosome-like nanovesicles (GELNs) were isolated and characterized for the first time [33]. Isolation protocol included pressing the juice of the grapes, followed by differential centrifugation and then sucrose gradient for final purification of the exosome-like nanoparticles. Size of the particles was measured using electron microscope and determined to be 380 nm, which is above the common range for exosomes which -nonetheless- were reported to display the similar characteristics. Zeta potential of the grape exosome-like nanovesicles was measured to be negative with average potential being -26.3 mV. For further assessment, lipidomic analysis of grape exosome-like nanovesicles was conducted. Results indicated that these nanovesicles are rich in phosphatidic acids (PA) with 53.2% and phosphatidylethanolamines (PE) with 26.1%.

To investigate the basis for this high level of PA, Ju et al conducted separate experiments using not just grape juice but whole grape. As a result, they showed that PA levels are higher in nanovesicles isolated from the total grape lysate and they conclude as there may be a selective sorting of PA. To further characterize the nanovesicles components, nucleic acid composition is checked via agarose gel electrophoresis for the detection of RNA components followed by mass spectrometry analysis for miRNAs. 96 miRNAs were identified. To test the effects of the GELNs in vivo, exosomes were administrated to mice by gavage, labelled with a fluorescent dye that binds to the lipid membrane. In 6 hours, nanovesicles were shown to accumulate in the gut, within the intestinal stem cells. In addition, intestinal stem cells have proliferated all over the intestine by Wnt pathway. Moreover, Ju et al demonstrated that genes regulated by the Wnt pathway are significantly upregulated after GELN administration. As the final part of the in vivo studies, GELNs were given to animals having dextran sulfate sodium (DSS)-induced colitis. When compared to the control group, mice treated with GELN shown to live longer by mediating the intestinal stem cell proliferation.

Grapefruit

For Nano technological purposes, grapefruit-derived nanovectors (GNVs) were also investigated [34]. Grapefruit nanoparticles are isolated with sucrose gradient ultracentrifugation from the grapefruit juice. Using electron microscope and dynamic light scattering, the size distribution was determined as around 250 nm. Localization of the GNVs are checked with using PKH26 dye and shown to be internalized within 12 hours. Cytotoxicity tests showed that no significant toxicity is found after the treatment of GNVs. In vivo studies were conducted by administering GNVs by different ways and where these exosomes localized. Results indicated that no pathological changes, fibrosis or necrosis was seen after the treatment with GNVs. All these results were encouraging for employing GNVs in drug delivery. For this purpose, chemotherapeutic agents, siRNAs, and proteins were loaded into GNVs. Results demonstrated that all of the agents are successfully delivered to the cells. GNVs showed that

drugs can be delivered efficiently to the site of disease and its biocompatibility gives an advantage in this process.

To investigate the interaction of gut immune system with food, grapefruit-derived nanovesicles (GDVs) are used as drug delivery system [35]. From the fruit pulp, grapefruit nanovesicles are isolated with sucrose gradient centrifugation. Electron microscope results showed that average size of the isolated nanovesicles were 210 nm with zeta potential being negative. Lipid analysis of the isolated nanovesicles indicated that they contain phosphatidylethanolamine and phosphatidylcholine with high ratios. Cytotoxicity assays were conducted in vivo and results showed that orally administrated nanovesicles have no side effects.

Pretreatment with grapefruit nanovesicles shown to protect the mice from DSS-induced colitis and increases its resistance by upregulating E-cadherin which is a component of adherent junctions. Also, they demonstrated that grapefruit nanovesicles decreased the expression of proinflammatory cytokines and chemokines, resulting in the reduction of damage caused by DSS-induced colitis. By labelling the nanovesicles with DiR dye, Wang et al demonstrated that nanovesicles localize mostly in the large intestine within 4 hours. Detailed analysis showed that nanovesicles are internalized by the macrophages located in the intestine. Also, they investigated the exosome uptake by macrophages and found that nanovesicles are taken by micropinocytosis and clathrin-dependent mechanisms. Protein expression analysis demonstrated that grapefruit nanovesicles up regulate the expression of HO-1 and IL-10, which are known as anti-inflammatory proteins, preventing colitis. All these results show that grapefruit nanovesicles can be taken up orally without any toxicity and used in the treatment of intestinal inflammatory diseases.

Another study involving usage of grapefruit derived nanovesicles as drug carriers was done to suppress brain tumor progression [36]. Exosome-like nanoparticles were isolated as explained previously [34], and sizes were determined around 100 nm. To efficiently transfect a host cell, nanoparticles were hybridized to polyethylenimine (PEI), called as pGNV. pGNVs were shown the have smaller size (80 nm in diameter) than regular nanovesicles. Total RNA extracted from EL4 cell line was fluorescently labelled and fused with pGNV and administered to mice. A fluorescent signal was detected in the brain tissue of the mice after dissection indicating that the nanoparticles successfully localized to the brain. To achieve improved receptor-ligand recognition/binding, pGNVs were coated with folic acid (FA) and this resulted with more efficient targeting of the brain cells. Furthermore, miR17 was loaded onto FA-pGNVs, which is known to regulate the natural killer cell activation and cancer cell apoptosis. FA-pGNV/miR17 treated mice resulted with the increase lifespan with brain tumor compared to those in the control group. As a result, it was seen that modified GNVs display a high potential for drug delivery to the tumor sites.

