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The Role of MSC Secretome and EV in Targeting Emerging and Persistent Viral Reservoirs Beyond Respiratory Viruses: A Narrative Review

Nur Dina Amalina[1,2,3]*, Faya Nuralda Sitompul[4], Ririn Rahmala Febri[5], Farahana Kresno Dewayanti[6], Izzati Rafidah[7], Fitri Hasnaulia Wargadipura[8]

*Correspondence:
amalinadina27@gmail.com

[1]Stem Cell and Cancer Research Indonesia, Central Java, Indonesia
[2]Pharmaceutical Sciences Department, Faculty of Medicine, Universitas Negeri Semarang, Central Java, Indonesia
[3]Biological Sciences Division, Nara Institute of Science and Technology, Nara, Japan
[4]Department of Signal Transduction, Research Institute of Microbial Diseases, The University of Osaka, Osaka, Japan
[5]Laboratory for Cell Systems, Institute for Protein Research, The University of Osaka, Osaka, Japan
[6]Department of Molecular Protozoology, Research Institute for Microbial Diseases, The University of Osaka, Osaka, Japan
[7]Department of Biomolecular Sciences and Engineering, SANKEN, The University of Osaka, Osaka, Japan
[8]Department of Metabolomics, Graduate School of Systems Life Sciences, Kyushu University, Fukuoka, Japan

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ABSTRACT

Background: Persistent viral infections remain a significant global health challenge, with viral reservoirs in anatomically and immunologically privileged sites evading conventional therapeutic approaches. Mesenchymal stem cells (MSCs) and their secreted factors, including the secretome and extracellular vesicles (EVs), have emerged as promising therapeutic modalities due to their immunomodulatory, anti-inflammatory, and tissue-regenerative properties. **Objective:** This narrative review synthesizes current evidence on the therapeutic potential of MSC-derived secretome and EVs in targeting viral reservoirs beyond respiratory infections, including human immunodeficiency virus (HIV), hepatitis viruses, herpesviruses, and emerging arboviruses. **Methods:** A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases for studies published between 2015 and 2025, focusing on MSC secretome, extracellular vesicles, viral reservoirs, and persistent viral infections. **Results:** MSC secretome and EVs demonstrate multifaceted antiviral mechanisms including direct viral inhibition, immunomodulation of host responses, tissue repair of virus-induced damage, and potential targeting of latent viral reservoirs. Evidence from in vitro, animal models, and limited clinical studies suggests efficacy against HIV latent reservoirs, chronic hepatitis B and C infections, cytomegalovirus reactivation, and dengue-induced pathology. Key bioactive components include microRNAs, cytokines, growth factors, and antimicrobial peptides that collectively modulate viral replication and host immunity. **Conclusion:** MSC-derived therapeutics represent a novel approach to addressing persistent viral infections, although significant challenges remain in standardization, scalability, delivery methods, and clinical translation. Future research should focus on optimizing EV production, identifying specific bioactive components, elucidating the mechanisms of reservoir penetration, and conducting rigorous clinical trials to establish the efficacy and safety profiles of these products.

Keywords: Mesenchymal stem cells, secretome, extracellular vesicles, viral reservoirs, cell-free therapy.

INTRODUCTION

Persistent viral infections represent a formidable challenge in modern medicine, affecting millions worldwide and contributing significantly to global morbidity and mortality (Borrow & Bhardwaj, 2018). Unlike acute viral infections, which are typically cleared by the host immune system, persistent infections establish a long-term presence within the host through various mechanisms, including latency, chronic active replication, and the establishment of anatomical reservoirs that evade immune surveillance (Virgin et al., 2009). These infections encompass a diverse array of pathogens, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV),

herpesviruses, human T-lymphotropic virus (HTLV), and various emerging arboviruses.

The establishment and maintenance of viral reservoirs constitute the primary obstacle to viral eradication. These reservoirs are located in anatomically privileged sites, such as the central nervous system (CNS), lymphoid tissues, liver, reproductive organs, and latently infected long-lived cells that harbor integrated or episomal viral genomes (Eisele & Siliciano, 2012). Current antiviral therapies, while often effective at suppressing active viral replication, fail to eliminate these latent reservoirs, necessitating lifelong treatment and risking viral rebound upon therapy discontinuation.

Mesenchymal stem cells (MSCs) are multipotent stromal cells first isolated from bone marrow that possess the capacity for self-renewal and differentiation into multiple lineages, including osteoblasts, adipocytes, and chondrocytes (Friedenstein et al., 1970; Pittenger et al., 1999). Beyond their regenerative potential, MSCs have garnered significant attention for their potent immunomodulatory properties, making them attractive candidates for treating inflammatory and immune-mediated conditions (Uccelli et al., 2008). MSCs can be isolated from various tissues, including bone marrow, adipose tissue, umbilical cord, placenta, and dental pulp, each source presenting distinct characteristics in terms of proliferation capacity, differentiation potential, and paracrine activity (Hass et al., 2011). Importantly, MSCs exert their therapeutic effects primarily through paracrine mechanisms rather than direct cellular engraftment and differentiation, secreting a complex array of bioactive molecules collectively termed the "secretome" (Caplan & Dennis, 2006).

The MSC secretome encompasses all factors secreted by MSCs, including soluble proteins, cytokines, chemokines, and growth factors, lipid mediators, nucleic acids, and extracellular vesicles (EVs) (Harrell et al., 2019). This secretome mediates diverse biological functions, including immunomodulation, angiogenesis, anti-apoptosis, anti-fibrosis, and antimicrobial activity (Vizoso et al., 2017). Extracellular vesicles represent a particularly important component of the MSC secretome. EVs are membrane-bound nanoparticles (30-1000 nm) released by cells that facilitate intercellular communication by transferring proteins, lipids, mRNAs, and microRNAs (miRNAs) to recipient cells (Théry et al., 2018). EVs are categorized based on their biogenesis into exosomes (30-150 nm, originating from multivesicular bodies), microvesicles (100-1000 nm, derived from plasma membrane budding), and apoptotic bodies (>1000 nm, released during apoptosis) (Kalluri & LeBleu, 2020). MSC-derived EVs (MSC-EVs) offer several advantages over cell-based therapies, including lower immunogenicity, reduced risk of tumorigenicity, easier storage and handling, the ability to cross biological barriers, and potential for targeted delivery through surface engineering (Hade et al., 2021). These characteristics position MSC-EVs as promising cell-free therapeutic agents for various diseases, including persistent viral infections.

