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THERAPEUTIC EFFECTS OF PLANT-DERIVED EXOSOMES ON DIFFERENT CANCER CELLS

Abstract

Plant-derived exosomes (PDEs) are natural extracellular vesicles. Research on them has called attention to advances in cancer treatment in recent years. Cancer is the global health crisis of our time and requires treatment that is effective, cost-effective, and has fewer side effects. New studies based on PDEs show that they have great potential to be considered as a therapeutic option. Research results show that the internal molecular charge of PDEs has less toxicity and they have effective anti-cancer activity. The main components of PDEs are lipids, proteins, DNA, and RNA. This review analyzed the available research on the factors that play a role in the effectiveness of the mechanism of action of plant-derived exosomes, based on their potential for medical purposes. As a result of the research, it was determined that the interaction with genes, the form of acquisition, which part of the plant to use, and whether or not an auxiliary agent is used, play an important role in the mechanism of action of such PDEs. It should be noted that the exosomes of each of the investigated plants did not have the same effect on all types of diseases, and their effectiveness varied depending on the diseases.

Keywords: *plant-derived exosomes (PDEs), cancer, DNA, RNA, gene*

Introduction

Human tissue is a cellular hybrid system between cells and the complete organ from a biomedical science perspective (Farley A. 2012:40). Human tissue is a system made up of cells with a specific composition and architecture that performs a specific function, and their cellular matrix (Andari S. 2023: 1053). Extensive studies have been conducted to identify molecules involved in the paracrine activity of stem cells to unlock new therapeutic variants in the concept of cellular based therapy. Plant exosome-like nanoparticles (PDENs) contain a variety of bioactive biomolecules. As an alternative cell-free therapeutic approach, they have the potential to deliver nano-bioactive compounds to the human body, thus leading to a variety of anti-inflammatory, antioxidant, and anti-inflammatory benefits (Andari, 2023: 1053). On the other hand, exosome-like particles of plant origin (PDEN) are believed to have the potential to deliver nano-bioactive compounds to the human body (Farley, 2012: 40). Given current advances and challenges, this work provides a comprehensive and concise overview of the role of PDENs as functional and useful biomolecules for biomedical applications and therapeutics.

Research Exosomes are biologically small cellular vesicles with a diameter of 30-150 nm and a density of 1.13-1.19 g/mL, and are excreted naturally by almost all eukaryotic cellular (Ratnadewi, 2023: 182). Because exosomes are considered an essential component, these vesicles resemble molecular components that contain charges such as DNA, RNA, lipids, and proteins and are released into the cellular matrix as a form of intercellular contact (Weaver, 2022: 102272). Cellular vesicles are membrane particles enclosed by a two-layer lipid, including apoptotic bodies, microvesicles, and exosomes. Organisms of all life forms can secrete cellular vesicles into the environment, which serves as an important link between cells and the environment, and also participates in various physiological processes (Willms, 2016: 22519). According to new evidence, plant cellular vesicles play an important role in regulating cross-border molecules with interacting organisms. In addition to transporting signaling molecules (nucleic acids, proteins, metabolic waste, etc.) to mediate cellular communication, the outer vesicles of plant cells themselves can function as functional molecules in cellular micromanagement across cellular boundaries (Zhao-Lin, 2022: 1006299). Several studies have shown that plants can produce vesicles in response to various biotic and abiotic environmental stresses, including pathogenic infections (Zhao-Lin, 2022: 1006299).

Plant-derived vesicles (PDVE) are structurally and functionally similar to animal-derived vesicles (MDVE) and contain large amounts of proteins, lipids, nucleic acids and metabolites necessary for inter-cell signaling relationship (An, 2006: 1009-1019; Alfieri, 2021: 498). In particular, signal transmission is between types. (Garaeva, 2021: 6489). Nucleic acids and proteins in herbal vesicles alter the physiological activities of animal cells (Mu, 2014: 1561). Unlike animal vesicles, PDVEs are easier and faster to extract, cost-effective and do not contain ethical problems (Fujita, 2018: 5772). Compared to synthetic lipid vesicles, PDVEs are safer. New emerging evidence suggests that PDVEs have good prospects in the development of nano-precision systems (Bokka, 2020: 1852).

Tumor micromanagement (TME) is completely different from the normal physiological environment and is a prerequisite for supporting the reproduction and metastasis of cancer cells. However, this unique TME also makes it difficult to treat cancer. For example, low TME pH may worsen before taking chemotherapeutic drugs. Inflammatory micromanagement significantly increases cancer prevalence, metastasis, and resistance to the drug. The relatively hypoxic environment facilitates neoangiogenesis and provides a constant food supply for the growth of cancer cells (Zhao, 2023: 6847). Also, chemotherapy does not perfectly target tumors and often cannot completely remove cancer cells and can even damage more normal cells while killing tumor cells (Behranvand, 2022: 507). Taking into account all these important indicators, the main objective of our work is to test the potential for plant exosome-like nanoparticles (PDENs) for biomedical purposes, by collecting and analyzing data from the latest relevant research and developments.

