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REVIEW

Exosomes: current knowledge and future perspectives

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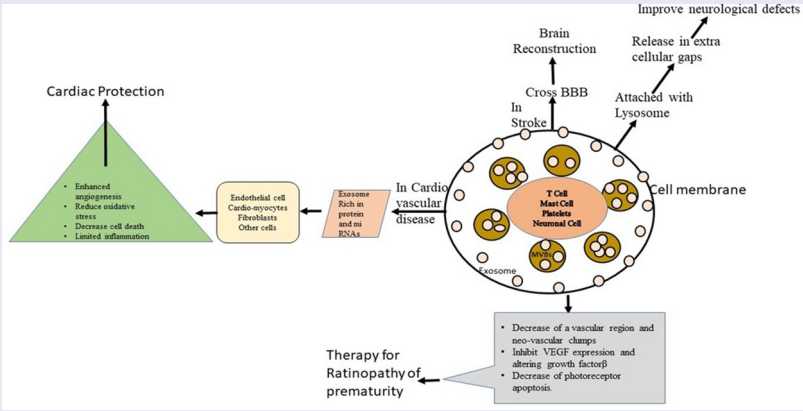
ABSTRACT

Exosomes are membrane-bound micro-vesicles that possess endless therapeutic potential for treatment of numerous pathologies including autoimmune, cardiovascular, ocular, and nervous disorders. Despite considerable knowledge about exosome biogenesis and secretion, still, there is a lack of information regarding exosome uptake by cell types and internal signaling pathways through which these exosomes process cellular response. Exosomes are key components of cell signaling and intercellular communication. In central nervous system (CNS), exosomes can penetrate BBB and maintain homeostasis by myelin sheath regulation and the waste products elimination. Therefore, the current review summarizes role of exosomes and their use as biomarkers in cardiovascular, nervous and ocular disorders. This aspect of exosomes provides positive hope to monitor disease development and enable early diagnosis and treatment optimization. In this review, we have summarized recent findings on physiological and therapeutic effects of exosomes and also attempt to provide insights about stress-preconditioned exosomes and stem cell-derived exosomes.



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1. Introduction

Biologically exosomes are natural therapeutic molecules having membranous vesicles (30–100 nm) which contain protein, lipid, and RNA in a particular living system. These exosomes contain a lipid bilayer membrane, surrounded by cytosol but do not contain any cellular organelles such as lysosomes, mitochondria, endoplasmic reticulum, or Golgi apparatus, etc.[1] They are released from T-cells, mast cells, dendritic cells, platelets, neuron cells, and epithelial cells present in the internal cellular spaces and body fluids (plasma, urine saliva, cerebrospinal fluid, colostrum, etc.).[1] Exosomes play an important role in the regulation of the immune system.[2] When the antigen is identified, the production of internal vesicles begins to take place in the presence of lysosomes. These vesicles are also called multi-vascular bodies (MVBs) which attach to the cellular membrane and result in the release of intracellular vesicles called exosomes. Further, the growth factors bind and activate receptors resulting in potentiation of various downstream pathways including stimulation of protein synthesis, production of MVBs and induction of

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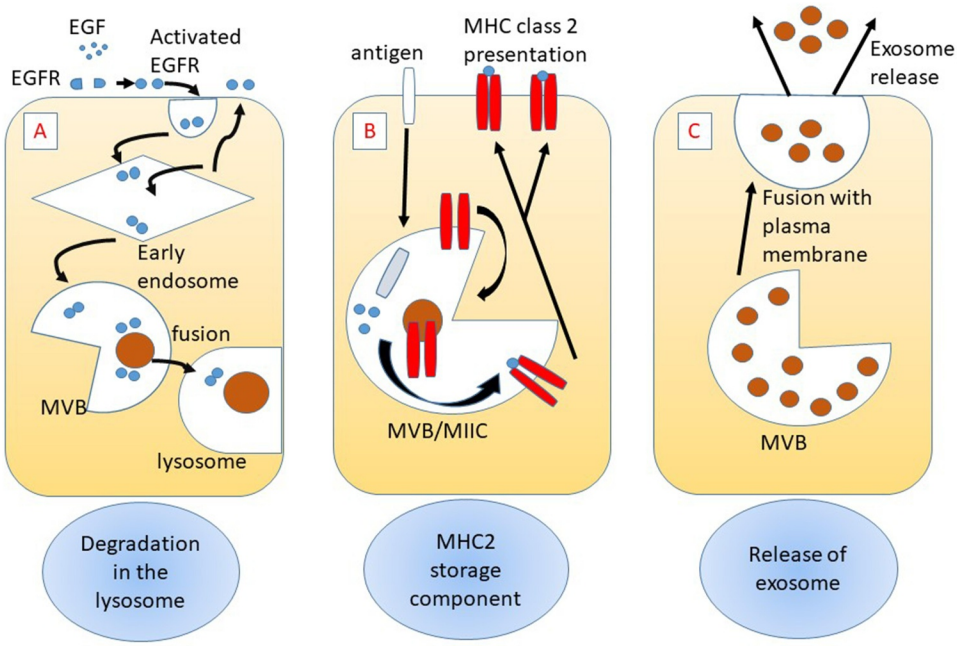

Figure 1. Different functions and fates of internalized vesicles.

various intracellular signaling pathways. This activation of signaling pathways is regulated directly or indirectly by lysosomes because of its involvement in the release of intracellular vesicles into the extracellular space (Figure 1).

The complicated layered protein enclosed in the exosome involves glycosyl-phosphatidyl-inositol (GPI) anchored protein, receptor ((Tumor Necrosis Factor Receptor 1) TNFR1), tetraspanins (Cluster of differentiation (CD81 and 82, CD9, CD63)), etc. Some other complex substances enfolded in exosomes include:

- Luminal proteins (cytokines and annexins).
- Presentation of antigen major histocompatibility complex 1&2 (MHC1 and 2), cell adhesion (milk fat globule epidermal growth factor 8 (MFGE8, integrin)) co-presentation molecules etc.
- Metabolic enzyme/fatty acids such as β-enolase, peroxidase, pyruvate kinase, and glyceraldehyde-3-phosphate dehydrogenase.
- Heat shock protein and chaperons (HSP20, HSP60, HSP70, HSP90)
- Protein associated with exosome biogenesis, i.e. ESCRT complex (endosomal sorting complexes required for transport such as ALIX (ALG-2 interacting protein X) and TSg101).
- Signaling proteins (Guanosine triphosphatase Harvey Rat sarcoma virus (GTPase Hras), Ras homolog gene family member A (RhoA), Guanine nucleotide-binding protein subunits-G-protein, Kinases, Ras-related protein (RAP1B))
- Protein associated with transcription and synthesis of proteins (Histone, transcription factors, ribosomal protein, ubiquitins, etc.)
- Protein associated with trading and joining of a membrane (ADP ribosylation factor (ARF), Rab protein, annexins)

1.1. Uptake of exosome

Exosomes are an important means of communication among cells. They are secreted from the donor cell within the extravascular environment and experience the wafting time in which they can flow all over the body fluids.[3] Exosomes are taken up by the receiver cell through various pathways. Inter-cellular movement of exosomes can be divided into the following three types:

(a) Exosomes can directly fuse with the plasma layer of the receiver cell to transport their internal contents to the receiver cell.[4]

(b) Target cell and exosomes transfer signal via interaction between receptor ligands.[5]
(c) Uptake of target cell exosome through various forms of endocytosis. This mechanism of endocytosis involves caveolin and clathrin-regulated endocytosis, raft-regulated endocytosis and receptors, phagocytosis, and micropinocytosis.[6]

1.2. Movement of exosome across different tissue barriers

Exosomes are small extracellular vesicles that play a crucial role in intracellular communication by transferring protein, lipid, and nucleic acids (RNA and DNA). The exosome is involved in various pathological and physiological processes, including development, immune response, and disease progression. The exosomes have the ability to bind different barriers such as the blood-brain barrier (BBB), intestinal barrier, placental barrier, pulmonary barrier, and skin barrier and cross them.

