ROYAL SOCIETY
OF CHEMISTRY

REVIEW

Check for updates

The emerging role of medical foods and therapeutic potential of medical food-derived exosomes

Jin-Young Hur,[a] SeonHyung Lee,[b] Woo-Ri Shin,[ab] Yang-Hoon Kim*[a] and Ji-Young Ahn ID *[a]

Medical food is consumed for the purpose of improving specific nutritional requirements or disease conditions, such as inflammation, diabetes, and cancer. It involves partial or exclusive feeding for fulfilling unique nutritional requirements of patients and is different from medicine, consisting of basic nutrients, such as polyphenols, vitamins, sugars, proteins, lipids, and other functional ingredients to nourish the patients. Recently, studies on extracellular vesicles (exosomes) with therapeutic and drug carrier potential have been actively conducted. In addition, there have been attempts to utilize exosomes as medical food components. Consequently, the application of exosomes is expanding in different fields with increasing research being conducted on their stability and safety. Herein, we introduced the current trends of medical food and the potential utilization of exosomes in them. Moreover, we proposed Medi-Exo, a exosome-based medical food. Furthermore, we comprehensively elucidate various disease aspects between medical food-derived exosomes (Medi-Exo) and therapeutic natural bionanocomposites. This review highlights the therapeutic challenges regarding Medi-Exo and its potential health benefits.

1. Introduction

In late 2019, the COVID-19 pandemic began to spread globally after the first confirmed human infection.[1] This catastrophe prompted increased global health awareness, which increased the production and demand for healthy diet, medicines, and vaccines.[2–4] However, the pandemic also caused disruptions in the distribution channels of these products. In addition, the probability of contracting the infectious disease was higher for people with other underlying diseases and once contracted they were more severely affected. Accordingly, people started to show interest in substances that are healthy to eat and in being healthy. Furthermore, they became focused on not contracting COVID-19 as was seen from the increased consumption of nutritional medical supplements and foods.[5]

Medical food is consumed or administered under the supervision of a physician.[6,7] Specifically, it is food with unique nutritional requirements determined by medical evaluation for the purpose of managing a specific diet for a disease or condition.[8,9] The first medical food to be released was Lofenalac (Lofenala®) in 1958, which was initially classified as a drug by

the FDA and then reclassified as medical food in 1972. Similar to Lofenala, early medical foods were mostly intended to meet special nutritional needs. Recently, the range of medical food has been expanded to include medical foods to manage various diseases, such as inflammation, osteoporosis, and venous insufficiency, and it is subdivided into different categories, such as functional foods, nutraceuticals, and dietary supplements.[7] Functional foods are naturally occurring and modified foods with bio-functionalities. Alternatively, nutraceuticals are ingredients or food bio-actives with bio-functionality.[10] Medical foods are consumed in the form of food and thus are different from medicines consumed in the form of pills. The medical foods in each of the above-mentioned categories can be classified according to the health status of the body and the purpose of administration. Dietary supplements, such as vitamins, amino acids, probiotics, and natural products, are added in medical food for various purposes.[8]

Recently, efforts have been made to use nanovesicles, such as liposomes and exosomes, as supplements for medical foods. All cells export extracellular vesicles (exosomes) containing different components and are classified according to their biosynthesis mechanisms.[11] Various exosomes inherit the characteristics of their cell origin, given that they include some of its components.[11,12] Exosomes are produced in the inner core of cells and contain nucleic acids, proteins, and lipids with a small size of 40 to 100 nm, and thus they can perform various functions and be naturally absorbed by cells.[13] Due to the

[a]*Department of Microbiology, Chungbuk National University, 1 Chungdae-Ro, Seowon-Gu, Cheongju 28644, South Korea. E-mail: jyahn@chungbuk.ac.kr; kyh@chungbuk.ac.kr; Fax: +82-43-264-9600; Tel: +82-43-261-2301; +82-43-261-3575*

[b]*Department of Bioengineering, University of Pennsylvania, 210 S 33rd St., Philadelphia, PA 19104, USA*

advantages of exosomes, they are used in various fields such as drug delivery, diagnosis, and treatment.[13–15] Firstly, exosomes are in the spotlight in the medical community due to their high homologous and low immune responses to avoid their decomposition in animals or patients. Secondly, exosomes can load various cargoes. In addition, the presence of a phospholipid bilayer is beneficial for fusion with the membranes of receptor cells. The structure of exosomes protects them from harsh conditions such as the digestive tract, including the acidic environment of the stomach, and in particular, exosomes derived from food can be absorbed from the intestine. They are transferred to other organs through the bloodstream and can function. Exosomes are also present in actual cooked or processed foods and are common and derived from various sources, ranging from grapes to human cells.[16] Exosomes have gained popularity due to their biocompatibility and low immunogenicity as effective delivery systems for therapeutics. Medical-purpose exosomes (Medi-Exo) with therapeutic potential are being applied for the treatment of inflammation, cancer, and cardiovascular disease as natural bionanocomposites.

In this review, we discuss the current trend of medical food components used for the treatment and prevention of different types of diseases. To address the limitations of conventional medical food, medical food-derived exosomes (Medi-Exo) are suggested as medical food (or additives) for the treatment of various diseases and health benefits (Scheme 1). Finally, the integration of food with extracellular vesicle (*e.g.*, exosomes) technology is at the forefront of this field.

2. Current knowledge of medical food

Medical food is a specialized type of food that has been developed specifically to address the treatment or management of specific diseases or health conditions. It serves various purposes, including the treatment of conditions such as Alzheimer's disease

and metabolic diseases, enhancing the quality of life for cancer patients, and even preventing certain conditions such as high risk of pre-eclampsia (Fig. 1). Based on its intended use, medical food can be categorized into three main groups, *i.e.*, supportive medical food, therapeutic medical food, and preventable medical food. Firstly, support medical food aims to improve the quality of life of patients by enhancing their immunity and supports their treatment indirectly. Secondly, the goal of treatment with medical food is to heal patients and help them regain their health. Finally, the prevention medical food can help high-risk people from getting sick (Table 1). Each category serves a distinct purpose in supporting the health needs and addressing specific medical conditions of individuals.

2.1 Support of diseases through medical food

Chemotherapy is a common treatment for cancer patients, but it has critical drawbacks. It can have effects not only on cancer cell but also normal cells, thus reducing immunity by decreasing the number of white blood cells.[26,27] Increasing immunity is essential to overcome the decreased immunity caused by cancer to protect patients from viral infections.[28,29] Firstly, due to the increasing immunity by nutrition,[30,31] proper nutriment supply can help both reduce the risk of infection and aid in overall treatment.[32,33] Secondly, the muscle mass of cancer patients affects their life after chemotherapy.[34] Cancer patients maintaining a good weight, muscle index, and muscle density have been shown to have an increased average survival period by approximately three times compared with a decrease in the above-mentioned characteristics in cancer patients (28.4 months and 8.4 months, respectively).[35] Particularly, the elderly often become unable to move gradually as they are confined to a bed for a long time. They may experience a decline in mobility as their muscles weaken and their strength decreases. Eventually, it becomes difficult for them to move again, and complications, such as pneumonia and pressure ulcers, are repeated, making it easier for their condition to gradually deteriorate.[36]

Scheme 1 The overview of Medi-Exo contents and its health benefits.

Fig. 1 Medical food and key compounds to treat diseases. The foods used as medical foods and the main ingredients contained in them are illustrated to show which diseases they can be used to treat.

Faber J. *et al.* examined the effects of a medical food rich in protein, leucine, fish oil, and certain oligosaccharides on 38 cancer patients receiving radiation therapy in a randomized, double-blind trial. The results showed that the group consuming the medical food had significantly higher levels of EPA and DHA integration in their white blood cells and reduced levels of the inflammatory medium PGE2 within a week.[17] Nicolaas E. P. Deutz *et al.* investigated how medical foods manufactured with high leucine and protein content could stimulate muscle protein synthesis in cancer patients, and the results showed that the medical foods increased the FSR muscle protein by 0.024% per hour compared to the beginning.[18]

Chronic stable angina is a type of angina caused by chronic stenosis due to arteriosclerosis.[37] The main objectives of treatment are to control symptoms, prevent myocardial infarction or sudden death, and manage coronary risk factors.[38] Proper management of blood pressure and blood sugar, weight, and cholesterol levels is important for managing chronic stable angina.[39] Many risk factors in CAD are associated with the reduction of nitrogen monoxide (NO). Hence, increasing the resistance to thrombosis and atherosclerosis by restoring NO activity using medical foods containing L-arginine and additional nutrients was investigated. Maxwell Andrew J. *et al.* divided their study into two treatment weeks and four recovery weeks.[19] Subsequently, they measured different metrics, including treadmill work, walking ECG readings, and quality of life ratings. The treadmill exercise capacity throughout the treatment period increased by 20% compared to the placebo

Table 1 Classification of medical foods and the treatment of diseases

Disease		Substances contained in medical food	Reference
(i) Support of diseases through medical food			
Cancer		High in protein and leucine and enriched with emulsified fish oil (containing EPA and DHA) and a specific oligosaccharide mixture	17
Cancer		40 g protein, based on casein and whey protein and enriched with 10% free leucine and other specific components	18
Angina secondary to atherosclerotic coronary artery disease (CAD)		L-Arginine	19
(ii) Treatment of diseases through medical food			
Aware of the pathogenesis	PKU (phenylketonuria)	LNAA (large neutral amino acids)	20
	Cow's milk allergy (CMA)	Hydrolyzed rice formula	21
Unaware of the pathogenesis	MS(motion sickness) in childhood periodic syndrome	*G. simplicifolia*, containing high concentrations of 5-HTP	22
	Mild Alzheimer's disease	Phosphatide precursors, vitamins B (for endogenous choline), vitamins C, vitamins E, selenium, and phospholipids	23
(iii) Prevention of diseases through medical food			
Population with high risk of pre-eclampsia		L-Arginine and antioxidant vitamins	24
Anemia in pregnancy		L-Methylfolate and high-dose vitamin B(12)	25

period. After two weeks of treatment, the total walking duration increased by 23%, and the pain-free walking distance increased. Positive outcomes were also seen in the quality of life, and in particular, there was high satisfaction with vitality (general happiness), housework, and work-related performance.

2.2 Treatment of diseases through medical food

2.2.1. Childhood cyclical syndrome. Esposito Maria *et al.* studied medical food for the treatment of childhood cyclical syndrome.[22] Childhood periodic syndrome is known as the pre-stage of migraines in children and adolescents, which is divided into cyclic vomiting syndrome (CVS), abdominal migraine (AM), and benign paroxysmal vertigo of childhood (BPVC).[40] It usually occurs in infancy or adolescence, manifests unexpectedly, recovers spontaneously, and is entirely normal between seizures, although the symptoms recur.[41]

In the case of childhood periodic syndrome, given that large-scale research is insufficient, it has been treated using medical food based on the mechanism of motion sickness symptoms. In particular, there is already a drug treatment for motion sickness, but it is used in adulthood for acute treatment of motion sickness, which is not suitable for children, and there is no preventive treatment for affected adults to date. The most famous theory for explaining motion sickness is the sensory collision theory, which a mismatch between visual and somatic senses, inducing nausea and vomiting. In addition, exceptionally, motion sickness is often considered a precursor to migraines. In the case of migraine attacks, the concentration of serotonin is lower than the normal level. Magnesium can relieve nerve excitement and muscle stiffness, which can improve motion sickness and migraines. Therefore, an experiment was conducted on 254 children using a seed extract of the 5-HTP-rich *Griffonia simplicifolia* Bail, a precursor of serotonin, and a compound containing magnesium. Consequently, the prevalence of children in the group who ingested the Griffonia/magnesium complex after 3 months was 36%, which was considerably lower than the prevalence of 73% in the control group.

2.2.2. Neurodegenerative disease. The exact mechanism and cause of Alzheimer's disease are still not clearly understood. Currently, it is known that a little protein called beta-amyloid is overproduced and deposited in the brain, harming brain cells.[42–45] In addition, the tau protein, which is crucial for maintaining the skeleton of brain cells, is damaged by oxidation, inflammation, and hyperphosphorylation, all of which may potentially cause damage to brain cells and have an impact on development.[46,47] A typical brain pathology finding, the neuroblast (or senile), is associated with the deposition of beta-amyloid proteins, and the bundle of nerve fibers is associated with tau protein hyperphosphorylation. Here, the loss of hippocampus and cortical synapses was considered to be the most closely associated, and thus researchers experimented with medical food containing nutrients that support the regeneration of synapses.[23] The nucleotide uridine, omega-3 polyunsaturated fatty acids, and choline are examples of foods that are known to promote synapse development. As a result of

the 12 weeks core study, improvements in language imaging work were found in 24% of patients in the control group and 40% in the active group. In addition, the significant intake of docosahexaenoic (DHA) and EPA was observed in the entire active group, and the plasma levels of vitamin E were significantly increased. Moreover, the response was calculated by combining the scores of ADAS-cog scale (cognition), ADCS-ADL scale (function), and CIBIC-plus (behavior), and the active group showed a higher response of 18.2% in comparison to the control group.

