



Antiviral Nanomedicine-Based Approaches against Epstein-Barr Virus Infection

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Abstract

Purpose of Review The Epstein-Barr virus (EBV) is a common virus around the globe with approximately 98% of adults testing positive against EBV. However, EBV infection typically begins early in the childhood. Owing to the ability to infect various body organ, EBV is linked to a broad spectrum of symptoms, diseases, and inflammatory conditions. Moreover,

since EBV exists in both latent and replicating forms in most healthy individuals, any disruption in the balance between the virus and its host can lead to the development of different diseases, including autoimmune disorders and cancer. Given these circumstances, we draw attention to the crucial need for developing prophylactic measures and treatments for EBV and its associated diseases.

Recent Findings We propose leveraging the advantages of nanomedicine, such as ferritin and iron oxide nanoparticles, for the creation of EBV vaccines. These advancements can also be applied to developing drugs to treat EBV-associated diseases, such as cancer, autoimmune disorders, and cytokine storm syndrome.

Summary We emphasize the urgency of having accessible EBV vaccines, as well as effective treatments for EBV-related diseases, especially when early diagnosis is involved. This approach, which includes comprehensive cytokine profiling for patients, can significantly enhance the effectiveness of treatment programs.

Introduction

Epstein-Barr virus (EBV), categorized as a gamma herpesvirus, is prevalent worldwide [1]. It has been reported that around 98% of adults are carriers of EBV [2], and this infection typically begins in early childhood [3]. Despite being recognized as the first oncogenic virus, EBV still lacks an available vaccine or a specific treatment option [4]. Some ongoing research efforts have resulted in limited experimental trials addressing this deficiency. Notably, EBV particles were initially observed using electron microscopy in the context of a case of malignant Burkitt's lymphoma in 1964 [5]. Burkitt's lymphoma is a B-cell neoplasm known to appear in atypical anatomical locations, including the mandible, nasopharynx, orbit, kidney,

adrenal glands, and ovaries. This virus primarily results in infectious mononucleosis and has close associations with both lymphatic and epithelial malignancies, including Burkitt's lymphoma (BL), Hodgkin's lymphoma (HL), Nasopharyngeal carcinoma (NPC), AIDS-associated B-cell lymphoma, and various lymphoproliferative diseases (LPDs) [6]. EBV can adopt two states, latency and lytic pathways, within its host cell, expressing viral latent or lytic genes to induce tumor cells in EBV-associated lymphoproliferative diseases [7]. The virus can exhibit four different types of latency patterns, namely type I, II, III, and W promoter (Wp) [8].

Virological overview of EBV

EBV, known as human herpesvirus 4, is composed of double-stranded DNA enclosed by an icosahedral capsid [9], further enveloped by a tegument and a host cell membrane containing integrated glycoproteins (Fig. 1). Infections resulting from EBV can manifest in various ways, ranging from asymptomatic cases to flu-like symptoms, or they can mimic the symptoms of infectious mononucleosis (IM) [10]. IM is a lymphoproliferative disease, typically self-limiting, and characterized by extensive activation of T-cells [11]. Nevertheless, EBV poses a significant life-threatening risk, especially for individuals with compromised immune systems [12].

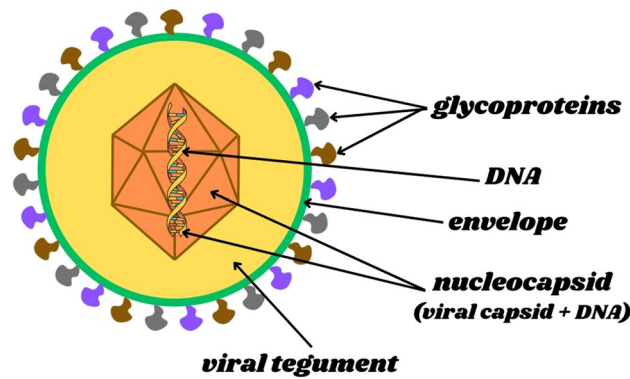


Fig. 1 Diagram displaying the fundamental structure of the Epstein-Barr virus (EBV).