(A) **Blood–brain barrier (BBB)**: BBB is known as a selective barrier between systemic circulation and the brain[7] and is mainly constituted by three barriers: endothelial cells (ECs), blood-cerebrospinal fluid barrier (BCSFB), and meningeal barrier.[8] These barriers separate the circulating blood from the CNS. Exosomes help transport specific cargoes across the BBB, stimulating intracellular communication between the brain and peripheral cells. Several transcellular mechanisms are involved in transporting the substances across the BBB including active efflux transport, adsorptive-mediated transcytosis, carrier-mediated transport, and receptor-mediated transport (involving transferrin receptors, foliate receptors, lipoprotein receptor-related proteins, scavenging receptors, interleukin-13 receptor a2, insulin receptors, and glutamate receptors).[9] In BBB, ECs are the main site that controls the transfer of exosomes. Exosomes from the blood flow move faster into the brain tissue when general mechanisms involved in EV uptake, such as endocytosis, micropinocytosis, phagocytosis, and plasma membrane fusion, are triggered upon by physical contact between circulating exosomes and BBB ECs. Furthermore, the entry of exosomes into the blood–brain barrier could be explained by three mechanisms, which include physical contact (fusion or ligand–receptor interaction, etc.), paracytosis, and transcytosis. Exosomes connect to and fuse with barrier-type ECs during this process, releasing cargo onto the cytosol. Gap junction-like communications start off as a result of particular receptors on the surface of ECs and exosome membrane proteins.[10] There are two potential stops along the transcytosis pathway. Exosomes are either directed to endosomes for destruction or for the entry into cells while the abluminal surface of ECs may receive exosomes from endosomes.[11]

(B) **Intestinal barrier**: It is a complex system that comprises of a single layer of epithelial cells that attach to the intestinal surface. It contributes as a critical defense mechanism by controlling the absorption of water and nutrients while preventing the entry of harmful substances, such as pathogens and toxins, into the bloodstream. Exosomes derived from intestinal cells consist of lipids, proteins, and microRNAs, which play an important role in maintaining the integrity of the intestinal barrier and modulating the immune response. They carry a diverse cargo of bioactive molecules, including chemokines, cytokines, and immune regulatory factors. They can bind with immune cells such as dendritic cells, macrophages, and T cells, which stimulates their function and promotes immune intolerance. By transferring anti-inflammatory factors to immune cells, it can suppress the inflammatory response and help maintain homeostasis.[12]

(C) **Placental barrier**: Placenta-derived exosomes are different from other exosomes due to the presence of some specific proteins, such as placenta-type alkaline phosphate (PLAP) and human leukocyte antigen G (HLA-G), as well as miRNA. It has been demonstrated that it is discharged from the placenta into the maternal circulation as

early as 7 weeks of gestation, and its concentration rises throughout the course of the pregnancy. This release is controlled by various factors comprising of mainly oxygen and glucose concentrations. The placenta barriers separate these maternal and fetal circulations. The release of exosomes correlates with placenta mass and contractility in normal pregnancy and is involved in the transfer of various molecules, including proteins and nucleic acids, across the placenta barrier.[13] These exosomes show another pathway by which the placenta interacts with the maternal system to induce maternal vascular adaptation to pregnancy and the progression of maternal–fetal vascular exchange. This interaction is important for normal fetal development.[14]

(D) **Pulmonary barrier**: It is referred to as the cellular layers that divide the lungs airspaces from the surrounding tissue and blood vessels. It plays a critical role as a crucial interface for gas exchange while providing protection against harmful substances. Exosomes are detected in lungs fluids, and some evidence suggests that they also help to maintain lungs homeostasis, immune response, and intracellular communication with the lungs, as we discussed in the intestinal barrier. This communication plays an important role in coordinating physiological processes, repairing damaged tissue, and responding to injury within the lungs.[15] However, understanding the function of exosomes in the pulmonary barrier is crucial for comprehending normal lung physiology, but it also has the potential to lead to the discovery of novel diagnostic indicators and treatment targets for lung disorders. It is important to keep in mind that the study of exosomes in relation to the pulmonary barrier is still not completely known, and more research is required to completely comprehend the workings of exosomal communication in the lungs as well as its functional significance.[16]

(E) **Skin barrier**: Skin is the largest organ of the human body and serves as a barrier to protect the body from the external environment and microbial invasion. The skin barrier is formed by the outermost layer, called the stratum corneum, which consists of dead skin cells implanted in a lipid-rich matrix. The skin cell-derived exosome participates in intercellular communication, carrying lipids, proteins, nucleic acids, and miRNA that can be transferred to neighboring cells and alter their functions. It is also involved in the maintenance of homeostasis by carrying important signaling molecules, growth factors, and enzymes that regulate cellular activities such as proliferation, differentiation, and apoptosis, as well as the production of organizational lipid within the stratum corneum, which is important for skin barriers. These exosomes also promote angiogenesis, cell migration, and tissue regeneration, which contribute to wound healing by enhancing the production of extracellular matrix components and modulating immune responses.[17]

1.3. Regulation of cell physiology through exosomes

Exosomes are considered to be an essential feature of the inner cell atmosphere and serve as a mediator for cell–cell interaction. They also act like immune stimulators having an immune triggering effect via conveying nucleic acid and protein to the receiver cell. Exosomes once secreted, may influence the behavior of the target cell or move toward the biological fluids and consequently extend to the distant location. Table 1 summarizes the role of exosomes derived from different cells and their physiological effects.

1.3.1. Role of exosome in CNS physiology

Exosomes are subtypes of extracellular vesicles (EVs) that change their composition to form intraluminal vesicles (ILVs), and further undergo modification to produce multi-vascular bodies (MVBs). MVBs attach to the lysosome plasma layer and release their constituents in extracellular gaps. These EVs play an important role in cell biology and physiology that includes the maintenance of stem cells and prevention of pathological conditions of disease.[18,19] It also has a prominent role

Table 1. Physiological effects and role of exosome.