2.2.3 Inflammatory disorder and allergy. Inflammation is one of the biological responses to harmful stimuli and is a phenomenon that occurs when immune cells, blood vessels, and inflammatory mediators are involved.[48,49] Inflammation appears with the purpose of cell damage inhibition, scar tissue removal, and tissue regeneration, but also causes tissue damage and disease, such as rheumatoid arthritis, dermatitis, asthma, and inflammatory bowel disease.[48,50–54] Therefore, although an inflammatory response may be necessary for the body, there are cases in which it is necessary to control or stop it. Curcumin, which is present in turmeric, suppresses the production of TNF-a, NF-kB, and COX-2, which are representative inflammatory mediators and reported to be effective in the treatment of inflammatory diseases.[55–57] Resveratrol is a phytoalexin found in berries such as raspberries and grapes.[58,59] Resveratrol inhibits the proliferation of spleen cells induced by IL-2 or allo-antigens and suppresses inflammatory cytokines of immune cells, thereby preventing inflammatory reactions effectively.[59] Dietary polyunsaturated fatty acids (PUFAs), which are abundant in fish, have been studied to regulate inflammation by suppressing the expression of COX-2, VEGFR2, and NF-kB, although the inhibitory mediators vary slightly depending on the type of PUFA.[60,61] Many food components that control inflammation have the potential to not only control inflammation, but also improve the diseases associated with it.[62]

Cow's milk allergy (CMA) is defined as an adverse effect on one or more milk proteins mediated by IgE or non-IgE mechanisms.[21] The prevalence rate for this common symptom in kids is about 4.9% of children aged <3 years. IgE-mediated reactions manifest as gastrointestinal, respiratory, and skin symptoms within 1 to 2 hours of ingestion, whereas non-IgE-mediated reactions include food protein-induced enteropathy (FPE) and food protein-induced allergic enteritis. It causes a variety of symptoms of food protein-induced allergic proctocolitis (FPIAP). Hypoallergenic milk powder is a diet for children who usually have this at one year of age and do not breastfeed.[63] Also, extensively hydrolyzed formula (eHF), which is generally proven to be hypoallergenic, is recommended, but hydrolyzed rice-based formulas (HRF) can be used as an alternative for infants who reject eHF or have severe CMA.[64] Anania Caterina *et al.*[64] reported the assessment of three factors, as follows: (i) the analysis of growth comes first. The growth discrepancies between infants with moderate or severe CMA and healthy children were not substantially different, and the growth trends of newborns fed HRF, soybean milk powder, and eHF were equivalent. Thus, they evaluated whether HRF could be a nutritionally appropriate alternative for infants. (ii) The

second is the symbolism of the taste of different formulations, which was evaluated by both adults and children, and the findings revealed that the preference for HRF was superior to eHF. (iii) The third is arsenic. Given that rice absorbs arsenic at a high rate, which is a non-threshold human carcinogen, the European Commission limits the amount of arsenic in newborn food to 0.10 mg kg^{-1}. In conclusion, the use of cheap and highly symbolic HRFs was evaluated to be useful in the treatment of CMA in 1 month-old infants.

2.2.4 Cardiovascular disease. Cardiovascular diseases include diseases such as coronary heart disease, heart failure, and hypertensive heart disease.[65] The causes of these diseases are diverse, including hypertension, dyslipidemia, oxidative stress, and inflammation.[66] Therefore, some anti-inflammatory, anti-cancer activity compounds can be utilized as anti-cardiovascular compounds.

Puerarin, an isoflavonoid present in kudzu, improves the NO and cGMP levels.[67,68] In addition, it enhances the level of phosphorylated eNOS protein and decreases the level of caveolin-1 and angiotensin II type 1-receptor. Through this process, puerarin has been reported to have an effect of lowering blood pressure, and may also contribute to the prevention of myocardial infarction.[67,69] Similar to puerarin, rutin, which is abundant in foods such as apples, figs, and asparagus, can lower blood pressure through eNOS signaling.[70,71] Additionally, it can inhibit coronary heart disease by regulating extracellular signal-regulated kinase 1/2 and Akt signaling. It has been reported that baicalin, which is abundant in Baikal skullcap, lowers blood pressure by acting on intracellular Ca^{2+} regulation.[72,73] Given that the number one cause of death worldwide is cardiovascular disease, efforts are being made to uncover the mechanisms of identified components or new functional components.[74]

2.2.5 Metabolic disorders. Diabetes is a metabolic disorder caused by high blood sugar levels,[75] which is divided into type 1 and type 2.[76] Type 1 has problems with the insulin produced by the pancreas and can be managed with insulin injection. In type 2, insulin is secreted normally, but due to insulin resistance, cells cannot accept insulin and the blood sugar rises. Type 2 is thought to have a problem with the insulin receptor, although its exact mechanism is not known. Therefore, studies are being conducted on compounds that can control insulin resistance.[76,77]

Ellagic acid is a component abundantly contained in pomegranate and *Castanea crenata* inner shell.[78] Although its exact mechanism has not been identified, it has been reported that it has activity to lower the blood glucose level and increase the insulin concentration.[79,80] Naringenin, a flavanone found in oranges, citrons, and grapefruit, has carbohydrate metabolism promoter, anti-inflammatory, and anti-oxidant effects.[81,82] Furthermore, it has been confirmed that it can alleviate diabetic nephropathy caused by type 2 diabetes. Berberine, one of the components of barberry, has also been found to have a hypoglycemic effect.[83,84] It is expected to help alleviate diabetic nephropathy by effectively reducing total cholesterol and low-density lipoprotein, but some complain of gastrointestinal adverse effects. Therefore, it needs to be used with caution.

Ingredients for diabetes, such as berberine, often have adverse effects. Thus, to overcome this, efforts to find new anti-diabetic sources are on-going.[85]

PKU is a condition in which phenylalanine hydroxylase activity is deficient or severely reduced, resulting in high plasma phenylalanine levels of 1000 mmol L^{-1}.[20] If left untreated, nerve cells in the cerebrum that are sensitive to phenylalanine levels can be damaged, resulting in catastrophic disorders such as microcephaly, epilepsy, severe cognitive impairment, behavioral issues, and even paralysis. Concolino *et al.* investigated a medical food called PheLNAA, which contains a lot of LNAA.[20] Seven of the 16 subjects successfully improved blood Phe control to more than the first final goal setting (30% reduction) four weeks after taking PheLNAA. These seven patients were found to have a 32% to 90% reduction in blood pH levels from the baseline throughout the study. Therefore, it was demonstrated that increased LNAA concentrations in PheLNAA medical foods significantly inhibit Phe transport from these patients to the gastrointestinal tract and BBB. Consequently, a novel approach for enhancing the diet and improving the adaptation of patients to the diet, which become restricted as they age, was offered.

Wang *et al.* combined the facts that the polymorphism of MTHFR reduces the L-methylfolic acid, serum methylcobalamin, and serum homocysteine levels and causes hypertension and DR, and methylation of homocysteine and B12 in their study.[86] They examined the effects of Ocufolin, a dietary supplement comprised of L-methylfolate and vitamin D, and eye-folate, a multivitamin with similar ingredients, on the progression of retinopathy in seven patients. Using fundus photography, all participants exhibited intraretinal hemorrhage, microaneurysms (MA), and reduced exudate.

2.2.6 Cancer. Aerobic metabolism produces reactive oxygen species, including superoxide and hydrogen peroxide, which oxidize biological components such as DNA, proteins, and lipids, causing cancer.[87] Oxidation is not the only cause of cancer, but because it is considered the most important cause, various studies have been conducted on antioxidant compounds that show anti-cancer effects.[88–90]

Astaxanthin is an alpha-hydroxyl-keto-carotenoid that is contained in various types of crustaceans such as shrimp and crab.[91] Astaxanthin is both a scavenger for free radicals and an oxidation protector.[92,93] Although the exact anti-cancer mechanism is still unknown, modification of gap junction communication is expected to affect anti-cancer activity.[94] Canthaxanthin, which is contained in foods such as eggs and paprika, also shows anti-cancer activity as a free radical scavenger.[95] Additionally, canthaxanthin has also been reported to inhibit the proliferation of human colon cancer cells and the development of skin tumors.[96,97] The chemopreventive activity of canthaxanthin has also been shown to be a result of gap junction communication modification.[98] Lycopene, which is typically contained in tomatoes, is a free radical scavenger together with astaxanthin and canthaxanthin.[99] Lycopene is known to inhibit the growth of human cancer cells. In particular, it has been reported to interfere with cell cycle progression and growth factor receptor signaling in prostate cancer.[100] In

addition to the above-mentioned components, antioxidant compounds such as lutein and fucoxanthin have been confirmed to have anti-cancer activity.[101,102]

2.3 Prevention of diseases through medical food

Pre-eclampsia (PE) is high blood pressure accompanied by excessive protein in the urine and is a problem that occurs only during pregnancy.[103] Pre-eclampsia can cause the placenta to peel off and deliver early, which increases the likelihood that newborns will have issues.[104] Also, the hands, fingers, neck, and feet of women may also swell, and if their pre-eclampsia is severe and untreated, seizures (eclampsia) or organ damage may occur. One of the major causes of morbidity and mortality in mothers and newborns is pre-eclampsia and eclampsia.[105] According to Vadillo-Ortega Felipe et al., hypertension disorder in mothers is caused by the promotion of maternal vasoconstriction due to a defective placenta and the activation or destruction of endothelial cells.[24] Therefore, it was decided that L-arginine administration will be beneficial for mothers who are at high risk for liver disease. L-Arginine is an endothelial-derived vasodilator and is used as a substrate for nitrogen oxide synthesis enzymes that show synthetic defects in liver disease. Women who had pre-eclampsia in the past or who had a family history of the condition received a bar containing L-arginine and antioxidant vitamins. The rate of pre-eclampsia or eclampsia declined to 13% in patients taking a combination of L-arginine and vitamins, and the premature delivery rate was only 11%. Additionally, it was discovered that at the start of the study there was no difference in the plasma concentration of L-arginine between the treatment groups. However, two neonatal deaths occurred in the placebo group and three in the vitamin group at birth, but not in the group that took both L-arginine and vitamins. This is related to extremely premature babies. Specifically, the intake of L-arginine and vitamin-added medical foods significantly reduced the risk of maternal pre-eclampsia, eclampsia, and premature birth.

Premature birth, natural miscarriage, and childbirth with underweight babies are all affected by anemia during pregnancy.[106] Furthermore, pregnant women with anemia are more likely to have a premature birth and mild labor contractions, resulting in prolonged delivery durations and an increased risk of excessive bleeding. In the study by Bentley Susan et al., the effect of medical foods that added L-methylfolate and vitamin B12 to the nutrition of existing prenatal vitamins (PNVs) as a control group was tested with PNVs.[25] The hemoglobin changed by −10.9 in the case of prenatal vitamins and merely by −4.0 in the case of medical food from the start of pregnancy until delivery. Additionally, prenatal vitamins had a 74.1% incidence of anemia and medicinal foods had a 39.7% incidence, both of which were significant outcomes.

3. Therapeutic aspects of natural bionanocomposites: exosomes

Exosomes are a type of extracellular vesicle (EV) that are released by cells into the extracellular space. They are small, spherical vesicles with an average diameter of less than 200 nm, and they possess a phospholipid bilayer structure. Exosomes can be found in various body fluids, including blood, urine, saliva, and milk. They play a crucial role in cell-to-cell communication and the transport of bioactive molecules, as well as molecules that are overexpressed in response to the specific condition or environment of cells. Exosomes contain a variety of bioactive molecules, including proteins, lipids, and nucleic acids such as RNA and DNA. Recently, milk-derived exosomes were discovered, which have been recognized as versatile bioactive materials. Subsequently, their potential application has been extended in various fields, including drug delivery, disease treatment, and cell communication.

Functional ingredients are low in concentration and are used by preparing extracts of raw food for their functions. However, commonly, it is not easy to isolate only the desired component from food, and thus food extracts contain various components in addition to the target component.[107,108] Consequently, adverse effects may be induced by unidentified ingredients. In this case, is relatively easy to identify the components of exosomes, and in addition to the target functional components, additional benefits from the proteins, lipids, and nucleic acids of exosomes can be obtained with higher efficiency.[109] Therefore, utilizing exosomes as a functional component of medical food can be a good strategy for obtaining health benefits (Table 2).