While the application of MSC secretome and EVs in respiratory viral infections, particularly COVID-19, has been extensively reviewed (Sengupta et al., 2020; Akbari & Rezaie, 2020), their potential in targeting persistent viral reservoirs beyond respiratory viruses remains incompletely synthesized. The unique immunomodulatory properties of MSC-derived products, coupled with their ability to penetrate tissue barriers and modulate host-pathogen interactions, suggest therapeutic utility in addressing latent and persistent viral infections. This narrative review aims to provide a comprehensive overview of the current research on the MSC secretome and extracellular vesicle (EV) applications in persistent viral infections, extending beyond respiratory viruses. We aim to elucidate the mechanisms by which MSC-derived therapies interact with viral reservoirs and modulate host immune responses, identify existing knowledge gaps and translational challenges, and propose future research directions to optimize the use of MSC-derived products in controlling or eliminating viral reservoirs.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

A comprehensive narrative review methodology was employed to synthesize current knowledge on MSC secretome and extracellular vesicles in targeting viral reservoirs beyond respiratory infections. Literature searches were conducted in October 2025 across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar.

The search strategy utilized combinations of keywords and Medical Subject Headings (MeSH) terms including: "mesenchymal stem cells" OR "mesenchymal stromal cells" OR "MSC" AND "secretome" OR "extracellular vesicles" OR "exosomes" OR "microvesicles" OR "conditioned medium" AND "viral reservoir" OR "latent infection" OR "persistent infection" OR "chronic viral infection" OR "HIV" OR "hepatitis" OR "herpesvirus" OR "cytomegalovirus" OR "arbovirus" OR "dengue" OR "Zika" OR "viral latency."

Inclusion and Exclusion Criteria

The review included original research articles, clinical trials, and relevant reviews published between 2015 and 2025 that focused on MSC secretome, conditioned medium, or EVs in the treatment of viral infections. Studies eligible for inclusion were those conducted in vitro, in vivo, or clinical settings, examining antiviral mechanisms and therapeutic efficacy. Only articles published in English and addressing persistent, latent, or chronic viral infections beyond primary respiratory viruses were considered. Studies exclusively focusing on acute respiratory viral infections including influenza, RSV, SARS-CoV-2, without broader mechanistic insights, articles lacking primary data or detailed mechanistic investigation, conference abstracts without available full texts, studies focusing solely on MSC cellular therapy without investigation of secretome or EV components, as well as duplicate or retracted publications were excluded.

Data Extraction and Synthesis

Relevant data were extracted from selected articles, including study design, MSC source, secretome/EV isolation and characterization methods, target virus, experimental models, key findings, proposed mechanisms, and clinical implications. Given the heterogeneity of study designs and outcomes, a narrative synthesis approach was employed rather than meta-analysis, organizing findings thematically by viral pathogen, mechanism of action, and therapeutic application.

Quality Assessment

This studies were critically evaluated considering experimental design rigor, reproducibility, appropriate controls, characterization of MSC-derived products according to International Society for Extracellular Vesicles (ISEV) guidelines (Théry et al., 2018), and translational relevance

RESULTS

Composition of MSC Secretome

The MSC secretome is a complex mixture of bioactive molecules that mediate therapeutic effects primarily through paracrine signaling. Proteomic analyses have revealed hundreds of secreted proteins with a wide range of functions. Major components include growth factors such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and brain-derived neurotrophic factor (BDNF). Immunomodulatory cytokines, such as interleukin-6 (IL-6), IL-10, prostaglandin E2 (PGE2), indoleamine 2,3-

dioxygenase (IDO), tumor necrosis factor-stimulated gene 6 protein (TSG-6), and galectin-1, play a crucial role in its immunoregulatory functions. Additionally, chemokines such as monocyte chemoattractant protein-1 (MCP-1/CCL2), stromal cell-derived factor-1 (SDF-1/CXCL12), interleukin-8 (IL-8/CXCL8), and RANTES (CCL5) facilitate cell recruitment and tissue repair. The secretome also contains antimicrobial peptides, including LL-37, β-defensins, hepcidin, and lipocalin-2, which provide direct antimicrobial and antiviral activities. Furthermore, extracellular matrix proteins, such as fibronectin, collagen, and laminin, as well as matrix metalloproteinases (MMPs), play a crucial role in tissue remodeling and regeneration. Together, these components make the MSC secretome a potent mediator of regenerative and immunomodulatory processes (Figure 1) (Harrell et al., 2019; Caplan & Dennis, 2006; Prockop & Oh, 2012; Ren et al., 2008; Krasnodembskaya et al., 2010; Maumus et al., 2013).

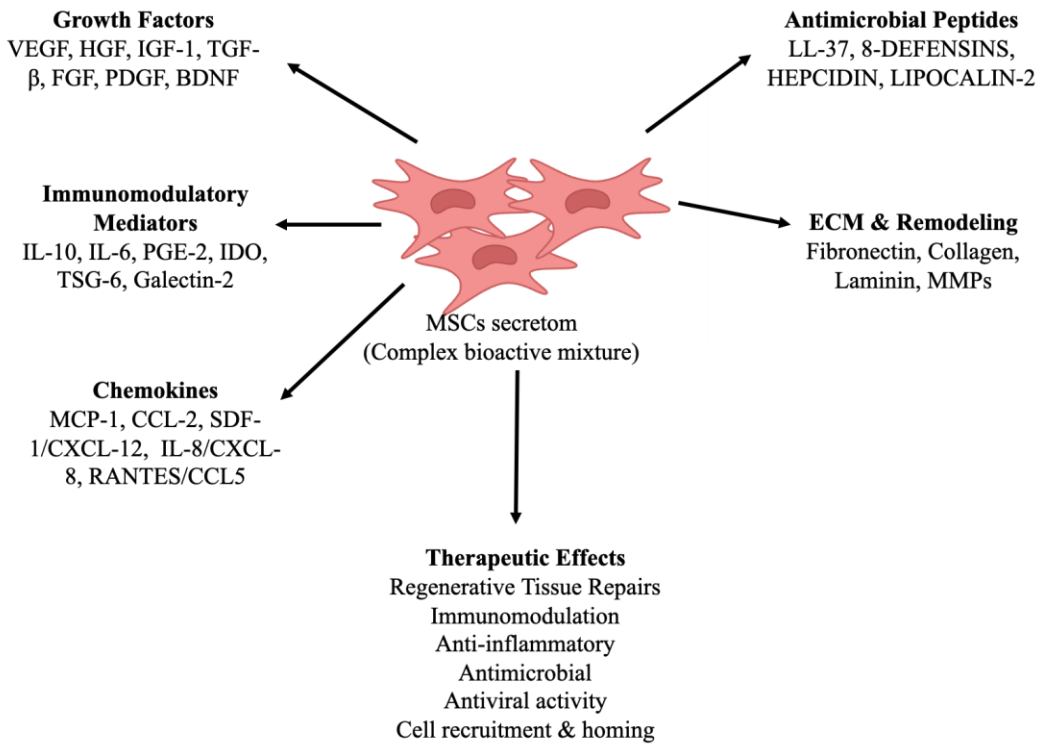

Figure 1. Schematic representation of the major bioactive components and therapeutic mechanisms of the mesenchymal stem cell (MSC) secretome.