The Epstein-Barr virus (EBV) typically infects through the mucosal surfaces of the mouth and throat. EBV primarily targets B cells in the immune system; the virus attaches itself to specific receptors on the surface of these cells, allowing it to gain entry. This initial attachment is facilitated by viral envelope glycoproteins interacting with cellular receptors [13]. After attachment, the virus fuses its envelope with the host cell membrane, and releasing its genetic material into the cell. This process allows the viral DNA to enter the host cell's nucleus. Once inside the nucleus, the EBV genome circularizes and starts replicating [13]. The virus utilizes the host cell's machinery to transcribe and translate its genes, producing viral proteins and new viral genomes. EBV can enter a latent phase where it remains in the host cell's nucleus without actively producing new viral particles. During latency, the viral genome persists in the infected cell and can periodically reactivate, leading to the production of new viruses. Infected B cells can release new viral particles, allowing the virus to spread to other cells [13]. In some cases, EBV can also infect epithelial cells in the mouth and throat, contributing to viral shedding and transmission through saliva [13].

Given that EBV can infect virtually any organ system in the body, it is associated with a wide array of diseases (Fig. 2) and inflammatory conditions (Fig. 3). These include autoimmune diseases (Fig. 4), vasculitis [14], organ failure [15], myocarditis [16], sudden death [17], disturbances in smell, taste, and hearing [18], thrombosis [11], cytokine storm syndrome [19], fatal anomalies [20], abortion [21], acute and chronic skin lesions [22], cancer, hemophagocytic syndrome, and severe coagulopathy [23, 24], chronic fatigue syndrome [25], chronic active EBV [22], ocular manifestations [26], hepatitis, pancreatitis [27], cholestasis, pneumonia, glomerulonephritis [28], enteritis [29], gastritis, cholecystitis [30], cystitis [31], adrenalitis [32], thyroiditis [33], encephalitis, cerebellar ataxia, Alzheimer's disease [34], and sarcoidosis [35].

There is an urgent requirement for the early detection and treatment of illnesses linked to EBV and the development of vaccines to protect against EBV infections. In most healthy individuals, EBV exists in two states: latent and replicating virus. A disturbance in the delicate balance between the virus and its host can lead to the emergence of various diseases [36]. Importantly, the interplay between psychological stressors and cellular factors can trigger the reactivation of EBV [34]. The nature of symptoms resulting from EBV

Infectious mononucleosis	Chronic active EBV	Chronic fatigue syndrome
Inflammations	Auto-immune diseases	Cancer
Organ(s) failure	Cytokine storm syndrome	Hemophagocytic syndrome
Thrombosis	Ocular manifestations	Skin lesions
Smell and taste loss or distortion	Cerebellar ataxia	Alzheimer`s disease
Sarcoidosis	Abortion	Fatal anomalies

Fig. 2 Epstein Barr virus-associated diseases.

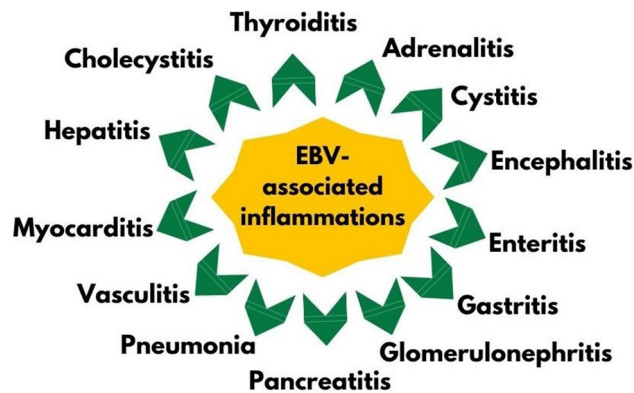


Fig. 3 Epstein Barr virus-associated inflammations.

infection varies and depends on factors such as stress levels, the individual's age, environmental conditions, and other pathogens. EBV reactivation can be triggered by specific factors, including immunosuppression, particular cytokines, or steroid hormones [37]. For example, during events like pregnancy or the rapid reduction of steroid use, EBV lytic replication can be facilitated by glucocorticoids, marked by increased expression of the immediate early *BZLF1* gene [38, 39].

