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Current updates on the epidemiology, pathogenesis and development of small molecule therapeutics for the treatment of Ebola virus infections

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ABSTRACT

Ebola virus disease (EVD) is a rare, highly contagious and a deadly disease with a variable fatality rate ranging from 30% to 90%. Over the past two decades, Ebola pandemic has severely affected the sub-Sahara region including Democratic Republic of the Congo (DRC), and Uganda. The causative agents of the most EVD cases are three distinct species out of six Ebolaviruses namely Zaire Ebolavirus (ZEBOV), Sudan Ebolavirus (SUDV) and Bundibugyo Ebolavirus (BDBV). In recent years, significant strides have been made in therapeutic interventions. Notably, the US Food and Drug Administration has approved two monoclonal antibodies: Inmazeb™ (REGN-EB3) and Ansuvimab or Ebanga™. Additionally, many small molecules are currently in the developmental stage, promising further progress in medical treatment. Addressing the critical need for preventive measures, this review provides an in-depth analysis of the licensed Ebola vaccines-Ervebo and the combination of Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo) as well as the vaccines which are currently being tested for their efficacy and safety in clinical studies. These vaccines might play an important role in curbing the spread and mitigating the impact of this lethal disease. The current treatment landscape for EVD encompasses both nutritional (supportive) and drug therapies. The review comprehensively details the origin, pathogenesis, and epidemiology of EVD, shedding light on the ongoing efforts to combat this devastating disease. It explores small molecules in various stages of the development, discusses patents filed or granted, and delves into the clinical and supportive therapies that form the cornerstone of EVD management. This review aims to provide the recent developments made in the design and synthesis of small molecules for scientific community to facilitate a deeper understanding of the disease and fostering the development of effective strategies for prevention, treatment, and control of EVD.

KEYWORDS: Ebola; Epidemic; Vaccine; Ebola virus disease

1. Introduction

Ebola virus disease (EVD; Ebola haemorrhagic fever) is a rare but severe contagious disease like Marburg virus disease[1,2]. EVD causes fatal illness to people and non-human primates with an average mortality rate of 50% but as high as 90%. Ebolavirus (EBOV) is a highly pathogenic non-segmented negative sense and single stranded RNA virus belonging to the Filoviridae family[1]. There are six characterized species in genus Ebolavirus *viz.*, Bundibugyo Ebolavirus (BDBV), Reston Ebolavirus (RESTV), Sudan Ebolavirus (SUDV), Taï Forest Ebolavirus (TAFV), Zaire Ebolavirus (ZEBOV), and Bombali Ebolavirus (BOMV) but only four of these cause EVD. Once contracted with the virus, signs and symptoms will start typically between 2 days and 3 weeks. Symptoms include fever, headache, sore throat, muscular pain that could cause internal bleeding, vomit of blood and eventually death if not treated on time[3]. Earlier, there was no specific treatment protocol for this viral disease and therefore the management was merely supportive in nature. However, as the pathogenesis of EVD became more understood over time, a few therapeutic agents have been granted emergency use authorization and some more are being developed. Efforts have also been made to develop vaccines to curb

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the spread and outbreak of this lethal disease. The outbreak of EVD in humans and in apes was first detected in Gabon and Republic of Congo between 2001 and 2003. It is believed that the Ebola infection in humans occurred due to infected fruit bats, as they were eaten by the local populations of Africa[4]. Ebola gets its name from the river named Ebola, present near to the Democratic republic of Congo (DRC), where the disease appeared first in 1976[5]. Soon after, this virus spread to other neighbouring countries in Africa and infected scores of people. Mortality and morbidity data[6] of EBOV outbreak in various countries from 2000 to 2023 is presented in Table 1.

EBOV formerly known as Ebola haemorrhagic fever, caused a major outbreak in sub-Saharan Africa on 3rd December 2014. It affected public health severely and post outbreak of EVD, the fatality rate varies from 30% to 90%. Western Africa, Guinea, Liberia, and Sierra Leone are the worst affected regions by Ebola infection. These regions have higher rates of illiteracy, poverty, inadequate health care facilities and extreme population mobility[7]. The large outbreak in sub-Saharan Africa was caused by three species of Ebola viruses: ZEBOV, SUDV and BDBV. Among all known species, the ZEBOV stands out as the most prolific in terms of fatalities and the frequency of outbreaks it has caused[8,9]. The greater epidemics were seen in Congo, Sudan, Gabon, and Uganda[10]. The effect of Ebola is mainly seen on people and non-human primates such as gorillas, monkeys, and chimpanzees. The exact cause of virus outbreak is unknown, but several studies have suggested it to be animal borne *i.e.*, it has come from bats or non-human primates. The virus spreads among people through direct contact with blood, animal tissue and body fluids of an infected person. If the healthy person encounters infected persons, the virus transmission occurs either by cut or mucous membrane of eyes, nose, or mouth[6]. The 6th outbreak was declared in Mubende District, in western Uganda on 20th September 2022 which was declared over on 11th January 2023. It has seen a total of 164 cases, 142 confirmed cases and 55 deaths with a fatality rate of 34%. The latest 14th outbreak of Ebola in DRC in April 2022 seen five confirmed cases with a 100% mortality rate (Table 1). The outbreak was declared over by the DRC Ministry of Health on 4th July 2022. Pregnant women having Ebola haemorrhagic fever are prone to frequent abortion[11]. During the Ebola epidemic in Yambuku, many pregnant women became infected due to vitamin injections with contaminated needles and syringes[12]. EVD infected women suffers