Cell or tissue obtained exosomes	Goal	Role/Consequences
Activation of B cell	CD4+ T cell	Stimulation of immune effects and balancing T cell
Plasma	T cell	Stop Th1 type oversensitivity effects and Th2 type allergic effects
Plasma	Lymphocyte and monocytes	Carrying particular exogenous siRNA focused MAPK pathway
Placenta	child and Foetus	Regulating activity of the T cell
Mouse mast cell	Marrow obtained mouse mast cell	Stimulated alteration of genetic materials.
Breast milk	New born	Stimulation of immune cell function of infants through miRNA associated T cell regulation and B cell distinction
Cancer involved fibroblast	Cancer in breast	Improvement of cell prominent activity
Metastatic melanoma cells	Bone marrow parent cell	Assisted tumor vasculogensis, invasion
Chronic myelogenous leukemia cells	Human endothelial cell	Initiation of angiogenic phenotype by secretion of IL8
Acute myeloid leukemia blasts and cells	progenitor cells like Ba/F3	Change of angiogenic, migratory and proliferative effects.
Endothelial cell	Smooth muscle cell	Movement of miRNA
Neuronal cells	Glial cell	Transportation of α synuclein

in neurological diseases as they serve to mediate information between nerves and glial cells. The pathological and physiological condition of exosomes makes it a possible drug transporting system by using direction for gene treatment toward targeting particular cells.[6]

1.4. Role of exosome in pathological states

1.4.1. Stroke

A stroke is a major medical emergency and a life-intimidating state. It is one of the leading causes of death prevalent all over the world. There are mainly two types of stroke

(a) Ischemic
(b) Hemorrhagic

Ischemic stroke reports for 87% of all strokes and is caused by thrombosis, blockage, or atherosclerosis in the major artery, leading to cerebral hypoxia and ischemia.[20]

Cerebral stroke (hemorrhagic stroke) is mainly caused due to bleeding in the brain by the rupture of a blood vessel. During the therapy of ischemic strokes, the main target is to restore the flow of blood. The two main methods used for the restoration of blood flow are thrombolysis by drugs (tissue plasminogen activator within 4–5 hr) and endovascular intracranial thrombectomy (extend potent life).[21]

The major problem in treatment lies in the identification of an appropriate biomarker for the treatment and diagnosis of stroke patients.[22] Exosomes may play a role in the management of stroke as they are synthesized from brain cells and can enter the cerebrospinal fluid by passing through BBB. Exosomes may also be released from the blood cells and pass through the endothelial cell wall during a stroke and can participate in stroke recovery through brain reconstruction. Secretion of exosomes from the destroyed central nervous cell may influence the spleen where they can enhance the release of pro-inflammatory cytokines and activation of T and B lymphocytes for regulation of immune inflammatory response. There are various types of exosomes with contain cystatin C and CD14 (cluster of differentiation 14), which may also be associated with the progression of brain atrophy in patients with vascular disease.[23] Transmission of mi-RNA and RNA among exosomes may play an important role in the stimulated brain restoration which may serve as an important regulator in the pathology and pathogenesis of ischemic stroke. Also, mi-RNA from exosomes has been known as a useful biomarker for the diagnosis, prognosis, and treatment of ischemic stroke (Figure 2).

The BBB gets damaged after the stroke. To repair the BBB and to upgrade angiogenesis, the pericytes attached to brain endothelial cells secrete exosomes which serve an important role in providing nutrition for neurogenesis. Neurons, oligodendrocytes, and astrocytes interact with each other through exosomes to regulate synaptic plasticity. Neurons linked with microglia regulate brain immune inflammation, and neurons and neural progenitor cells secrete exosomes to regulate peripheral immunity after being stimulated by external substances which pass through the BBB. After the stroke, brain endothelial cells secrete exosomes that regulate neural progenitor cells to differentiate into

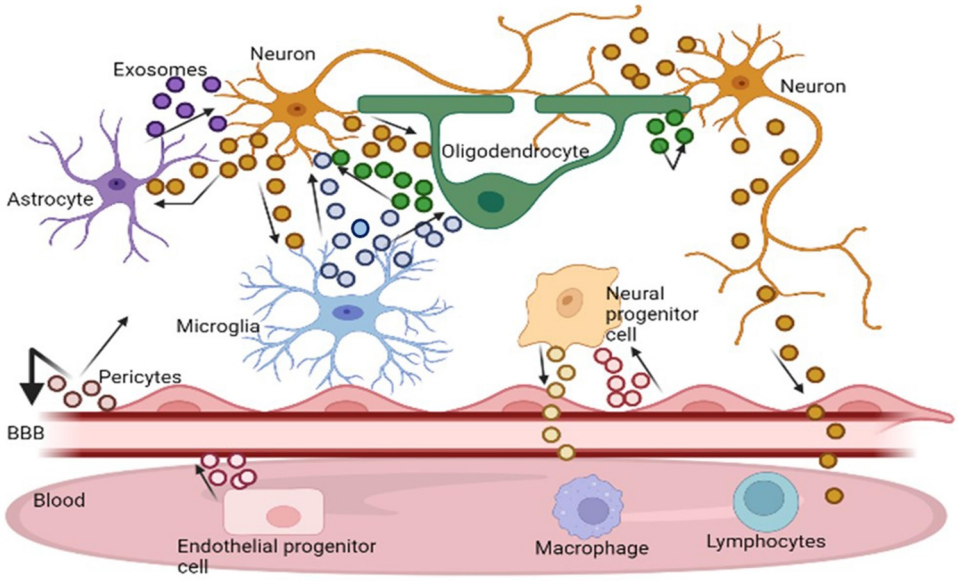

Figure 2. Exosome associated in brain reconstruction after stroke.

oligodendrocytes which participate in myelination. In conclusion, the exosomes have an important therapeutic role in protecting against damage after stroke as they exert long-term neuroprotective effects, regulate peripheral immune response, and participate in brain reconstruction events such as enhanced angiogenesis and axonal dendritic remodeling.

1.4.2. Neurodegenerative diseases

It is one of the major causes of death and dysfunction and also leads to a heavy burden on the healthcare system. Exosome proves as a favorable prognostic biomarker and gives therapeutic approaches in brain injury and neurodegenerative diseases. Various studies showed that exosomes can be involved in neuroinflammation regulation, development in physiological neurogenesis, and positive effects on neurological diseases. Neurodegenerative diseases caused due to accumulation of intracellular or extracellular insoluble proteins are collectively referred to as cerebral proteinopathies.[24]

Examples

(a) Alzheimer's disease is caused by an accumulation of β-amyloid protein and involvement of microtubules like Tau protein.
(b) Parkinson's disease occurs by aggregation of neuronal end protein alpha-synuclein.
(c) Amyotrophic lateral sclerosis (ALS) occurs by aggregation of transactive response DNA binding protein (TDP43) that may influence transcription inhibitors and superoxide dismutase1 (SOD1)
(d) Huntington's Disease is caused by aggregation of mutant Huntington's protein (mHP)

This aggregation or accumulation is the result of an abnormal protein clearance pathway which may disturb protein homeostasis. The neurological disorder induced through the development of irreversible disability of neurons and synapse acts as a marker of this type of disease. It has been represented that various types of cells in the CNS such as oligodendrocytes and astrocytes released exosomes. Exosome act as a potential carrier and may participate in the pathogenesis of neurodegenerative disorder and can serve in inter-neuron communication.[25] Table 2 summarizes the role of exosomes that act as biomarkers for various neurodegenerative disorders.

1.4.2.1. Alzheimer's disease (AD). It is also a common neurodegenerative disease with major symptoms of dementia. This disorder reduces cognitive capability, normal physiological brain condition, and capability to accomplish actions of daily life. The important reason for AD is aggregation of

Table 2. Exosomes as Biomarkers in Neurodegenerative Disorders.