Exosomes are produced by endocytosis.[110,111] Exosomes are colloidal nanoparticles and their surface charge is reflected by their zeta potential, which is considered as one of the characteristics of exosomes.[112,113] Exosomes secreted by animal cells have a spherical structure formed of a lipid bilayer.[114] Similar to most plant-derived vesicles, nano-vesicles have a simple lipid bilayer like eukaryotic cell membranes and are structurally spherical.[115] The composition of exosomes is not random and their function and composition depend on the cell of their origin.[116,117] Similar to normal cell membranes, the membrane components of exosomes are composed of lipids, carbohydrates and proteins.[118–120] The unique characteristics of exosomes have attracted significant attention in clinical applications as both diagnostic biomarkers and therapeutic cargo carriers. One of their appealing attributes is their reduced immunogenicity, which is a result of their biocompatibility and bilayer lipid structures.[121] These structures effectively shield the encapsulated cargo from degradation, making exosomes an attractive option as a therapeutic vector. Moreover, exosomes offer the advantage of accommodating various cargoes, and their ability to fuse with the receptors in the call membrane makes them highly efficient for the delivery of cargo. However, although exosomes are considered promising vectors, their components have gained greater popularity in the medical community due their potential in treating inflammation, cancer, and cardiovascular diseases.[122] In addition, due to their ability to represent metabolic stages of cell/organ origin and their important role in major pathological processes, exosomes are considered new and promising biomarkers for a wide range of diseases (Fig. 2). Mesenchymal stem cell-derived exosomes (MSC-exosomes) are one of the exosomes that show potential for the regeneration of

Table 2 Exosomal components as biomarkers

Exosomal components	Disease	Associated molecules	Reference
Protein	Prostate cancer	CD9	126
	Breast cancer	CD81	127
	Melanoma	TRIP2, VLA-4, HSP70, HSP90	128
	Pancreatic cancer	Glypican-1	129
	Colorectal cancer	CD147, CD9	130
	Chronic hepatitis C	CD81	131
	Alzheimer's disease	Exosomal amyloid peptides, Thr-181	132
	Parkinson's disease	DJ-1, α-synuclein	133
Nucleic acid	Type 2 diabetes	miRNA-1249-3p	134
	Myocardial infarction	miRNA-125b-5p	135
	Acute myocardial infarction	miRNA-93-5p	136
	Oral squamous cell carcinoma	miR-155	137
	Liver cancer	miR-26a	138
	Colorectal cancer	miR-146a-5p, miR-155-5p	139
	Pancreatic ductal adenocarcinoma	miR-196a, miR-124, miR-1226-3p	140
	Breast cancer	BCL-2 siRNA	141
	Bladder cancer	PLK-1 siRNA	142

tissue damage. Mesenchymal stem cells have been reported to alleviate type 2 diabetes in animals and clinical trials, and it was confirmed that MSC-exosomes are also effective in treating type 2 diabetes.[123] Treatment with MSC-exosomes in a type 2 diabetic rat model reduced blood sugar levels and restored phosphorylation of insulin receptor substrate 1 and protein kinase B.[124] In addition, it has been confirmed that they alleviate diabetes and restore insulin secretion through muscle cell glucose transporter expression, liver glycogen storage increase, and B-cell death suppression.[125]

3.1 Exosomal proteins

Various proteins exist on the surface of exosomes, and proteins derived from the parent cells play a major role in intracellular communication.[143] Proteins with various roles such as targeting, adhesion, and T-cell stimulation are present in the exosome membrane.[144] In particular, tetraspanins are abundant, which

are involved in cell penetration, invasion, and fusion (Fig. 3A). Heat shock proteins (HSP70 and HSP90) are involved in antigen binding and antigen presentation in stress response.[145] Exosomes contain various proteins such as membrane transport proteins, heat shock proteins, and enzymes to play functional roles, and highly abundant proteins can be used to distinguish exosomes as biomarkers.[144,146] For example, CD9 and CD81 were found to be positive as exosomal protein markers in prostate cancer[126] and breast cancer cell lines,[127] respectively. Additionally, TRIP2, VLA-4, HSP70, and HSP90 were identified as potential diagnostic biomarkers for melanoma[128] and CD147 and CD9 for colorectal cancer.[130] It has also been reported that glypican-1, a surface protein of exosomes, is exclusively present in the serum of pancreatic cancer.[129] Exosomes can serve as biomarkers in various diseases besides cancer. In the case of hepatitis C patients, an increase in exosomal CD81 has been observed.[131] Furthermore, exosomal amyloid peptides and
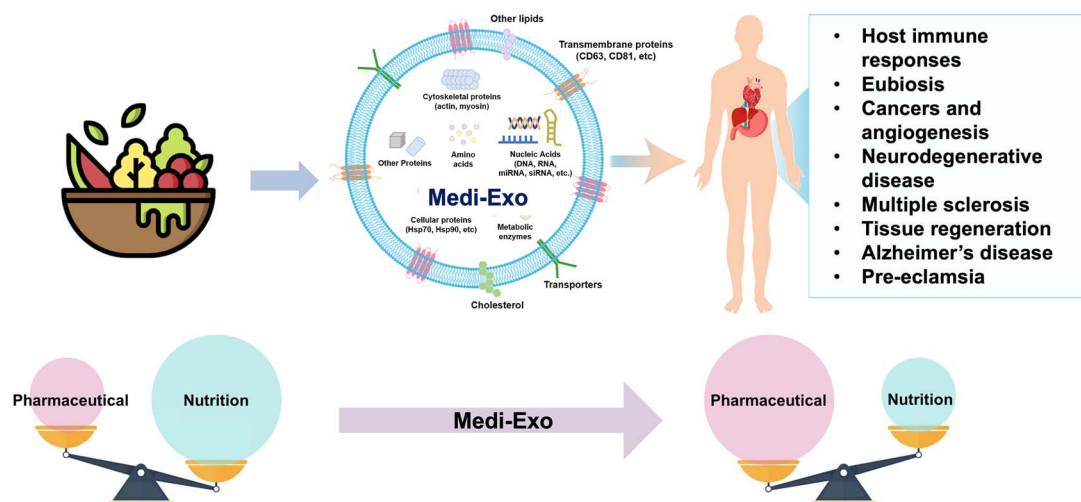

Fig. 2 A schematic representation of biogenesis and uptake of exosomes.
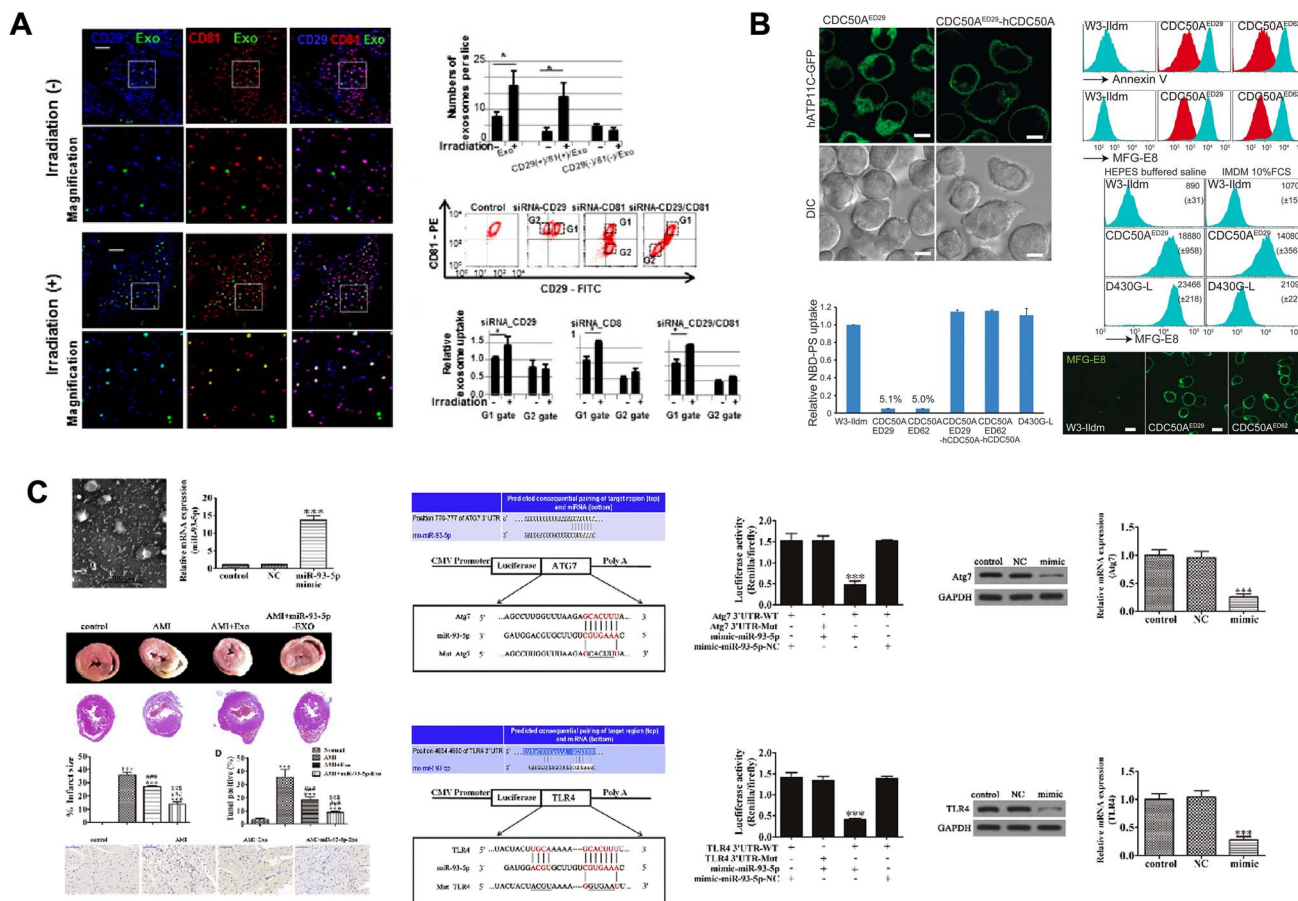
Fig. 3 Exosome components: a diverse array of therapeutic agents. (A) Cellular uptake of exosomes through the CD29/CD81 complex formation. This figure has been adapted from Ref. Hazawa *et al.* with permission from Elsevier, copyright 2014.[203] (B) Caspase-mediated cleavage of phospholipid flippase for apoptotic phosphatidylserine exposure for engulfment of diseases. This figure has been adapted from Ref. Segawa *et al.* with permission from Science, copyright 2014.[151] (C) miR-93-5p-containing exosomes treatment attenuates acute myocardial infarction-induced myocardial damage. This figure has been adapted from Ref. Liu *et al.* with permission from CellPress, copyright 2018.[161]

phospho-tau (Thr-181) have been implicated in Alzheimer's disease,[132] while DJ-1 and α-synuclein are potentially associated with the diagnosis of Parkinson's disease.[133] In the case of exosomes derived from animal cells, it is known that the proteins contained in the cells of their origin are also contained in the exosomes in relative abundance.[147] However, it has been reported that plant-derived exosomes contain relatively simpler proteins than animal cell-derived exosomes.[148]

3.2 Exosomal lipids

Lipids in exosome membranes are essential components of their lipid bilayer structure.[119] It contains lipids such as cholesterol, sphingolipids, and phosphatidylserines, and most of the lipids of exosomes are found in their outer membrane due to their formation process.[149,150] In general, sphingomyelin is predominantly found in the outer leaflet of exosomes, while phosphatidylserine is found in their inner leaflet. Alternatively, it appears that phosphatidylethanolamine is randomly distributed in their bilayer (Fig. 3B).[151] The lipid composition varies depending on the type of cell of origin, but interestingly, it differs greatly between exosomes and their parent cells.[152]

However, a similar lipid composition is shown between exosomes from a single cell line. The higher the content of sphingomyelin, desaturated lipids, and cholesterol in the exosome membrane than in the parent cell, the greater the stiffness and resistance to degradation of the exosome, and the more effective the delivery of substances such as proteins and nucleic acids.[143,153]

3.3 Exosomal nucleic acids

Exosomes may include RNAs and DNAs such as mRNAs, miR-NAs, and lncRNAs that were present in their cell of origin.[154] Exosomes contain abundant miRNAs and genomic DNA, and contain up to 500 different miRNAs. Exosomes carry their nucleic acids into the target cells, which are then transcribed and translated to affect the cells.[155] The nucleic acids can be stably detected in the circulatory system and protected from RNase degradation by the stability of exosomes. Consequently, exosomal miRNA is a potential candidate as an ideal biomarker in clinical diagnostics. Exosomes have demonstrated remarkable sensitivity and specificity, particularly in diverse cancer types. The nucleic acids encapsulated within exosomes can be

categorized into several classes, including messenger RNA (mRNA), microRNA (miRNA), small interfering RNA (siRNA), circular RNA (circRNA), and long non-coding RNA (lncRNA). The type and amount of nucleic acids in exosomes, especially lncRNAs and circRNAs, are greatly affected by the health status of their origin. Utilizing these characteristics, RNAs in exosomes can be used as disease diagnostic markers.[156] miRNAs contained in exosomes have many effects on cells based on cell-to-cell communication such as angiogenesis, hematopoiesis, and tumorigenesis.[157]

It has been confirmed that natural killer (NK)-derived exosomes derived from lean mice attenuate insulin resistance and inflammatory response in type 2 diabetes.[158] miRNA-1249-3p accumulates in NK-derived exosomes. miRNA-1249-3p targets SKOR1, which regulates the formation of SMAD6/MYD88/SMURF1.

The hypoxic bone marrow mesenchymal stem cell (BM-MSC) exosomes extracted by inducing hypoxia in BM-MSCs were found to increase the therapeutic effect by concentrating miR-NAs, showing therapeutic effects in the myocardium.[159] A particularly high concentration of miRNA-125b-5p was accumulated in the exosomes of hypoxic BM-MSCs.[159,160]

Adipose-derived stromal cells (ADSCs) contain miRNA-93-5p, and the cardioprotective effect of this exosome was confirmed *in vitro* and *in vivo* (Fig. 3C).[161] *In vitro*, miRNA-93-5p effectively inhibited hypoxia-induced autophagy and inflammatory cytokine expression by targeting Atg7 and TLR4.

