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REVIEW ARTICLE

Extracellular vesicles and endothelial dysfunction in infectious diseases

Linfang Zhang[1,2] | **Jingshu Chi**[2,3] | **Hao Wu**[2] | **Xiujuan Xia**[2] | **Canxia Xu**[3] | **Hong Hao**[2] | **Zhenguo Liu**[2]

[1]Department of Gastroenterology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

[2]Center for Precision Medicine and Division of Cardiovascular Medicine, Department of Medicine, University of Missouri School of Medicine, Columbia, Missouri, USA

[3]Department of Gastroenterology, the Third Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence
Zhenguo Liu, Center for Precision Medicine and Division of Cardiovascular Medicine, Department of Medicine, University of Missouri School of Medicine, 1 Hospital Drive, CE306, Columbia, Missouri 65212, USA.
Email: liuzheng@health.missouri.edu

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of mortality and morbidity globally. Studies have shown that infections especially bacteraemia and sepsis are associated with increased risks for endothelial dysfunction and related CVDs including atherosclerosis. Extracellular vesicles (EVs) are small, sealed membrane-derived structures that are released into body fluids and blood from cells and/or microbes and are critically involved in a variety of important cell functions and disease development, including intercellular communications, immune responses and inflammation. It is known that EVs-mediated mechanism(s) is important in the development of endothelial dysfunction in infections with a diverse spectrum of microorganisms including *Escherichia coli*, *Candida albicans*, SARS-CoV-2 (the virus for COVID-19) and *Helicobacter pylori*. *H. pylori* infection is one of the most common infections globally. During *H. pylori* infection, EVs can carry *H. pylori* components, such as lipopolysaccharide, cytotoxin-associated gene A, or vacuolating cytotoxin A, and transfer these substances into endothelial cells, triggering inflammatory responses and endothelial dysfunction. This review is to illustrate the important role of EVs in the pathogenesis of infectious diseases, and the development of endothelial dysfunction in infectious diseases especially *H. pylori* infection, and to discuss the potential mechanisms and clinical implications.

KEYWORDS
cardiovascular diseases, endothelial dysfunction, exosomes, extracellular vesicles, *Helicobacter pylori*, infectious diseases

1 | INTRODUCTION

Despite in-depth understanding and effective controls of the traditional cardiovascular risk factors, including diabetes mellitus (DM), hypertension (HTN), hyperlipidaemia, smoking, and obesity, cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality in developed countries, including the USA (Tsao et al., 2023). Accumulating data has shown that infectious diseases caused by microorganisms, such as bacteria, viruses and parasites, play an important role in the pathogenesis of CVDs including atherosclerosis (Sipilä et al., 2023; Wang et al., 2022). Several mechanisms have been linked to the increased risk of CVDs associated with infections, including (but not limited to) inflammation, oxidative stress, coagulation and immune dysregulation, in response to the type and severity of infections, host reactions, and environmental factor (Levi et al., 2003; Reali et al., 2021; Seeherman & Suzuki, 2021; Stotts et al., 2023). It has been demonstrated that *Chlamydia pneumoniae* upregulates the expressions of multiple enzymes, such as NADPH oxidase (NOX) and cyclooxygenase in vascular endothelial cells, NOX and

cytochrome oxidase in macrophages, and lipoxygenase in platelets, thus increasing the productions of reactive oxygen species (ROS) and inflammatory cytokines and promoting the development and progression of both early and late stages of atherosclerosis (Azenabor et al., 2005; Kälvegren et al., 2005; Kreutmayer et al., 2013). In addition, microbes and/or microbial molecules like lipopolysaccharide (LPS) from *C. pneumoniae* (Juvonen et al., 1997), and the virulence factor urease from *Helicobacter pylori* (Farsak et al., 2000) can activate endothelial cells, leading to excessive ROS formation and endothelial inflammation and dysfunction through increased expressions of proinflammatory cytokines and adhesion molecules including TNF-α, IL-6, IL-8, IL-1β, and intercellular adhesion molecule-1 (ICAM-1) (de et al., 2019; Wang et al., 2023).

Extracellular vesicles (EVs) are a class of very diverse, small, sealed membrane-derived structures that are critically involved in intercellular communications through transport of a wide spectrum of bioactive molecules including (but not limited to) proteins, lipids and microRNAs (Abels & Breakefield, 2016). They are naturally generated and released from almost all types of cells including endothelial cells and cardiomyocytes (Abels & Breakefield, 2016). Some Microorganisms have also been shown to produce EV-like vesicle that can interact with endothelial cells and modulate their functions (Kifle et al., 2020; Kim et al., 2019). Among these vesicles, the outer membrane vesicles (OMVs), which are released from Gram-negative bacteria and display a similar structure to cell-derived EVs, are important mediators of bacteria-host communications and potential modulators of CVDs (Ho et al., 2016; Wang et al., 2021). A recent study has shown that OMVs generated by *Porphyromonas gingivalis* significantly increased endothelial permeability and potentiated vascular oedema by cleaving endothelial intercellular junction proteins, suggesting that OMVs may act in concert with the whole bacteria to enhance CVD risk (Farrugia et al., 2020). Similarly, OMVs from *Escherichia coli* have been shown to trigger NF-κB translocation to the nucleus, leading to the up-regulation of adhesion molecules and cytokines, increased recruitment of leukocytes, and ultimately activating the endothelium and initiating the inflammatory cascade in endothelial cells (Kim et al., 2013). Therefore, during infections, EVs can originate from activated host cells, pathogens, or from a mixture of both and play an important role in the pathogenesis of CVDs.

H. pylori is a spiral, gram-negative microaerobic bacterium and colonizes in the epithelium of human stomach in about half of the global population (Hooi et al., 2017). Aside from its pathogenic effect on gastric diseases (Lee et al., 2016; Robinson & Atherton, 2021; Vakil, 2010; Wang et al., 2009), growing evidences reveal that *H. pylori* may be related to numerous extra-gastric diseases such as haematological diseases (especially idiopathic thrombocytopenia), neurological abnormalities, dermatological pathologies, and autoimmune disorders like inflammatory bowel diseases, chronic liver disease, and DM (Emilia et al., 2007; Marignani et al., 1997; Robinson, 2015; Sawayama et al., 2005; Zhou et al., 2013). Studies with human subjects and animal models have demonstrated that *H. pylori* infection, especially with the CagA-positive *H. pylori* infection, may lead to endothelial dysfunction, and significantly increases the risk of CVDs including HTN (Migneco et al., 2003), atherosclerosis (Xia et al., 2022), and ischemic stroke (Diomedi et al., 2004) with largely undefined mechanisms due to the presence of gastric tissue barrier and the unique *H. pylori* survival and growth environment. However, recent studies revealed that EVs released from *H. pylori*-infected gastric mucosa carry *H. pylori*-specific proteins (Xia et al., 2022), miRNAs (Li et al., 2019), and other pathogenic factors into the circulation, triggering vascular inflammation and oxidative stress, and leading to endothelial dysfunction. These findings may provide an explanation for endothelial dysfunction in patients with *H. pylori* infection.

This review will: (1) provide a brief overview on the structure and function of EVs from cells and microorganisms; (2) summarize the role of EVs in CVDs; (3) describe the relationships between infectious diseases like *H. pylori* infection and endothelial dysfunction, and (4) discuss the role of EVs in mediating the effect of infectious agents like *H. pylori* on endothelial function and potential mechanisms. Since *H. pylori* infection is one of the most common infections globally and leads to significant endothelial dysfunction through EV-mediated mechanism, thus, this will be used as an example to discuss the important role of EVs in the development of endothelial dysfunction in infectious diseases in detail in this review.