Name of disease	Origin	Composition	Function	Clinical application
Alzheimer's Disease	Plasma	REST, HSF-1, LAMP1, IRS	Neurological Damage	Premature Identification
Alzheimer's Disease	Serum	miR-135a, miR-193b, miR-384	Neurological Damage	Advance Identification
Alzheimer's Disease	Plasma and CSF	Aβ, NFT	Neurological Damage	Advance Identification
Parkinson Disease	CSF	α –SYN, DJ-1, miR-409, miR-153, miR-485-5p	Neurological Damage	Pre mature Identification
Parkinson Disease	CSF	3p,miR-433, miR-136-3p,miR19b-3p,miR-132-5p, miR-10a-5p, miR-873-3p, miR-370	Neurological Damage	Advance Identification
Prion Disease	Plasma	PrPSc	Neurological Damage	Fast Identification
Prion Disease	Serum	miR-143-3p, miR-451a,mir-146a-5p, miR-142-3p, miR-let-7b,miR-429-3p, miR141-3p,miR-20 family	Neurological Damage	Advance Identification
Amyotrophic lateral sclerosis	Peripheral blood and serum	TDP-43	Neurological Damage	Rapid Discovery
Amyotrophic lateral sclerosis	Plasma	miR-183-5p, miR-193a-5p, miR-9-5p, miR-15a-5p	Neurological Damage	Advance Identification
Huntingtons Disease	Plasma	mHtt	Neurological Damage	Advance Identification
Huntingtons Disease	Plasma	miR-877-5p, miR-22-5p, miR-30d-5p, miR-223-5p	Neurological Damage	Advance Identification

REST: Repressor element 1-silencing transcription factor, LAMP: Lysosome associated membrane protein, IRS: Insulin receptor substrate, SYN: Synuclein, NFT: Neurofibrillary tangles, DJ-1: Protein deglycase, PrPSc: Primarily of scrapie prion protein.

Aβ plaque and neurofibrillary tangles (NFT) which is produced by Tau protein over phosphorylation.

The pathological condition can be divided into two parts:

(a) Amyloid Plaque
(b) NFT

The aggregation of Aβ in oligomers (which are responsible for the formation of amyloid plaque) occurs at the very early stage of the development of disease. Almost 5.5 million Americans have been identified with AD and it is expected that it will increase by 13.8 million in 2050. There is increasing evidence of exosomes associated with the transfer of Tau and Aβ proteins, but the major role is still controversial. Some studies represent that transfer of exosome of these two proteins may involve in the mechanism of decomposition of neuronal microtubule and affect the axonal transport, which leads to a lack of neurons and death of a cell, but in other studies, exosome have been found to show the capability to decrease amyloid β protein in brain introduced by microglia. It also can transmit neuroprotective substances between cells. Various studies show that disease-related protein in exosomes have been found in cerebrospinal fluid (CSF) or plasma samples of protein with AD which represents exosomes as an AD biomarker. Some other studies show that neuronal exosome detected from the plasma of AD patients contains autolysosome protein and changed the level of lysosome-associated membrane protein 1 (LAMP1). In exosomes separated from the plasma sample, change has been detected in Tau and Aβ levels, and thus, they can serve as predictors of AD. There are various neurogenic exosomes linked proteins in the plasma of patients with AD, involving repressor element 1-silencing transcription factor (REST), LAMP1, heat shock factors1 (HSF-1), phosphorylated type 1 insulin receptor substrate (IRS), and the level of these changes within 10 years after diagnosis of AD. The expression level of miR-135a, miR-384, and miR-193b are compared in serum isolated from the exosome of a normal individual and neurodegenerative patient with either Parkinson's disease dementia (PPD), vascular dementia (VaD) or mild cognitive impairment (MCI). The results of the comparison show that the other two small RNA and microRNA 384 have a good ability to transform PDD, VaD, and AD. For advanced diagnosis of Alzheimer's disease. The composition of miR-193b, miR-384, miR-135a seems more useful. These experiments represent that exosomes can show a new direction for the prevention and identification of disease. It also

shows that exosomes produced by various brain tissue cells would play an important therapeutic role in the progression and alteration of AD.[26]

1.4.2.2. Parkinson's disease (PD). It is the most common motor disorder and second most common neurodegenerative disease in CNS and it occurs mostly in old age. The risk of this disease increases as the age progresses. The clinical symptoms are muscle stiffness, static tremors, slow movement, instability in posture, and other types of symptoms associated with dyskinesia. These symptoms occur via variance within the excitatory neurotransmitter (acetylcholine) and inhibitory neurotransmission (dopamine) in the part of the brain, i.e. substantia-nigra of patients with PD. These signals are not produced rapidly after transformation. The very first symptom is shown only due to the lack of dopaminergic neurons in substantia-nigra and striatum. PD patients also show dementia and depression. It has been also represented that misfolded and accumulated α-syn (alpha-synuclein) is the most important constituent of axons and Lewy bodies in an assumed and infrequent type of PD. The secretion of exosomes is mainly linked with intracellular protein delivery with the endosomal-lysosomal process. So maybe their biological characteristic is linked to Parkinson's disease. The main reason for having Parkinson's disease is also linked to the molecular state associated with inoperative protein delivery to lysosome and endosome and this condition has become a definite amalgamate cellular pathway in the pathogenesis of infrequent PD. Various studies show that exosomes transfer toxic α-synuclein between cells which is associated with the progression of PD.[26] It has also been observed that exosomes have the ability to offer neuroprotection in PD as they have an affinity to remove misfolded protein which may hamper the production of neural stem cells. Also, Glial cells and brain neurons can remove and decrease dangerous metabolites with the help of exosome extravasation. Furthermore, they also reduce harmful proteins (alpha-synuclein) in the cell, and various other studies show that exosomes can reduce neuronal stress.

The mitochondrial dysfunction and oxidative stress associated with PD may affect the misfolded alpha-synuclein accumulation, and that is why the biomarkers such as DJ1 (mitochondrial dysfunction-related gene) and alpha-synuclein have the capacity for exact determination of PD.[26] The determination of noninvasive biochemical markers for this disorder is the rational way to target drug research. Quantitative studies have found that exosomes derived from the brain cells of patients with PD can be utilized as the best biomarker for PD. It may involve neurons-derived exosomes (NDE), astrocytes-derived exosomes (ADE), and oligodendrocytes-derived exosomes (ODE). One research found that the plasma ODE and NDE levels enhanced significantly at the early stage of patients with PD and that levels of ODE were linked with the complexity of the disease. This also modified the brain cell capability to eliminate neuro-toxic substances. The research also shows the exosome protein derived by plasma, i.e. clusterin, accompanied by C1R gene division and apo lipoprotein A1 may be used as a biomarker for knowing PD development.[27] A recent study found that the signaling of brain insulin can mediate neuronal survival via the mitogen-activating protein kinase (MAPK) and phosphoinositide 3-kinase protein kinase B (AKT) downregulated pathway and is involved in the pathogenesis of PD. Change in PD condition can be also measured by insulin signaling markers through exosomes derived from the brain and neuronal CSF studies.