When exosomes loaded with miR-26a were tested on class B type 1-expressing liver cancer cells, it was found that the upregulation of miR-26a led to a decrease in cell migration and proliferation rates.[138] This was attributed to the reduction in the levels of key proteins involved in G1/S transition, which halted the cells in the G1 phase and inhibited the progression of the cell cycle.

Many estrogen receptor-positive (ER+) breast cancer patients exhibit overexpression of the anti-apoptotic protein BCL-2.[141] This protein, being an estrogen-responsive gene, promotes disease progression and enhances the survival of tumor cells, allowing cancer cells to evade programmed cell death. NK cell-derived exosomes were used as a carrier for BCL-2 targeted siRNAs, and it was found that exosomes loaded with siBLC-2 activated mitochondria-dependent apoptosis in malignant breast cancer cell lines.

Upon loading PLK-1 siRNA into exosomes and co-culturing them with an invasive bladder cancer cell line, it was discovered that the gene expression of PLK-1 was inhibited, resulting in the induction of apoptosis.[142]

4. Treatment and prevention of diseases through food-derived exosomes

Pathogenesis is defined as the occurrence and development of disease. The prevention, management, and treatment of numerous diseases depend on an understanding of their etiology and progression.[162] This is owing to the fact that the mechanical properties of the tissue or cellular environment play

a role in the progression or development of many diseases (Fig. 2).[163]

Food-derived exosomes (FDE) are exposed to the gastrointestinal environment after food consumption (Table 3). However, the lipid bilayer surrounding FDE prevents their degradation under the conditions of the digestive tract, including the acidic environment of the stomach. Therefore, substances loaded within FDE are not broken down in the gastrointestinal tract. They are safely absorbed through the intestines, affecting the whole body.[164] FDE absorbed through the intestinal walls reach peripheral organs *via* the bloodstream.[165] This stability and mechanism have been evaluated for their potential use in the treatment and prevention of various diseases. Exosomes not only serve as carriers but also contain substances that contribute to therapy.[166] For example, exosomes derived from blueberries carry miRNAs such as miR-156e, which have shown effectiveness against cardiovascular inflammation.[167] Additionally, the stability of exosomes is utilized for the delivery of methotrexate.[168] FDE originate not only from fruits but also from various sources, including milk and broccoli.

4.1 Food-derived exosomes

Food-derived exosomes (FDE) have a variety of potential functions for the treatment and prevention of diseases. FDE contain biomaterials such as microRNAs, proteins, and lipids. They regulates gene expression, cellular processes, and signaling pathways in target cells. FDE also play a role in cell-to-cell communication, potentially influencing physiological processes and immune responses, and they can used as therapeutic agents. Some types of FDE contain biomaterial molecules with anti-inflammatory properties, which means they can reduce inflammation-associated disease. Thus, it is crucial to highlight that FED have functions in the treatment and prevention of diseases, and here we provide a detailed explanation of some various diseases.

Raimondo S. *et al.* found that the juice of *Citrus limon* L. contains nanoparticles that can be considered exosome-like nanovesicles, and isolating these nanovesicles and co-culturing them with various cells resulted in a decrease in the growth of tumor cell lines (A549, SW480, and LAMA84). Furthermore, they confirmed an increased expression of the pro-apoptotic molecules, Bad and Bax, indicating the promotion of tumor cell apoptosis.[181]

Ahn G. *et al.* extracted physiologically active exosomes (Mi-Exo) from bovine milk. They confirmed their cytoprotective effect through antioxidant activity and anti-inflammatory effects, and also discovered that they contain TGF-β3, which reduces scar formation. The authors described their potential as a therapeutic material to minimize scars and keloids, such as skin tissue damage.[170]

Nanoparticles derived from broccoli target DCs, inducing tolerogenic DCs and preventing mouse colitis. Deng Z. *et al.* treated a mouse colitis model with broccoli-derived nanoparticles for 10 days. Although the mice treated only with DSS exhibited weight loss, those treated with the broccoli-derived nanoparticles did not show any weight loss. Moreover, it was confirmed that broccoli-derived nanoparticles can be efficiently

Table 3   Derived exosomes and their targeted diseases

Food source	Therapeutic components of Medi-Exo	Extraction methods	Target mechanism or disease	Reference
Honey	miR-4057	Ultracentrifugation and filtration	Acute liver injury	185
Grapefruit	Exosome + luciferase siRNA	Purified on sucrose after centrifugation	Colon cancer	186
	Exosome component + miR17	Purified on sucrose after centrifugation	Brain tumor	187
	Exosome + methotrexate	Purified on sucrose after centrifugation	Inflammatory gut disease	168
Grape	Lipids	Purified on a sucrose step gradient after centrifugation	Dextran sulfate sodium-induced colitis	188
	Exosomes	Purified on a sucrose step gradient after centrifugation	Intestinal stem cell	189
Blueberry	miR-156e, miR-162, miR-319d	Sequential centrifugation, ultra-filtered and centrifugation	Cardiovascular inflammation	167
Lemon	Citrus nanovesicles	Centrifuged and transferred to a 30% sucrose/D_2O cushion and ultracentrifugation	Cancer cell proliferation	181
Broccoli	Lipids	Sequential centrifugation, sucrose purification and ultracentrifugation	Mouse colitis	171
Ginger	Exosome + cancer-specific ligands	Membrane filtration, differential ultracentrifugation, and equilibrium density gradient ultracentrifugation	Nasopharyngeal cancer	190
	Exosome with doxorubicin (Dox)	Centrifugation, sucrose purification and ultracentrifugation	Colon cancer	191
	siRNA-CD98	Centrifugation, sucrose purification and ultracentrifugation	Ulcerative colitis	192
	Ath-miR167a	Centrifugation, sucrose purification and ultracentrifugation	DSS-induced colitis	193
	mi-RNA125	Centrifugation and ultracentrifugation	Chronic colitis and colitis-associated cancer(CAC)	194
	Shogaol	Centrifugation, ultracentrifugation, sucrose step gradient and ultracentrifugation	Alcohol-induced liver damage	169
	DMT1 siRNA	Centrifugation, mixing with FA, dry and add equal volume Hepes buffer	Hereditary hemochromatosis	195
Milk	Curcumin	Use miRCURY™ Exosome isolation kit (Exiqon)	Adenocarcinoma	196
	Exosome + anthocyanins	Differential ultracentrifugation	Lung tumor	197
	Exosome + Dox, EPT1, Ce6	Differential centrifugation	Oral squamous cell carcinoma	198
	Has-miR-148a-3p	Sequential centrifugation and ultracentrifugation	Lung tumor	199
	Lactoferrin and α-lactalbumin	Differential ultracentrifugation	Breast cancer	172
	GRP94	Ultracentrifugation and extraction	Necrotizing enterocolitis	200
	miR-148a	Centrifugation, filtration and ultracentrifugation	Osteoarthritis	201
Moringa	miRNA-160h, miRNA-166, and miRNA-159c	Filtration and ultracentrifugation	Tumorigenesis	202

absorbed by dendritic cells (DCs), suggesting a novel therapeutic strategy for regulating gut immune homeostasis through dietary means and the treatment and prevention of diseases.[171]

When Badawy A. A. *et al.* confirmed the inhibitory effect of camel milk-derived exosomes on the MCF7 human breast cancer cell line and found that they inhibited cell migration and exhibited dose-dependent anti-proliferative activity. Furthermore, they observed reduced inflammation, angiogenesis, and metastasis in tumor tissues, as well as the inhibition of oxidative stress. In conclusion, it was confirmed that camel milk exosomes partially induced cell apoptosis in cancer cells.[172]

4.2   Host immune responses

Honey-derived exosomes have been shown to suppress inflammation by inhibiting the formation of the nucleotide-binding domain and leucine-rich repeat related (NLR) family, pyrin domain containing 3 (NLRP3) inflammasome (Fig. 4A).[173] Honey-derived exosomes did not affect the inflammasome protein levels, but prevented oligomerized NLRP3 from recruiting apoptotic speck protein (ASC). It was confirmed from the immunofluorescence staining results that the visualized spots were significantly reduced with the honey-derived exosome treatment. In addition, miRNA-4057 in the honey-derived exosomes strongly inhibited the self-cleavage of Casp1 after NLRP3 inflammasome activation, thereby inhibiting the inflammatory response. However, miRNA-4057 from the honey-derived exosomes did not reduce the expression levels of IL-6 and TNF-a, which are inflammatory cytokines. However, even if the inflammatory cytokine level was not reduced, it was proven that the honey-derived exosomes inhibited the inflammatory response through the formation of inflammasomes and inhibition of Casp1 self-cleavage.

Ginger-derived exosomes contain the bioactive constituents of ginger, 6-gingerol and 6-shogaol, in addition to normal exosome components. Ginger-derived exosomes decreased pro-inflammatory cytokines such as TNF-a, IL-6, and IL-1b and increased anti-inflammatory cytokines IL-10 and IL-22.[87] It was proven that ginger-derived exosomes can prevent and improve inflammatory diseases by targeting the inflamed intestinal mucosa and reducing damage factors and promoting healing factors.

4.3   Eubiosis

The composition of the microbial community in the intestines is influenced by factors such as the genetic makeup, environment, and diet of the host. The microbial community produces signaling molecules and metabolites that impact various important functions in the intestines, including colonization, movement, digestion, permeability, secretion, energy extraction, mucosal immunity, and barrier effects. Moreover, certain components of the microbial community or groups of microorganisms can enter other organs such as the brain, liver, and pancreas through the circulatory system, influencing their functions. Essentially, the interactions between the immune system of the host and the microbial community are crucial for maintaining intestinal balance. However, if the equilibrium between the host and the microbial community is disrupted, it can lead to diseases. When

the microbial communities are in balance, this is referred to as eubiosis, whereas an imbalance is called dysbiosis, which can contribute to both infectious and non-infectious diseases.[174] It is widely recognized that the intestinal microbial community regulates the expansion of specific subsets of lymphocytes. T helper 17 (TH17) cells, a specific type of CD4+ T helper cells, play a significant role in the development of autoimmune diseases by producing inflammatory cytokines such as IL17A, IL17F, and IL-22. These TH17 cells accumulate in the intestine, indicating that the gut itself induces the maturation of TH17 cells. Another subset of CD4+ T helper cells known as forkhead box P3 (FOXP3)+ regulatory T cells (Tregs) is also abundant in the intestines and contributes to maintaining intestinal balance. The development of intestinal Treg cells has been shown to rely, at least partially, on the presence of microbial communities, as observed by a significant reduction in the intestinal lamina propria of germ-free mice.[175] Research has discovered that exosomes derived from milk have an impact on ulcerative colitis. To investigate this, a study used mice with a specific genetic modification in their intestines (kindlin 2 intestine-specific knockout mice) induced by tamoxifen treatment. These mice were administered either a control solution of PBS or a suspension of exosomes in PBS for four days. The results demonstrated that the addition of exosomes led to the significant reversal of the colitis state, resembling the condition of normal mice. Additionally, their colon appeared clean without the presence of bloody stool (Fig. 4B).[176] Several studies have shown that imbalances in the gut microbiota can induce inflammatory responses and contribute to the progression of rheumatoid arthritis (RA) in both RA patients and animal models. In the case of new-onset rheumatoid arthritis (NORA) patients, *Prevotella copri* was found in their gut, making these individuals more susceptible to RA. When dominant *P. copri* from RA patients was inoculated into mice that were raised in a germ-free environment, it induced arthritis through a mechanism involving Th17 cells. Furthermore, a decrease in the expression of claudin-1 and occludin, which are important proteins for maintaining gut barrier function, was observed before the onset of RA. In the lamina propria, which is located beneath the epithelial cells of the gut, there was an increase in CD3+ T cells, dendritic cells, and B cells in NORA patients. The lamina propria contains T cells, dendritic cells, B cells, and stromal cells, and Paneth cells promote the differentiation of both Th17 and Treg cells. The components found in milk can enhance gut barrier function and microbial diversity, thereby limiting the inflammatory process and protecting the gut.[164] Extracellular vesicles (EVs) derived from human breast milk have been shown to have a protective effect on intestinal epithelial cells, reducing cell death caused by oxidative stress by activating the MAPK pathway.[177]

