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Review Article

Extracellular vesicles: Function, resilience, biomarker, bioengineering, and clinical implications

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Abstract

Extracellular vesicles (EVs) have emerged as key players in intercellular communication, disease pathology, and therapeutic innovation. Initially overlooked as cellular debris, EVs are now recognized as vital mediators of cell-to-cell communication, ferrying a cargo of proteins, nucleic acids, and lipids, providing cellular resilience in response to stresses. This review provides a comprehensive overview of EVs, focusing on their role as biomarkers in disease diagnosis, their functional significance in physiological and pathological processes, and the potential of bioengineering for therapeutic applications. EVs offer a promising avenue for noninvasive disease diagnosis and monitoring, reflecting the physiological state of originating cells. Their diagnostic potential spans a spectrum of diseases, including cancer, cardiovascular disorders, neurodegenerative diseases, and infectious diseases. Moreover, their presence in bodily fluids such as blood, urine, and cerebrospinal fluid enhances their diagnostic utility, presenting advantages over traditional methods. Beyond diagnostics, EVs mediate crucial roles in intercellular communication, facilitating the transfer of bioactive molecules between cells. This communication modulates various physiological processes such as tissue regeneration, immune modulation, and neuronal communication. Dysregulation of EV-mediated communication is implicated in diseases such as cancer, immune disorders, and neurodegenerative diseases, highlighting their therapeutic potential. Bioengineering techniques offer avenues for manipulating EVs for therapeutic applications, from isolation and purification to engineering cargo and targeted delivery systems. These approaches hold promise for developing novel therapeutics tailored to specific diseases, revolutionizing personalized medicine. However, challenges such as standardization, scalability, and regulatory approval need addressing for successful clinical translation. Overall, EVs represent a dynamic frontier in biomedical research with vast potential for diagnostics, therapeutics, and personalized medicine.

Keywords: *Bioengineering for drug delivery, Cellular resilience, Clinical therapeutics, Disease biomarker, Extracellular vesicles*

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Introduction

Extracellular vesicles (EVs) have garnered immense interest in biomedical research due to their diverse roles in intercellular communication, disease pathogenesis, and therapeutic potential. These small membrane-bound vesicles are released by virtually all cell types into the extracellular environment and play crucial roles in mediating cell-to-cell communication [1-4]. Initially dismissed as cellular debris, EVs are now recognized as essential mediators of intercellular communication, delivering a cargo of proteins, nucleic acids, and lipids to recipient cells. This review aims to provide a comprehensive overview of the multifaceted roles of EVs, focusing on their utility as biomarkers for disease diagnosis, their functional significance in physiological and pathological processes, and the burgeoning field of bioengineering for therapeutic applications.

As biomarkers, EVs offer a promising avenue for noninvasive disease diagnosis and monitoring. The cargo carried by EVs reflects the physiological state of the originating cells, making them valuable sources of diagnostic information [5-7]. Various studies have highlighted the

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diagnostic potential of EVs in cancer, cardiovascular diseases, neurodegenerative disorders, and infectious diseases [8-17]. Furthermore, the stability of EVs in bodily fluids such as blood, urine, and cerebrospinal fluid enhances their utility as biomarkers, offering advantages over traditional diagnostic methods [8-16].

Beyond their diagnostic utility, EVs play essential roles in intercellular communication and modulate various physiological and pathological processes. EVs facilitate the transfer of bioactive molecules such as microRNAs (miRNAs), proteins, and lipids between cells, thereby influencing recipient cell function and behavior. In normal physiology, EVs participate in processes such as tissue regeneration, immune modulation, and neuronal communication [18-22]. When a cell faces adversity, EVs come bearing gifts of resilience. For instance, EVs carry and deliver antioxidant enzymes such as superoxide dismutases, catalase, peroxiredoxin, glutathione peroxidase, glutathione S-transferase, and thioredoxin [23], acting as molecular firefighters to quench oxidative stress, preserve cellular integrity, and facilitate resilience [23-27]. Conversely, dysregulation of EV-mediated communication has been implicated in disease pathogenesis, including cancer progression, immune disorders, and neurodegenerative diseases [1-4].

Understanding the functional significance of EVs in health and disease is therefore crucial for elucidating novel therapeutic targets and strategies.