1.4.2.3. Prion disease. It is a contaminated spongiform encephalopathy (TSE) which is distinguished by spongiform egg developmental loss of neuronal function and structure. It is a mortal neurodegenerative disorder that occurs mainly in CNS and peripheral nervous system (PNS) and can be transferred between animals and humans. The extent of appreciable misfolded prion protein (PrPSc) with β sheet confirmation is the pathological condition of prion disease. It is secreted via misfolding of common prion protein (PrPC) which has α helical structure. PrPC is highly present in exosome and PrPC (disease-related type) are also shown in exosome. The exosome having PrPC can be involved in the transfer of the virus in various tissues and can regulate the progression of the disease. Studies indicate that the administration of prion-infected exosomes in animals can spread the disease.[28] At present the main well-defined transfer route of prion shows the contact between cell and cell,

nanotube tunnel, and exosome.[29] Current research on the participation of miRNA in exosomes with infectious prions is incomplete and the clinical condition of prion infection indicates the positive upregulation of miR142-3p, miR-145a-5p, miR143-3p, miR-146a-5p, miR-451a, miR-320, miR150-5p, miR-let-7b, miR320 and also negative regulation inhibition of miR-141-3p, miR429-3p and all appendage of the miR-200 family and 182 other miRNA bunches. miRNAs are most important as biomarkers of the disease of prion, but additional studies are necessary to recognize particular miRNAs in body fluids which may have the ability as a biomarker for the determination and treatment of prion disease.[30]

1.4.3. Role of exosomes in cardiovascular diseases

Cardiovascular disease is one of the most common causes of death in living beings with almost one in every four deaths being related to cardiac disorders. The heart of a human being is composed of 2–3 billion cardio-myocytes, which report for almost one-third of the overall number of cells in the heart.[31] This also involves a broad arrangement of extra-cellular cells like a cell of smooth muscle, fibroblast, endothelial cells, cells related to the immune system, mast cells, and various connective tissue and stem cells of the heart[32]. It is observed that the local cell and cell-cell communication serves in the management of cardiac homeostasis and also the transfer of hypertrophic stimuli response.[33] This type of communication among cells mainly involves growth factors regulated autocrine/paracrine, adiponectin-regulated endocrine signals, and interaction between cell-matrix and signaling via an adhesive molecule that involves integrins which may regulate ventricular growth in exchange via various humoral mediators and movement of growth factors. Exosomes are a kind of extracellular vesicles which have 30–100 nm size range. Production of exosomes from the cell was previously suggested to be a process through which cells rejected their cellular waste.[34,35] But over the years, exosomes have come out to play an important role in intracellular interactions that are associated with normal physiology. Examples include development of cardiac muscles, formation of vesicles during reticulocyte maturation, and myocardial angiogenesis.[8,36] Table 3 summarizes the pathological effects of Exosomes in various Cardiovascular diseases.

1.4.3.1. Exosome in cardio-myocyte hypertrophy.

Studies have proved that cardiac stress (such as due to cardiac valve disease, systemic hypertension and myocardial contravention) may lead to cardio-myocyte hypertrophy, fibroblast proliferation and release of extracellular matrix protein as well as pro-inflammatory cytokines.[37,38] Recently, some researchers represented a distinctive process through which cardiac fibroblasts regulate the hypertrophic effects of cardiomyocytes via the delivery of exosomes of miR-21.

Firstly, the researchers recognized the cardiac fibroblast production and release of exosomes by using an approach of RNA sequencing. Then, they identified that miRNA was found to be rich in exosomes obtained from rats especially infant rat's heart fibroblast. The most promising results were obtained by Bang et al. that the fibroblast may deliver exosome of miRNA-21 which is picked up through cardiomyocytes, and then it may regulate the action of SORBS2 (sarcoplasmic protein sorbin and SH3 domain containing protein2) and PDLIM5 (PDZ and LIM domain5) resulting in a considerable increment in the size of cardiomyocyte cell, thus resulting in cardiac hypertrophy[39] (Figure 3).

Table 3. Pathological effect of exosome in cardio-vascular diseases.

Site of exosomes release	Exosome's function	Effects mediated by
Neonatal rat cardiac fibroblasts	Improve cardiac myocyte hypertrophy	miR-21
Goto-kakizaki rat cardio myocytes	Decrease myocardial endothelial cell mediation, formation and migration	miR-320
Platelets via patients with sepsis	Cause endothelial cell apoptosis and cardiac dysfunction	NADPH, NOS, PDI
16K PRL-treated HUVECs (Human Umbilical Vein Endothelial Cells)	Decrease metabolic activity in cardiomyocytes	miR-146a
Heart and plasma of patient with acute peripartum cardiomyopathy	miR-146a rich exosome are involved with dilated with cardiomyopathy	miR-146a

1.4.3.2. Exosome in peri-partum cardiomyopathy (PPCM). PPCM is a serious cardiomyopathy condition occurring in many pregnant women.[40] It is distinguished by unexpected heart attacks in the last trimester of pregnancy and in the starting month of postpartum. 16-K Da N terminal protein chip(16KPRL) linked with the prolactin (PRL) through cathepsin D, is said to be a possible factor in the initiation of PPCM. But the fundamental molecular mechanism remains obscure. At present, some researchers suggested that 16KPRL may also be responsible for miR-146a expression in endothelial cells (ECs), resulting in obstruction of angiogenesis as well as increased secretion of miR-146a-rich exosome through ECs.

The exosome of the endothelial cell can be picked up by cardiomyocytes leading to the promotion of miR-146a levels. In response to this, the expression of neurogenic locus notch homolog protein 1(Notch1), trafficking kinesin-binding protein 1(Trak1), Erbb4 (miR-146a target) was inhibited in cardio-myocytes, resulting in damaged metabolic activity and contractile functions. These results show that miRNA depends on the intracellular interaction system between ECs and cardiomyocytes through exosomes and this can serve as an important biomarker in peripartum cardiomyopathy (PPCM) induced heart failure (Figure 4)

1.4.3.3. Exosome in diabetic cardio-myopathy. Diabetes influences almost 80% of the US population and it is estimated that over 400 million people will be affected by diabetes by 2030 (Vickers NJ 2017). Diabetes is a combination of metabolic diseases characterized by higher levels of blood glucose either because of loss of (type1) or resistance to (type2) insulin.[41] In the case of diabetes with higher glucose levels in the bloodstream, it may result in dysfunction of endothelial cells and refraction of microvascular cells.[42] The abnormal myocardial angiogenesis caused due to diabetes is mainly responsible for the development of ischemic CVS

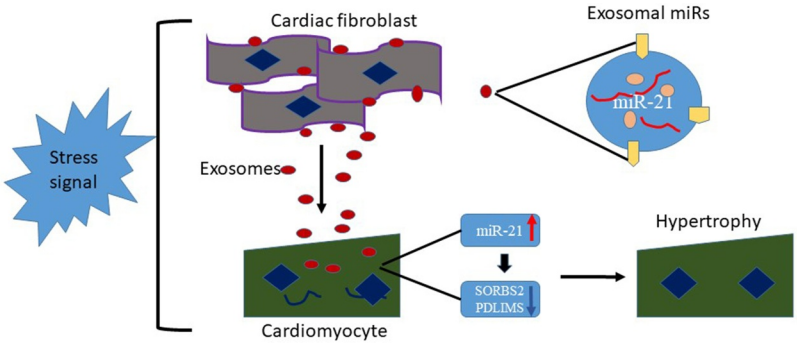

Figure 3. Stress induced cardiomyocyte hypertrophy regulation through exosome of miR-21.