2 | OVERVIEW OF THE STRUCTURE AND FUNCTION OF EVS FROM CELLS AND MICROORGANISMS

EVs are small membrane-bound particles that are secreted by a variety of cells and can mainly be classified into three groups based on their biogenesis, size, content, release pathways and function: exosomes, microvesicles, and apoptotic bodies (Raposo & Stoorvogel, 2013). Exosomes are the smallest type of EVs with a diameter of 30 to 150 nm (average 40–100 nm), and are generated from the inward budding of endosomal membrane, resulting in the formation of multivesicular bodies (MVBs) that fuse with the plasma membrane and release intraluminal vesicles (ILVs) as exosomes (Pegtel & Gould, 2019).

Exosome formation is a complex process that involves the endosomal sorting complex required for transport (ESCRT) machinery and other accessory proteins (Théry et al., 2002). ESCRT is composed of four subcomplexes: ESCRT-0, -I, -II and -III, that are responsible for recognition, concentration, and invagination of specific cargo molecules into the endosomal membrane. ESCRT-0 binds to ubiquitinated cargo and sequentially recruits ESCRT-I, ESCRT-II and ESCRT-III to form a spiral-shaped filament that drives the inward budding of endosomal membrane and the scission of ILVs. ILVs are the precursors of exosomes that are released when MVBs fuse with the plasma membrane. ESCRT machinery can also interact with other proteins, such as ALIX, TSG101, VPS4 and HD-PTP, that regulate the size, shape and composition of ILVs (Théry et al., 2002).

EVs including exosomes are universally present in blood, saliva, urine, cerebrospinal fluid, lymphatic fluid, breast milk, amniotic fluid, and other body fluids, and continuously secreted from most types of eukaryotic cells including (but not limited to) B cells, T cells, dendritic cells, reticulocytes, platelets, endothelial cells, smooth muscle cells and stem cells (Buzas, 2023; Song et al., 2020). EVs can be produced by different mechanisms, including cytoskeletal rearrangement, membrane blebbing, calcium influx, phospholipid asymmetry, or cell activation (D'Souza-Schorey & Schorey, 2018). Certain microorganisms including *P. gingivali*, *Fusobacterium nucleatum* and *H. pylori* have also been shown to produce exosome-like vesicle from the outer membrane of gram-negative bacteria (Liu et al., 2021; Ma et al., 2023; Wang et al., 2021). These vesicles are spherical structures with a diameter of 20 to 300 nm and a trilamellar membrane composed of phospholipids, LPS and outer membrane proteins (OMPs) (Sartorio et al., 2021). OMVs can be formed via two main mechanisms: budding or blebbing of the outer membrane, or explosive cell lysis induced by endolysins (Kulp & Kuehn, 2010). The biogenesis and release of OMVs are influenced by various factors, such as lipoproteins, phospholipids, quorum-sensing molecules, flagella and environmental stress. OMVs have diverse functions in bacterial physiology and pathogenesis, such as nutrient acquisition, protein transport, DNA transfer, toxin delivery, immune modulation and virulence factor delivery (Collins & Brown, 2021; Koeppen et al., 2016; Kulp & Kuehn, 2010; Pan et al., 2023).

The surface proteins of EVs are important for their function and uptake by the target cells. EVs from different sources share many typical markers, including transmembrane proteins including tetraspanins (CD9, CD63, CD81 and CD82), major histocompatibility complex (MHC), and cytosolic proteins like heat shock proteins (HSP-70 and HSP-90) (Doyle & Wang, 2019). EVs also have significant heterogeneity in their surface proteins, depending on their origin and biogenesis pathway. For example, exosomes from cancer cells may express cancer-related markers such as CD9, CD63 and CD81 which are involved in tumor progression, invasion and metastasis (Ashraf Malik et al., 2019; Miki et al., 2018; Ondruššek et al., 2023), while exosomes from immune cells may express HLA-DR/DP/DQ since these cells are involved in antigen presentation, immune regulation and inflammation (Vincent-Schneider et al., 2002). The cargo of each unique EVs population varies greatly based on the cell and tissue types of origin. A variety of proteins, lipids, RNAs (including mRNA, microRNA and tRNA), DNA, and other diverse bioactive molecules have been identified in EVs (Pegtel & Gould, 2019). According to the latest database on EV contents, ExoCarta (http://www.exocarta.org), 41,860 proteins, more than 7540 RNA, and 1116 lipid molecules have been identified from different cell types and organisms (ExoCarta, 2016).

Production, secretion, transportation and membrane fusion of various EVs represent a unique and complex mode of intercellular and interorgan system communications. For example, Leishmaniasis is a parasitic disease caused by Leishmania species, which infects and multiplies in macrophages and other phagocytic cells. EVs from infected cells or activated cells can carry protein, lipids and RNAs that have different functions in leishmaniasis pathogenesis. EVs can carry parasite proteins, such as Leishmania surface glycoprotein (gp63), which can degrade the immune receptors and impair the immune response (da Silva Lira Filho et al., 2021). EVs can also carry microRNA, downgrade inflammatory response in neighbouring macrophages and induce macrophage polarization (Ganguly et al., 2022). Therefore, EVs and their bioactive substances can be potentially used as biomarkers for disease diagnosis, drug delivery and prediction of disease prognosis and clinical outcomes for infectious disease (Choi et al., 2020; Hu et al., 2021; Jung et al., 2023).

3 | ROLES OF EVS IN THE PATHOGENESIS OF INFECTIOUS DISEASES

Infectious diseases are the clinical manifestations of interactions between hosts and infectious microbes, including bacteria, viruses, fungi and parasites. Recent studies have demonstrated that EVs are critically involved in the development of many infectious diseases as summarized in Table 1. Numerous factors are involved in the roles of EVs in the pathogenesis of infectious diseases. The interactions between infected organisms and EVs are very complex and have not been well understood. Potential roles of EVs in infectious diseases are: (1) spreading infections. It has been reported that EVs from hepatitis C virus (HCV)-infected cells can transfer viral RNA and proteins that can initiate or sustain infection in other cells (Aydin et al., 2021). (2) Inhibiting or promoting the growth of pathogens. It has been shown that mesenchymal stem cell-derived EVs can attenuate influenza, SARS-CoV-2, urinary tract infections, intestinal infections and sepsis (Manzoor et al., 2023). (3) Modulating immune responses. Splenic mononuclear cells from mice with treatment of EVs from Salmonella-infected antigen-presenting cells could increase $CD4^+$ T cells in response to the challenge of Salmonella antigens (Hui et al., 2021). Considering the stability of EVs and their immunogenicity and enrichment of pathogen molecules, EVs also have potential values on vaccine preparations or serve as diagnostic biomarkers of microbial infections (Cho et al., 2020; Jung et al., 2023). Additionally, the ability of EVs to transport diverse molecules to target cells suggests their potential for drug or therapy delivery (Choi et al., 2020). Thus, EVs play a major role in the pathogenesis of infections and may have potential values in diagnosis and therapies.

TABLE 1 The roles of extracellular vesicles (EVs) in the pathogenesis of infectious diseases.