Biomarkers of extracellular vesicles

Extracellular vesicles as diagnostic biomarkers in disease

Numerous studies have demonstrated the diagnostic potential of EVs in a wide range of diseases, including cancer, cardiovascular disorders, neurodegenerative diseases, and infectious diseases. EVs carry a diverse cargo of biomolecules, including proteins, nucleic acids, and lipids, derived from their parent cells. These molecular signatures reflect the physiological state and pathological alterations of the originating cells, making EVs valuable sources of diagnostic information. Moreover, the presence of EVs in easily accessible bodily fluids such as blood, urine, and cerebrospinal fluid enables noninvasive sampling, facilitating their utility in disease diagnosis and monitoring [8-16]. For instance, EVs present in saliva contain proteins and RNAs that function as biomarkers for oral cancer, periodontitis, and Sjögren's syndrome, aiding in their early detection and disease monitoring [28]. Moreover, EVs found in serum, plasma, and urine carry liver-specific enzymes, cytokines, and miRNAs, serving as indicators of liver injury and fibrosis, thereby offering a noninvasive approach to diagnose and assess liver disease progression [29]. In the realm of neurodegenerative diseases, EVs in cerebrospinal fluid, plasma, and serum may encapsulate amyloid-β, tau, and α-synuclein, whose presence and levels can contribute to the diagnosis and comprehension of conditions such as Alzheimer's and Parkinson's diseases [30]. Similarly, in autoimmune diseases, EVs derived from serum, plasma, urine, and synovial fluid express autoantigens, cytokines, and miRNAs associated with these conditions, providing insights into autoimmune status and disease activity, notably in rheumatoid arthritis and systemic lupus erythematosus [31]. Moreover, EVs sourced from various bodily fluids, including serum, plasma, urine, saliva, ascites, and pleural effusion, are valuable resources for cancer diagnosis, as they can be analyzed for tumor-specific antigens and nucleic acids, facilitating early detection, diagnosis, prognosis, and monitoring of diverse cancers [32]. Here, we summarized examples on the potential use of EVs as diagnostic markers in Table 1.

Surface marker profiling of extracellular vesicles

Profiling surface markers on EVs has become a valuable strategy for delineating EV subpopulations and understanding their functional diversity in health and disease. The surface markers, such as tetraspanins (such as CD9, CD63, and CD81), integrins, and annexins, are proposed to have a crucial role in facilitating interactions with target cells [33-35]. They serve as key identifiers for EV identification and characterization, although their presence may fluctuate depending on the EV subtype and cellular origin. Furthermore, EVs can exhibit cell- and tissue-specific markers reflective of their parent cell type or origin, thereby enhancing the complexity of their surface protein profile [33-35]. For instance, microparticles, a subset of circulating EVs, predominantly derived from platelets, exhibit high expression levels of platelet markers CD41 and P-selectin [36,37], suggesting their platelet origin. Notably, some populations of EVs exhibit elevated levels during periods of stress [17,28-32], indicating their potential suitability as markers for diseases. These surface markers are crucial for cell recognition and cargo delivery, thereby influencing EV function and biological effects. Identification of surface markers associated with specific EV subtypes provides valuable insights into their physiological roles and pathophysiological implications [38-42].

Extracellular vesicle cargo: Molecular signatures and disease associations

The molecular cargo carried by EVs holds critical information regarding disease pathogenesis and progression. EVs from diseased cells exhibit distinct molecular signatures,

Table 1: Potential use of extracellular vesicles as diagnostic markers

Disease	EV source	Biomarker potential (EV cargo: Diseases)	Reference
Oral diseases	Saliva	Proteins and RNAs: Oral cancer, periodontitis, and Sjögren's syndrome	[28]
Liver failure	Serum, plasma, urine	Liver-specific enzymes, cytokines, and miRNAs: Liver injury and fibrosis	[29]
Neurodegenerative diseases	Cerebrospinal fluid, plasma, serum	Amyloid-β, tau, α-synuclein: Neurodegenerative disorders	[30]
Autoimmune diseases	Serum, plasma, urine, synovial fluid	Autoantigens, cytokines, and miRNAs: Autoimmune diseases	[31]
Cancer	Serum, plasma, urine, saliva, ascites, pleural effusion	Tumor-specific antigens, and nucleic acids: Cancers	[32]

EV: Extracellular vesicles, miRNAs: MicroRNAs

including specific proteins, miRNAs, and lipids, which correlate with disease status and prognosis. Understanding the composition and dynamics of EV cargo in different disease contexts provides valuable insights into disease mechanisms and potential diagnostic markers. Moreover, the association between EV cargo and disease phenotype offers opportunities for developing targeted diagnostic approaches and personalized medicine strategies [43-47].