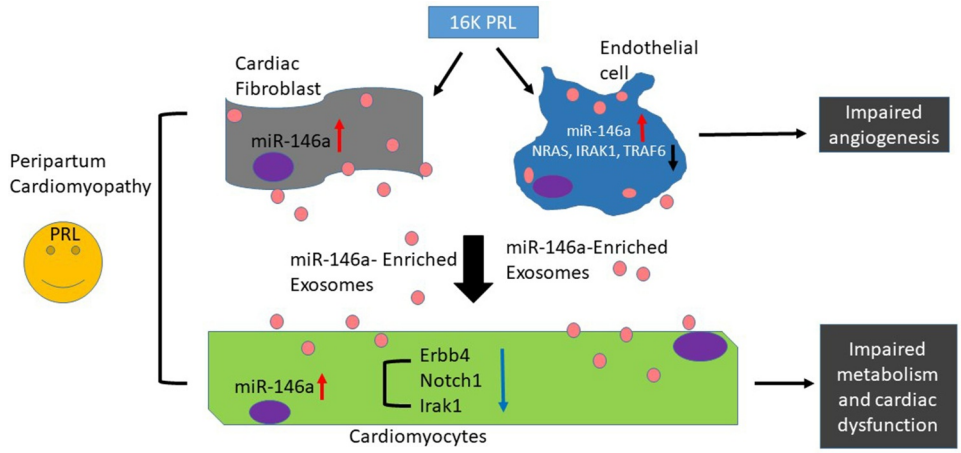

Figure 4. Role of exosomes in peripartum cardiomyopathy.

disease (Vickers NJ et al., 2017). Inside the human heart, the endothelial cells serve an important role in the survival of cardiomyocytes and contraction of myocardial fibers.[43] But during stress conditions such as in the case of hyperglycemia, whether cardiomyocytes can influence the function of an endothelial cell is probably unknown.

Diabetic cardiomyocytes contain greater levels of miR-320 in exosomes and decreased levels of HSP20 protein and miR-126, when compared with normal cardiomyocytes. This downregulates the expression of erythroblast transformation specific-2 (Ets-2) and IGF1 in the endothelial cell which leads to obstruction in blood vessels and inhibition in the proliferation of ECs (Figure 5).

1.4.3.4. Role of exosome in septic cardiomyopathy.

Cardiovascular disturbance plays an important role in the cause of mortality involved with sepsis; a dysfunction that initiates through general infections.[44] There is gripping proof that myocardial decline is observed in more than 40% of sepsis patients,[45] and this effect may involve exosomes. Sepsis is activated through responsive immune effects to contamination, which can lead to multiple organ deterioration.[46] Inflammation caused by sepsis leads to the clotting of blood, consequently leading to loss of nutrients and oxygen supply to essential organs such as the heart. CVS dysfunction is a big factor in the contribution of mortality involved with sepsis. Heart-blood barrier (HBB), which is formed by cardiac endothelial cells, cardiac fibroblast, and other cells regulates the microenvironment for proper function and protection against harmful substances. Dysfunction of HBB contributes to the pathogenesis of sepsis. The implication of cytokines such as TNFα, IL-6, reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as superoxide, nitric oxide, and per oxy-nitrile depress the functions of myocardial tissue. However, various recent studies have shown that the exosome presence in the plasma of a patient with sepsis may lead to cardiac and vascular dysfunction and also coagulation.[2]

Some researchers investigated that, in sepsis, the increased production of NO (nitric oxide) and the presence of liposaccharides (LPS) can activate the secretion of exosomes from various platelets, which contain a large amount of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase,

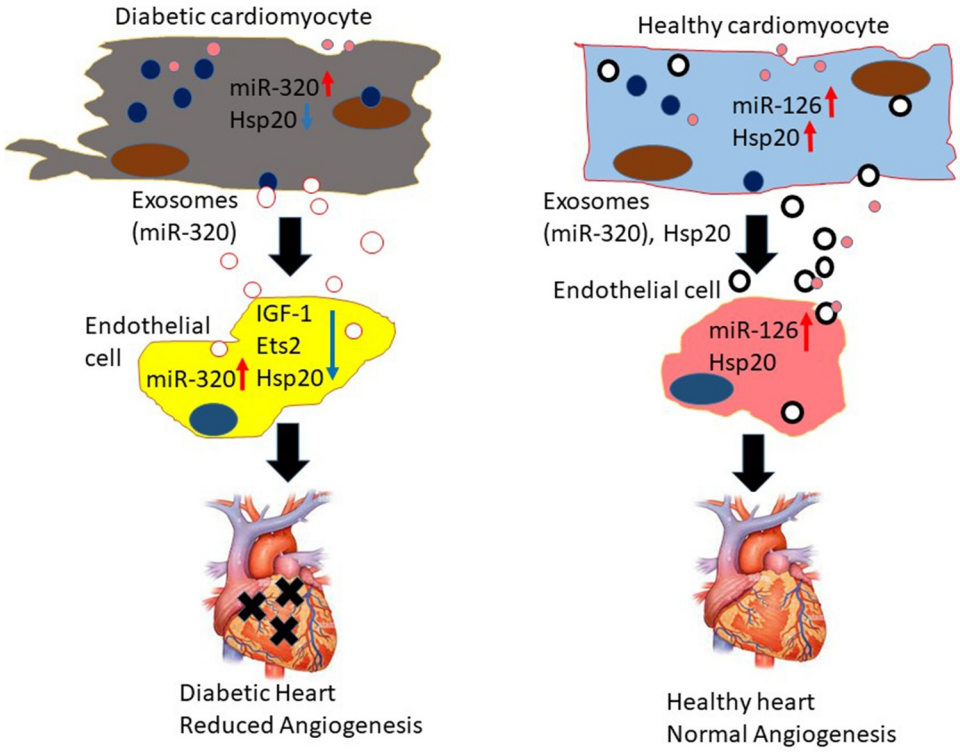

Figure 5. Role of exosomes in diabetic cardiomyopathy.

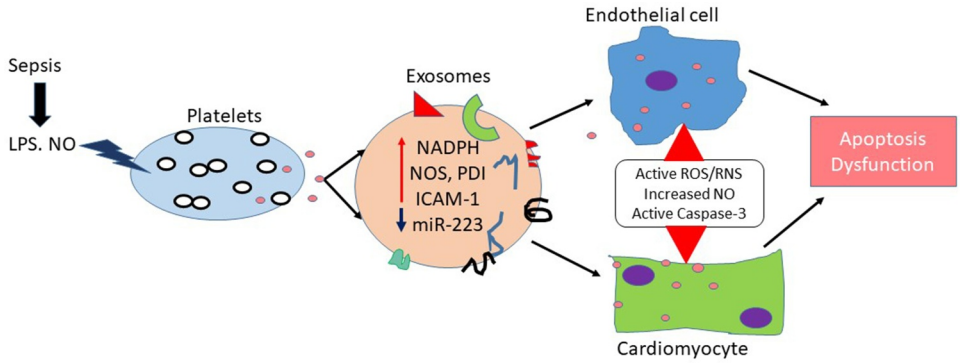

Figure 6. Role of exosomes in septic cardiomyopathy.

protein disulfide isomerase (PDI) and nitric oxide synthase as investigated through western blotting. These effects of exosomes were increased via pre-exposure to LPS. This confirms that the exosome obtained from the septic platelets contains NOS, which may form NO in the exosome and may also induce the production of NO in the heart. And thus may help in alleviating the dysfunctions caused due to cardiomyopathy (Figure 6).