Extracellular Vesicles: Cargo and Function

MSCs-derived EVs function as critical mediators of intercellular communication by delivering a variety of functional biomolecules to recipient cells. Comprehensive characterization of MSC-EVs has revealed a diverse cargo that includes proteins such as tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), membrane trafficking proteins (Alix and TSG101), cytoskeletal proteins, and various enzymes. Nucleic acids are also prominent within EVs, with microRNAs (miRNAs) being the most extensively studied. Specific miRNAs, such as miR-21, miR-23a, miR-125b, miR-145, miR-146a, and members of the let-7 family, have been implicated in mediating immunomodulatory and antiviral effects. Beyond miRNAs, MSC-EVs contain mRNAs, long non-coding RNAs (lncRNAs), and DNA fragments. The lipid composition of EVs comprises cholesterol, ceramides, sphingomyelin, phosphatidylserine, and other bioactive lipid mediators, all of which contribute to the structural integrity and biological activity of EVs. Notably, the molecular

composition of MSC secretome and EVs varies based on the tissue source of MSCs, donor characteristics, culture conditions, and environmental stimuli such as priming or preconditioning. This variability offers opportunities to optimize therapeutic applications of MSC-derived EVs (Lötvall et al., 2014; Ferguson et al., 2018; Record et al., 2014; Ti et al., 2015).

Mechanisms of Antiviral Activity

MSC secretome and EVs exert antiviral effects through multiple interconnected mechanisms rather than a single mode of action. These mechanisms can be broadly categorized into direct antiviral effects, immunomodulation, tissue repair and regeneration, and targeting potential reservoirs.

a. Direct Antiviral Mechanisms

MSC-derived secretome and EVs demonstrate multiple antiviral mechanisms contributing to their therapeutic potential. Viral entry can be inhibited by MSC-derived factors that block viral attachment and entry into host cells. Several studies have demonstrated that soluble factors in the MSC secretome compete with viral receptors or downregulate receptor expression, such as ACE2, CCR5, and CXCR4, on target cells, thereby limiting viral access. In addition, MSC-EVs transfer antiviral microRNAs (miRNAs), including miR-146a, miR-29a, and members of the let-7 family, which directly target viral genomes or cellular genes essential for viral replication. The secretome also induces the expression of interferon-stimulated genes (ISGs), establishing an antiviral state within recipient cells. Furthermore, certain MSC-derived factors interfere with the late stages of the viral life cycle, including viral assembly, maturation, and release; however, this aspect is less extensively studied compared to the mechanisms affecting entry and replication. These diverse actions enable MSC secretome and EVs to disrupt various stages of viral infection, suggesting broad potential antiviral effects (Khatri et al., 2018; Lim et al., 2020; Mao et al., 2019; Alcayaga-Miranda et al., 2017).

b. Immunomodulatory Mechanisms

Immunomodulatory activity is a hallmark of the MSC secretome and EVs in regulating immune responses during viral disease. The suppression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IFN-γ, is accompanied by an increase in the secretion of anti-inflammatory mediators such as IL-10 and TGF-β (Reis et al., 2018). These changes are mediated through signaling pathways involving prostaglandin E2 and indoleamine 2,3-dioxygenase, as well as direct transfer of immunoregulatory microRNAs via EVs. The reduction of excessive inflammation by MSC-derived products is particularly effective in preventing tissue damage and promoting healing during persistent or chronic viral infections (Harrell et al., 2019).

The secretome also influences innate immunity by driving macrophage polarization toward an anti-inflammatory M2 phenotype, which is characterized by elevated IL-10 and reduced TNF-α and IL-12 production (Majka et al., 2017). Additionally, EVs modulate the function of natural killer cells and dendritic cells, resulting in altered antiviral immune responses. Immunomodulatory effects are context-dependent, varying according to the level of inflammation and the specific microenvironment encountered by MSC-derived products (Prockop & Oh, 2012).

Regulation of adaptive immunity involves the inhibition of T cell proliferation, the promotion of regulatory T cell populations, and changes in B cell function, including alterations in antibody production. Transfer of microRNAs through EVs alters T cell metabolism and function, which may affect immune surveillance during latent or chronic viral infection. Rather than simple immunosuppression, MSC secretome and EVs help restore immune homeostasis and promote balanced antiviral responses (Németh et al., 2009).

c. Tissue Repair and Regeneration

The MSC secretome demonstrated significant restorative effects in the context of chronic viral infection–induced tissue injury. Its bioactive components exerted anti-apoptotic, angiogenic, anti-fibrotic, and regenerative influences that collectively supported tissue repair and functional recovery. Growth factors, such as HGF, IGF-1, and VEGF, reduce the apoptosis of infected or damaged cells, thereby preserving tissue integrity (Gnecchi et al., 2008). The secretion of VEGF, FGF, and other angiogenic mediators enhanced neovascularization, resulting in improved tissue perfusion and regeneration within affected organs (Kinnaird et al., 2004). Furthermore, the secretome exhibited strong anti-fibrotic actions by downregulating collagen deposition, suppressing myofibroblast differentiation, and remodeling the extracellular matrix through MMP activity (Caplan & Correa, 2011), which is particularly relevant for preventing cirrhotic progression in chronic hepatitis. In addition, MSC-derived paracrine signals activated endogenous stem and progenitor cells, further promoting the repair and regeneration of injured tissues (Bi et al., 2007).

d. Targeting Viral Reservoirs

The MSC secretome, particularly its EV component, exhibited properties suggestive of a novel and incompletely defined capacity to target latent viral reservoirs. EVs demonstrated the ability to cross the blood–brain barrier (BBB) via mechanisms such as transcytosis and direct endothelial membrane fusion, enabling potential delivery of therapeutic cargo to central nervous system viral reservoirs (Alvarez-Erviti et al., 2011). Systemically administered MSC-EVs showed preferential retention in specific organs including the liver, spleen, and lungs, indicating tissue tropism that may be harnessed to reach reservoir sites in these locations (Wiklander et al., 2015). In addition, EVs utilized diverse cellular entry routes endocytosis, membrane fusion, and receptor-mediated uptake—ensuring efficient cargo delivery even to latently infected cells (Mulcahy et al., 2014). Emerging data further suggest that MSC-derived factors may modulate epigenetic regulators of viral latency, raising the possibility of latency reversal (“shock”) in conjunction with clearance strategies (“kill”) to achieve functional elimination of persistent infections (Yin et al., 2020).