Intracellular cargo profiling of extracellular vesicles

Intracellular cargo profiling of EVs provides crucial insights into their functional diversity and molecular signatures, allowing for the characterization of EV subtypes and their roles in health and disease. For example, the utility of EV-encapsulated miRNAs was explored as potential diagnostic markers for prostate cancer [48,49]. By analyzing miRNA profiles in EVs isolated from the blood plasma of both prostate cancer patients and healthy individuals, distinct expression patterns of certain miRNAs such as miR-140-3p, miR-150-5p, and miR-23b-3p were identified in the patient group, demonstrating promising diagnostic accuracy for prostate cancer [49]. Research also validated the presence of these EV-associated miRNAs in blood plasma, demonstrating their accurate measurability and highlighting their potential as noninvasive diagnostic and monitoring tools for cancer [48]. Accordingly, the cargo carried by EVs encompasses a diverse array of biomolecules, including proteins, nucleic acids, lipids, and metabolites, which reflect the physiological state and pathological alterations of the parent cells. By analyzing the intracellular cargo of EVs, researchers can elucidate their roles in various biological processes and disease pathogenesis [28-30,32,50-53].

Functional roles of extracellular vesicles

Biogenesis and secretion of extracellular vesicles

The biogenesis and secretion of EVs are intricate processes orchestrated by various cellular mechanisms [54-56]. Exosomes, small EVs ranging from 50 to 150 nm, originate from the endosomal system through the inward budding of the endosomal membrane, forming intraluminal vesicles (ILVs) within multivesicular bodies (MVBs). This process involves the endosomal sorting complex required for transport (ESCRT) machinery, responsible for sorting ubiquitinated proteins into ILVs, although ESCRT-independent pathways, involving lipids, tetraspanins, and proteins like syntenin-1, also contribute [54-56]. Once formed, MVBs are transported to the cell periphery and can fuse either with lysosomes for degradation or with the plasma membrane, facilitated by proteins such as SNAREs and Rab GTPases, leading to exosome release into the extracellular space. Microvesicles, with diameters ranging from 100 to 1000 nm, form through outward budding and fission of the plasma membrane, regulated by the cytoskeleton and involving phospholipid reorganization, including phosphatidylserine externalization and cytoskeleton-protein interactions [55]. Apoptotic bodies, typically ranging from 1 to 5 μm in size, are discharged during the advanced stages of apoptosis, carrying cellular debris and organelles from deteriorating cells [57]. Their timely clearance by phagocytic cells is essential to prevent the release of potentially harmful intracellular contents into the extracellular space [57], which can be identified as the sub-G1 population through flow cytometry [58-60]. Concurrently, microparticles commonly refer to circulating EVs found in the bloodstream [17,61]. These meticulously regulated mechanisms mirror the physiological state of the cell and carry significant implications for intercellular communication and the onset of disease [54-56].

Intercellular communication and target cell signaling modulation via extracellular vesicles

EVs serve as potent vehicles for intercellular communication, facilitating the transfer of biomolecules between cells. By shuttling proteins, nucleic acids, and lipids, EVs enable the exchange of molecular information, influencing recipient cell behavior and function. This communication occurs locally within tissues and organs, as well as systemically throughout the body, thereby modulating various physiological processes and contributing to homeostasis [1-4].

Extracellular vesicle-mediated signal induction

EVs can induce signaling in target cells by presenting surface molecules that interact with cell-surface receptors. For example, EVs bearing ligands for receptor tyrosine kinases (RTKs) can activate signaling cascades that promote cell survival and proliferation [4]. Following are two examples of EV-mediated signal induction. (1) Interactions between surface proteins and ligands: EVs can display a diverse array of surface proteins that engage with receptors on target cells. For instance, angiopoietin-2 present on the surface of EVs has the capability to bind to the Tie2 receptor on recipient cells, thereby initiating downstream cellular signaling associated with angiogenesis, such as phosphatidylinositol 3-kinase (PI3K)/Akt/endothelial nitric oxide synthase and syndecan-4/syntenin pathways [62]. Similarly, EVs containing Toll-like receptor ligands have the ability to stimulate immune cells, prompting the secretion of cytokines and chemokines pivotal for instigating and sustaining immune responses [63]. (2) Activation of RTKs: EVs are capable of transporting ligands and/or receptors of RTKs, which, upon binding to their corresponding receptors on target cells, instigate a series of phosphorylation events [64,65]. This cascade consequently triggers various intracellular signaling pathways, including but not limited to the PI3K/Akt and MAPK pathways, which play significant roles in governing cell survival, proliferation, and differentiation [66].