1.5. Protective mechanism of exosome in myocardium

Various studies have indicated that exosome obtained from ischemic cell or any stem cell provide cardio-protection, and this may have a positive effect in the therapy of cardiovascular disease. The endothelial barrier in the myocardium is important for maintaining proper tissue perfusion and disruption in this barrier prevents the discharge of harmful molecules, which induces cardiovascular disease. Exosomes contribute in the regulation of this endothelial barrier function by transferring specific protein, lipid, and nucleic acid.

1.5.1. Exosome from mesenchymal stem cell prevents cardiovascular disorders

Various types of stem cells (such as adult stem cells, embryonic stem cells, or pluripotent stem cells) have been explored for their therapeutic effectiveness in Cardiovascular disorders.[47,48] Stem cells produce various type of factors which includes microRNA, proteins, growth factors, proteasome, antioxidants, exosome, etc. Mesenchymal Stem cells (MSC) obtained exosomes have gathered widespread attention in the treatment of various types of Cardiovascular disorders. Studies involving langendroff representation of reperfusion injury have shown that pure exosomes can decrease barricade size in the heart of mice (Lia RC et al., 2010). Some researchers explain that a single IV bolus of exosome, 5 min earlier to reperfusion effects decreases the barricade size by 45% in mice.[49] They also observed that exosome therapy reinstates redox condition in the heart of mice within 30 min, which is proved by the upregulated level of NADPH and ATP and decreased oxidative stress. These results show that the exosome consists of various enzymes such as glyceraldehyde3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (PGK), enolase (ENO), phosphoglucomutase (PGM), pyruvate kinase m2 isoform (PKm2) that are essential for the generation of ATP. Additionally, activation of CD73 (the main enzyme accountable for the production of external cellular adenosine by releasing adenine nucleotides) and phosphorylation of PFKFB3 (promoter of phosphor fructose kinase) are closely covered in MSC obtained exosome. It may have therapeutic possibilities for patients who are suffering from myocardial infarction. Similar to the above studies, research has been done on the murine model of hypoxia-induced hypertension (HPH), where it was observed that MSC-obtained exosome (MEX) transfer in vivo plays a vital role in the prevention of repressed HPH and vascular remodeling.

1.5.2. Exosome from blood stem cell regulates myocardial angiogenesis

It is already assumed that the blood/hematopoietic stem cell (HSCs) can reconstruct heart tissue by transforming it into cardiomyocytes.[50] But several

studies have shown that some of the implanted HSCs can survive and these cells then evolve into cardiomyocytes.[51] Nevertheless, it has been observed that implantation of these all HSCs can markedly improve cardiac function in various human and animal models. Implantation of HSCs releases various paracrine factors which include vascular endothelial growth factors (VEGF), insulin growth factors (IGF), hepatocyte growth factors (HGF), fibroblast growth factors (FGF), etc. Recently, a study showed that CD34+ stem cells of humans could release exosomes having cup-shaped structures that expressed phosphatidylserine, CD63, and tumor susceptibility gene 101 (TSG101). With the help of in vitro model, it had been observed that CD34+ exosome reproduced the activity of angiogenic CD34+ cells via increasing viability of the endothelial cell, tube-like development on matrigel, and proliferation. In the in vivo study, the author proves that both CD34+ exosome and CD34+ cell was responsible for the production of the vessel-like structure of endothelial cell along with enhancing the length of an endothelial cell. This shows that the CD34+ exosomes are the main paracrine CD34+ component cell factor involved in the growth of vessels. The molecular mechanism behind CD34+ exosome-regulated angiogenesis is not recognized. It may be attributed to angiogenic signaling cascade activation or complete transformation of contents of exosome (protein/RNAs) within the cytosol. A study revealed that the exosome CD34+ is rich in pro-angiogenic miR-130a and miR-126, when compared to the CD34- exosome (Figure 7). But the extent to which these exosomal miR regulate and cause molecular changes in the receiver cell needs to be further clarified.

1.5.3. Exosome from cardiac progenitor cell provides cardio-protection

Cardiac progenitor cell secretes exosomes and these exosomes contain matrix metalloproteinase (MMPs) and external cell matrix metalloproteinase inducer (EMMPRIN), which plays a vital role in the regulation of external cell-matrix and also activate MMP. Additionally, guanine, adenine, thymine, adenine-4 (GTAT4)-effective miR-451 is present in large amounts in these exosomes. Some studies confirmed that cardiac progenitor cell (CPC)-obtained exosome may regulate the migration of endothelial cells. Further, some studies showed that CPC exosomes released in acute myocardial ischemia/reperfusion model in mice inhibited cardiomyocyte apoptosis by 53%. Also, studies have proved that human myocardial cells produce “Spheres” in vitro which are also referred to as cardio-spheres (CSs). These CSs consists of both committed progenitors and primitive cells for the three main type of cell located in the heart (i.e. smooth muscle cell, cardiomyocytes, and endothelial cell) which indicate a novel source for cardiac regeneration. Several studies have revealed that cardio sphered derived cells (CDCs) may regulate reproduction and functional development in the human heart. Recently, research showed that CDC-

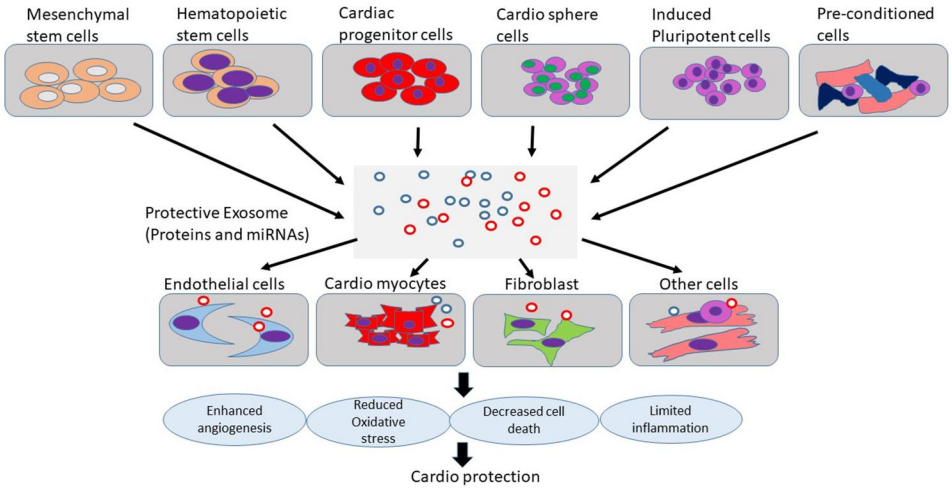

Figure 7. Cardio-protective role of exosome.

Table 4. Protective mechanism of exosomes in heart diseases.