Applications in Specific Viral Infections

a. Human Immunodeficiency Virus (HIV)

HIV persistence despite effective antiretroviral therapy (ART) remains a major obstacle to achieving a definitive cure, primarily due to the presence of latently infected CD4+ T cells, especially within the long-lived memory T cell subset that serves as the principal viral reservoir (Eisele & Siliciano, 2012). Preclinical investigations have provided encouraging evidence for the therapeutic potential of MSC-derived products in the treatment of HIV infection. Human adipose-derived MSC-EVs were shown to inhibit HIV replication in infected peripheral blood mononuclear cells (PBMCs) by transferring miRNAs that target the HIV-1 long terminal repeat (LTR) and cellular co-receptors, leading to reduced expression of CCR5 and CXCR4 on CD4+ T cells and consequently limiting viral entry (Martínez-Garza et al., 2020). In addition, the bone marrow-derived MSC secretome suppressed HIV replication in a humanized mouse model, resulting in a 70% decrease in viral loads compared to controls, accompanied by the upregulation of antiviral restriction factors, such as APOBEC3G and tetherin (Kim et al., 2021).

The chronic immune activation typical of HIV infection under ART, MSC-EVs exhibited pronounced immunomodulatory effects by lowering inflammatory markers, including IL-6, TNF-α, and D-dimer in plasma from HIV-infected individuals ex vivo (Nazari-Jahantigh et al., 2020). Additionally, MSC secretome treatment restored impaired T cell functions and promoted Treg expansion, potentially mitigating chronic inflammation while preserving antiviral immune responses.

Preliminary findings also suggest that MSC-derived components may influence HIV latency; EV-associated miRNAs and histone deacetylase (HDAC) inhibitors could contribute to latent virus reactivation as part of "shock and kill" approaches, although further studies are warranted to confirm this concept (Archin et al., 2012; Turner & Margolis, 2017). Beyond systemic effects, MSC-EVs demonstrated neuroprotective actions by crossing the blood–brain barrier, reducing neuroinflammation, and enhancing neuronal survival in models of HIV-associated neurocognitive disorders (HAND) (Ru et al., 2019). While a phase I/II clinical trial in HIV/HBV co-infected patients confirmed the safety and immune restorative capacity of MSC infusions (Pang et al., 2018), dedicated clinical evaluation of MSC secretome and EV-based therapies for HIV remains limited, representing a critical unmet area for translational research (Table 1).

b. Hepatitis B Virus (HBV)

HBV infection, affecting an estimated 296 million individuals worldwide, persists due to the stability of the covalently closed circular DNA (cccDNA) reservoir within hepatocytes, which current nucleoside analog therapies cannot eradicate (World Health Organization, 2021). The MSC secretome has demonstrated hepatoprotective, antiviral, immunomodulatory, and anti-fibrotic properties in HBV models. In HBV-infected liver tissue, MSC-conditioned medium reduced hepatocyte apoptosis and inflammation through HGF and IL-10 secretion (Salomone et al., 2019). Umbilical cord MSC-derived EVs inhibited HBV replication in both HepG2.2.15 cells and primary human hepatocytes, lowering HBsAg and HBeAg secretion by 40–50% and reducing intracellular HBV DNA levels; this effect was mediated by transfer of miR-199a-3p targeting the HBV polymerase gene and HBx-interacting protein (Wang et al., 2020).

In terms of immune regulation, MSC secretome partially restored HBV-specific T cell activity while attenuating excessive inflammatory responses in mouse models (Zhao et al., 2021), suggesting that balanced immunomodulation could enhance antiviral efficacy without exacerbating immunopathology. The secretome also exerted potent anti-fibrotic effects by decreasing hepatic stellate cell activation, reducing collagen accumulation, and promoting matrix remodeling via MMPs (Lee et al., 2019), benefits that occur independently of direct viral suppression and may complement ongoing antiviral therapy. Clinically, randomized controlled trials using MSC therapy have shown improved liver function and reduced fibrosis in patients with decompensated HBV-related cirrhosis (Li et al., 2016). However, dedicated investigations into the impact of MSC secretome or EVs on cccDNA reservoirs in HBV patients remain limited, marking a key area for future research.

c. Hepatitis C Virus (HCV)

Despite the high cure rates achieved with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection, challenges persist in the form of treatment failures, reinfection, extrahepatic manifestations, and management of advanced fibrosis beyond viral clearance (Pawlotsky, 2020). The MSC secretome has shown anti-HCV activity through multiple mechanisms. Bone marrow MSC-derived EVs inhibited HCV replication in Huh7.5 hepatoma cells by approximately 60%, an effect mediated by transfer of antiviral miRNAs such as let-7f and miR-196, which targeted both viral genome sequences and host factors critical for viral replication (Mohamadnejad et al., 2016).

In addition to direct antiviral effects, MSC-conditioned medium reduced hepatocyte apoptosis and inflammation in HCV-infected liver cells via secretion of anti-apoptotic and anti-inflammatory mediators (Watanabe et al., 2019), offering therapeutic value even when DAAs achieve viral elimination. The clinically most advanced application of MSC therapy in HCV involves the management of advanced liver disease and cirrhosis. Multiple clinical trials have reported improved liver function, decreased fibrosis markers, and better quality of life following MSC infusions in HCV-related cirrhosis patients (Sakaida et al., 2018), effects attributed to the combined regenerative, anti-fibrotic, and anti-inflammatory actions of the secretome. Furthermore, given HCV's capacity to cause

Table 1. Summary of MSC Secretome and Extracellular Vesicle Applications in Persistent Viral Infections