4.4   Cancers and angiogenesis

Moringa-derived exosomes lowered the viability of leukemia cells and increased apoptosis by decreasing B-cell lymphoma 2 protein expression and reducing the mitochondrial membrane potential.[178] Cytotoxicity was shown in BCL2 positive cells, and these results were expected to be caused by miRNAs in moringa-derived exosomes, and thus the miRNA expression profile was
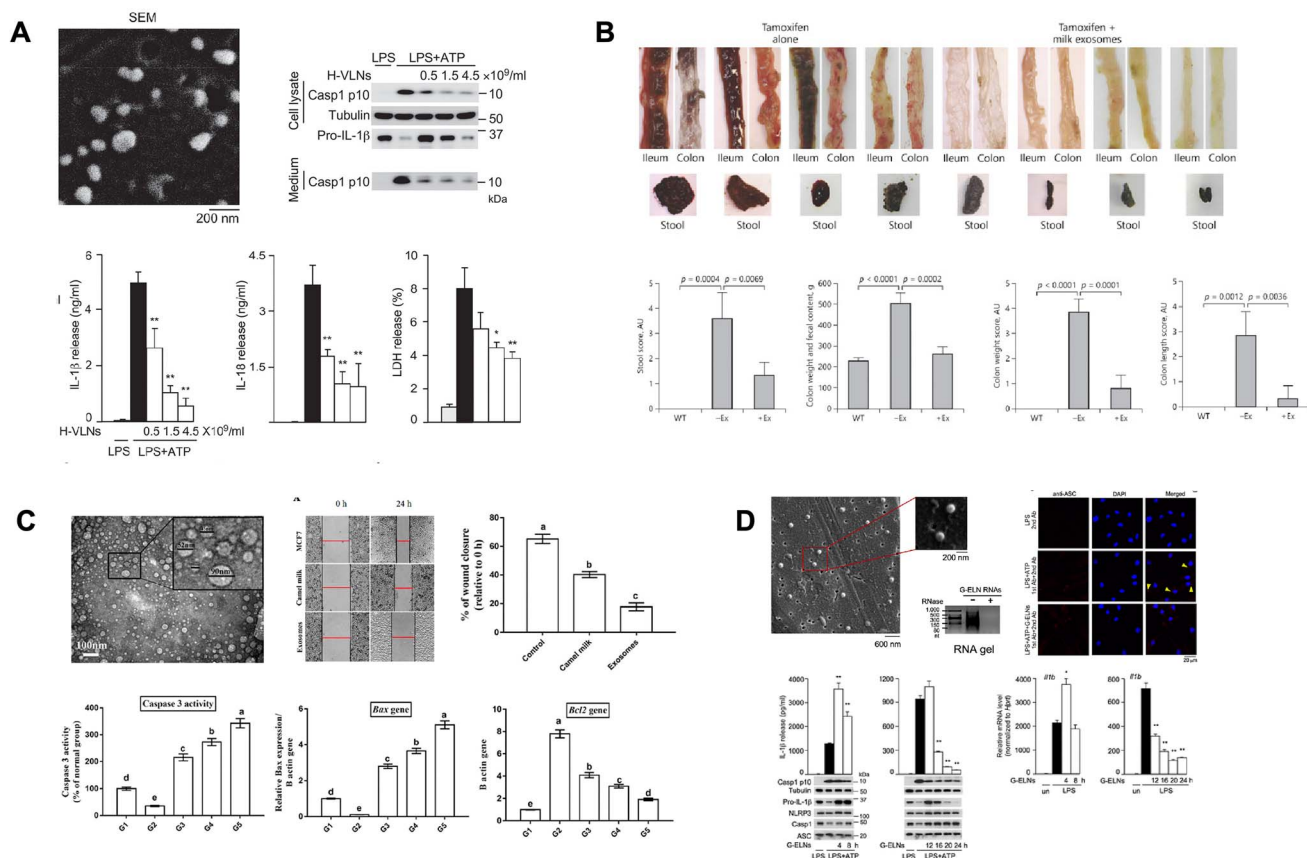
Fig. 4 The treatment and prevention of diseases through food-derived exosomes. (A) The anti-inflammatory effect of vesicle-like nanoparticles in honey. This figure has been reproduced from Ref. Chen *et al.* with permission from Wiley, copyright 2021.[173] (B) Milk exosomes prevent intestinal inflammation in a mouse model for ulcerative colitis. This figure has been reproduced from Ref. Stremmel *et al.* with permission from Karger, copyright 2020.[176] (C) The tumor therapeutic effect of camel milk and its exosomes on MCF7 cells *in vitro* and *in vivo* for cancer cells. This figure has been adapted from Ref. Badawy *et al.* with permission from Sage, copyright 2021.[179] (D) Exosome-like nanoparticles in ginger can inhibit the NLRP3 inflammasome activity. This figure has been adapted from Ref. Chen *et al.* with permission from ACS, copyright 2019.[182]

confirmed. The moringa-derived exosomes contained miRNA-160h, miRNA-166, and miRNA-159c, which are expected to inhibit the transcription of the BCL2 protein involved in tumorigenesis. In a similar study, miRNAs did not affect the cell viability in PBMCs, highlighting the anti-tumor activity of moringa-derived miRNAs.

Although it is not known which component is responsible for the effect, camel milk exosomes have been confirmed to have various anticancer effects against breast cancer *in vitro* and *in vivo* (Fig. 4C).[179,180] Their apoptosis-inducing ability for MCF7 breast cancer cells was confirmed by changes in the expression level of various apoptosis marker mRNAs. Bax was up-regulated by a minimum of 2.79 ± 0.12-fold to a maximum of 5.11 ± 0.22-fold and Bcl2 was up-regulated by a maximum of 4.09 ± 0.22-fold and a minimum of 1.92 ± 0.11-fold in mammary tumor tissue from mice treated with camel milk and camel milk exosomes. In rats treated with camel milk and camel milk exosomes, the mRNA levels of the lipid peroxidation biomarkers malondialdehyde (MDA) and iNOS were significantly reduced, and the oxidative stress markers superoxide dismutase, glutathione peroxidase and catalase increased, resulting in increased resistance to oxidation. Additionally, there was a decrease in

inflammatory cytokine mRNA and an increase in immune cells. The effects were higher in camel milk exosomes than in camel milk, and the potential of camel milk exosomes as an anti-cancer treatment was proven by combining several pieces of evidence. To test the effects of exosomes on tumor cell growth, A549, SW480 (human lung and colorectal adenocarcinoma cell lines), and LAM84 (chronic myeloid leukemia cell line) were treated with *Citrus limon* L. juice-derived nanovesicles.[181] It was observed that the treated groups formed fewer colonies compared to the untreated control group. Furthermore, to evaluate the mechanism of tumor growth inhibition, the expression of various molecules was tested, revealing an increase in the expression of the pro-apoptotic genes Bad and Bax and a decrease in the expression of the anti-apoptotic genes survivin and Bcl-xl. Additionally, activation through the TNF-related apoptosis-inducing ligand (TRAIL)/DR5 pathway, consisting of the TRAIL signal and the receptor Dr5, which controls the apoptotic process, was confirmed.

LAM cells were xenografted into NOD/SCID mice, and lemon-derived nanovesicles were locally (intratumoral) or intraperitoneally (IP) administered three times a week. The results, as shown in the figure below, demonstrated that the mice treated with the

lemon-derived nanovesicles formed smaller tumors compared to the control group. Therefore, this suggests that citrus limon nanovesicles reduce tumor growth *in vivo* through the induction of TRAIL-mediated cell apoptosis and inhibition of cytokine secretion associated with angiogenesis.

4.5 Neurodegenerative disease

Recently, neuroinflammation has been recognized as a significant factor in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Inflammasomes are a complex of proteins that is formed when the body encounters danger signals from pathogenic infections or cellular stress. One specific type of inflammasome, known as NLRP3 (nucleotide-binding domain and leucine-rich repeat-containing family, pyrin domain containing 3), recruits Casp-1 to assemble a multi-protein complex (Fig. 4D).[182] Activation of the NLRP3 inflammasome by Casp-1 leads to the production of IL-1β and IL-18 and triggers a form of cell death called pyroptosis.

In a recent experiment using bone marrow-derived macrophages from C57BL/6J mice, various essential oil nanoemulsions (ELNs) derived from ginseng, aloe vera, grapefruit, garlic, turmeric, dandelion, lavender, cactus, and ginger were cultured together. Most of these ELNs demonstrated weak inhibitory or stimulatory effects on the release of IL-1β and the levels of Casp1 p10 upon activation of the NLRP3 inflammasome. However, the G-ELN (ginseng essential oil nanoemulsion) showed a strong inhibitory effect on the release of IL-1β and IL-18, as well as the levels of Casp1 p10 during NLRP3 inflammasome activation. Importantly, G-ELN did not significantly affect the levels of the cytokines IL-6 and TNFα induced by LPS, suggesting that G-ELN has minimal impact on the general inflammatory response of macrophages. Furthermore, it was observed that lipids, among the components of G-ELN, play a role in its anti-inflammasome activity.

4.6 Multiple sclerosis

Multiple sclerosis (MS) is a condition characterized by the immune system's attack on myelin, a protective covering of nerve fibers. This attack disrupts the communication between the brain and the body, potentially leading to difficulties in independent walking when nerve fibers suffer permanent damage or deterioration. Presently, although there is no cure for MS, treatment focuses on accelerating recovery from attacks, modifying the progression of the disease, and managing symptoms. Autoimmune reactions of TCD4 cells primarily drive the development of MS, and the presence of myelin oligodendrocyte glycoprotein (MOG) on the outer layer of the myelin sheath facilitates the access of brain inflammation-inducing proteins such as myelin basic protein (MBP) and proteolipid protein (PLP). Strategies to induce antigen-specific tolerance in MS treatment involve modifying the structure, dosage, or administration route of the antigen. Butyrophilin (BTN) is a protein that shares over 50% amino acid similarity with the relevant domain of MOG. It has been identified in milk-derived exosomes and the milk fat globule membrane (MFGM), which are vesicular structures found in milk.[183]

4.7 Tissue regeneration

Wound healing refers to the process of replacing damaged tissue with newly generated tissue. The successful transition from inflammation to tissue regeneration, involving distinct phases of inflammation, proliferation, and remodeling, is crucial for the restoration of the extracellular matrix (ECM) and blood vessels. Macrophages play a versatile role in regulating each stage of wound healing. Fibroblasts and endothelial cells are also vital in the remodeling of the ECM and the formation of new blood vessels, which are essential for wound closure. Epigenetic factors, such as transcription factors and microRNAs (miRNAs), are known to be involved in the transition from inflammation to proliferation.

Milk-derived extracellular vesicles (EVs) have been shown to possess the ability to enhance the proliferation of fibroblasts by approximately 40–50% and endothelial cells by 20–30%. The extent of fibroblast proliferation was dependent on the concentration of milk EVs. In tube formation experiments using endothelial cells, milk EVs promoted an increase in both the branch point number and total tube length by approximately 2–30%. Moreover, milk EVs stimulated the proliferation and migration of fibroblasts (NIH-3T3 cells) and facilitated capillary formation in endothelial cells (SVEC4-10). Conversely, EVs derived from serum did not exhibit similar effects, possibly due to the presence of various pro-inflammatory factors in the serum. Consequently, milk EVs were identified as promoters of wound healing. Colostrum EVs and mature milk EVs exhibited higher expression levels of wound healing-related proteins compared to serum EVs. Specifically, colostrum EVs displayed increased expression of IL-4, which supports anti-inflammatory responses, and ECM accumulation in comparison to other types of EVs. Treatment with milk EVs resulted in a reduction in the expression of Smad7, a key inhibitor of the TGF-β signaling pathway involved in epithelialization, a crucial signaling pathway in wound healing. Additionally, miRNA21, which is known to promote wound healing through the Smad7-Smad2/3-elastin pathway, was upregulated in colostrum EVs.

In a mouse model of excisional wound healing, colostrum EVs labeled with Flamma 675 *N*-hydroxysuccinimide (NHS) were observed to remain in the skin for over 3 days before gradually decreasing and found to be distributed in the organs of mice following subcutaneous injection of EVs. The wound closure rate was significantly accelerated in the group treated with colostrum EVs compared to the control group (saline treatment). Notably, the mice receiving additional treatment with EVs starting on the 4th day after injury (Colos EVs-D4 group) exhibited significantly improved wound closure rates compared to the colostrum EV group.[184]

5 Conclusion

Medical food for specific nutritional requirements or the improvement of medical conditions has recently gained significant attention. The consumption of medical food has shown therapeutic effects in various diseases, ranging from Alzheimer's disease to metabolic disorders, and is available for sale as a formulated product.

Exosomes may also play a prominent role as medical materials as stable vectors and diagnostic biomarkers. Exosomes have a stable structure with a lipid bilayer and their ability to contain various proteins and nucleic acids make them suitable as a therapeutic agent. Furthermore, exosomes can remain stable in strong acidic environments because they consist of lipids. Accordingly, exosomes can act as carriers that can be absorbed by human tissue for the delivery of cargo to the target site. Also, they have been widely discussed for their potential use as diverse biomarkers, particularly in various types of cancer. They have been shown to have therapeutic effects in various diseases, ranging from metabolic to neurodegenerative disorders. Also, an advantage of exosomes is the availability of various natural and food-derived exosomes in our daily lives.

Exosomes in medical food (Medi-Exo) reveal health benefits and demonstrate potential to improve human diseases and provide new therapeutic approaches as natural bionanocomposites. They originate from natural food or sources and are composed of a lipid bilayer membrane enclosing a variety of biomolecules, which allows them to interact with target cells efficiently. Thus, with further studies on exosomes, they can be become a powerful component in medical food as "Medi-Exo".