Transfer of functional protein and lipid components

EVs can deliver functional proteins to recipient cells, which can directly modulate cellular signaling pathways. This includes the transfer of active enzymes that can alter the phosphorylation status of proteins within the target cell, thereby affecting signal transduction [54]. In addition, lipids are critical components in the EVs' membrane and play a crucial role in the interaction between EVs and cells [4]. For example, phosphatidylserine indirectly engages with the growth arrest-specific protein 6 (Gas6). This interaction forms the phosphatidylserine-Gas6 complex, which subsequently activates the MER tyrosine kinases located on macrophage surfaces, initiating EV uptake and inducing an anti-inflammatory phenotype [67].

Gene regulations

EVs often contain RNA molecules, including miRNAs, messenger RNAs (mRNAs), and long noncoding RNAs. These RNAs can be delivered to recipient cells and regulate gene expression by modulating mRNA stability or translation. miRNAs, in particular, are known to play a significant role in post-transcriptional gene regulation [4,55]. In addition, epigenetic regulation is also involved in EV-mediated gene regulation [68,69].

Role of extracellular vesicles in normal physiology and pathophysiology to persist resilience

EVs participate in various physiological processes, including tissue repair, immune regulation, and neuronal communication. In normal physiology, EVs contribute to maintaining tissue homeostasis and orchestrating cellular responses to environmental cues. Similarly, EVs have demonstrated a crucial function in maintaining cellular and physiological resilience during periods of stress [24,25]. However, dysregulation of EV-mediated signaling pathways is implicated in the pathogenesis of numerous diseases, including excessive inflammation, cancer, cardiovascular disorders, kidney pathology, neurodegenerative diseases, and pathogen invasions [18-22,70,71]. Unraveling the roles of EVs in both normal physiology and pathophysiology is critical for harnessing their therapeutic potential and developing innovative strategies for disease intervention.

Bioengineering approaches for manipulating extracellular vesicles

Isolation and purification techniques

Bioengineering advancements have led to the development of innovative methods for the isolation and purification of EVs from biological fluids and cell culture supernatants. These techniques enable the efficient extraction of EV populations with high purity and yield, facilitating downstream analyses and therapeutic applications. From traditional ultracentrifugation to emerging microfluidic-based approaches, the continuous refinement of isolation techniques enhances our ability to harness the potential of EVs for diagnostic and therapeutic purposes [72-75]. However, despite these advantages, certain limitations persist within these methods. Here, we outline the advantages and disadvantages of currently utilized EV purification methods in Table 2.

Engineering extracellular vesicle cargo for therapeutic applications

Bioengineering strategies allow for the modification and manipulation of EV cargo, including proteins, nucleic acids, and lipids, to enhance their therapeutic efficacy. By engineering EV cargo, researchers can tailor their molecular composition and functional properties to target specific cellular pathways or disease processes. This approach holds promise for the development of novel therapeutics for a wide range of diseases, including cancer, neurodegenerative disorders, and inflammatory conditions, by exploiting the natural delivery capabilities of EVs [82-89].

Strategies for targeted delivery and controlled release

Bioengineering approaches enable the design of EV-based delivery systems with enhanced targeting specificity and controlled release kinetics. Through surface modification and encapsulation techniques, EVs can be engineered to target specific cell types or tissues and deliver therapeutic payloads with precision. Moreover, bioengineered EVs can be engineered to respond to external stimuli, allowing for the spatiotemporal control of cargo release. These strategies hold great potential for overcoming biological barriers, improving drug delivery efficiency, and minimizing off-target effects in therapeutic applications [90-95].