EBV contains genes that code for proteins with both sequence and functional similarity to human proteins, allowing them to regulate EBV-infected cells [22]. Among these proteins, cytokines play a crucial role [40]. While cytokines are essential in facilitating the innate immune response, persistent or dysregulated cytokine activity can potentially lead to pathological conditions, such as severe chronic active EBV development. This highlights the intricate interplay between pro-inflammatory and anti-inflammatory cytokines, a defining aspect of inflammation. Severe chronic active EBV infection results from the clonal expansion of either T- or NK cytotoxic cells,

Systemic lupus erythematosus	Auto-immune hepatitis
Rheumatoid arthritis	Sjogren's syndrome
Multiple sclerosis	Grave's disease
Auto-immune thyroid disorders	Celiac disease
Auto-immune thyroid disorders	Kawasaki disease
Nervous system vasculitis	Vitiligo
Auto-immune adrenocortical insufficiency	Generalized pustular psoriasis

Fig. 4 Epstein Barr virus-associated autoimmune diseases.

leading to elevated levels of both pro-inflammatory and anti-inflammatory cytokines, including interleukin (IL)-1, interferon- α (IFN- α), IL-13, IL-15, tumor necrosis factor (TNF)- α , and transforming growth factor (TGF)- β [14].

Additionally, EBV-induced myocarditis can lead to congestive heart failure [41]. Thus, we emphasize the critical importance of early diagnosis and treatment of EBV to reduce the risk of mortality. The presence of a cytokine storm is a distinctive feature of hemophagocytic lymphohistiocytosis (HLH), marked by significantly elevated levels of IFN- α , soluble CD25, as well as a marked increase in IL-6, IL-10, and IL-18. Therefore, it is imperative to underscore the significance of evaluating cytokine profiles in patients with EBV-associated diseases [19]. The open reading frame (ORF) of EBV *BILF1* promotes immunosuppression and contributes to oncogenic processes [42]. Therefore, compounds that act as inverse agonists for BILF1 have the potential to inhibit cellular transformation and serve as promising candidates for therapeutic intervention [43]. *BILF1* encodes a protein responsible for targeting the major histocompatibility complex (MHC) class I molecules, leading to their degradation within lysosomes, which compromises their recognition by immune T-cells [44].

EBV remains the first human virus known to directly contribute to the development of lymphoid and epithelial cancers [45]. Additionally, EBV has been linked to various malignancies, including post-transplant lymphoproliferative disorders, which are the most common forms of cancer arising after organ transplantation [1]. The lifelong presence of EBV in the body during its latent phase explains the prolonged nature of autoimmune diseases, often marked by recurring exacerbations of symptoms [46]. Normally, the immune system works to keep the viral load minimal. However, instances of immunosuppression can trigger EBV reactivation, causing it to transition to the lytic phase [22]. While NK cells typically identify and eliminate virally infected

cells, certain EBV proteins can disrupt this mechanism, hindering early viral control and potentially leading to infectious mononucleosis (IM) or severe primary viral infections [47].

Mortality resulting from EBV infection primarily results from the development of hemophagocytic lymphohistiocytosis (HLH), characterized by hypercytokinemia, often referred to as cytokine storm syndrome. Hypercytokinemia leads to cellular damage, organ dysfunction, and ultimately, death [19]. However, the clinical course of HLH varies, ranging from rapid-onset multi-organ failure within hours to prolonged symptoms resembling IM that persist over months [48]. Notably, patients with acute or chronic EBV symptoms exhibit significantly elevated levels of IL-1, IL-2, IL-6, and IFN- α in their serum [19]. Therefore, our objective is to emphasize the importance of both preventive and therapeutic preparedness for EBV and its associated conditions, harnessing the potential benefits of nanomedicine.

Prophylactic and therapeutic aspects of nanomedicine against EBV

Nanomedicine offers a multifaceted approach encompassing both prophylactic and therapeutic dimensions in combating Epstein-Barr virus (EBV) infections [49, 50]. In the prophylactic realm, engineered nanomaterials serve as a potential avenue for vaccine delivery, leveraging their unique properties to enhance vaccine efficacy and immune response. These nanovaccines can be tailored to mimic viral components, stimulating robust immune reactions against EBV before infection [49, 50]. On the therapeutic front, nanomedicine showcases promise in targeted drug delivery, enabling precise transport and release of antiviral agents to infected cells or tissues. Moreover, nanoparticles with surface modifications can specifically recognize and bind to EBV-infected cells, delivering therapeutic payloads such as antivirals or immunomodulators directly to the viral targets. Nanomedicine's ability to enhance drug stability, bioavailability, and target specificity holds substantial potential in shaping both preventative and treatment strategies against EBV infections [49, 50]. Continued research in this domain aims to optimize nanomedicine approaches, offering new avenues to combat EBV and related diseases.