Type of infection	Main diseases	EVs content (Active substances) (EVs from both pathogens and target cells)	Main function
Bacteria			
M. tuberculosis	Tuberculosis	***M. tuberculosis* antigen**: Antigen 85B, Antigen 85C, Apa, BfrB, GlcB, HspX, KatG and Mpt64 (Kruh-Garcia et al., 2014). **RNA**: hsa-miR-1246, hsa-miR-2110, hsa-miR-370-3P, hsa-miR-28-3p, and hsa-miR-193b-5p (Lyu et al., 2019). **Proteins**: heat shock protein70 (HSP70), CD81, major histocompatibility complex-I (MHC-I) and tumor susceptibility gene101 (TSG101) (Zhang et al., 2021).	•Suppressing immune response: lipoprotein from EVs can suppress IFN-γ induced MHCII and CD64 expression (Singh et al., 2011). •Presenting antigen: MHC-II and *M. tuberculosis* antigen complexes from EVs and plasma membrane-derived microvesicles were able to present exogenous antigenic peptide to T hybridoma cells (Ramachandra et al., 2010). •Promoting intracellular Mtb survival: EVs miRNA-18a promotes *M. tuberculosis* survival in macrophages via negatively regulating autophagy by inhibiting ataxia telangiectasia mutated (ATM) (Yuan et al., 2020).
Streptococcus pneumoniae	Pneumoniae	***S. pneumoniae* antigen**: capsular polysaccharides 14 of *S. pneumoniae* (Cps14-CRA) (Colino & Snapper, 2007); **Cytokines**: interleukin-36γ (Colino & Snapper, 2007)	•Activating T lymphocyte to induce a protective immune response: *S. pneumoniae* Cps14-CRA expressed on the surface of BMDC-derived EVs induced Cps14-specific Ig responses and specifically protected against a lethal challenge with Pn14 (Colino & Snapper, 2007).
Staphylococcus aureus	Bacteraemia, Infective endocarditis, skin and soft tissue infections	**RNA**: mRNAs, lncRNA, miRNA (**Cai et al., 2018**; **Chen et al., 2021**). **Proteins**: complement 3 (C3), integrin alpha-6 (ITGA6), apolipoprotein A1 (APOA1), annexin A2 (ANXA2), tripeptidyl peptidase II (TPP2), keratin 8 (KRT8), and recombinant desmoyokin (AHNAK) (**Zhu et al., 2023**).	•Preventing cell damage: exosomal lncRNA associated with FAS translational regulation (lnc-AFTR) exerted anti-inflammatory and anti-apoptotic effects by inhibiting the activation of TNF signalling pathway and mitogen-activated protein kinases (MAPK) signalling pathway (Chen et al., 2022). •Enhancing inflammatory responses: EVs from *S. aureus* increased the production of pro-inflammatory mediators (IL-6, thymic stromal lymphopoietin, macrophage inflammatory protein-1α, and eotaxin) by dermal fibroblasts (Hong et al., 2011).
Parasite			
P. yoelii	Malaria	**Proteins**: parasite proteins (Martín-Jaular et al., 2016) (rhoptry proteins, serine repeat antigens, fam-a proteins, YIR proteins) and *P. yoelii* infected mice proteins (Martin-Jaular et al., 2011) (Alpha 2 macroglobulin, Complement component 3 and Albumin).	•Activating immune response against infection: infected reticulocytes-derived EVs were able to elicit a spleen-dependent protective response against malaria (Martín-Jaular et al., 2016). •Promoting inter-cellular communications and antigen presentation: reticulocyte-derived EVs carry antigens and are involved in immune modulation (Martin-Jaular et al., 2011).
T. gondii	Toxoplasmosis	**MiRNA**: miR-146a-5p, miR-155-5p, miR-21-5p, miR-29c-3p and miR-125b-5p (da Cruz et al., 2020).	•Modulating macrophage activation and against acute parasite infection: EVs from *T. gondii* increase the production of IL-12, TNF-α and IFN-γ in macrophages; BALB/c mice immunized with *T. gondii* EVs showed both humoral and cellular immune responses and exhibited a prolonged survival time (Li et al., 2018). •Regulating host cell proliferation and cell cycle: EVs from *T. gondii*-infected cells showed attenuation of cell proliferation and slight enhancement of S phase in rat myoblast cells. various exosomal miRNAs were crucial for the regulation of target genes related to cell proliferation (Kim et al., 2016).
S. japonicum	Schistosomiasis S	**MiRNA**: miRNA-33 (Wang et al., 2022); miR-92a-3p, miR-146a-5p and miR-532-5p (Cai et al., 2020); ***S. japonicum* surface antigens**: 22.6 kDa tegumental antigen, tegument antigen, and major egg antigen (Zhu et al., 2016);	•Promoting liver fibrosis in a cross-species manner: miRNA-33 from egg-derived EVs of *S. japonicum* can promote liver fibrosis and inhibiting the expression of miRNA-33 decreases fibrosis (Wang et al., 2022). •Preventing autoimmune diseases: EVs from DCs treated with *S. japonicum* soluble egg antigen (SEA; SEA-treated DC exosomes) decrease the severity of acute dextran sulfate sodium (DSS)-induced colitis (Wang et al., 2017).

(Continues)

TABLE 1 (Continued)

Type of infection	Main diseases	EVs content (Active substances) (EVs from both pathogens and target cells)	Main function
Virus			
***Epstein–Barr virus* (EBV)**	Epithelial and lymphoid malignancies	**EB particles**: EBV nuclear antigen EBNA1 and latent membrane proteins LMP1 and 2A; proteins (Mrad et al., 2021); lncRNAs: MALAT1, AFAP1-AS1 and AL359062 (He et al., 2017).	•Inducing an inflammatory response: EVs expressing EBV proteins correlate with disease activity and induce an inflammatory response in onocyte-derived macrophages (Mrad et al., 2021). •Serving as prognostic biomarkers for nasopharyngeal carcinoma (NPC): high levels of the lncRNAs were closely related to advanced NPC tumour node metastasis stages and EBV infection (He et al., 2017). •Altering the microenvironment and enhancing the pathogenesis of EBV-related malignancies: EBV product-containing EVs promote the phenotypes of cancer-associated fibroblasts by stimulating YAP1 signalling and production of the immunosuppressive cytokines IL8, CCL2, and IL6 (Lee et al., 2022).
Influenza A virus (IAV)	Respiratory tract disease	**RNAs**: miRNA composition (miR-21-3p, miR-26a-5p, miR-23a-5p, miR-548c-5p) and mRNA composition (RPL13A, MKNK2 and TRIB3) (Zabrodskaya et al., 2022);	•Suppressing immune defense genes: EVs from IAV-infected cells reduce the immune response of neighbouring intact cells, leading to more effective IAV replication (Zabrodskaya et al., 2022). •Promoting M1 polarization and recruitment of macrophages: EVs from the supernatant of IAV-infected cells promote the recruitment and polarization of peritoneal M1 macrophages (Xia et al., 2022).
Fungi			
Cryptococcus neoformans	Cryptococcosis	**Cryptococcal pathogens**: Sec6 (Panepinto et al., 2009), α-Galactosyl epitopes (Vallejo et al., 2011) Polysaccharides, lipids (Rodrigues et al., 2008)	•Promoting microbes to invade the host and contribute to the infection: Exosomes-like vesicles cross the cell wall to reach the extracellular space, contributing to capsule growth or getting into host tissues (Panepinto et al., 2009).

3.1 | Roles of EVs in bacterial infections

EVs are involved in various infectious diseases caused by bacteria such as *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *H. pylori* and *Salmonella typhimurium* (Bhatnagar et al., 2007; Hong et al., 2011; Smith et al., 2017; Zahmatkesh et al., 2022). Both host- and bacteria-derived EVs can transmit and release pathogen-related virulence factors during bacterial infections. It is reported that EVs from cytotoxin-associated gene A (CagA)-expressing *H. pylori* infected gastric epithelial cells contain and deliver CagA, a virulence factor, to distant organs and tissues, leading to direct or indirect damages to various cells and tissues, such as intestinal epithelial cells, endothelial cells and immune cells (Guo et al., 2022; Wang et al., 2016; Xia et al., 2020). OMV-derived β-lactamase from coinfecting pathogens such as non-typeable *Haemophilus influenzae* and *M. catarrhalis* may contribute to hydrolyses of amoxicillin and protect Group A *streptococci* from the bactericidal effect of amoxicillin, playing a critical role in the pathogenesis and outcome of the infection (Schaar et al., 2014).

EVs can either have anti-infectious or pro-infectious effects depending on the types of bacteria, the host cells, and the EV cargo. Studies have shown that the EVs from host cells carrying *Mycobacterium tuberculosis* antigens such as the major histocompatibility complex class II molecules (MHC-II) and 19-kDa lipoprotein, could activate T cells and induce a protective immune response by initiating innate responses and stimulating inflammatory response (Bhatnagar et al., 2007; Ramachandra et al., 2010). However, some EVs from *Mycobacterium tuberculosis*-infected macrophages and mesenchymal stem cells (MSCs), carrying immunosuppressive cytokines and microRNAs, can suppress macrophage activation and promote intracellular survival of *Mycobacterium tuberculosis* by modulating immune responses (Singh et al., 2011; Yuan et al., 2020). Studies are needed to investigate the mechanism(s) for the beneficial effects of EVs on the control of infections, which would help develop novel immunotherapy to eliminate bacterial infections like *Mycobacterium tuberculosis*.