Virus	Primary Reservoir Site	Key Mechanisms of MSC-Derived Therapeutics	Major Findings	Clinical Status	Key References
HIV	CD4+ memory T cells, CNS, lymphoid tissue	• Reduction of CCR5/CXCR4 co-receptor expression • Enhanced antiviral restriction factors (APOBEC3G, tetherin) • Immunomodulation and Treg expansion • BBB penetration and neuroprotection • Potential latency modulation	• MSC-EVs reduced HIV replication in PBMCs via miRNA transfer targeting LTR and co-receptors • 70% reduction in viral load in humanized mice • Reduced inflammatory markers (IL-6, TNF-α) • Neuroprotective effects in HAND models	Phase I/II trials completed in HIV/HBV co-infected patients showing safety and immune reconstitution Studies of acellular products lacking	Martínez-Garza et al., 2020; Kim et al., 2021; Nazari-Jahantigh et al., 2020; Ru et al., 2019; Pang et al., 2018
HBV	Hepatocyte cccDNA	• Inhibition of HBV polymerase via miR-199a-3p • Hepatocyte protection (HGF, IL-10) • Anti-fibrotic effects • Immune restoration	• 40-50% reduction in HBsAg and HBeAg secretion • Decreased intracellular HBV DNA • Reduced hepatic stellate cell activation • Partial restoration of HBV-specific T cell responses	RCTs showing improved liver function and reduced fibrosis in cirrhotic patients cccDNA reservoir studies needed	Wang et al., 2020; Salomone et al., 2019; Zhao et al., 2021; Lee et al., 2019; Li et al., 2016
HCV	Hepatocytes	• Transfer of antiviral miRNAs (let-7f, miR-196) • Anti-apoptotic signaling • Anti-fibrotic and regenerative effects • Immunomodulation for extrahepatic manifestations	• 60% reduction in HCV replication in Huh7.5 cells • Reduced hepatocyte death and inflammation • Improved liver function in cirrhosis • Enhanced quality of life	Multiple trials in HCV-related cirrhosis showing clinical benefit Adjunct to DAA therapy	Mohamadnejad et al., 2016; Watanabe et al., 2019; Sakaida et al., 2018; Cacoub et al., 2016

Virus	Primary Reservoir Site	Key Mechanisms of MSC-Derived Therapeutics	Major Findings	Clinical Status	Key References
CMV	CD34+ hematopoietic progenitors, myeloid cells	• Suppression of immediate-early gene expression via miR-148a and miR-21 • Balanced immunomodulation • Prevention of reactivation	• Inhibition of CMV reactivation from latency • Reduced inflammation during reactivation • Maintained antiviral immunity	Clinical use in HSCT recipients showing reduced CMV reactivation and improved outcomes Mechanisms incompletely defined	Tan et al., 2021; Ball et al., 2013; Reeves & Sinclair, 2008
HSV-1/2	Sensory neuron ganglia	• Enhanced type I interferon responses • Transfer of antiviral miRNAs • Neuroprotection • Accelerated wound healing	• Reduced HSV-1 replication in keratinocytes • Improved wound healing in murine cutaneous infection • Protection of neurons from viral damage	Preclinical only Clinical potential for HSV encephalitis and recurrent infections	Li et al., 2018; Whitley & Roizman, 2001
EBV	Memory B cells	• Suppression of excessive inflammation • Maintenance of EBV-specific T cell responses • Caution regarding reactivation risk	• Reduced inflammation in hemophagocytic lymphohistiocytosis • Preserved antiviral immunity • Concerns about lymphoproliferation	Preclinical Careful patient selection needed	Zhang et al., 2017; Young & Rickinson, 2004
VZV	Dorsal root ganglia	• Neuroprotection • Anti-inflammatory effects • Analgesic properties	• Reduced neuroinflammation in ganglionitis models • Neuronal survival support • Potential for postherpetic neuralgia	Preclinical only Limited VZV-specific studies	Han et al., 2016; Gershon et al., 2015

Virus	Primary Reservoir Site	Key Mechanisms of MSC-Derived Therapeutics	Major Findings	Clinical Status	Key References
Dengue	Monocytes/macrophages (transient)	• Suppression of cytokine storm (IL-6, TNF-α, IL-1β) • Endothelial barrier stabilization via TSG-6, PGE2 • Platelet preservation • Vascular protection	• Reduced vascular leak in murine severe dengue • Improved survival • Stabilized endothelial barriers via VEGF and angiopoietin-1 • Enhanced megakaryopoiesis	Phase I trial completed showing safety and trends toward clinical benefit Phase II ongoing	Lim et al., 2018; Lim et al., 2020; Lee et al., 2017; Shi et al., 2014
Zika	Neural progenitor cells, CNS	• Neuroprotection of neural progenitors • Delivery of neurotrophic factors • Anti-inflammatory effects • Support for neurogenesis • Modest direct antiviral activity	• Reduced ZIKV-induced neural progenitor cell death • Partial rescue of brain development defects in mice • 40% reduction in viral replication • Promoted neurogenesis	Preclinical only Therapeutic window questions for congenital syndrome	Souza et al., 2018; Regmi et al., 2019; Krauer et al., 2017
HTLV-1	CD4+ T cells	• Reduction of inflammatory cytokines • Neuroprotection in HAM/TSP • Protection from immune-mediated damage • Caution in ATL risk	• Reduced inflammatory cytokine production by infected T cells • Protection of neural cells from immune damage • No evidence of promoting malignancy	Preclinical Clinical trials warranted for HAM/TSP with careful monitoring	Nakamura et al., 2019; Shimizu et al., 2020; Gessain & Cassar, 2012
Chikungunya	Joints (chronic inflammation)	• Anti-inflammatory effects in synovium • Cartilage repair support • Tissue regeneration	• Reduced synovial inflammation in mice • Cartilage repair support • Addressed chronic arthralgia	Preclinical only Clinical potential for post-acute arthritis	Silva et al., 2021; Burt et al., 2017
West Nile	CNS neurons	• Neuroprotection • Reduction of neuroinflammation • Support for neurological recovery	• Reduced CNS viral loads in mice • Decreased neuroinflammation	Preclinical only Potential for neuroinvasive disease	Kumar et al., 2020; Petersen et al., 2013

Virus	Primary Reservoir Site	Key Mechanisms of MSC-Derived Therapeutics	Major Findings	Clinical Status	Key References
		• Modest direct antiviral effects	• Improved neurological outcomes and survival		

Abbreviations: ATL, adult T-cell leukemia/lymphoma; BBB, blood-brain barrier; cccDNA, covalently closed circular DNA; CNS, central nervous system; CMV, cytomegalovirus; DAA, direct-acting antiviral; EBV, Epstein-Barr virus; HAND, HIV-associated neurocognitive disorders; HAM/TSP, HTLV-1-associated myelopathy/tropical spastic paraparesis; HBV, hepatitis B virus; HCV, hepatitis C virus; HGF, hepatocyte growth factor; HSV, herpes simplex virus; HSCT, hematopoietic stem cell transplantation; HTLV-1, human T-lymphotropic virus type 1; IL, interleukin; LTR, long terminal repeat; miRNA, microRNA; MSC, mesenchymal stem cell; PBMC, peripheral blood mononuclear cell; PGE2, prostaglandin E2; RCT, randomized controlled trial; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; TSG-6, tumor necrosis factor-stimulated gene 6 protein; VEGF, vascular endothelial growth factor; VZV, varicella-zoster virus; ZIKV, Zika virus.