Source of exosome	Function of exosome	Effects of cargo
Human CD34+ cell: CD34+ modified by Sonic hedgehog (shh)	Improved angiogenesis and decrease barricade size in mice after acute myocardial	miR-130a, miR-126, shh protein
Human cardiac progenitor cell (CPC)	Decrease cardio myocyte cell death and increase cardiac function after administration of exosome	miR-132, miR-210, miR-146a-3p
Human ES9.E1-derived MSCs	In myocardial ischemic-reperfused mice	GAPDH, PGK, PGM, ENO
Stem cell of mouse mesenchymal	In vivo transportation of IPC exosome, decrease infraction size	miR-199a-3p, miR-22, miR-21,
Human cardiosphere obtained cells	Administration of into selected mouse heart.	miR-22, miR-146a, miR-210
Mouse mesenchymal stromal cell	IV administered exosome reduce vascular remodeling	miR-17, miR-204

obtained exosomes can replicate CDC-induced positive therapeutic effects and the other actions of CDCs on the barricade of a mouse heart. They also observed that miR-146a is rich in CDC exosomes and miR-146a provides protective action of CDC exosomes to a great extent. Overall CDC exosome has an important role in the regulation of signaling and particularly the miRNAs moves through these exosomes which have a protective role in the murine model of myocardial infarction (MI).[52]

Table 4 summarizes the protective mechanism of exosomes in various heart diseases

1.6. Exosome in eye diseases

Exosomes is also released from the cells present in the eye such as the cornea, conjunctiva, and retina. Exosomes consist of nucleic acid (DNA and RNA), lipids, and proteins, which are associated with the mother cell and have a vital range of biological functions. It regulates the proper functioning of tissue barrier integrity in the eye such as the blood retinal barrier (BRB), and corneal epithelial barrier by transferring specific proteins and lipids to the specific cell.

1.6.1. Diabetic retinopathy

Diabetic retinopathy (DR), one of the most dangerous and complex abnormalities associated with diabetes has three important phases, proliferative DR, non-proliferative DR, and pre-proliferative diabetic retinopathy. Diabetic molecular edema characterized by macula and vascular leakage is a subtype of the non-proliferative type of diabetic retinopathy.[53,54] Proliferative DR shows symptoms of hypoxia and neovascularization. In this condition, the BBB becomes compromised, resulting in increased vascular permeability and leakage of fluid and protein into retinal tissue. This barrier dysfunction is a critical factor for the pathogenesis of the disease. The pathological phenomenon behind DR is mainly retinal ischemia-reperfusion injury (IRI). Retinal IRI results in a lack of necessary nutrients and temporary hypoxia. Reperfusion then results in the secretion of an excess amount of ROS, associated inflammatory response and oxidative stress. Overall, IRI is mainly responsible for the cause of apoptosis, necrosis, and autophagy leading to damage of neurons, mainly in Retinal Ganglion cells (RGCs).[55] The role of exosomes released from mesenchymal stem cells (MSCs) in ocular tissue shows that DR can be alleviated after intravitreal administration of MSCs obtained from exosomes.[14] A researcher revealed the influence of exosome on retinal ischemia with the help of intravitreal administration of hypoxia cultured exosome consisting of angiogenic mediated ingredients via human MSCs and balanced level of saline in oxygen-induced retinopathy (OIR) model of a mouse where he found that the exosome therapy improves retinal fineness and reduced retinal ischemia when compared with a controlled group. Some studies also show the exosome protective role in diabetic microangiopathy. Further studies are required to validate the protective role of exosomes in diabetic retinopathy.

1.6.2. Macular degeneration related to age

The retina is a pulpy and clear membrane that is responsive to light and connected with an internal membrane of choroid by the external membrane of retinal pigment epithelium (RPE).[56] It consists of a monolayer of pigment epithelial cells, that are sensitive to ROS and oxidative stress because of their anatomical function and position. Age-related macular deterioration, which occurs mainly in old age especially after 50 years old, results in blindness and this has

been observed widely in many developed countries. Based on clinical abstract and pathological alteration, age-related macular degeneration (AMD) can be classified into wet AMD and dry AMD. Wet AMD also called neo-vascular AMD is characterized by choroidal neovascularization (CNV) that results in retinal and choroidal hemorrhage. In comparison to dry AMD, wet AMD causes serious visual disturbance. Neo vascularization does not occur in dry AMD. Dry AMD is also called atrophic AMD. Retinal pigment epithelium (RPE) forms the external blood-retinal barrier (BRB) and oxidative stress damages the function of this barrier and thus, plays an important role in the pathogenesis of AMD.[57] Various types of retinal cells can produce and release exosomes like retinal astroglial cells (RAC) and numerous studies have shown that retinal pigment epithelium (RPE) cell under stressed conditions secretes large amounts of exosomes consisting of vascular endothelial growth factor receptor 2 (VEGFR2) which increases the production of new blood vessels. Several studies also show that exosomes may act as a biomarker for the diagnosis of AMD, especially as a novel biomarker for the neovascular AMD diagnosis.[58]

1.6.3. Glaucoma and traumatic optic neuropathies

Glaucoma is a group of diseases characterized by atrophy of the optic nerve, visual decline, and visual area defects. Pathologically enhanced intraocular pressure (IOP) and inadequate blood supply to the optic nerves are the major risk factors in glaucoma. The blood optic nerve barrier (BONB) consists of several cellular components including astrocytes, pericytes, and endothelial cells, which regulate the exchange of molecules between blood vessels and optic nerve tissue. Disruption in BONB has been observed in glaucoma. There are two types of glaucoma-

(a) Open-angle glaucoma
(b) Closed-angle glaucoma

These are further divided into primary and secondary glaucoma.[59] Patients who are suffering from primary glaucoma have raised IOP, but its main reason is not identified. When there is no increment in IOP, then it is a subtype of primary open-angle glaucoma (POAG).[60] Secondary glaucoma occurs by raised IOP and this results in the loss of retinal ganglionic cells (RGCs) due to elevated IOP that mainly occurs through raised production or/and a decrease in the discharge of aqueous humor (AH). Hence, the reduction of intraocular pressure in the retinal ganglionic cells (RGCs) is the major pathway of glaucoma therapy. Trabecular meshwork (TM) which can clear out AH can be explored to decrease IOP, and this may be employed for clinical therapy of Glaucoma.[61] A study has shown that an exosome is released by a primary cell of non-pigmented ciliary epithelium (NPCE) as well as an NPCE cell line and this exosome down-regulates Wnt signaling through miR-29b. The trabecular meshwork (TM) is regulated by wnt signaling and treatment of the TM cell line by using the sample of exosome can stimulate the TM Wnt signaling which can play a very important role in IOP reduction and thus, Glaucoma therapy.

Another scientist also observed that the exosome obtained through NPCE cells are associated with wnt signaling proteins regulation in TM cells, thus confirming the role of exosomes in the treatment of Glaucoma. Further, some studies reported the role of exosomes in primary open-angle glaucoma (POAG) in which gene expression of TM in patients having POAG was compared to that of a healthy subject. It was found that the gene expression of TM in POAG causes alteration of Q368X myocilin. However, a protein linked with exosome, which includes matrix GLA protein (γ-carboxyglutamic acid), TIMP2 (Tissue inhibitors of metalloproteinases2), SPARC (secreted protein acidic and rich in cysteine) communicate through some of TM attributed gene, that varies in non-myocilin POAG person.[62,63] But still, the therapeutic action of exosomes from multiple tissues on traumatic optic neuropathies[64,65] and glaucoma needs to be substantially explored.

2. Summary and conclusion

The exosomes exist in our body fluids, viz., urine, amniotic fluid, blood, and pleural effusion in diseased as well as healthy physiological conditions. These are the microvesicles that enter the interstitial space and then, gain access into the circulation. The exosomal secretions function as communication mediators between cells and serve an

important role in both physiological as well as pathological processes. The clinical application of exosomes is still in its nascent stage, and further, studies are required to substantiate the use of exosomes as therapeutic drugs in clinical setups. Needless to say, exosomes represent a promising future landmark in the therapeutic world.

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Data availability statement

The data that support the findings of this study are openly available in the references in the public domain.

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