EVs from endothelial cells can carry both host and bacterial components that may modulate immune responses. It was reported that EVs released from human endothelial cells during sepsis contain microRNA-99a/b, which can suppress the expression of mTOR, a key regulator of cell metabolism and survival, in recipient cells. This may lead to a prolonged and exaggerated inflammatory response and contributes to sepsis-induced organ failure (Fitzpatrick et al., 2022). It was also demonstrated that

rickettsial-infected, endothelial cell-derived EVs can carry rickettsial antigens and induce immune responses in macrophages and dendritic cells, leading to dysfunction of the recipient brain microvascular endothelial cells (Liu et al., 2021). Therefore, endothelial EVs may play a critical role in the function and integrity of the vascular barrier and subsequent fluid homeostasis and prevention of pathogen invasion.

3.2 | Roles of EVs in viral infections

Viral infections are very common and frequently associated with significant damages to many cells and organ systems. Recent studies have demonstrated that EVs released from cells infected with a variety of viruses, including (but not limited to) SARS-CoV-2, Epstein-Barr Virus (EBV), HPV and HIV, are involved in viral spread, host immunity and microenvironment modifications (Chen et al., 2021, 2022; Feng et al., 2020; Tong et al., 2020).

The relationship between EVs and viral infections is complex and multifaceted. EVs can modify viral pathogenesis by regulating the host immune response, inflammation, apoptosis, and tissue damages during viral infection, depending on the types of viruses and the host cells. EVs can promote viral infection by transferring viral components or facilitating virus entry into target cells. It was reported that EVs from HIV-infected cells can transfer HIV-encoded miRNAs and proteins that modulate the expression of host genes and promote viral replication and latency (Kadiu et al., 2012; Sadri Nahand et al., 2020). On the other hand, EVs from the culture supernatant of CD8(+) T-cells can inhibit HIV-1 replication by suppressing CCR5-tropic (R5) and CXCR4-tropic (X4) replication through a protein moiety (Tumne et al., 2009). Semen EVs inhibit HIV-1 RNA expression by inhibiting the recruitment of transcription factors NF-$\varkappa$B and Sp1, as well as RNA Pol II, to the promoter region in the 5′-long terminal repeat (LTR) of HIV-1 (Welch et al., 2018). In addition, viruses and EVs have similar biophysical features because of their small size and comparable molecular composition, which makes them hard to distinguish (Raab-Traub & Dittmer, 2017).

Increasing evidence suggests that human viruses can hijack EVs to deliver viral components and even infectious viruses, providing additional routes of transmission and escape from immune recognition and facilitating viral persistence in the infected host. For example, the budding of HIV-1 at the plasma membrane (Lorizate et al., 2013) and the secretion of HCV from host cells (Ramakrishnaiah et al., 2013; Tamai et al., 2012) hijack the EV biogenesis mechanisms of infected cells to enhance their dissemination through exploiting the ESCRT pathway. It has been shown that intact rotaviruses and noroviruses have been found within EVs (Santiana et al., 2018). Thus, EVs could incorporate and transmit both viral and host factors, prompting or attenuating immune responses during viral infections via multiple mechanisms.

The Coronavirus Disease 2019 (COVID-19) that is caused by SARS CoV-2 infection is associated with severe respiratory diseases and significant damages to other important organ systems including heart, liver, brain and vasculature (Akter & Clemente-Casares, 2023; Dufour et al., 2022; Stein et al., 2022; Xu et al., 2023). EVs have receptors for SARS CoV-2 entry like CD9 and ACE2, which may be involved in promoting SARS CoV-2 infection (Andreu & Yáñez-Mó, 2014; Wang et al., 2020). Upon entrance into cells, SARS CoV-2 or its components may be packaged into EVs for secretion (Barberis et al., 2021). Proteomic analysis of the serum EVs from SARS CoV-2 infected patient has identified several molecules that are critically involved in immune responses, inflammation, and activation of coagulation and complement pathways, suggesting a potential significant role of EVs in tissue damages and multiple organ dysfunctions in patients with COVID-19 (Barberis et al., 2021). In addition, EVs released from the cells can carry a significant amount of information on disease state, serving as potential biomarkers for diagnosis and treatment of COVID-19 (Kawasaki et al., 2022; Mazini et al., 2021; Mimmi et al., 2023; Sengupta et al., 2020).

3.3 | Roles of EVs in parasitic infections

Studies have also shown that EVs play a vital role in host-pathogen interactions during parasitic infections, including *Schistosoma mansoni, Schistosoma japonicum* and *Toxoplasma gondii* (Kifle et al., 2020; Wang et al., 2022; Zhu et al., 2022). During parasitic infections, EV generation can be enhanced or inhibited by various factors, such as the types of parasites, the stages of infection, the host cell type, and the environmental conditions. EV formation is a complex process that can be modulated by both the host and the parasite during parasitic infection. A recent study has demonstrated that the ESCRT-III machinery participates in the production of EVs and protein export during *Plasmodium falciparum* infection (Avalos-Padilla et al., 2021). *P. falciparum* proteins PfBro1, PfVps32 and PfVps60 interact with the host ESCRT-III complex and mediate the inward budding of the endosomal membrane to form MVBs, which can release EVs upon fusion with the plasma membrane. Alternatively, these proteins can induce the outward budding and shedding of plasma membrane to generate microvesicles that contain parasite proteins. Data also demonstrated that disrupting the PfVps60 gene reduces the productions of EVs (Avalos-Padilla et al., 2021).

Parasites release EVs in the host environment before invasion into host cells (Silverman et al., 2010). These EVs contain parasite-specific bioactive substances including proteins, RNA, lncRNA and nucleic acids. In human protozoan parasitic diseases such as malaria, African sleeping sickness, Chagas disease, leishmaniasis and toxoplasmosis, EVs serve as a carrier of effector molecules that modulate the host immune response to establish infection (da Silva Lira Filho et al., 2021; Dias-Guerreiro

et al., 2021; Higuchi et al., 2018; Li, Xiu, et al., 2018; Oxendine Harp et al., 2023). It was reported that Leishmania EVs can transfer Leishmania RNA virus 1 (LRV1), a virus that infects Leishmania and enhances its virulence, to macrophages and induce type-I interferon responses (Atayde et al., 2019). Similarly, Giardia lamblia can produce and release exosome-like vesicles (ElVs) that have similar characteristics to exosomes from other eukaryotic cells (Moyano et al., 2019). ElVs can modulate the parasite growth, adherence, and immune evasion by delivering parasite-derived or host-derived molecules to recipient cells. ElVs may have potential applications as biomarkers or therapeutics for giardiasis (Gavinho et al., 2020). Thus, Parasite-derived EVs can transfer virulence factors and drug-resistance markers, modify host cell gene expression, and promote parasite adherence and host cell proliferation, may critically contributing to the outcome of parasitic infections.

Vascular endothelium can serve as a site of infection and replication for many protozoan parasites, such as Plasmodium, *Schistosoma mansoni* and *Echinococcus multilocularis* (Kifle et al., 2020; Liu et al., 2023; Yang et al., 2017). Formation and/or release of EVs from the host and/or the invading parasites can be significantly affected by the interactions between the infected endothelial cells and parasites. These EVs can carry parasite-derived molecules and trigger endothelial dysfunction. It has been demonstrated that EVs or exosome-like vesicles (ELVs) and microvesicles (MVs) from *Schistosoma mansoni* could be internalized by both human endothelial cells and monocyte cells, leading to differential expressions of important genes associated with cell contraction, coagulation, and arachidonic acid metabolism, as well as immune responses in endothelial cells (Kifle et al., 2020). The same study also revealed that antibodies against recombinant tetraspanin proteins from the surface of EVs from *S. mansoni* effectively attenuated the uptakes of EVs by both endothelial cells and monocytes. Thus, EVs may play important roles in host-parasite interactions and the pathogenesis of diseases with parasites and may serve as a potential target for prevention and treatment of parasite infections and related conditions.