extrahepatic complications including cryoglobulinemia, glomerulonephritis, and neurological disorders (Cacoub et al., 2016), the immunomodulatory potential of MSC secretome may help address these systemic manifestations, although targeted studies remain limited.

d. Herpesviruses

The herpesvirus family, comprising eight distinct viruses, establishes lifelong persistence in humans by maintaining latency within specific cell types and anatomical niches (Pellett & Roizman, 2013). In cytomegalovirus (CMV) infection, latency occurs in CD34+ hematopoietic progenitor cells and myeloid lineage cells, with periodic reactivation posing risks, especially to immunocompromised individuals (Reeves & Sinclair, 2008). While certain contexts suggest MSCs might support CMV replication, more recent findings indicate that MSC-EVs can suppress CMV reactivation, as EV-associated miR-148a and miR-21 downregulate immediate-early viral genes required for latency escape (Tan et al., 2021). Concurrently, MSC secretome modulates immune responses to minimize inflammatory damage during reactivation while retaining antiviral efficacy. Clinically, MSC therapy in hematopoietic stem cell transplant recipients has correlated with reduced CMV reactivation rates and improved outcomes, though the relative contributions of direct antiviral activity versus immunomodulation remain uncertain (Ball et al., 2013).

In herpes simplex virus (HSV) infection, HSV-1 and HSV-2 persist in sensory neurons, leading to recurrent mucocutaneous lesions and occasional encephalitis (Whitley & Roizman, 2001). Umbilical cord MSC-EVs demonstrated anti-HSV-1 actions by reducing viral replication in keratinocytes, enhancing wound healing, and boosting type I interferon responses in a murine cutaneous infection model, partly through delivery of antiviral miRNAs (Li et al., 2018). Neuroprotective factors within MSC secretome could potentially mitigate neuronal injury in HSV encephalitis, although this possibility requires further validation. Epstein-Barr virus (EBV), latent in memory B cells, is linked to malignancies and post-transplant lymphoproliferative disorders (Young & Rickinson, 2004). MSC-derived immunomodulatory factors have been shown to curb excessive inflammation in EBV-associated hemophagocytic lymphohistiocytosis while preserving EBV-specific T cell function (Zhang et al., 2017); however, the immunosuppressive profile of MSCs raises theoretical concerns about promoting EBV reactivation or lymphoproliferation, warranting careful clinical assessment.

Varicella-zoster virus (VZV), latent in dorsal root ganglia, can cause herpes zoster and postherpetic neuralgia in older or immunocompromised individuals (Gershon et al., 2015). The

neuroprotective and analgesic properties of MSC secretome suggest potential for mitigating VZV-related neurological sequelae, with preliminary data indicating reduced neuroinflammation and enhanced neuronal survival in experimental viral ganglionitis models, though studies directly addressing VZV remain limited (Han et al., 2016).

e. Dengue Virus

Dengue virus (DENV) is the most prevalent arthropod-borne viral infection worldwide, with severe manifestations such as vascular leak, hemorrhage, and multi-organ dysfunction primarily driven by immune-mediated pathology rather than direct viral cytotoxicity (Guzman & Harris, 2015). The MSC secretome offers a promising therapeutic approach by modulating the hyperinflammatory responses underlying severe dengue. In a murine model of severe infection, MSC-conditioned medium reduced vascular leakage and improved survival by suppressing proinflammatory cytokines (IL-6, TNF-α, and IL-1β) and preserving endothelial barrier function, effects mediated through the secretion of TSG-6 and PGE2 (Lim et al., 2018).

Endothelial stabilization represents a key protective mechanism, as dengue-associated vascular permeability is a major determinant of disease severity. MSC-EVs enhance endothelial integrity by transferring regulatory miRNAs and delivering angiogenic mediators, including VEGF and angiopoietin-1 (Lee et al., 2017). Additionally, given that thrombocytopenia contributes to dengue hemorrhagic manifestations, MSC secretome components including thrombopoietin and megakaryopoiesis-promoting factors support platelet production and may alleviate hematologic complications (Shi et al., 2014). Clinically, phase I evaluation of MSC therapy in severe dengue confirmed safety and demonstrated trends toward reduced plasma leakage and accelerated clinical recovery in treated patients (Lim et al., 2020). A larger phase II trial is ongoing, and future studies focusing on acellular MSC secretome and EV formulations are anticipated to further delineate optimal strategies for dengue immunomodulation and vascular protection.

f. Zika Virus

Zika virus (ZIKV) has emerged as a major global health concern due to its strong association with congenital neurological defects, particularly microcephaly, and with adult neurological syndromes such as Guillain-Barré syndrome (Krauer et al., 2017). The MSC secretome has demonstrated significant neuroprotective and reparative potential in experimental ZIKV infection. Umbilical cord MSC-derived EVs were shown to reduce ZIKV-induced neural progenitor cell death in vitro and to partially rescue brain development abnormalities in infected mice, promoting neural cell survival, attenuating neuroinflammation, and enhancing neurogenesis through the delivery of neurotrophic factors and regulatory miRNAs (Souza et al., 2018).

Beyond neuroprotection, MSC-conditioned medium exerted modest direct antiviral activity, reducing ZIKV replication by approximately 40% in infected cells via induction of interferon-dependent antiviral signaling pathways (Regmi et al., 2019). However, the therapeutic effectiveness of MSC secretome in congenital Zika syndrome remains highly dependent on timing. While MSC-derived factors may mitigate ongoing neural injury and promote repair during later stages of gestation or postnatal life, structural brain malformations caused by early fetal infection are likely irreversible. Current research therefore focuses on defining the optimal therapeutic window in which intervention with MSC secretome or EVs can effectively prevent or reduce the severity of ZIKV-induced developmental abnormalities.

g. Human T-Lymphotropic Virus (HTLV-1)

Human T-cell leukemia virus type 1 (HTLV-1) infects an estimated 5–10 million individuals globally and is responsible for diseases including adult T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), with persistent infection

occurring within CD4+ T cells (Gessain & Cassar, 2012). In HAM/TSP, chronic spinal cord inflammation and demyelination are driven by excessive immune activation against HTLV-1. The MSC secretome's anti-inflammatory and neuroprotective properties position it as a potential therapeutic candidate. In vitro studies demonstrated that MSC-conditioned medium reduced inflammatory cytokine output from HTLV-1-infected T cells and protected neural cells from immune-mediated injury (Nakamura et al., 2019), supporting the rationale for clinical trials aimed at ameliorating neurological disability in HAM/TSP. The use of MSC-derived therapies warrants cautious consideration. While no current data indicate that MSC secretome promotes HTLV-1-related malignancies, theoretical concerns remain that immune modulation might alter tumor risk or progression. Consequently, applications in HTLV-1 carriers should involve careful patient selection, rigorous monitoring, and integration within controlled clinical settings to ensure safety and efficacy (Shimizu et al., 2020).