Targeting glycoproteins

A ferritin nanoparticles vaccine was developed to prevent viral infections [51]. This was accomplished by attaching ferritin to a truncated domain from the EBV gp350 protein, containing the crucial receptor-binding site required for B-cell infection [52]. In comparative studies with the soluble gp350 antigen, the nanoparticle-based vaccine demonstrated significant improvement, neutralizing antibody levels 10 to 100 times higher in mice

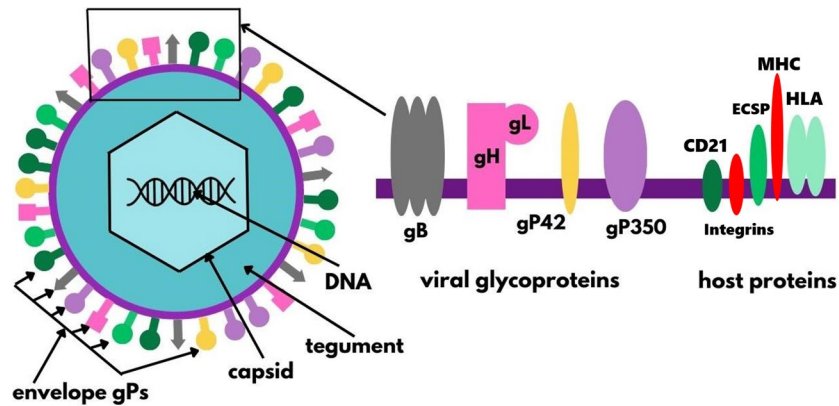


Fig. 5 Schematic illustration showing the Epstein Barr virus envelope glycoproteins (entry complex) and putative host-derived membrane proteins; CD21 (complement receptor type 2), Integrins, ECSP (Epithelial cell surface proteins), Major histocompatibility complex (MHC) molecules, and HLA (Human leukocyte antigen) Class I and II molecules.

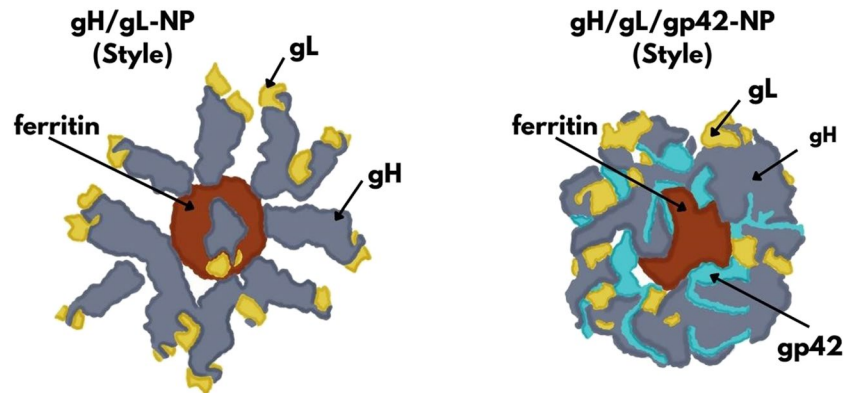


Fig. 6 Ferritin nanoparticles-based Epstein Barr virus-vaccines. Glycoprotein H (gH), glycoprotein L (gL), and glycoprotein 42 (gp42) are the viral surface glycoproteins.

and non-human primates. Additionally, this vaccine conferred protective immunity in a mouse model subjected to a lethal viral challenge [51].

EBV glycoproteins, including gH/gL, gp42, and gB (Fig. 5), have demonstrated higher immunogenicity than the previously favored gp350 antigen [4]. Utilizing distinct EBV antigens, such as gH in combination with gL or with gp42 within a ferritin nanoparticle vaccine (Fig. 6), facilitates the generation of neutralizing antibodies. These antibodies effectively inhibit virus-cell fusion and protect against a broader range of cell types beyond preventing B-cell infection [53]. Clinical trials have recently been initiated to assess the efficacy of an mRNA vaccine known as mRNA-1189. This vaccine comprises four distinct mRNAs encoding gH, gL, gp42, and gp220, along with a ferritin-gp350 nanoparticle vaccine [4].