Conclusion

In six runs, PDENs reportedly kept tumor growth in vowels. Broccoli is known to inhibit the growth of miR159 breast cancer cells across borders (Zhao-Lin, 2022: 1006299). Ginseng extracellular vesicles, dependent on TLR4 and MyD88, promote the transformation of tumor-associated macrophages from the M2 phenotype to the M1 phenotype and inhibit the growth of melanoma (Cao, 2019: 326). Cellular vesicles extracted from the leaves and stems of the dendrobium inhibit the expression of TYR, TRP-1, and TRP-2, the gene MITF, and tyrosine-related proteins associated with melanin production, causing melanin reduction in melanoma cells (Yang, 2021: 259). In addition to cellular vesicles, grapefruit extracellular vesicles have been shown to stop melanoma cell cycles at point G2/M and inhibit melanin proliferation (Zhao-Lin, 2022: 1006299). Asparagus cell-to-cell vesicles inhibit the proliferation of cancer cells by decreasing the expression levels of Ki67 and PCNA in liver cancer cells and increasing the protein levels of AIF, Bax, and Bak. Caspase-9 causes the breakdown of key cellular proteins, including the DNA repair enzyme PARP, resulting in the death of cancer cells (Zhao-Lin, 2022: 1006299). In addition, citrus lemon

exosomes have been shown to specifically inhibit a variety of tumor cell lines by reaching the tumor area and activating apoptotic cell death by trailer-mediated cancer: A549 (human lung cancer cell line), SW480 (human colorectal adenocarcinoma cell line), LAMA84 (chronic myeloid blood cancer cell line) cancer cell proliferation (Raimondo, 2015: 19514). Cellular vesicles derived from garlic have anti-cancer properties against A498 (the cell line of human renal carcinoma). In tumor cells treated with cellular vesicles of garlic, expression levels of proapoptotic genes such as p53, Bax, Cas3, and Cas9 increased significantly and expression levels of Bcl-2 antiapoptotic genes decreased significantly. As a potent angiogenic factor, VEGF secretion, which adversely affects tumor angiogenesis in cancer cells, was significantly reduced (Ozkan, 2021: 14773). Consequently, plant cellular vesicles are able to prevent the proliferation and metastasis of cancer cells activate cellular apoptosis, and interfere with the tumor cell life cycle through immune pathways (macrophages and B lymphocytes) and direct effects. However, it should be noted that each of the plant exosomes did not achieve successful results in all directions and are not effective in the same diseases. As mentioned above, each herbal exosome has had successful results in different diseases. Even these results were influenced by which parts of the plants were used and by which they were obtained.

In addition to these, bitter melon exosomes in combination with the chemotherapeutic drug 5-fluorouracil (5-FU) increase cytotoxicity and reduce 5-FU resistance during oral squamous cell carcinoma cell (OSCC) therapy by lowering the expression of inflammatory NLRP3. Extracellular vesicles of bitter melon cause apoptosis in oral squamous cell carcinoma cells by stimulating mitochondrial damage by ROS-mediated administration, a process probably mediated by MAP30 protein (Yang, 2021: 259). To inhibit the development of the brain tumor, miR17 was capsulated in greiffuteczosomes coated with folic acid and polyethyleneimine, miR17 was rapidly delivered to the brain intranasally, and GL-26 was selectively received by cancer cells. GL-26 induced the expression of MHC1 in cancer cells, killing cancer cells and leading to the activation of healthy cells (Zhao-Lin, 2022: 1006299). Some research groups have combined grapefruit-derived vesicles with aptamer HA1 to load the chemotherapeutic drug azithromycin to target and kill HER2+ breast cancer cells (Tang, 2020: 186). Coating grapefruit exosomes with membranes of activated leukocytes increases the expression of LFA-1 or CXCR1 and CXCR2 and improves the involvement of grapefruit exosomes in cancer cells. Capsulated doxorubicin in grapefruit exosomes was successfully delivered to CT26 colon cancer and had a tumor-killing effect (Zhao-Lin, 2022: 1006299). These research findings suggest that, in practical applications, in addition to using the original herbal extraselular vesicles directly as a medicinal product, we are able to point out that the role of supportive genes to enhance its targeting, specific tumor-specific ability, as well as the differences in the chemical compound used as a means of capsulization to increase activity, could open bright doors in the future for a large number of chronic and oncological diseases to continue furthering these investigations for the long-term mechanism of action of exosomes and at the same time for effective and economically appropriate therapeutic use.

In the research analyzed, extracellular vases of various plants have been found to have significant results in the treatment of chronic diseases, whether oncological or human. The plants used in the analyzed studies and the diseases in which their exosomes are affected are shown in Table 1.

Table 1.
Diseases in which exosomes of various plants are most effective:

1	Ginger	Colon cancer, inflammation of the lungs, oral diseases, colitis
2	Greyfurt	Regeneration of intestinal tissue and tumor
3	Lemon	Liver, spleen, and kidney tumors, stomach cancer
4	Rice	Blood sugar and metabolizes regulation
5	Broccoli	Breast cancer
6	Ginseng	Melanoma
7	Blackberry	Insulin Resistance and Liver Fungal Disorder
8	Dendrobium	Melanoma
9	Beech tree	Cervical cancer caused by the human papillomavirus
10	Asparagus	Liver cancer
11	Maize	Intestinal tumors
12	Garlic	Renal carcinoma
13	Bitter melon	Brain tumor

We have determined that the mechanisms of action of exosomes derived from the roots, leaves, fruits, and stems of plants used at the time of our investigation are different, but also that the effect of acquired vesicles on genes varies and may affect the expression of genes. If so, it makes sense to say that these exosomes are similar to human exosomes, in that PDENs, such as stem cells, have the ability to recognize troublesome cells and tissues without affecting tissues other than damaged tissues (healthy) in the body. Because research is ongoing in this direction, more plants, genes, and diseases should be involved in the research to confirm these findings. We cannot say that each of the plant-based exosomes is necessarily capable of affecting the entire oncology or any disease. An analysis of the studies found that each of the plants examined could have different effects on one or more diseases, which showed different effects on each plant that did not apply to exosomes derived from all parts of a plant. In ginger and lemon plants, more than one part was different and yielded significant results in the same direction. It should also be noted that the mechanisms of excretion, impurities, and concentration play a role in the mechanism of action. Lastly, the role of herbal exosomes in cancer treatments will be tremendous. This allows not only the ability to selectively target cancer cells but also the importance of specific plant parts.

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