Optimization Strategies for Enhanced Therapeutic Efficacy

The composition and therapeutic potency of MSC-derived secretome and extracellular vesicles (EVs) can be substantially enhanced through optimized priming, engineering, and delivery strategies (Table 2). Preconditioning MSCs with specific stimuli prior to secretome collection modifies their paracrine output and functional efficacy (Ti et al., 2015). Inflammatory priming using cytokines such as IFN-γ, TNF-α, and IL-1β augments immunomodulatory activity by upregulating IDO, PGE2, and other anti-inflammatory mediators, resulting in primed MSC-EVs with superior inflammation-suppressive effects relative to naïve vesicles (Waterman et al., 2012). Similarly, hypoxic preconditioning (1–5% O_2) enhances MSC survival, proliferation, and secretion of angiogenic and neuroprotective factors, including VEGF, HGF, and BDNF, producing EVs with increased neuroprotective potency, particularly relevant for neurotropic viral infections (Ejtehadifar et al., 2015). Culturing MSCs in three-dimensional spheroids further improves the yield and bioactivity of secreted factors, enriching anti-inflammatory and regenerative components compared to conventional two-dimensional culture (Bartosh et al., 2010). Genetic modification of MSCs to express therapeutic genes—such as cytokines, growth factors, or antiviral proteins—can precisely tailor secretome composition for targeted efficacy, though this approach may raise regulatory concerns (Wang et al., 2019). Additionally, priming with viral antigens or inactivated viruses represents an emerging strategy to enhance antiviral secretome properties, though it remains largely unexplored (Khatri et al., 2018).

EV engineering techniques have also advanced the capacity for therapeutic cargo loading and tissue-specific targeting. Approaches such as electroporation, sonication, freeze–thaw cycles, and saponin permeabilization enable the encapsulation of antiviral drugs, specific miRNAs, or proteins into EVs (Luan et al., 2017). Surface modification with targeting ligands—such as antibodies, peptides, or aptamers—can improve delivery precision to tissues or cells harboring viral reservoirs; for example, EVs expressing HIV-1 envelope proteins could selectively target latently infected CD4+ T cells (Antes et al., 2018). Hybrid systems combining EVs with synthetic nanoparticles or liposomes further enhance vesicle stability, loading efficiency, and targeting capabilities while retaining biological compatibility (Sato et al., 2016).

Table 2. Optimization Strategies for Enhanced Therapeutic Efficacy of MSC Secretome and EVs

Strategy Category	Approach	Key Mechanism/Outcome	Example References
MSC Priming and Preconditioning	Inflammatory priming with IFN-γ, TNF-α, IL-1β	Upregulates IDO, PGE2, and anti-inflammatory factors; primed MSC-EVs show enhanced inflammation reduction	Waterman et al., 2012
	Hypoxic preconditioning (1–5% O_2)	Increases MSC survival/proliferation; boosts VEGF, HGF, BDNF secretion; enhances neuroprotective effects	Ejtehadifar et al., 2015
	3D spheroid culture	Enhances secretome yield; increases anti-inflammatory and regenerative factor production	Bartosh et al., 2010
	Genetic modification of MSCs	Overexpression of cytokines, growth factors, antiviral proteins; enhances targeted effects	Wang et al., 2019
	Viral antigen priming	Exposure to viral antigens/inactivated virus may enhance antiviral secretome properties	Khatri et al., 2018
EV Engineering and Targeting	Cargo loading (electroporation, sonication, freeze-thaw, saponin, co-incubation with engineered donor cells)	Increases delivery of antiviral drugs, miRNAs, therapeutic proteins into EVs	Luan et al., 2017
	Surface modification with targeting ligands (antibodies, peptides, aptamers)	Directs EVs to specific cell/tissue targets such as HIV reservoirs	Antes et al., 2018
	Hybrid approaches (EV-nanoparticle/liposome fusion)	Improves stability, loading capacity, and targeting while retaining bioactivity	Sato et al., 2016
Delivery Routes and Formulations	Systemic administration (IV infusion)	Broad distribution for disseminated infections; mitigated clearance via PEGylation/albumin conjugation	Wiklander et al., 2015
	Local administration	Targeted tissue delivery (intrahepatic, intrathecal, intra-articular) for higher local concentration	Wiklander et al., 2015
	Intranasal delivery	CNS targeting via olfactory/trigeminal pathways for neurotropic viral infections	Long et al., 2017

Strategy Category	Approach	Key Mechanism/Outcome	Example References
	Formulation strategies (lyophilization, encapsulation, long-acting forms)	Enhances stability, storage potential, and clinical practicality	Haghparast et al., 2018

The therapeutic success of MSC secretome and EV-based interventions also depends on appropriate delivery routes and formulation technologies. Systemic administration via intravenous infusion facilitates widespread biodistribution for disseminated viral infections, although rapid hepatic and splenic clearance poses a limitation; strategies such as PEGylation and albumin conjugation have been proposed to extend circulation time (Wiklander et al., 2015). Local administration through site-directed injection—such as intrahepatic for hepatitis, intrathecal for central nervous system infections, or intra-articular for arboviral arthritis—enables high local concentrations while minimizing off-target exposure. Intranasal delivery offers a noninvasive route for central nervous system targeting through olfactory and trigeminal pathways, providing particular relevance for neurotropic viral infections (Long et al., 2017). Moreover, formulation improvements including lyophilization, encapsulation, and long-acting preparations enhance the stability, storage, and clinical feasibility of MSC-derived therapeutics (Haghparast et al., 2018).

Challenges and Limitations

Significant heterogeneity exists in MSC characteristics depending on tissue source, donor age and health, culture conditions, and passage number, leading to considerable variability in secretome composition and therapeutic potency that complicates clinical translation (Samsonraj et al., 2017). The absence of standardized protocols for MSC isolation, expansion, secretome harvesting, and EV purification results in products with varying purity and bioactive profiles (Moll et al., 2019). In contrast, quality control under ISEV guidelines requires specialized resources that are often unavailable in routine production settings (Théry et al., 2018). Batch-to-batch variability and the lack of validated potency assays hinder regulatory approval and cross-study comparability (Galipeau et al., 2016). Mechanistically, the therapeutic effects of MSC secretome and EVs in viral infections remain incompletely defined, with their pleiotropic actions mediated by complex mixtures of bioactive molecules varying by pathological context. Key questions persist regarding their ability to penetrate and act upon latent viral reservoirs, as direct evidence of EV accumulation in such sites is limited. Most studies focus on short-term outcomes without clarifying the long-term effects on viral persistence, host immunity, or disease progression.