Ginger

Ginger derived nanoparticles (GDN) have been shown to protect the body from alcohol induced liver damage [37]. GDNs were harvested by grinding the ginger roots followed by differential centrifugation and sucrose gradient centrifugation. Characterization shows that GDNs have an average of 300 nm diameter, with negative zeta potential. Lipid analysis showed that GDN is mostly enriched in phosphatidic acids. Localization of ginger nanoparticles in vivo showed that these particles localize mostly in the liver and lymph nodes in 12 hours. Uptake mechanism was studied by treatment with endocytosis inhibitors and results showed that the uptake of GDN was decreased in the presence of these inhibitors, suggesting that endocytosis is required for the successful internalization of the GDNs. Oral administration of GDN to mice has been shown to increase the expression of antioxidant genes such as HO-1 in the liver, just after 6 hours. Ethanol-fed animals are used as the model of the alcohol-induced liver injury. Administration of GDNs to these animals promoted a decrease in the abundance of lipid droplets in the liver, and triglyceride levels. Consequently, combination of these results showed that GDNs have the capacity to protect mice from alcohol-induced liver damage.

Lemon

Raimondo and colleagues were firstly demonstrated the effect of citrus limon-derived nanovesicles on cancer cell proliferation and tumor growth [38]. Isolation of nanovesicles was performed with ultracentrifugation, and purification with sucrose gradient. Isolated nanovesicles were measured to be 50-70 nm in size, under electron microscope. To visualize the localization and the uptake of these nanovesicles by recipient cells, isolated nanovesicles were treated with PKH26 dye, which binds to its lipid membrane. Results indicated that the nanovesicles were taken up by these cells 3 hours following the treatment and localized into the cytoplasm. As an in vitro approach, citrus-derived nanovesicles are introduced into cancer cell lines A549 (human lung carcinoma), SW480 (human colorectal adenocarcinoma) and LAMA84 (chronic myeloid leukemia) with the doses of 5 μg/ml and 20 μg/ml.

Results indicated that citrus-derived nanovesicles decreased cell viability on cancer cell lines, whereas increased the cell viability on healthy cell lines, such as HUVEC (human umbilical vein endothelial cell). It also demonstrated that the treatment of these nanovesicles increased the expression of pro-apoptotic genes BAD and BAX while decreasing the expression of Bcl-xl according to the gene expression analysis. Further investigation showed that TRAIL-mediated cell death was regulated after the treatment of lemon derived exosomes. To investigate the effect of these nanovesicles in vivo, nanovesicles were introduced into CML xenograft model mice, which were treated with LAMA84 cell line a week before the administration of nanovesicles. Results indicated that tumor size have been suppressed after the treatment via TRAIL-mediated pathway.

Broccoli

Effects of the Broccoli-derived nanoparticle (BDN) on the immune system were investigated [39]. Broccoli derived nanovesicles are isolated with sequential centrifugation followed by column filtration. Isolated nanoparticles were analyzed under electron microscope and determined to have an average size of 32.4 nm in diameter. Effects of BDNs were investigated in mouse colitis model induced with dextran sulfate sodium (DSS). DSS-induced colitis in mouse model has known to be T cell independent [40]. Therefore to determine the anti-inflammatory effect of BDNs, mice were treated with T-cells and BDNs. According to these findings, BDNs treated mice didn't develop colitis indicating the inflammation is could be inhibited with BDN supplementation. Once BDNs were orally administrated to mice, these vesicles are found to be taken up by dendritic cells in the colon of the mice. Furthermore, within the dendritic cells, BDNs activate adenosine monophosphate-activated protein kinase (AMPK), which is known as an anti-inflammatory enzyme. All these results indicated that broccoli derived nanoparticles have a modulatory role in gut immune system.

Wheat

One of the latest studies has been shown to have an important contribution to wound healing by applying exosomes obtained from wheat juice at Yeditepe University. In this study, exosome isolation was made from wheat grass and charcterized according to the size and surface exosome specific markers. Moreover cytotoxity assay was performed on HDF (human dermal fibroblast cell line), HUVEC (human umbilical vein endothelial cell) and Hacat (keratinocyte cell line) cell lines with different concentrations and no lethal effects were observed. In addition, scratch assay was performed and siginificant effect on wound healing was observed to negative control. In this study, effect of wheat exosome on genes such as collagen type I by performing Real Time PCR. The important role of wheat exosome on vascularization also indicated this study via tube formation assay [41].

Conclusion

Mammalian exosomes are proven to be secreted from various cell lines including cancer cells and are currently being used for diagnostic purposes. Exosome-like nanoparticles from edible plants are isolated with similar characteristics and their content has similarities with mammalian cells. Recent studies show that edible plant-derived exosomes or nanoparticles can be used as natural therapeutic agents against various diseases. In vivo studies showed that these exosomes act as drug carriers which can target specific locations. In addition, natural existence nanoparticles in edible plants provide biocompatibility and absence of toxicity both of which are desired features from an agent in therapeutic applications. All in all, in this review it was mentioned that plant derived edible exosomes have a significant potential to be used as a drug delivery system for the treatment of diseases in the future.

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