3.4 | Roles of EVs in fungal infections

Fungi are eukaryotic microbes that have typical nucleus, nuclear membranes, nucleolus and organelle. Although there are more than 6 million fungal species worldwide, less than 1% are known to infect human subjects (Köhler et al., 2017). The most common human fungal pathogens include *Cryptococcus neoformans*, *Aspergillus fumigatus* and *Candida albicans* (Idnurm & Lin, 2015; Nobile & Johnson, 2015; Paulussen et al., 2017). Like infections with bacteria and viruses, during fungal infection, either the host cells or the fungi could produce EVs that contain related pathogenic factors such as polysaccharides, lipids, nucleic acids, and toxins, and then deliver these pathogenic factors to distal host cells, contributing to the regulation of inflammatory responses of host cells and fungal colonization (Gandhi et al., 2022; Rodrigues et al., 2008; Souza et al., 2008, 2022). Indeed, it has been reported that *C. neoformans* produces EVs during in vitro growth and animal infection. The vesicular compartments, which are transferred to the extracellular space, contain glucuronoxylomannan (GXM), a component of the cryptococcal capsule, and important lipids such as glucosylceramide and sterols, thus modulating the extracellular environment and contributing to the pathogenesis of *C. neoformans* infection (Rodrigues et al., 2007).

Growing evidence suggests that there are significant interactions between fungal infection and endothelial dysfunction (Le et al., 2019; Naik & Mohammed, 2023). Fungal infection can induce endothelial dysfunction by activating inflammatory pathways, triggering oxidative stress, and impairing nitric oxide production (Qin et al., 2019; Qin et al., 2022). It was found that *C. neoformans*-derived microvesicles (CnMVs) can enhance the traversal of the blood-brain barrier (BBB) by *C. neoformans* in vitro. CnMVs can fuse with human brain microvascular endothelial cells (HBMECs), enhance *C. neoformans* infection of the brain, and thus playing an important role in the pathogenesis of cryptococcal meningoencephalitis (Huang et al., 2012). A very recent study, using techniques including microarray analysis and real-time quantitative PCR to determine the changes of miRNAs in macrophage-derived exosomes (exo-miRNAs), showed a marked alteration in exo-miRNAs with an increased permeability and ROS accumulation in human umbilical vein endothelial cells (HUVEC) during cryptococcal infections. The data revealed that five exo-miRNAs were significantly increased with the level of exo-miR-4449 being the highest, while two were reduced. The data also showed that exo-miR-4449 could be internalized by HUVEC and increase their monolayer permeability (Li et al., 2024). Thus, EVs derived from both activated cells and fungi play an important role in endothelial dysfunction associated with fungal infection.

4 | INFECTIOUS DISEASES AND ENDOTHELIAL DYSFUNCTION

Endothelial cells play a critical role in maintaining the integrity of vascular structure and function, and endothelial dysfunction is associated with many disease conditions especially CVDs, including (but not limited to) HTN, atherosclerosis, coronary artery disease, peripheral vascular disease, DM and chronic kidney failure (Alexander et al., 2021; Carrizzo et al., 2018; Figueir et al., 2012; Santoro et al., 2010; Zhang et al., 2023). The mechanisms for endothelial dysfunction are complex and multifactorial, including (but not limited to) impaired vascular homeostasis, reduced nitric oxide (NO) bioavailability, increased oxidative stress and inflammation (Clapp et al., 2004; Pirro et al., 2017). Many genetic and environmental factors as well as physical and pathological

conditions are closely associated with endothelial dysfunction, including HTN, DM, hyperlipidaemia, smoking, stress and ageing (Abu-Saleh et al., 2021; Golbidi et al., 2020; Jia et al., 2019; Wong et al., 2010).

Existing evidence clearly indicates that there is a close relationship between infectious diseases and endothelial cell dysfunction. A wide spectrum of bacterial and viral pathogens and/or associated substances have been detected in human atherosclerotic plaques (Xue et al., 2021) or CVDs including myocarditis, endocarditis and pericarditis (Aljohani et al., 2022; Faraji et al., 2018; Lin et al., 2023). The infectious agents could trigger a series of biochemical and pathophysiological reactions, including increases in leukocyte adhesion to endothelium, increased vascular permeability and inflammation, leading to endothelial dysfunction (Joffre & Hellman, 2021; Robles et al., 2022; Yang et al., 2022). Indeed, it has been demonstrated that endothelium-dependent relaxation of aorta was significant attenuated in apolipoprotein E-knockout (apoE-KO) mice with intranasal inoculation (both single and repeated) of *C. Pneumoniae* with the mechanisms associated with NO-mediated pathway and cyclooxygenase-dependent vasoconstricting products (Liuba et al., 2000). Mice with intranasal inoculation of *C. Pneumoniae* also exhibit inflammation of the arterial wall, intimal migration of smooth muscle cells, and foam cell formation (Liuba et al., 2000). Acute intratracheal inoculation of *C. pneumoniae* in pigs causes significant endothelial dysfunction of both resistance and epicardial coronary vessels with decreased endothelium-dependent reactivity of coronary microcirculation and increased pro-coagulant status, potentially contributing to acute coronary syndrome (Liuba et al., 2003). Application of *P. gingivalis* to white rabbits significantly increases atherosclerotic lesion formation in the aorta (Jain et al., 2003).

Several epidemiological and observational studies have shown the association between infections and endothelial dysfunction as well as CVDs. A prospective observational study of 101 patients with sepsis and 50 healthy controls revealed that septic patients had higher levels of endothelial activation markers, such as soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), and von Willebrand factor (vWF), and lower levels of endothelial progenitor cells (EPCs), which are involved in endothelial repair. Endothelial dysfunction in sepsis can lead to increased vascular permeability, leukocyte adhesion, platelet activation and microthrombosis, leading to organ failure and even death. Recent studies have demonstrated a strong relationship between COVID-19 and endothelial dysfunction. A study by Haffke et al. (2022). revealed that SARS-CoV-2 infection induced significant endothelial dysfunction in COVID-19 patients, as evidenced by increased levels of endothelial biomarkers (such as endothelin-1, endocan, and angiopoietin-2). Many post-COVID-19 patients have been shown to exhibit a significant endothelial dysfunction as reflected by a diminished reactive hyperaemia index (<1.67), while not observed in healthy subjects (Haffke et al., 2022). COVID-19 patients have been reported to have low-grade endotoxemia that could activate NOX-2, leading to increased oxidative stress and endothelial dysfunction. Compared with controls, patients with COVID-19 pneumonia had significantly higher levels of LPS, soluble Nox2-derived peptide (sNOX-2-dp), hydrogen peroxide (H_2O_2), and inflammatory cytokines such as TNF-α and IL-6. Conversely, flow-mediated dilation (FMD), hydrogen peroxide breakdown activity (HBA) and NO bioavailability were significantly decreased in the subjects with COVID-19 pneumonia (Ciacci et al., 2023).

Mechanistically, infectious agents may contribute to endothelial dysfunction and CVDs through either directly by the infections and damage to the vascular endothelium or indirectly through a dysregulated immune response with the release of excessive inflammatory cytokines and activation of endothelium (Juvonen et al., 1997; Kreutmayer et al., 2013; Reali et al., 2021). Vascular inflammation plays an important role in the initiation and progression of atherosclerosis and other CVDs (Libby, 2021). Infectious agents trigger a dysregulated immune response by activating innate and adaptive immunity, releasing excessive inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (Dewi et al., 2004), or stimulating the production of ROS (Azenabor et al., 2005). The inflammatory cytokines and ROS can subsequently impair endothelial function by reducing vasodilation, enhancing leukocyte adhesion and migration, promoting coagulation and thrombosis, and stimulating vascular remodelling. Moreover, EVs may also mediate some of these effects by transferring molecular signals between different cell types and tissues (which will be discussed below).