Safety considerations center on the potential for context-dependent immunosuppression, which may predispose individuals to opportunistic infections; however, clinical trials have not consistently demonstrated increased infection rates (Galipeau et al., 2016). Donor-derived MSC products may carry endogenous viruses such as CMV or EBV, necessitating rigorous screening to prevent transmission risks (Arav et al., 2021). Theoretical concerns about tumor promotion, particularly in oncogenic viral contexts like EBV, HTLV-1, or HBV, have not been substantiated in clinical studies, with some evidence suggesting anti-tumor properties (Hmadcha et al., 2020). Additionally, interactions between MSC-EV biogenesis pathways and viral dissemination mechanisms require careful pathogen-specific evaluation (Urbanelli et al., 2019).

Manufacturing and scalability challenges include the need for extensive MSC expansion, which risks senescence, reduced potency, and genetic instability (Bonab et al., 2006), alongside

inherently low EV yields that demand large culture volumes and optimized collection systems such as bioreactors (Patel et al., 2017). While EVs demonstrate superior stability compared to live cells, the long-term storage effects on their functionality remain underexplored, underscoring the importance of developing robust formulations suitable for widespread clinical distribution (Kusuma et al., 2018). Cost-effectiveness is a crucial factor for deploying interventions in viral diseases prevalent in resource-limited settings. From a regulatory perspective, MSC secretome and EVs occupy an ambiguous classification between biologics and cell therapies, with evolving guidance from agencies such as the FDA and EMA addressing GMP-compliant manufacturing, appropriate categorization, and trial design considerations, including endpoint selection, biomarker validation, and comparator strategies (Lener et al., 2015; Mendicino et al., 2014).

DISCUSSION

This review consolidates current evidence delineating the therapeutic potential of mesenchymal stromal cell (MSC)–derived secretome and extracellular vesicles (EVs) in the management of persistent viral infections beyond the respiratory spectrum. Collectively, the findings highlight that MSC-derived acellular therapeutics constitute a multimodal therapeutic platform that integrates direct antiviral activity, immunomodulation, tissue repair, and, potentially, viral reservoir modulation. Unlike conventional antiviral agents that act through discrete molecular targets, MSC secretome and EVs exert broad, pleiotropic effects across multiple pathological pathways. Among these, immune regulation emerges as the principal mechanism, as MSC-derived factors consistently demonstrated the ability to attenuate hyperinflammation, reestablish immune homeostasis, and mitigate immunopathology—key determinants of disease severity in chronic viral infections. Nonetheless, achieving an optimal balance between suppressing detrimental inflammation and preserving antiviral defenses remains a critical translational challenge. Despite a growing body of preclinical evidence supporting efficacy across diverse viral models, clinical translation remains nascent, with most data derived from cellular MSC therapies rather than purified acellular or EV-based formulations. Variations in viral species, disease stage, and host immune milieu further underscore the context-dependent nature of MSC-derived interventions and the necessity for tailored therapeutic frameworks.

When situated within the broader therapeutic landscape, MSC secretome and EVs represent a complementary adjunct to existing antiviral regimens rather than a competing modality. By addressing pathological dimensions such as tissue injury, immunopathology, and persistent inflammation—domains inadequately targeted by conventional antivirals—MSC-derived products could augment the efficacy and durability of virological control. Compared with live MSC therapy, acellular formulations offer superior safety, scalability, and standardization, while retaining the paracrine and immunoregulatory activities responsible for therapeutic benefit. Moreover, in contrast to highly specific immunotherapies such as therapeutic vaccines or engineered T cell platforms, MSC secretome confers a broader immunomodulatory spectrum and exhibits dual antiviral–regenerative capacity, making it particularly relevant for chronic viral diseases with concurrent tissue damage such as hepatitis B and HIV-associated organ injury.

From a mechanistic perspective, the capacity of MSC-EVs to engage and modulate latent viral reservoirs remains a pivotal but incompletely understood question. Features including their nanoscale size, ability to traverse biological barriers, and propensity for cellular uptake by diverse cell types—including those harboring latent infection—form the theoretical basis for reservoir engagement. Early studies suggest partial epigenetic modulation of viral latency, raising the possibility of controlled “shock and kill” strategies; however, rigorous demonstration of EV accumulation, functional impact within sanctuary sites, and integration into combinatorial latency-reversal frameworks is still lacking. Rather than complete viral eradication, MSC-derived

interventions may ultimately contribute to functional cure paradigms, achieving sustained viral suppression and immune normalization without total reservoir elimination. Addressing fundamental knowledge gaps—including biodistribution, pharmacokinetics, and long-term viro-immunologic outcomes—will be essential to substantiate this potential.

Advancing MSC secretome and EV-based therapies toward clinical application requires a structured translational roadmap that integrates preclinical standardization, early-phase dose-escalation trials, and late-phase randomized controlled studies incorporating mechanistic virological endpoints. Standardization of MSC source selection, culture parameters, and isolation methods must be accompanied by validated potency assays and Good Manufacturing Practice (GMP)–compliant production pipelines. In parallel, personalized therapeutic frameworks—encompassing patient stratification, individualized product optimization, rational combination with antiviral or immunotherapeutic modalities, and biomarker-guided treatment monitoring—are anticipated to enhance clinical precision and efficacy profiles.

Ultimately, responsible clinical development requires consideration of both ethical and global equity principles. Ensuring accessibility in resource-limited settings, transparent communication of uncertainties during early-phase trials, and equitable distribution of manufacturing technologies remain imperative to prevent therapeutic disparity. Furthermore, strategic investment in MSC-derived biologics should complement rather than displace established cost-effective interventions, including vaccination and public health measures. Future research should prioritize mechanistic dissection, comparative optimization of MSC sources, establishing scalable GMP standards, and refining regulatory frameworks that recognize MSC-derived secretome and EVs as a distinct, evidence-based class of bioactive therapeutics with transformative potential in virology and regenerative medicine.

CONCLUSION

MSCs–derived secretome and extracellular vesicles represent a next-generation class of acellular biologics with broad therapeutic promise for persistent viral infections. Through integrated antiviral, immunomodulatory, and regenerative activities and potential modulation of latent viral reservoirs, these products address key pathogenic mechanisms not targeted by conventional antivirals. Accumulating preclinical data and early clinical observations substantiate their safety and biological activity. However, translation remains contingent on the standardization of manufacturing, elucidation of the mechanism, and rigorous clinical evaluation. Under intrinsic scalability, low immunogenicity, and mechanistic versatility, MSC-derived secretome and EVs hold considerable potential as adjunctive therapies in the rational design of curative strategies against chronic and refractory viral infections.

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