Biomedical applications of biosimulating artificial extracellular vesicles

Artificial EVs represent a cutting-edge approach in biomedical research, offering versatile platforms for mimicking the natural functions of EVs with enhanced controllability and tenability [96-98]. These synthetic vesicles are engineered to replicate key characteristics of native EVs, including their size, morphology, and surface properties, while providing advantages in cargo loading, targeting specificity, and therapeutic efficacy. By modulating the lipid composition, surface modifications, and cargo content of artificial EVs, researchers can tailor their properties for a wide range of biomedical applications, from drug delivery and disease diagnosis to regenerative medicine [96-98].

For instance, artificial EVs have been extensively explored for drug delivery applications, leveraging their biocompatibility, biodegradability, and cargo-loading capacity. These synthetic vesicles can encapsulate a variety of therapeutic agents, including small molecules, nucleic acids, and proteins, offering precise control over drug release kinetics and biodistribution [96-99]. By modifying the surface of liposomes with targeting ligands or antibodies, researchers can augment their specificity for afflicted tissues or cells, thereby enhancing therapeutic outcomes while minimizing off-target effects [96-99]. For instance, lectin-conjugated liposomes, such as P-selectin, E-selectin, L-selectin, and galectins, demonstrate the ability to deliver drugs specifically to inflamed and injured cells, enabling precise drug delivery to individual dying cells at a single-cell resolution [99]. These engineered synthetic vesicles can be tailored to encapsulate hydrophobic or hydrophilic drugs, imaging agents, or contrast agents, facilitating multimodal imaging and targeted therapy across various disease scenarios. Overall, the biomedical utilization of artificial EVs shows significant promise in advancing personalized medicine approaches and addressing unmet clinical needs [96-99].

Future perspectives and challenges

Emerging technologies and trends in extracellular vesicle research

The rapid evolution of technologies, such as single-vesicle analysis, advanced imaging techniques, and high-throughput sequencing, promises to unveil new insights into the biology and functions of EVs. Moreover, the integration of multi-omics approaches and systems biology strategies will

Table 2: Benefits and drawbacks of currently used extracellular vesicle isolation and purification methods

Purification method	Principle	Advantages	Disadvantages	Reference
Density gradient centrifugation	Separating EVs from other components based on their buoyant density by using a density gradient medium	High purity, preserves EV integrity and function	Time-consuming, low yield, requires large sample volume, may alter EV composition	[76,77]
Size exclusion chromatography	Separating EVs from other components based on their size by using a porous matrix	High purity, preserves EV integrity and function, compatible with different sample types	Low yield, requires large sample volume, may lose small EVs	[76,78]
Ultrafiltration	Separating EVs from other components based on their size by using a semipermeable membrane	High yield, fast, scalable, compatible with different sample types	Low purity, may damage EVs, may cause membrane fouling	[76-78]
Precipitation	Precipitating EVs from the solution by using organic solvents, polymers, or salts	High yield, fast, scalable, compatible with different sample types	Low purity, may damage EVs, may alter EV composition, may introduce contaminants	[76,78]
Immunoaffinity capture	Capturing EVs from the solution by using antibodies against specific EV surface markers	High specificity, high purity, enables subpopulation analysis	Low yield, expensive, requires prior knowledge of EV markers, may cause cross-reactivity or steric hindrance	[76,78,79]
Microfluidics	Manipulating EVs in microscale channels by using various physical or biochemical forces	High throughput, high purity, high sensitivity, enables multiplex analysis, preserves EV integrity and function	Expensive, complex, requires specialized equipment and expertise, may introduce contaminants	[80,81]

EV: Extracellular vesicle

enable the comprehensive characterization of EV cargo and their roles in health and disease [100-103]. Additionally, the emergence of organoid and organ-on-a-chip models offers sophisticated platforms for studying EV-mediated intercellular communication and disease mechanisms in physiologically relevant contexts [104-106].

Clinical translation and therapeutic potential of engineered extracellular vesicles

The clinical translation of engineered EVs holds immense promise for revolutionizing personalized medicine and therapeutic interventions. Engineered EVs offer targeted drug delivery, immunomodulatory effects, and regenerative potential for various diseases, including wound healing, cancer, neurodegenerative disorders, and inflammatory conditions [107,108]. However, the consistent isolation of EVs poses technical challenges, compounded by the intricate analyses necessary for their efficient study, which may hinder the utilization of pure EV populations as reliable biomarkers. Although biomarker identification holds significance for enhancing the diagnosis, monitoring, prediction, and prognosis of the diseases, prioritizing reproducibility and user-friendliness is paramount [109]. Moreover, the transition of EV-based therapies from experimental stages to practical clinical applications encounters obstacles concerning scalability, standardization of manufacturing processes, and regulatory approval. Overcoming these challenges will be essential for unlocking the therapeutic promise of engineered EVs in clinical contexts. Based on existing literature, we outline potential future directions of EV research in Table 3.