Although many opportunities lie ahead, the Medi-Exo technique as nascent technology faces limitations and challenges. Typically, to facilitate the application of exosomes in various disease treatments, it is essential to have confidence in their safety or toxicity for humans. Addressing this limitation will require efforts to understand the clear identification and mechanism of disease treatment using exosomes. Understanding the biodistribution of exosomes and their clearance mechanisms is crucial for their therapeutic application. Exosome therapy is a novel technology that is still undergoing clinical research and requires further investigation. It needs extensive clinical trials to establish its efficacy and safety in humans. The identification of exosomes often requires highly efficient extraction methods from food or natural materials, which can provide novel biomarkers. However, these food or natural materials suffer from poorly defined compositions, which may be problematic for identifying the detail information of exosomes. Ongoing efforts to find novel biomarkers of exosomes as natural materials may hold the key to addressing this problem. Despite these limitations, Medi-Exo for diseases such as inflammation, cancer, and metabolic disorders is expected to yield beneficial results through various applications in biology and medicine mechanisms.

Abbreviations

EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
PGE2	Prostaglandin E2
FSR	Fractional synthesis rate
CAD	Coronary artery disease
ECG	Electrocardiogram
TNF-a	Tumor necrosis factor a
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
COX-2	Cyclooxygenase-2
VEGFR2	Vascular endothelial growth factor receptor 2
IgE	Immunoglobulin E
CMA	Cow's milk allergy
eNOS protein	Endothelial NOS protein
BBB	Blood–brain barrier
MTHFR	Methylenetetrahydrofolate reductase
DR	Diabetic retinopathy
CD9	Cluster of differentiation 9
CD63	Cluster of differentiation 63
CD81	Cluster of differentiation 81
HSP70	Heat shock protein 70
HSP90	Heat shock protein 90
CD147	Cluster of differentiation 147
Thr-181	Phospho-tau
DJ-1	Parkinson's disease protein 7
Atg7	Autophagy-related 7
TLR4	Toll-like receptor 4
BCL-2	B-cell lymphoma 2
siBLC-2	Bcl2 siRNA
PLK-1	Polo-like kinase 1
NLR	Nucleotide-binding domain leucine-rich repeat containing
NLRP3	Nucleotide-binding domain and leucine-rich repeat protein-3
ASC	Recruiting apoptotic speck protein
Casp1	Cysteine–aspartic acid protease 1 (caspase-1)
PBMCs	Peripheral blood mononuclear cells
Bax	Apoptosis regulator
Bad	BCL2 associated agonist of cell death
Bcl-xl	B-cell lymphoma-extra large
NOD/SCID	Nonobese diabetic/severe combined immune deficiency
MOG	Myelin oligodendrocyte glycoprotein
MBP	Myelin basic protein
PLP	Proteolipid protein
BTN	Butyrophilin
ECM	Extracellular matrix
Smad7	SMAD family member 7, decapentaplegic homolog 7

Author contributions

J.-Y. H. and S. H. L. wrote the manuscript with input from all authors. Both W.-R. S and J.-Y. A. contributed to the final version of the manuscript. Y.-H. K. supervised the project. J.-Y. A. devised the project, the main conceptual ideas and proof outline.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

References

1 M. Ciotti, M. Ciccozzi, A. Terrinoni, W.-C. Jiang, C.-B. Wang and S. Bernardini, *Crit. Rev. Clin. Lab. Sci.*, 2020, **57**, 365–388.

2 R. Forman, S. Shah, P. Jeurissen, M. Jit and E. Mossialos, *Health policy*, 2021, **125**, 553–567.

3 J. Sultana, S. Crisafulli, F. Gabbay, E. Lynn, S. Shakir and G. Trifirò, *Front. Pharmacol.*, 2020, **11**, 588654.

4 C. Rodríguez-Pérez, E. Molina-Montes, V. Verardo, R. Artacho, B. García-Villanova, E. J. Guerra-Hernández and M. D. Ruíz-López, *Nutrients*, 2020, **12**, 1730.

5 *Fi Global Insights 2021 Trend Guide*, 2021.

6 B. P. Ciampa, E. Reyes Ramos, M. Borum and D. B. Doman, *J. Gastroenterol. Hepatol.*, 2017, **13**, 104–115.

7 J. L. Holmes, A. Biella, T. Morck, J. Rostorfer and B. Schneeman, *Curr. Dev. Nutr.*, 2021, **5**, nzaa172.

8 R. Casale, Z. Symeonidou, S. Ferfeli, F. Micheli, P. Scarsella and A. Paladini, *Pain Ther.*, 2021, **10**, 225–242.

9 N. Ramalingum and M. F. Mahomoodally, *Adv. Pharmacol. Sci.*, 2014, **2014**, 354264.

10 C. M. Hasler, *J. Nutr.*, 2002, **132**, 3772–3781.

11 Y. Zhang, Y. Liu, H. Liu and W. H. Tang, *Cell Biosci.*, 2019, **9**, 19.

12 Y. Zhang, J. Bi, J. Huang, Y. Tang, S. Du and P. Li, *Int. J. Nanomed.*, 2020, **15**, 6917–6934.

13 C. Yang, M. Zhang and D. Merlin, *J. Mater. Chem. B*, 2018, **6**, 1312–1321.

14 T. D. Brown, K. A. Whitehead and S. Mitragotri, *Nat. Rev. Mater.*, 2020, **5**, 127–148.

15 B. Zhou, K. Xu, X. Zheng, T. Chen, J. Wang, Y. Song, Y. Shao and S. Zheng, *Signal Transduction Targeted Ther.*, 2020, **5**, 144.

16 P. Akuma, O. D. Okagu and C. C. Udenigwe, *Front. Sustain. Food Syst.*, 2019, **3**, 23.

17 J. Faber, M. Berkhout, U. Fiedler, M. Avlar, B. Witteman, A. Vos, M. Henke, J. Garssen, A. Van Helvoort and M. Otten, *Clin. Nutr.*, 2013, **32**, 338–345.

18 N. E. P. Deutz, A. Safar, S. Schutzler, R. Memelink, A. Ferrando, H. Spencer, A. van Helvoort and R. R. Wolfe, *Clin. Nutr.*, 2011, **30**, 759–768.

19 A. J. Maxwell, M. P. Zapien, G. L. Pearce, G. MacCallum and P. H. Stone, *J. Am. Coll. Cardiol.*, 2002, **39**, 37–45.

20 D. Concolino, I. Mascaro, M. Moricca, G. Bonapace, K. Matalon, J. Trapasso, G. Radhakrishnan, C. Ferrara, R. Matalon and P. Strisciuglio, *Eur. J. Clin. Nutr.*, 2017, **71**, 51–55.

21 J. Walsh, R. Meyer, N. Shah, J. Quekett and A. T. Fox, *Br. J. Gen. Pract.*, 2016, **66**, e609–e611.

22 M. Esposito, F. Precenzano, M. Sorrentino, D. Avolio and M. Carotenuto, *J. Med. Food*, 2015, **18**, 916–920.

23 P. Scheltens, P. J. Kamphuis, F. R. Verhey, M. G. O. Rikkert, R. J. Wurtman, D. Wilkinson, J. W. Twisk and A. Kurz, *Alzheimer's Dementia*, 2010, **6**, 1–10.

24 F. Vadillo-Ortega, O. Perichart-Perera, S. Espino, M. A. Avila-Vergara, I. Ibarra, R. Ahued, M. Godines, S. Parry, G. Macones and J. F. Strauss, *Bmj*, 2011, **342**, d2901.

25 S. Bentley, A. Hermes, D. Phillips, Y. A. Daoud and S. Hanna, *Clin. Ther.*, 2011, **33**, 204–210.

26 L. Zitvogel, L. Apetoh, F. Ghiringhelli and G. Kroemer, *Nat. Rev. Immunol.*, 2008, **8**, 59–73.

27 S. Senapati, A. K. Mahanta, S. Kumar and P. Maiti, *Signal Transduction Targeted Ther.*, 2018, **3**, 7.

28 T. Kawai and S. Akira, *Nat. Immunol.*, 2006, **7**, 131–137.

29 V. T. DeVita, T. S. Lawrence and S. A. Rosenberg, *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, Lippincott Williams & Wilkins, 2008.

30 R. K. Chandra and S. Kumari, *J. Nutr.*, 1994, **124**, 1433S–1435S.

31 M. Gershwin, *Nutrition and Immunity*, Elsevier, 2012.

32 M. R. Mainous and E. A. Deitch, *Surg. Clin. North Am.*, 1994, **74**, 659–676.

33 J. C. Frost and A. J. Baldwin, *Clin. Med.*, 2021, **21**, e272.

34 F. Pin, M. E. Couch and A. Bonetto, *Curr. Opin. Support Palliat.*, 2018, **12**, 420.

35 L. Martin, L. Birdsell, N. MacDonald, T. Reiman, M. T. Clandinin, L. J. McCargar, R. Murphy, S. Ghosh, M. B. Sawyer and V. E. Baracos, *J. Clin. Oncol.*, 2013, **31**, 1539–1547.

36 A. Kamiya, T. Hayashi, R. Sakon, K. Ishizu, T. Wada, S. Otsuki, Y. Yamagata, H. Katai and T. Yoshikawa, *BMC Surg.*, 2022, **22**, 220.

37 R. Kones, *Vasc. Health Risk Manage.*, 2010, **6**, 635.

38 D. R. Zanger, A. J. Solomon and B. J. Gersh, *Am. Fam. Physician*, 2000, **61**, 129–138.

39 E. M. Ohman, *N. Engl. J. Med.*, 2016, **374**, 1167–1176.

40 A. A. Gelfand, *Curr. Opin. Neurol.*, 2013, **26**, 262–268.

41 D. Spiri, V. E. Rinaldi and L. Titomanlio, *Ital. J. Pediatr.*, 2014, **40**, 1–11.

42 X. Sun, W.-D. Chen and Y.-D. Wang, *Front. Pharmacol.*, 2015, **6**, 221.

43 D. J. Selkoe, *Annu. Rev. Neurosci.*, 1994, **17**, 489–517.

44 S. M. Khan, D. S. Cassarino, N. N. Abramova, P. M. Keeney, M. K. Borland, P. A. Trimmer, C. T. Krebs, J. C. Bennett, J. K. Parks and R. H. Swerdlow, *Ann. Neurol.*, 2000, **48**, 148–155.

45 S. Sadigh-Eteghad, B. Sabermarouf, A. Majdi, M. Talebi, M. Farhoudi and J. Mahmoudi, *Med. Princ. Pract.*, 2015, **24**, 1–10.

46 R. Medeiros, D. Baglietto-Vargas and F. M. LaFerla, *CNS Neurosci. Ther.*, 2011, **17**, 514–524.

47 C. Bancher, C. Brunner, H. Lassmann, H. Budka, K. Jellinger, G. Wiche, F. Seitelberger, I. Grundke-Iqbal, K. Iqbal and H. Wisniewski, *Brain Res.*, 1989, **477**, 90–99.

48 L. Chen, H. Deng, H. Cui, J. Fang, Z. Zuo, J. Deng, Y. Li, X. Wang and L. Zhao, *Oncotarget*, 2018, **9**, 7204–7218.

49 J. M. Bennett, G. Reeves, G. E. Billman and J. P. Sturmberg, *Front. Med.*, 2018, **5**, 316.

50 A. J. Guimond, K. Shiba, E. S. Kim and L. D. Kubzansky, *Psychoneuroendocrinology*, 2022, **141**, 105746.

51 E. H. Choy and G. S. Panayi, *N. Engl. J. Med.*, 2001, **344**, 907–916.

52 D. Y. Leung, M. Boguniewicz, M. D. Howell, I. Nomura and Q. A. Hamid, *J. Clin. Invest.*, 2004, **113**, 651–657.

53 A. Kay, *J. Allergy Clin. Immunol.J. Clin. Invest.*, 1991, **87**, 893–910.

54 D. C. Baumgart and S. R. Carding, *Lancet*, 2007, **369**, 1627–1640.

55 N. J. Olsen, *Minerva Med.*, 2011, **102**, 33–40.

56 Y. Peng, M. Ao, B. Dong, Y. Jiang, L. Yu, Z. Chen, C. Hu and R. Xu, *Drug Des., Dev. Ther.*, 2021, **15**, 4503–4525.

57 I. Rinkunaite, E. Simoliunas, M. Alksne, D. Dapkute and V. Bukelskiene, *BMC Complementary Med. Ther.*, 2021, **21**, 39.

58 H. I. Rocha-Gonzalez, M. Ambriz-Tututi and V. Granados-Soto, *CNS Neurosci. Ther.*, 2008, **14**, 234–247.

59 T. Meng, D. Xiao, A. Muhammed, J. Deng, L. Chen and J. He, *Molecules*, 2021, **26**(1), 229.

60 C. N. Serhan, S. Yacoubian and R. Yang, *Annu. Rev. Pathol.: Mech. Dis.*, 2008, **3**, 279–312.

61 M. Piotrowska, A. Binienda and J. Fichna, *Mol. Cell. Endocrinol.*, 2021, **538**, 111448.

62 B. Sears and C. Ricordi, *J. Obes.*, 2011, **2011**, 431985.

63 L. Panahipour, A. A. Tabatabaei and R. Gruber, *J. Dairy Sci.*, 2020, **103**, 6771–6781.

64 C. Anania, I. Martinelli, G. Brindisi, D. De Canditiis, G. De Castro, A. M. Zicari and F. Olivero, *J. Clin. Med.*, 2022, **11**, 4823.