5 | *H. pylori* INFECTION AND ENDOTHELIAL DYSFUNCTION

H. pylori is a gram-negative bacterium that colonizes in human gastric epithelium in a significant portion of general population in the world with infection rates ranging from 30% to 50% in developed countries, and up to 80% in developing countries, especially in Asia (Hooi et al., 2017). Accumulating data supports the concept that *H. pylori* infection leads to significant endothelial dysfunction and development of CVDs including atherosclerosis, coronary artery disease (CAD), HTN and stroke (Migneco et al., 2003; Sawayama et al., 2005; Zhou et al., 2013). A study in 2011 with 42 subjects (31 patients with *H. pylori* infection and 11 controls) reported that eradication of *H. pylori* with triple therapy significantly improved endothelial dysfunction (Blum et al., 2011). A recent study with young subjects without any known cardiovascular risk factors has shown that, compared with controls, patients with *H. pylori* infection exhibit a significant reduction in endothelium-dependent flow-mediated dilation (FMD) of branchial artery (Xia et al., 2020). When the patients with *H. pylori* infection were treated with BIS-based quadruple oral anti-*H. pylori* therapy (100 mg furazolidone, 100 mg doxycycline, 5 mg ilaprazole, and 220 mg colloidal bismuth tartrate, twice a day for 2 weeks), their endothelium-dependent FMD of the brachial artery was effectively restored (Xia et al., 2020). These data strongly suggest that *H. pylori* infection attenuates endothelial cell function in human subjects.

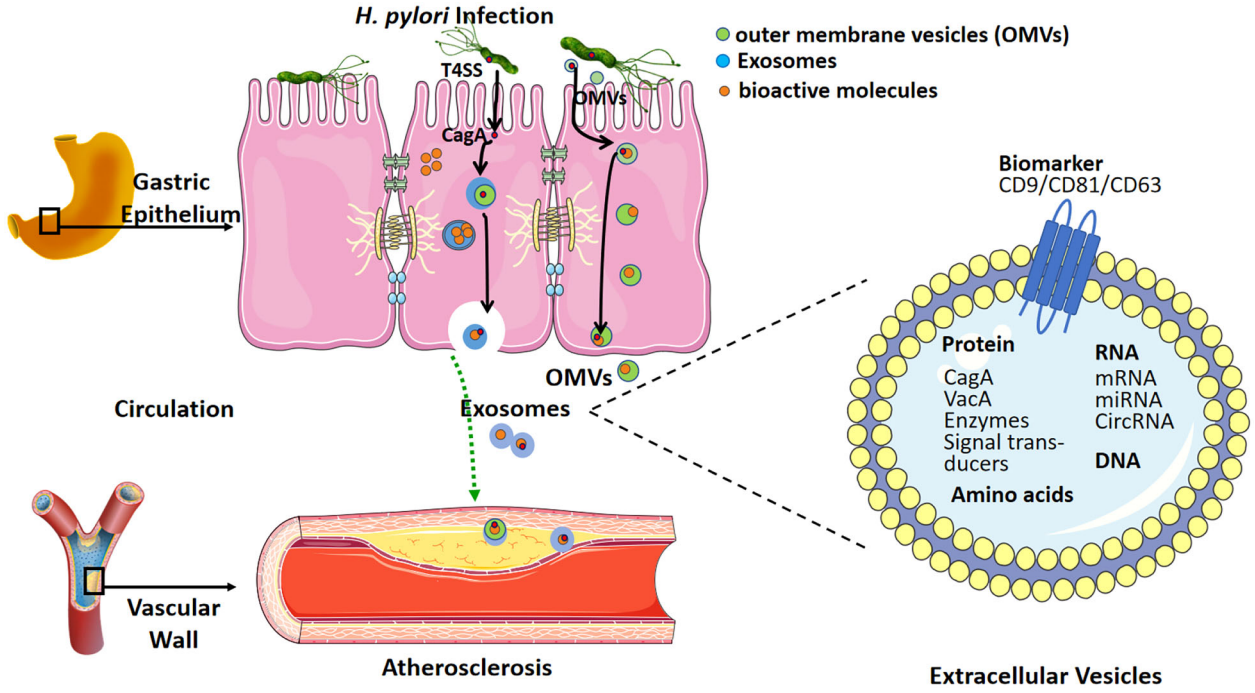

FIGURE 1 Structure and components of EVs derived from gastric epithelial cells with *H. pylori* infection. EVs attach to the cell surface of nearby or distant gastric epithelial cells and then enter the blood circulation through the lamina propria and are subsequently internalized by the host cells. EVs can contain different types of cell surface proteins, intracellular protein, RNA, DNA, amino acids, and metabolites. EV, extracellular vesicles; DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

Animal studies have also demonstrated that acetylcholine (Ach)-induced endothelium-dependent relaxation was significantly reduced in mice 1 week after *H. pylori* infection without change in nitroglycerin (NTG)-induced endothelium-independent relaxation (Xia et al., 2020). The impaired Ach-induced endothelium-dependent relaxation persisted for as long as the infection was present for at least 24 weeks in the infected mice without change in vascular contraction to either phenylephrine or potassium chloride, while NTG-induced endothelium-independent relaxation remained intact (Xia et al., 2020). In addition, *H. pylori* eradication with anti-*H. pylori* therapy effectively restored the endothelium-dependent vasorelaxant response to Ach. These data have demonstrated that *H. pylori* infection selectively impairs endothelium-dependent relaxation, not endothelium-independent relaxation, of aorta in mice that are similar to the findings in human subjects with *H. pylori* infection. These data also suggest that *H. pylori* infection-induced impairment of endothelium-dependent vascular function is reversible if treated on time (within 6 months of infection in mice).

A few mechanisms have been proposed for the development of vascular diseases associated with *H. pylori* infection. One hypothesis suggests that chronic infections such as chronic *H. pylori* infection may produce low-grade inflammatory response, thus increasing the risk for adverse cardiovascular events (Krupa et al., 2021; Li et al., 2021). Indeed, *H. pylori* infection of primary human endothelial cells is reported to increase the productions of inflammatory cytokines IL-6 and IL-8 (especially IL-8) in endothelial cells (Tafreshi et al., 2018), thus, ultimately leading to atherosclerosis. Other proposed mechanisms on *H. pylori* infection-induced CVDs include endothelial barrier disruption, oxidative modifications, inflammation, and molecular mimicry (de et al., 2019; Negrini et al., 2020; Takemura et al., 1996; Tobin et al., 2008).

However, *H. pylori* do not enter the blood circulation themselves because of the gastric tissue barrier and a unique survival and growth environment. Endothelial cells are directly exposed to circulating substances, and recent studies have demonstrated that exosomes, which could translocate bacteria and their bioactive components from the gastric mucosa into the systemic circulation as shown in Figure 1, play an important role in endothelial dysfunction with *H. pylori* infection (Qiang et al., 2022), which will be discussed in detail below.

6 | ROLE OF EVS IN ENDOTHELIAL DYSFUNCTION IN INFECTIOUS DISEASES

Recent studies have indicated that circulating EVs are important mediators of endothelial dysfunction, vascular inflammation, and thrombosis by modulation of NO production, oxidative stress, inflammation and coagulation. It has been reported that EVs from mature dendritic cells increased endothelial inflammation and atherosclerosis via TNF-α mediated activation of

NF-κB pathway (Gao et al., 2016). PKH67-labelled exosomes have been shown to be translocated into aortic endothelial cells after intravenous injection in C57BL/6 mice. Weekly injection of 20 μg exosomes from mature dendritic cells for 12 weeks could increase the burden of atherosclerotic lesions in ApoE$^{-/-}$ mice. In addition, inhibition of exosome secretion with GW4869 could attenuate endothelial inflammation by mature dendritic cells in vitro (Gao et al., 2016).