Considerations in extracellular vesicle-based therapeutics

With the advancement of EV-based therapeutics, regulatory considerations become increasingly important [119]. Regulatory frameworks need to be established to ensure the safety, efficacy, and quality of engineered EV products. In addition, the ethical implications of modifying EV cargo and engineering EVs for specific therapeutic purposes should be carefully evaluated. Collaborative efforts among researchers, clinicians, and regulators are essential to navigate these complex ethical and regulatory landscapes and facilitate the responsible development and deployment of EV-based therapeutics [119].

Conclusion

EVs represent dynamic mediators of intercellular communication and hold immense potential in biomedical research and clinical applications. This review provides a comprehensive overview of the multifaceted roles of EVs, emphasizing their utility as biomarkers for disease diagnosis, their functional significance in physiological and pathological processes, and the burgeoning field of bioengineering for therapeutic applications. The diagnostic potential of EVs as biomarkers offers a promising avenue for noninvasive disease diagnosis and monitoring. Their unique molecular cargo, reflective of the physiological state of originating cells, makes EVs valuable sources of diagnostic information. Moreover, the stability of EVs in bodily fluids enables their utility in disease diagnosis across a wide range of conditions, from cancer to infectious diseases. In addition to their diagnostic utility, EVs play essential roles in intercellular communication, influencing various physiological and pathological processes. Their ability to transfer biologically active cargo between cells modulates recipient cell behavior and function, impacting processes such as tissue regeneration, immune modulation, and disease progression. Dysregulation of EV-mediated communication is implicated in numerous diseases, highlighting the importance of understanding their functional roles in health and disease. Bioengineering approaches offer exciting opportunities for manipulating EVs for therapeutic applications. From isolation and purification techniques to engineering EV cargo and designing targeted delivery systems, bioengineering strategies enable precise control over EV properties and functions.

Table 3: Potential future focuses of extracellular vesicle research

Future focus	Description	Reference
EV biogenesis and secretion	Understanding the molecular mechanisms and regulation of EV formation and release from different cell types and under different conditions	[110,111]
EV cargo and function	Identifying the composition and function of EVs in various physiological and pathological processes, and elucidating the factors that determine the sorting and transfer of EV cargo	[110-112]
EV heterogeneity and subpopulations	Characterizing the diversity and specificity of EVs based on their origin, size, shape, surface markers, and molecular content, and developing methods to isolate and analyze EV subpopulations	[113]
EV detection and quantification	Developing novel and standardized methods and technologies to detect and quantify EVs in different samples, and establishing reliable and reproducible EV quality control and validation criteria	[114]
EV engineering and modification	Improving the stability, specificity, and delivery efficiency of EVs, and modifying their molecular content and surface properties, using various methods such as genetic manipulation, chemical modification, and physical loading	[112,115]
EV-based therapeutics and drug delivery	Exploring the potential of EVs as natural and biocompatible carriers of therapeutic agents or immunostimulatory molecules, and optimizing their targeting and biodistribution	[110,112,115,116]
EV-based biomarkers and diagnostics	Exploiting the diagnostic and prognostic value of EVs as sources of disease-specific biomolecules, and developing sensitive and specific EV-based assays and biosensors	[110]
EV-based inter-kingdom communication	Investigating the role of EVs in mediating the interactions between different kingdoms of life, such as plants, animals, fungi, and bacteria, and their implications for health and disease	[55,117,118]

EV: Extracellular vesicle

These advancements hold great promise for developing novel therapeutics for a wide range of diseases, revolutionizing personalized medicine and therapeutic interventions. Looking ahead, emerging technologies, clinical translation, and regulatory considerations will shape the future landscape of EV research and applications. Continued interdisciplinary collaboration and innovation are essential for overcoming challenges and harnessing the full potential of EVs in biomedical research and clinical practice. By leveraging the versatility and adaptability of EVs, we can pave the way for transformative advancements in diagnostics, therapeutics, and personalized medicine.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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