65 G. D. Flora and M. K. Nayak, *Curr. Pharm. Des.*, 2019, **25**, 4063–4084.

66 R. Hajar, *Heart Failure Rev.*, 2017, **18**, 109–114.

67 Y. X. Zhou, H. Zhang and C. Peng, *Front. Pharmacol*, 2021, **12**, 771793.

68 W. Shi, R. Yuan, X. Chen, Q. Xin, Y. Wang, X. Shang, W. Cong and K. Chen, *Am. J. Chin. Med.*, 2019, **47**, 19–38.

69 H. Wenjun, W. Jing, L. Tao, M. Ling, Y. Yan, Z. Xiaorong and Z. Rui, *Med. Sci. Monit.*, 2015, **21**, 1700–1706.

70 A. Carrizzo, M. Ambrosio, A. Damato, M. Madonna, M. Storto, L. Capocci, P. Campiglia, E. Sommella, V. Trimarco, F. Rozza, R. Izzo, A. A. Puca and C. Vecchione, *Mol. Nutr. Food Res.*, 2016, **60**, 2304–2311.

71 L. Lv, Y. Yao, G. Zhao and G. Zhu, *Exp. Ther. Med.*, 2018, **15**, 506–512.

72 L. Ding, C. Jia, Y. Zhang, W. Wang, W. Zhu, Y. Chen and T. Zhang, *Biomed. Pharmacother.*, 2019, **111**, 325–330.

73 L. Xin, J. Gao, H. Lin, Y. Qu, C. Shang, Y. Wang, Y. Lu and X. Cui, *Front. Pharmacol*, 2020, **11**, 583200.

74 H. C. Kim, *Glob. Adv. Health Med.*, 2021, **3**, 134–141.

75 A. E. Kitabchi, G. E. Umpierrez, J. M. Miles and J. N. Fisher, *Diabetes Care*, 2009, **32**, 1335–1343.

76 I. Tuma, *Vnitr. Lek.*, 2007, **53**, 486–488.

77 S. Padhi, A. K. Nayak and A. Behera, *Biomed. Pharmacother.*, 2020, **131**, 110708.

78 J. Long, Y. Guo, J. Yang, S. M. Henning, R. P. Lee, A. Rasmussen, L. Zhang, Q. Y. Lu, D. Heber and Z. Li, *Food Funct.*, 2019, **10**, 6582–6588.

79 N. Fatima, R. M. Hafizur, A. Hameed, S. Ahmed, M. Nisar and N. Kabir, *Eur. J. Nutr.*, 2017, **56**, 591–601.

80 A. Ahad, A. A. Ganai, M. Mujeeb and W. A. Siddiqui, *Chem.-Biol. Interact.*, 2014, **219**, 64–75.

81 M. Oza and Y. Kulkarni, *Int. J. Pharma Sci. Res.*, 2016, **7**, 14–24.

82 S. J. Tsai, C. S. Huang, M. C. Mong, W. Y. Kam, H. Y. Huang and M. C. Yin, *J. Agric. Food Chem.*, 2012, **60**, 514–521.

83 J. Yin, H. Xing and J. Ye, *Metabolism*, 2008, **57**, 712–717.

84 J. H. Zhang, J. F. Zhang, J. Song, Y. Bai, L. Deng, C. P. Feng, X. Y. Xu, H. X. Guo, Y. Wang, X. Gao, Y. Gu, C. Jin, J. F. Zheng, Z. Zhen and H. Su, *Am. J. Chin. Med.*, 2021, **49**, 1399–1415.

85 P. Tiwari, *J. Diabetes Res.*, 2015, **2015**, 340838.

86 J. Wang, C. Brown, C. Shi, J. Townsend, G. R. Gameiro, P. Wang and H. Jiang, *Eye Vis.*, 2019, **6**, 1–11.

87 M. Aghajanpour, M. R. Nazer, Z. Obeidavi, M. Akbari, P. Ezati and N. M. Kor, *Am. J. Cancer Res.*, 2017, **7**, 740–769.

88 J. D. Hayes, A. T. Dinkova-Kostova and K. D. Tew, *Cancer Cell*, 2020, **38**, 167–197.

89 B. Perillo, M. Di Donato, A. Pezone, E. Di Zazzo, P. Giovannelli, G. Galasso, G. Castoria and A. Migliaccio, *Exp. Mol. Med.*, 2020, **52**, 192–203.

90 T. Khaldi, N. Chekchaki, Z. Rouibah, K. Chouala, H. Cheniti, M. Boumendjel, F. Taibi, M. Messarah and A. Boumendjel, *J. Toxicol. Environ. Health Sci.*, 2022, **14**, 291–300.

91 J. Hu, W. Lu, M. Lv, Y. Wang, R. Ding and L. Wang, *Rev. Bras. Farmacogn.*, 2019, **29**, 24–29.

92 B. P. Chew, J. S. Park, M. W. Wong and T. S. Wong, *Anticancer Res.*, 1999, **19**, 1849–1853.

93 H. Kurihara, H. Koda, S. Asami, Y. Kiso and T. Tanaka, *Life Sci.*, 2002, **70**, 2509–2520.

94 H. Jyonouchi, S. Sun, K. Iijima and M. D. Gross, *Nutr. Cancer*, 2000, **36**, 59–65.

95 T. Tanaka, M. Shnimizu and H. Moriwaki, *Molecules*, 2012, **17**, 3202–3242.

96 P. Palozza, N. Maggiano, G. Calviello, P. Lanza, E. Piccioni, F. O. Ranelletti and G. M. Bartoli, *Carcinogenesis*, 1998, **19**, 373–376.

97 M. M. Mathews-Roth and N. I. Krinsky, *Photochem. Photobiol.*, 1985, **42**, 35–38.

98 L. X. Zhang, R. V. Cooney and J. S. Bertram, *Cancer Res.*, 1992, **52**, 5707–5712.

99 X. Zhang, Q. Wang, B. Neil and X. Chen, *China Med. J.*, 2010, **123**, 2231–2236.

100 H. S. Kim, P. Bowen, L. Chen, C. Duncan, L. Ghosh, R. Sharifi and K. Christov, *Nutr. Cancer*, 2003, **47**, 40–47.

101 A. Ronco, E. De Stefani, P. Boffetta, H. Deneo-Pellegrini, M. Mendilaharsu and F. Leborgne, *Nutr. Cancer*, 1999, **35**, 111–119.

102 A. Iannone, C. Rota, S. Bergamini, A. Tomasi and L. M. Canfield, *J. Biochem. Mol. Toxicol.*, 1998, **12**, 299–304.

103 P. August and B. M. Sibai, *Clinical features and*, diagnosis, accessed December 2022, https://www.uptodate.com/contents/preeclampsia-clinical-features-and-diagnosis.

104 J. M. Roberts and C. Escudero, *Pregnancy Hypertension*, 2012, **2**, 72–83.

105 A. Nakimuli, S. Nakubulwa, O. Kakaire, M. O. Osinde, S. N. Mbalinda, N. Kakande, R. C. Nabirye and D. K. Kaye, *BMC Pregnancy Childbirth*, 2016, **16**, 1–8.

106 O. Api, C. Breyman, M. Çetiner, C. Demir and T. Ecder, *Turk. J. Obstet. Gynecol.*, 2015, **12**, 173–181.

107 K. Kumar, A. N. Yadav, V. Kumar, P. Vyas and H. S. Dhaliwal, *Bioresour. Bioprocess.*, 2017, **4**, 18.

108 A. Lama-Munoz and M. D. M. Contreras, *Foods*, 2022, **11**(22), 3671.

109 Y. Zhang, Y. Liu, H. Liu and W. H. Tang, *Cell Biosci.*, 2019, **9**, 1–18.

110 S. Gurung, D. Perocheau, L. Touramanidou and J. Baruteau, *Cell Commun. Signaling*, 2021, **19**, 1–19.

111 M. Alfieri, A. Leone and A. Ambrosone, *Pharmaceutics*, 2021, **13**, 498.

112 G. Midekessa, K. Godakumara, J. Ord, J. Viil, F. Lättekivi, K. Dissanayake, S. Kopanchuk, A. Rinken, A. Andronowska and S. Bhattacharjee, *ACS Omega*, 2020, **5**, 16701–16710.

113 E. Beit-Yannai, S. Tabak and W. D. Stamer, *J. Cell. Mol. Med.*, 2018, **22**, 2001–2006.

114 Y. Zhang, J. Bi, J. Huang, Y. Tang, S. Du and P. Li, *Int. J. Nanomed.*, 2020, **15**, 6917.

115 T. Karamanidou and A. Tsouknidas, *Int. J. Mol. Sci.*, 2021, **23**, 191.

116 H. Wei, Q. Chen, L. Lin, C. Sha, T. Li, Y. Liu, X. Yin, Y. Xu, L. Chen and W. Gao, *Int. J. Biol. Sci.*, 2021, **17**, 163.

117 S. Gurunathan, M.-H. Kang and J.-H. Kim, *Int. J. Nanomed.*, 2021, **16**, 1281.

118 T. Skotland, K. Sandvig and A. Llorente, *Prog. Lipid Res.*, 2017, **66**, 30–41.

119 T. Skotland, N. P. Hessvik, K. Sandvig and A. Llorente, *J. Lipid Res.*, 2019, **60**, 9–18.

120 W. Zhang, X. Jiang, J. Bao, Y. Wang, H. Liu and L. Tang, *Front. Immunol.*, 2018, **9**, 90.

121 M. Lu and Y. Huang, *Biomaterials*, 2020, **242**, 119925.

122 Q. Shen, Z. Huang, J. Yao and Y. Jin, *J. Adv. Res.*, 2022, **37**, 221–233.

123 Y. Sun, H. Shi, S. Yin, C. Ji, X. Zhang, B. Zhang, P. Wu, Y. Shi, F. Mao, Y. Yan, W. Xu and H. Qian, *ACS Nano*, 2018, **12**, 7613–7628.

124 J. Xiong, H. Hu, R. Guo, H. Wang and H. Jiang, *Front. Endocrinol.*, 2021, **12**, 646233.

125 J. Y. Kim, W.-K. Rhim, Y.-I. Yoo, D.-S. Kim, K.-W. Ko, Y. Heo, C. G. Park and D. K. Han, *J. Tissue Eng.*, 2021, **12**, 20417314211008626.

126 F. H. Jansen, J. Krijgsveld, A. van Rijswijk, G.-J. van den Bemd, M. S. van den Berg, W. M. van Weerden, R. Willemsen, L. J. Dekker, T. M. Luider and G. Jenster, *Mol. Cell. Proteomics*, 2009, **8**, 1192–1205.

127 V. Luga, L. Zhang, A. M. Viloria-Petit, A. A. Ogunjimi, M. R. Inanlou, E. Chiu, M. Buchanan, A. N. Hosein, M. Basik and J. L. Wrana, *Cell*, 2012, **151**, 1542–1556.

128 H. Peinado, M. Alečković, S. Lavotshkin, I. Matei, B. Costa-Silva, G. Moreno-Bueno, M. Hergueta-Redondo, C. Williams, G. García-Santos and C. M. Ghajar, *Nat. Med.*, 2012, **18**, 883–891.

129 S. A. Melo, L. B. Luecke, C. Kahlert, A. F. Fernandez, S. T. Gammon, J. Kaye, V. S. LeBleu, E. A. Mittendorf, J. Weitz and N. Rahbari, *Nature*, 2015, **523**, 177–182.

130 Y. Yoshioka, N. Kosaka, Y. Konishi, H. Ohta, H. Okamoto, H. Sonoda, R. Nonaka, H. Yamamoto, H. Ishii and M. Mori, *Nat. Commun.*, 2014, **5**, 3591.

131 M.-W. Welker, D. Reichert, S. Susser, C. Sarrazin, Y. Martinez, E. Herrmann, S. Zeuzem, A. Piiper and B. Kronenberger, *PLoS One*, 2012, **7**, e30796.

132 S. Saman, W. Kim, M. Raya, Y. Visnick, S. Miro, S. Saman, B. Jackson, A. C. McKee, V. E. Alvarez and N. C. Lee, *J. Biol. Chem.*, 2012, **287**, 3842–3849.

133 Z.-H. Zhao, Z.-T. Chen, R.-L. Zhou, X. Zhang, Q.-Y. Ye and Y.-Z. Wang, *Front. Aging Neurosci.*, 2019, **10**, 438.

134 Y. Wang, M. Li, L. Chen, H. Bian, X. Chen, H. Zheng, P. Yang, Q. Chen and H. Xu, *Signal Transduction Targeted Ther.*, 2021, **6**, 409.

135 L.-P. Zhu, T. Tian, J.-Y. Wang, J.-N. He, T. Chen, M. Pan, L. Xu, H.-x. Zhang, X.-T. Qiu and C.-C. Li, *Theranostics*, 2018, **8**, 6163.

136 J. Liu, M. Jiang, S. Deng, J. Lu, H. Huang, Y. Zhang, P. Gong, X. Shen, H. Ruan and M. Jin, *Mol. Ther.–Nucleic Acids*, 2018, **11**, 103–115.