In infectious diseases, such as sepsis, tuberculosis, and COVID-19, exosomes (both host- and pathogen-derived) can enter the circulation and transmit and release the pathogen-related virulence factors in endothelial cells, leading to endothelial dysfunction. Micro RNAs (miRNAs) are short non-coding RNAs that regulate gene expressions and a large number of miRNAs are critically involved in the regulation of endothelial cell function (Santulli, 2016). MiRNAs are important part of exosome cargos, and exosomes and exosomal miRNAs are well known to be associated with the development and progression of endothelial dysfunction and atherosclerosis. It has been demonstrated that exosomal miR-27b-3p could efficiently enter vascular endothelial cells and activate NF-κB pathway by downregulating PPARα, leading to vascular inflammation and subsequent atherogenesis in ApoE$^{-/-}$ mice (Tang et al., 2023). A recent study investigated the effect of exosomal miRNAs on endothelial cells during sepsis, and demonstrated that miR-1-3p expression was significantly increased in the plasma exosomes from rats with cecal ligation and puncture (CLP)-induced sepsis, septic patients, and LPS-stimulated HUVECs in vitro. Upregulation of miR-1-3p inhibits cell proliferation, promotes apoptosis and cytoskeleton contraction, increases monolayer endothelial cell permeability and membrane injury by targeting stress-associated endoplasmic reticulum protein 1 (SERP1), resulting in endothelial dysfunction and weakening vascular barrier function (Gao et al., 2021). On the other hand, exosomes could alleviate inflammation in sepsis. A study revealed that exosomes from adipose-derived stem cells (ADSCs) suppressed the excessive inflammatory response and ROS and prevented cell injury and ferroptosis of pulmonary microvascular endothelial cells in association with increased expression of GPX4. ADSCs-derived exosomes could also attenuate lung injury and improve animal survival in mice with CLP-induced sepsis (Shen et al., 2023).

7 | ROLE OF EXOSOMES IN MEDIATING THE EFFECT OF *H. pylori* INFECTION ON ENDOTHELIAL FUNCTION AND POTENTIAL MECHANISMS

Exosomes can cross the physiologic barrier such as cell membrane and blood-brain barrier and deliver their cargos to brain cells within highly protected anatomical regions (Yang et al., 2015). Recently, it has been shown that *H. pylori* infection significantly impairs endothelial function in male mice through an exosome-mediated mechanism(s) (Zhang et al., 2023). Inhibition of exosome secretion with GW4869 effectively preserves endothelial function in mice with *H pylori* infection (Xia et al., 2020). Data from a recent study has revealed that CagA$^+$ *H. pylori*, not CagA$^-$ *H. pylori*, infection significantly impairs endothelial function, and enhances atherosclerosis *via* exosomes-mediated ROS formation in mice. Treatment with CagA-containing exosomes released from human epigastric epithelial cells (GES-1) co-cultured with CagA$^+$ *H. pylori*, not with CagA$^-$ *H. pylori*, significantly increases intracellular ROS production in endothelial cells and impairs their function (Xia et al., 2022). Therefore, exosomes released from the *H. pylori*-infected gastric epithelial cells, carrying various bioactive components including proteins, lipids, carbohydrates and nucleic acids, enter circulation and then into endothelial cells, leading to endothelial dysfunction as shown in Figure 2.

7.1 | miRNAs

Accumulating data have shown that exosome-transmitted miRNAs play important roles in *H. pylori* infection-induced endothelial dysfunction (Li et al., 2019). It is reported that *H. pylori* infection increases the expression of miR-25 in gastric epithelial cells and increases the levels of exosome-transmitted miR-25 in peripheral blood in human subjects (Li et al., 2019). Studies have revealed that Kruppel-like factor 2 (KLF2) is a direct target of exosome-transmitted miR-25 in vascular endothelial cells. In addition, the miR-25/KLF2 axis is involved in the regulation of NF-κB signalling pathway, and significantly increases the expressions of IL-6, monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), and ICAM-1, leading to increased levels of inflammation in endothelial cells (Li et al., 2019). Treatment of HUVECs with a variety of *H. pylori*-derived products enhances the expressions of various miRNAs including miR-21, miR-155 and miR-663 in the cells that are associated with inflammation, apoptosis and necrosis of endothelial cells (Kalani et al., 2021). It is also reported that aqueous extract of CagA$^+$ *H. pylori* is more potent than that of CagA- *H. pylori* on inducing apoptosis and necrosis of HUVECs (Kalani et al., 2017).

7.2 | CagA

H. pylori has multiple strains and based on the presence of CagA, *H. pylori* is divided into two major categories: CagA-positive and CagA-negative *H. pylori*. The majority of patients in East Asian countries with *H. pylori* infection (>90%) are infected

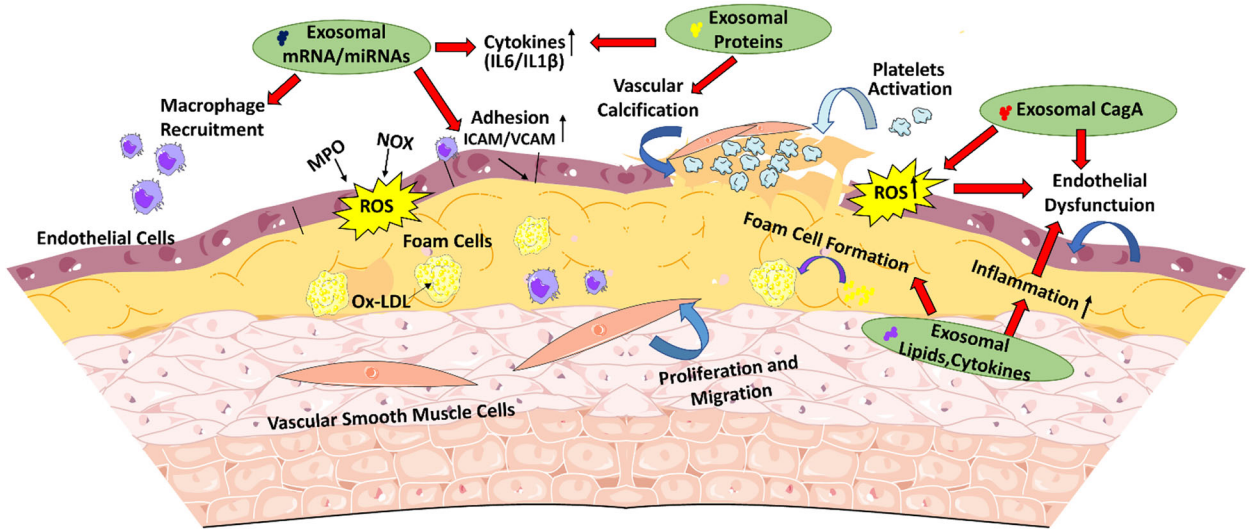

FIGURE 2 Exosomes from *H. pylori* infected gastric epithelial cells are associated with atherosclerosis. During *H. pylori* infection, the virulence factor CagA, miRNA and various molecules are delivered into circulation with exosomes. CagA-containing exosomes play important roles in *H. pylori* infection-induced endothelial dysfunction through various mechanisms, including increased productions of inflammatory cytokines, ROS production and macrophage-derived foam cell formation. Exosome-transmitted miRNAs significantly increases the expressions of IL-6, MCP-1, VCAM-1, and ICAM-1, leading to increased levels of inflammation in endothelial cells. ICAM-1, intercellular adhesion molecule-1; miRNA, micro ribonucleic acid; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule-1.