Table 1. Ebola virus disease (EVD) outbreaks between 2000 and 2023[5].

Species	Year	Location	Number of cases	Number of death (%)
Sudan Ebolavirus	2000	Uganda	425	224 (53)
Zaire Ebolavirus	2001	Republic of the Congo	59	44 (75)
Zaire Ebolavirus	2001	Gabon	65	53 (82)
Zaire Ebolavirus	2003	Republic of the Congo	35	29 (83)
Zaire Ebolavirus	2003	Republic of the Congo	143	128 (90)
Zaire Ebolavirus	2004	Russia	1	1 (100)
Zaire Ebolavirus	2004	Sudan	17	7 (41)
Zaire Ebolavirus	2005	Republic of the Congo	12	10 (83)
Bundibugyo Ebolavirus	2007	Uganda	131	42 (32)
Zaire Ebolavirus	2007	Democratic Republic of the Congo	264	187 (71)
Zaire Ebolavirus	2008	Democratic Republic of the Congo	32	15 (47)
Reston Ebolavirus	2008	Philippines	6*	0
Sudan Ebolavirus	2011	Uganda	1	1 (100)
Sudan Ebolavirus	2012	Uganda	17	7 (41)
Bundibugyo Ebolavirus	2012	Democratic Republic of the Congo	38	13 (34)
Zaire Ebolavirus	2014	Democratic Republic of the Congo	69	49 (71)
Zaire Ebolavirus	2014	Sierra Leone	28610	11308 (40)
Zaire Ebolavirus	2014	Italy	1	0
Zaire Ebolavirus	2014	Mali	8	6 (75)
Zaire Ebolavirus	2014	Nigeria	20	8 (40)
Zaire Ebolavirus	2014	Senegal	1	0
Zaire Ebolavirus	2014	Spain	1	0
Zaire Ebolavirus	2014	United Kingdom	1	0
Zaire Ebolavirus	2014	United States	4	1 (25)
Zaire Ebolavirus	2017	Democratic Republic of the Congo	8	4 (50)
Zaire Ebolavirus	2018	Democratic Republic of the Congo, Uganda	3470	2287 (66)
Zaire Ebolavirus	2018	Democratic Republic of the Congo	54	33 (61)
Zaire Ebolavirus	2020	Democratic Republic of the Congo	130	55 (42)
Zaire Ebolavirus	2021	Democratic Republic of the Congo	12	6 (50)
Zaire Ebolavirus	2021	Guinea	23	12 (52)
Zaire Ebolavirus	2021	Democratic Republic of the Congo	11	9 (82)
Zaire Ebolavirus	2022	Democratic Republic of the Congo	6	6 (100)
Sudan Ebolavirus	2022	Uganda	164	55 (34)

*Asymptomatic.

from major complications such as haemorrhagic manifestations and neurologic complications compared to other EVD patients[13].

This review covers a detailed overview of EVD including its origin, pathogenesis, epidemiology, approved pharmacotherapy and vaccines, small molecules in development, clinical and supportive therapy along with preventive measurements.