137 P. Kirave, P. Gondaliya, B. Kulkarni, R. Rawal, R. Garg, A. Jain and K. Kalia, *Oncotarget*, 2020, **11**, 1157.

138 G. Liang, S. Kan, Y. Zhu, S. Feng, W. Feng and S. Gao, *Int. J. Nanomed.*, 2018, **13**, 585.

139 D. Wang, X. Wang, Y. Song, M. Si, Y. Sun, X. Liu, S. Cui, X. Qu and X. Yu, *Cell Death Dis.*, 2022, **13**, 380.

140 C. Wang, J. Wang, W. Cui, Y. Liu, H. Zhou, Y. Wang, X. Chen, X. Chen and Z. Wang, *OncoTargets Ther.*, 2021, **14**, 1441.

141 K. Kaban, C. Hinterleitner, Y. Zhou, E. Salva, A. G. Kantarci, H. R. Salih and M. Märklin, *Cancers*, 2021, **13**, 2397.

142 K. A. Greco, C. A. Franzen, K. E. Foreman, R. C. Flanigan, P. C. Kuo and G. N. Gupta, *Urology*, 2016, **91**, 241.

143 S. Gurung, D. Perocheau, L. Touramanidou and J. Baruteau, *Cell Commun. Signaling*, 2021, **19**, 47.

144 Q. Hu, H. Su, J. Li, C. Lyon, W. Tang, M. Wan and T. Y. Hu, *Precis. Clin. Med.*, 2020, **3**, 54–66.

145 M. F. Tsan and B. Gao, *J. Leukocyte Biol.*, 2009, **85**, 905–910.

146 S. Samanta, S. Rajasingh, N. Drosos, Z. Zhou, B. Dawn and J. Rajasingh, *Acta Pharmacol. Sin.*, 2018, **39**, 501–513.

147 R. Mears, R. A. Craven, S. Hanrahan, N. Totty, C. Upton, S. L. Young, P. Patel, P. J. Selby and R. E. Banks, *Proteomics*, 2004, **4**, 4019–4031.

148 S. Di Gioia, M. N. Hossain and M. Conese, *Open Med.*, 2020, **15**, 1096–1122.

149 J. Donoso-Quezada, S. Ayala-Mar and J. González-Valdez, *Traffic*, 2021, **22**, 204–220.

150 S. Xie, Q. Zhang and L. Jiang, *Membranes*, 2022, **12**, 498.

151 K. Segawa, S. Kurata, Y. Yanagihashi, T. R. Brummelkamp, F. Matsuda and S. Nagata, *Science*, 2014, **344**, 1164–1168.

152 S. E. Sedykh, E. E. Burkova, L. V. Purvinsh, D. A. Klemeshova, E. I. Ryabchikova and G. A. Nevinsky, *Extracellular Vesicles and Their Importance in Human Health*, 2020, pp. 1–28.

153 J. Donoso-Quezada, S. Ayala-Mar and J. Gonzalez-Valdez, *Traffic*, 2021, **22**, 204–220.

154 F. Chen, N. Wang, H.-Y. Tan, W. Guo, C. Zhang and Y. Feng, *Cancer Biol. Ther.*, 2019, **20**, 583–592.

155 S. Mathivanan, H. Ji and R. J. Simpson, *J. Proteomics*, 2010, **73**, 1907–1920.

156 J. Wang, B.-L. Yue, Y.-Z. Huang, X.-Y. Lan, W.-J. Liu and H. Chen, *Int. J. Mol. Sci.*, 2022, **23**, 2461.

157 M. Ahmadi and J. Rezaie, *J. Transl. Med.*, 2020, **18**, 1–17.

158 Y. Wang, M. Li, L. Chen, H. Bian, X. Chen, H. Zheng, P. Yang, Q. Chen and H. Xu, *Signal Transduction Targeted Ther.*, 2021, **6**, 409.

159 L. P. Zhu, T. Tian, J. Y. Wang, J. N. He, T. Chen, M. Pan, L. Xu, H. X. Zhang, X. T. Qiu, C. C. Li, K. K. Wang, H. Shen, G. G. Zhang and Y. P. Bai, *Theranostics*, 2018, **8**, 6163–6177.

160 X. F. Zhang, T. Wang, Z. X. Wang, K. P. Huang, Y. W. Zhang, G. L. Wang, H. J. Zhang, Z. H. Chen, C. Y. Wang, J. X. Zhang and H. Wang, *Mol. Ther.–Nucleic Acids*, 2021, **26**, 347–359.

161 J. Liu, M. Jiang, S. Deng, J. Lu, H. Huang, Y. Zhang, P. Gong, X. Shen, H. Ruan, M. Jin and H. Wang, *Mol. Ther.–Nucleic Acids*, 2018, **11**, 103–115.

162 S. Baron, *Medical microbiology*, University of Texas Medical Branch at Galveston, Galveston (TX), 4th edn, 1996.

163 S. Mostowy and A. R. Shenoy, *Nat. Rev. Immunol.*, 2015, **15**, 559–573.

164 K. K. Ayyar and A. C. Moss, *Front. Pharmacol*, 2021, **12**, 1295.

165 J. Munir, M. Lee and S. Ryu, *Adv. Nutr.*, 2020, **11**, 687–696.

166 R. Anusha and S. Priya, *Mol. Nutr. Food Res.*, 2022, **66**, 2200142.

167 M. De Robertis, A. Sarra, V. D'oria, F. Mura, F. Bordi, P. Postorino and D. Fratantonio, *Biomolecules*, 2020, **10**, 742.

168 B. Wang, X. Zhuang, Z.-B. Deng, H. Jiang, J. Mu, Q. Wang, X. Xiang, H. Guo, L. Zhang and G. Dryden, *Mol. Ther.*, 2014, **22**, 522–534.

169 X. Zhuang, Z.-B. Deng, J. Mu, L. Zhang, J. Yan, D. Miller, W. Feng, C. J. McClain and H.-G. Zhang, *J. Extracell. Vesicles*, 2015, **4**, 28713.

170 G. Ahn, Y.-H. Kim and J.-Y. Ahn, *Nanoscale Adv.*, 2021, **3**, 528–537.

171 Z. Deng, Y. Rong, Y. Teng, J. Mu, X. Zhuang, M. Tseng, A. Samykutty, L. Zhang, J. Yan and D. Miller, *Mol. Ther.*, 2017, **25**, 1641–1654.

172 A. A. Badawy, M. A. El-Magd and S. A. AlSadrah, *Integr. Cancer Ther.*, 2018, **17**, 1235–1246.

173 X. Chen, B. Liu, X. Li, T. T. An, Y. Zhou, G. Li, J. Wu-Smart, S. Alvarez, M. J. Naldrett, J. Eudy, G. Kubik, R. A. Wilson, S. D. Kachman, J. Cui and J. Yu, *J. Extracell. Vesicles*, 2021, **10**, e12069.

174 V. Iebba, V. Totino, A. Gagliardi, F. Santangelo, F. Cacciotti, M. Trancassini, C. Mancini, C. Cicerone, E. Corazziari and F. Pantanella, *New Microbiol.*, 2016, **39**, 1–12.

175 H. E. Al-Rashidi, *Saudi J. Biol. Sci.*, 2022, **29**, 1628–1643.

176 W. Stremmel, R. Weiskirchen and B. C. Melnik, *Inflamm. Bowel Dis.*, 2020, **5**, 117–123.

177 J. Aarts, A. Boleij, B. C. Pieters, A. L. Feitsma, R. J. van Neerven, J. P. Ten Klooster, L. M'Rabet, O. J. Arntz, M. I. Koenders and F. A. van de Loo, *Front. Immunol.*, 2021, **12**, 703277.

178 M. Potesta, V. Roglia, M. Fanelli, E. Pietrobono, A. Gismondi, S. Vumbaca, R. G. Nguedia Tsangueu, A. Canini, V. Colizzi, S. Grelli, A. Minutolo and C. Montesano, *Cell Death Discovery*, 2020, **6**, 43.

179 A. A. Badawy, M. A. El-Magd and S. A. AlSadrah, *Integr. Cancer Ther.*, 2018, **17**, 1235–1246.

180 A. A. Badawy, R. Q. A. Othman and M. A. El-Magd, *Mol. Cell. Toxicol.*, 2021, DOI: 10.1007/s13273-021-00163-4.

181 S. Raimondo, F. Naselli, S. Fontana, F. Monteleone, A. L. Dico, L. Saieva, G. Zito, A. Flugy, M. Manno and M. A. Di Bella, *Oncotarget*, 2015, **6**, 19514.

182 X. Chen, Y. Zhou and J. Yu, *Mol. Pharmaceutics*, 2019, **16**, 2690–2699.

183 A. Mokarizadeh, K. Hassanzadeh, M. Abdi, H. Soraya, M. R. Faryabi, E. Mohammadi and A. Ahmadi, *Med. Hypotheses*, 2015, **85**, 141–144.

184 H. Kim, D. E. Kim, G. Han, N. R. Lim, E. H. Kim, Y. Jang, H. Cho, H. Jang, K. H. Kim and S. H. Kim, *Adv. Healthcare Mater.*, 2022, **11**, 2102027.

185 X. Chen, B. Liu, X. Li, T. T. An, Y. Zhou, G. Li, J. Wu-Smart, S. Alvarez, M. J. Naldrett and J. Eudy, *J. Extracell. Vesicles*, 2021, **10**, e12069.

186 Q. Wang, X. Zhuang, J. Mu, Z.-B. Deng, H. Jiang, L. Zhang, X. Xiang, B. Wang, J. Yan and D. Miller, *Nat. Commun.*, 2013, **4**, 1867.

187 X. Zhuang, Y. Teng, A. Samykutty, J. Mu, Z. Deng, L. Zhang, P. Cao, Y. Rong, J. Yan and D. Miller, *Mol. Ther.*, 2016, **24**, 96–105.

188 S. Ju, J. Mu, T. Dokland, X. Zhuang, Q. Wang, H. Jiang, X. Xiang, Z.-B. Deng, B. Wang and L. Zhang, *Mol. Ther.*, 2013, **21**, 1345–1357.

189 M. R. Ghiasi, E. Rahimi, Z. Amirkhani and R. Salehi, *Adv. Biomed. Res.*, 2018, **7**, 125.

190 Z. Li, H. Wang, H. Yin, C. Bennett, H.-g. Zhang and P. Guo, *Sci. Rep.*, 2018, **8**, 14644.

191 M. Zhang, B. Xiao, H. Wang, M. K. Han, Z. Zhang, E. Viennois, C. Xu and D. Merlin, *Mol. Ther.*, 2016, **24**, 1783–1796.

192 M. Zhang, X. Wang, M. K. Han, J. F. Collins and D. Merlin, *Nanomedicine*, 2017, **12**, 1927–1943.

193 Y. Teng, Y. Ren, M. Sayed, X. Hu, C. Lei, A. Kumar, E. Hutchins, J. Mu, Z. Deng and C. Luo, *Cell Host Microbe*, 2018, **24**, 637–652.

194 M. Zhang, E. Viennois, M. Prasad, Y. Zhang, L. Wang, Z. Zhang, M. K. Han, B. Xiao, C. Xu and S. Srinivasan, *Biomaterials*, 2016, **101**, 321–340.

195 X. Wang, M. Zhang, S. R. Flores, R. R. Woloshun, C. Yang, L. Yin, P. Xiang, X. Xu, M. D. Garrick and S. Vidyasagar, *Mol. Ther.*, 2019, **27**, 493–506.

196 M. Vashisht, P. Rani, S. K. Onteru and D. Singh, *Appl. Biochem. Biotechnol.*, 2017, **183**, 993–1007.

197 R. Munagala, F. Aqil, J. Jeyabalan, A. K. Agrawal, A. M. Mudd, A. H. Kyakulaga, I. P. Singh, M. V. Vadhanam and R. C. Gupta, *Cancer Lett.*, 2017, **393**, 94–102.

198 Q. Zhang, Q. Xiao, H. Yin, C. Xia, Y. Pu, Z. He, Q. Hu, J. Wang and Y. Wang, *RSC Adv.*, 2020, **10**, 28314–28323.

199 R. Munagala, F. Aqil, J. Jeyabalan and R. C. Gupta, *Cancer Lett.*, 2016, **371**, 48–61.

200 B. Li, A. Hock, R. Y. Wu, A. Minich, S. R. Botts, C. Lee, L. Antounians, H. Miyake, Y. Koike and Y. Chen, *PLoS One*, 2019, **14**, e0211431.

201 B. C. Pieters, O. J. Arntz, J. Aarts, A. L. Feitsma, R. J. van Neerven, P. M. van der Kraan, M. C. Oliveira and F. A. van de Loo, *Mol. Nutr. Food Res.*, 2022, **66**, 2100764.

202 M. Potestà, V. Roglia, M. Fanelli, E. Pietrobono, A. Gismondi, S. Vumbaca, R. G. Nguedia Tsangueu, A. Canini, V. Colizzi and S. Grelli, *Cell Death Discovery*, 2020, **6**, 43.

203 M. Hazawa, K. Tomiyama, A. Saotome-Nakamura, C. Obara, T. Yasuda, T. Gotoh, I. Tanaka, H. Yakumaru, H. Ishihara and K. Tajima, *Biochem. Biophys. Res. Commun.*, 2014, **446**, 1165–1171.