with CagA$^+$ *H. pylori* (Covacci et al., 1993). CagA is a major virulence factor in *H. pylori*, which encodes the CagA protein and can be translocated into host cells through the type IV secretion system (T4SS) (Cover et al., 2020). Epidemiological data and meta-analysis have revealed a much stronger correlation between infection with CagA$^+$*H. pylori* strains and atherosclerosis in patients compared to that of CagA$^-$ *H. pylori* strains (Mayr et al., 2003; Tahmina et al., 2022). CagA has been found in the serum-derived exosomes of patients and mice infected with CagA$^+$ *H. pylori* (Shimoda et al., 2016; Xia et al., 2020). In vitro study (Xia et al., 2020) has demonstrated that exosomes from the conditioned media of human gastric epithelial cells (GES-1) co-cultured with CagA$^+$ *H. pylori* or from the serum exosomes from patients or mice with *H. pylori* infection contain CagA protein, and significantly decreased endothelial functions with decreased migration, tube formation and proliferation. In vivo study has shown that inhibition of exosome secretion with GW4869 effectively preserved endothelial function in mice with *H. pylori* infection (Xia et al., 2020). On the other hand, exosomes from the conditioned media of GES-1 cells co-cultured with CagA$^-$ *H. pylori* or from the serum exosomes from mice with CagA$^-$ *H. pylori* infection have no significant effect on endothelial function (Xia et al., 2022). A recent study has shown that overexpression of CagA protein selectively in vascular endothelial cells significantly attenuates endothelial cell function and promotes the development of atherosclerosis in a mouse model, possibly through activation of the pro-inflammatory transcription factor STAT3 (Tahmina et al., 2022). Thus, CagA-containing exosomes can enter circulation and may be transmitted to distant organs, contributing to the pathogenesis of extra-gastric diseases associated with CagA-positive *H. pylori* infection, including endothelial dysfunction and atherosclerosis.

7.2.1 | Oxidative stress

ROS have been considered an important contributing factor to the development of endothelial dysfunction and a wide range of CVDs including HTN and atherosclerosis (Batty et al., 2022; Ferroni et al., 2006). *H. pylori* infection, especially CagA$^+$ *H. pylori* infection can increase ROS levels through various mechanisms, including increased productions of inflammatory cytokines and CagA-containing exosomes mediated mechanism (Xia et al., 2022). Recent studies have demonstrated that serum exosomes from mice with CagA$^+$ *H. pylori* infection, and exosomes from conditioned media of human GES-1 cells co-cultured with CagA$^+$ *H. pylori* increase intracellular ROS production and inhibits the function of endothelial cells with decreased migration, tube formation, and proliferation, which are effectively prevented with treatment of N-acetylcysteine (Xia et al., 2022). Inhibition of exosomes release with GW4869 also effectively prevents aortic ROS production as well as aortic endothelial dysfunction and atherosclerosis in mice with CagA$^+$ *H. pylori* infection (Xia et al., 2022). Interestingly, exosomes from CagA$^-$ *H. pylori* infected mouse serum or from GES-1 cells co-cultured with CagA$^-$ *H. pylori* have no significant effect on intracellular ROS production in endothelial cells or the function of endothelial cells (Xia et al., 2022). These data suggest that CagA-containing exosomes play a critical role in increased ROS production and endothelial cell dysfunction in *H. pylori* infection.

There are substantial sex differences in many CVDs including atherosclerosis and coronary artery disease (Ramirez & Sullivan, 2018; Sato et al., 2022; Vakhtangadze et al., 2021). A recent study investigated the role of exosomes in mediating the sex differences in endothelial cell dysfunction with *H pylori* infection (Zhang et al., 2023). Data showed that exosomes from the serum of male mice, but not from the serum of female mice with *H. pylori* infection, significantly increased intracellular ROS in mouse brain microvascular endothelial cells (bEND.3 cells) and inhibited their function with decreased migration, tube formation and proliferation compared with control, which could be reversed by treatment of N-acetylcysteine. In vivo studies demonstrated that *H. pylori* infection impaired acetylcholine-induced endothelium-dependent aortic relaxation in male but not female mice in association with a significant increase in aortic ROS selectively in male mice, not in female mice (Zhang et al., 2023).

7.2.2 | Regulation of macrophage functions

Macrophages play a critical role in the productions of inflammatory cytokines and ROS and are closely associated with endothelial dysfunction and development of CVDs (Rosenfeld et al., 1990; Vendrov et al., 2023; Zhang et al., 2021). *H. pylori* has been shown to recruit macrophages to the gastric mucosa to produce proinflammatory cytokines and chemokines, leading to local inflammation and damage to the gastric mucosa (Tang et al., 2021). It was reported that CagA-containing exosomes from *H. pylori* infected GES-1 cells can be taken up by macrophages in circulation and promotes macrophage-derived foam cell formation and enhances atherosclerotic lesion development by downregulating the expression of transcriptional factors PPARγ and LXRα, and thus suppressing the transcription of cholesterol efflux transporters and enhancing foam cell formation (Yang et al., 2019). Treatment of Raw264.7 cells with the exosomes from CagA-positive *H. pylori*-infected GES-1 cells significantly increases the percentage of foam cells, the total cholesterol content, and cholesterol ester in the cells (Yang et al., 2019).

8 | UNANSWERED QUESTIONS

The field of EVs and endothelial dysfunction in infectious diseases is rapidly expanding, but there are still many gaps and challenges that need to be addressed to advance this field. There is no comprehensive review article to examine the relationship between EVs and endothelial dysfunction associated with infectious diseases. The mechanisms and functions of EVs from many different infectious agents and different types of immune cells, such as macrophages, dendritic cells, T cells, and B cells, during infectious diseases are unclear. It is also unknown how EVs mediate the crosstalk between endothelial cells and other types of cells, such as platelets, smooth muscle cells, fibroblasts, stem cells and immune response cells in response to infections and related tissue inflammation and damages. Infectious diseases are very diverse and dynamic in nature and their clinical manifestations and courses of disease development and progression may change rapidly and dramatically in a short period of time. It is unclear if EVs and their cargos from the hosts and/or the infectious agents could change accordingly with the stages of infectious disease development and progression and how. Sex, age, and ethnic background may play an important role in the clinical outcomes of infectious diseases. Very little data are available regarding the differences in EVs and their cargos and potential contributions to the pathogenesis and/or clinical outcomes of infectious diseases associated with sex, age and ethnic background.

These questions are important because EVs play a key role in the development and progression of infectious diseases and endothelial dysfunction and associated CVDs, and thus may have an important impact on the prevention and/or treatment of infectious diseases. In addition, EVs may have potential applications as biomarkers for diagnosis and prognosis of infectious diseases as well as preventive and/or therapeutic values. Therefore, it is important to adequately address these questions to achieve the optimal outcomes for the prevention, diagnosis, and treatment of infectious diseases using comprehensive and systematic as well as innovative approaches to fully characterize EVs from the hosts and the infectious agents at different stages of diseases.

9 | CONCLUSIONS

CVDs remain the leading cause of morbidity and mortality for both men and women in the world today. EVs carry various bioactive components including miRNAs, proteins and lipids and are involved in the development of CVDs. Various infections are associated with increased risk for CVDs, and EVs play an important role in the pathogenesis of disease development associated with infectious agents including virus, fungi and bacteria. *H. pylori* infection has been shown to significantly increase the risk for CVDs including HTN and atherosclerosis. EVs from *H. pylori* infected gastric epithelium can enter the circulation and endothelial cells, and increase intracellular ROS production, leading to endothelial dysfunction. The mechanisms for EVs-mediated ROS production and endothelial dysfunction are complex and likely multi-factorial, including inflammatory cytokines, specific mRNAs, miRNAs, proteins like CagA, and modification of macrophage function. Understanding the roles of EVs and the bioactive substances in their cargos could serve as a fingerprint and biomarkers for the development and progression of CVDs,

and help defining the mechanism for CVDs and developing new strategies to prevent and treat CVDs associated with *H. pylori* infection and other infectious diseases.

AUTHOR CONTRIBUTIONS

Linfang Zhang: Investigation; writing—original draft; writing—review and editing. **Jingshu Chi**: Investigation; validation. **Hao Wu**: Writing—original draft. **Xiujuan Xia**: Investigation. **Canxia Xu**: Writing—review and editing. **Hong Hao**: Supervision. **Zhenguo Liu**: Conceptualization; methodology; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

ORCID

Linfang Zhang https://orcid.org/0000-0002-0715-8885

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