SiRNA delivery

Small interfering RNA (siRNA) is a type of RNA molecule involved in gene silencing, acting as a potent tool to regulate gene expression [54]. In the context of treating rheumatoid arthritis (RA), an autoimmune condition linked to Epstein-Barr virus (EBV) infection, siRNA technology holds promise. siRNA works by targeting and binding to specific messenger RNA (mRNA) sequences, leading to mRNA degradation and hindering the translation of proteins essential for disease progression [54]. In RA, siRNA therapy could potentially target genes involved in the inflammatory response, suppressing the overactive immune system characteristic of the disease [54–58]. This approach offers the advantage of precise targeting, potentially reducing off-target effects commonly associated with traditional medications. However, challenges persist, such as effective delivery of siRNA to the affected joints and ensuring sustained therapeutic levels [54–58]. Additionally, off-target effects and potential immune responses to the siRNA delivery system are among the drawbacks that need to be addressed for successful clinical application in RA treatment associated with EBV infection [54–58].

The use of nanoparticle as a drug delivery system introduces innovative approaches to address certain medical conditions, including rheumatoid arthritis (RA), an autoimmune disease associated with EBV infection [59, 60]. It is important to note that prolonged use of synthetic and biological DMARDs (disease-modifying anti-inflammatory drugs), NSAIDs (non-steroidal anti-inflammatory drugs), and glucocorticoids can lead to adverse effects affecting gastrointestinal, hepatic, cardiac, and renal functions [59, 61–63]. A significant portion of patients do not respond positively to existing RA treatments or may develop a tolerance to these therapies over time. Unlike traditional medications, nanocarriers are intentionally designed to deliver drugs precisely to the site of joint inflammation, thus avoiding systemic side effects [59]. Instances of this approach involve directing therapeutic substances toward cell receptors or employing small interfering RNAs (siRNAs) to reduce the activity of genes associated with particular signaling pathways. [60, 61]. SiRNAs have been used to inhibit EBV replication by selectively targeting the protease (PR) gene [64••]. The EBV PR is encoded by the *BVRF2* gene and plays a crucial role in viral capsid maturation and packaging of viral DNA in the later stages of the EBV lytic cycle.

Surface-coated nanoparticles

Surface-modified nanoparticles present an innovative approach for delivering cytokines in combating Epstein-Barr virus (EBV) infections. These nanoparticles undergo specific surface alterations, empowering them to effectively transport and release cytokines, vital immune signaling molecules, to targeted sites [49, 50, 65]. In the context of EBV, these modified nanoparticles can

be engineered with surface ligands or antibodies that recognize and bind to receptors present on immune cells implicated in combating the virus. By encapsulating cytokines within these nanoparticles, their controlled and targeted release at infection sites can modulate the immune response against EBV [49, 50, 65]. This precision delivery enhances the efficacy of the cytokines, potentially mitigating EBV infection severity and associated symptoms [49, 50, 65]. Nevertheless, challenges regarding nanoparticle stability, ensuring compatibility within the body, and precise targeting of infected cells remain pivotal for the successful application of surface-modified nanoparticles in delivering cytokines against EBV infections. Ongoing research endeavors aim to refine and optimize these nanoparticles, holding promise for augmenting therapeutic strategies against EBV.

Surface-coated nanoparticles (Fig. 7) have been employed, similar to those used for delivering RA medications, by influencing immune cells like macrophages in inflamed joints [66, 67]. This therapeutic approach is used to manage conditions characterized by excessive cytokine production, particularly IL-6. Notably, EBV viremia levels are correlated with IL-6 levels [27]. IL-6 receptor monoclonal antibody obstructs IL-6 binding to its receptor, thus disrupting IL-6's activities. This intervention leads to the improvement of immunological and hematological abnormalities, as well as the relief of systemic inflammatory symptoms, including cachexia. Importantly, it demonstrates potent therapeutic efficacy while maintaining high safety and general tolerability [68].

Targeting human Epidermal Growth Factor Receptor (EGFR)

The human epidermal growth factor receptor (EGFR) is overexpressed in around one-third of epithelial malignancies, spanning various types such as head and neck, colorectal, breast, ovarian, prostate, bladder, and lung

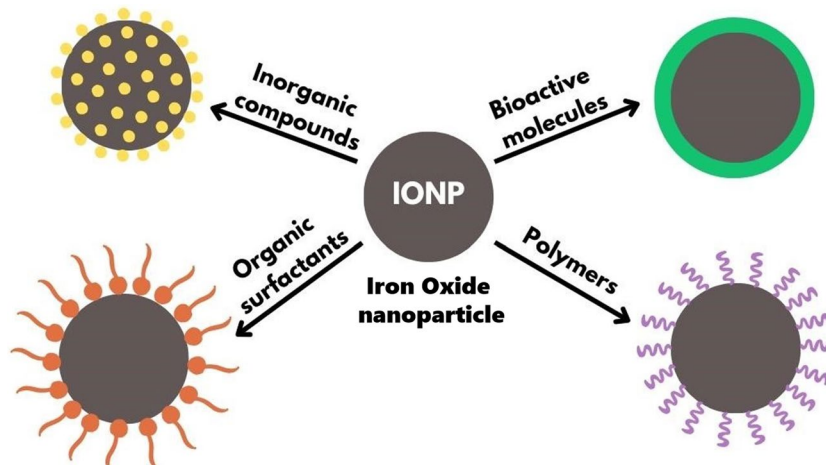


Fig. 7 Surface-coated nanoparticles.

cancers [69]. Dysregulated and persistent EGFR activation plays a pivotal role in promoting tumor growth and progression. This includes fostering heightened cell proliferation, facilitating cell cycle advancement, promoting tumor angiogenesis, facilitating invasion and metastasis, as well as hindering the programmed cell death process [70–72]. Superparamagnetic iron oxide nanoparticles (SPIONs) have been employed to leverage these insights for therapeutic purposes. They are conjugated with various substances, notably by conjugating the anti-EGFR monoclonal antibody cetuximab to dextran coated SPIONs using periodate oxidation. Cetuximab blocks ligand binding to EGFR, inhibiting ligand-induced phosphorylation and activating the EGFR tyrosine kinase. Notably, SPIONs have demonstrated superior sensitivity, reduced toxicity, and a longer plasma half-life than paramagnetic gadolinium chelates. Research findings indicate that SPIONs not only retain the therapeutic effects of cetuximab but also have the ability to specifically target tumors expressing EGFR [69]. The therapeutic potential of cetuximab-polyethylene glycol (PEG)-dextran SPIONs (cet-PEG-dex SPIONs) for addressing EGFR-expressing tumors was explored *in vitro*. This included Western blot analysis, evaluating the reduction in surface EGFR levels, assessing apoptosis, and conducting an antibody-dependent cell-mediated cytotoxicity (ADCC) assay [73].

Conclusion and future prospective

EBV is a ubiquitous herpesvirus associated with several diseases, including infectious mononucleosis and various cancers. EBV is known for its global prevalence, with nearly 98% of adults exhibiting serological positivity, and the infection typically commences during early childhood. Furthermore, EBV is distinguished by its latency and ability to persist in our bodies throughout our lifetime. Additionally, its capacity to infect various organs, systems, and tissues makes it associated with a wide array of diseases. The need for available vaccines against EBV infection and treatments for the associated diseases is pressing, especially when considering early diagnosis. A comprehensive understanding of patients' cytokine profiles can significantly enhance treatment programs' effectiveness. Nanomedicine offers a versatile platform for developing novel and highly targeted antiviral approaches against EBV infection. These approaches may significantly improve treatment outcomes, reduce side effects, and offer curative options for EBV-associated diseases. Nanoparticles can be designed to deliver antiviral drugs specifically to the infected cells by encapsulating or attaching antiviral agents to enhance drug delivery and stability and reduce systemic toxicity.

In addition, nanoparticles can be engineered to serve as carriers for antigens, enhancing the efficiency of vaccines (nano-vaccines) against EBV, which can elicit a stronger and longer-lasting immune response. By utilizing nanoparticles to deliver siRNA or microRNA inhibitors that can specifically target and silence viral genes and hinder the replication and gene expression of EBV. Meanwhile, nanoparticles can be used to deliver CRISPR-Cas9 or other

gene-editing tools to directly modify viral genes within the infected cells, potentially providing a curative approach to EBV-associated diseases. Importantly, research into nanoparticles that can target and disrupt the latent EBV reservoirs may provide a means of preventing viral reactivation and associated diseases like lymphomas and nasopharyngeal carcinoma.

Author contribution

M.A., C.A.C.A., A.F.A, R.F. E.N., M.A.R., M.M.: conceptualization and design. M.A., C.A.C.A., A.F.A, R.F. E.N., M.A.R.: literature search, data extraction and analysis. M.A., C.A.C.A., I.M.B, A.M.A.R.: original manuscript writing. All authors contributed to revision and approved the final version of the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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