2. Life cycle and transmission of Ebola

The EVD is a rare and a deadly disease. EBOV has a thread like filamentous structure with a large non-segmented, negative strand RNA of 19 kb size. The virus is transmitted through the bodily fluids and the blood of the infected person. It can enter through the abrasions, cut and injuries, *via* the mucosal surfaces and parental transmission[14]. EBOV is made up of seven genes (*NP, VP35, VP40, GP, VP30, VP24, L*) which codes for ten proteins such as nucleoprotein (NP), 4 viral proteins (VP) 24, 30, 35, 40, glycoprotein (GP), soluble glycoprotein (s-GP), small soluble glycoprotein (ssGP), -peptide and RNA-dependent RNA polymerase (RdRp; L)[15,16]. The VP40 is the most abundant viral protein present under the viral envelope and helps in maintaining structural integrity, Ebola virion maturation and budding. The VP24 is a minor component of virions and helps in nucleocapsid formation. The GP is present in the viral envelope and helps in receptor bindings and fusion. The NPs, VP30, VP35 and RdRp enclose the genetic materials and the protein shell capsid[17–19]. The EBOV attaches to the target cell by binding of transmembrane virus envelope GP1 to cell surface factor and enter the cell by the receptor-mediated endocytosis. Acidification and the fusion of virus with the host membrane mediates the release of EBOV nucleocapsid in the cytoplasm. After membrane fusion, the ribonucleoprotein is released from virion and serves as a template to produce negative sense genome progeny. The negative sense genome progeny is associated to the nucleocapsid proteins. The GP and sGP modified with the Golgi body and endoplasmic reticulum (ER). The nucleocapsid proteins, negative sense genome progeny, and the membrane protein *i.e.*, VP24, VP40 and GP assembled to form the complete virion and transport to budding site of plasma membrane and bud from the cell surface.

3. Anti–Ebola therapy

The previous outbreaks revolutionized the clinical management of the Ebola patients to control, contain and prevent the further spread of the outbreak. During the 13th outbreak in DRC, the country was able to limit the infections to a total of 11 cases and 6 deaths. Unfortunately, patients are at high risk of mortality as very limited drugs are available for the treatment of EVD. Therefore, measures to reduce the spread of infections and treatment of Ebola include both nutritional (supportive) and drug therapy. Figure 1 shows the different treatment strategies adopted for the treatment of Ebola.

3.1. Vaccines

During 2018-2020 Ebola outbreak in DRC, the first-ever multi-drug randomized control trial was conducted to evaluate the effectiveness and safety of vaccines and other treatment for Ebola patients under an ethical framework.

As of 2023, only two Ebola vaccines have been licensed against Zaire Ebolavirus (ZEBOV): Ervebo and a combination of Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo) which is delivered in two doses. The Ervebo vaccine (recombinant vesicular stomatitis virus-Zaire Ebola virus Ebola Zaire Vaccines; V920, rVSV G-ZEBOV-GP or rVSV-ZEBO; Merck's) is a single-shot, live-attenuated, vectored vaccine which is based on recombinant vesicular stomatitis virus which expresses the ZEBOV glycoprotein[20]. This vaccine was tested successfully for efficacy in a randomized trial in Guinea. This vaccine gives 97.5% efficacy. When rapid immunity is required, a single shot of rVSV-ZEBOV is important[21]. This vaccine is made up of rice-derived recombinant human serum albumin and it contains live-attenuated recombinant vesicular stomatitis virus[22]. In November 2019, the European Medical Agency (EMA) licensed the Ervebo and in December 2019, the vaccine was licensed by the US Food and Drug Administration (FDA), prequalified by the World Health Organization (WHO) for use in individuals aged 18 or older[23]. Later it expanded the approval for people aged 1 to 17 years old as a single dose administration (except for pregnant and breast-feeding women) for protection against EVD caused by ZEBOV.

The marketing authorization of the second vaccine Zabdeno and Mvabea was approved by the EMA in May 2020 for individuals 1 year and older. The Zabdeno-Mvabea vaccine was developed by



Figure 1. Different strategies currently used to treat and manage Ebola virus disease.

Johnson & Johnson. It is a monovalent replication incompetent adenoviral vector serotype 26 (Ad26) vaccine, which encodes the full-length GP of EBOV Mayinga variant. It is indicated for the active immunization of individuals aged 18 years and older who are at risk of infection[24]. The vaccine is delivered in 2 doses: Zabdeno is administered first (prime) and after 8 weeks the second dose of Mvabea is given as a boost. The two-dose regimen is not suitable for any outbreak where there is a requirement of instant protection.

3.1.1. Ebola vaccines under development

Over the past few years, there has been improved characterization of clinical course of EVD[25]. Some vaccines have been developed for the Ebola and immunogenicity and the safety of these developed vaccines were evaluated in various clinical trials. In 2017, Coller *et al*. described the development of V920 Ebola vaccine. V920 vaccine is a live-attenuated, chimeric virus which is based on recombinant vesicular stomatitis virus (rVSV) backbone. The G glycoprotein of rVSV is deleted in V920 and substituted by GP of Zaire Ebola virus (rVSV-ZEBOV-GP) attenuating the virus. During phase Ⅰ clinical trial, 800 adults and 40 paediatric subjects received V920. The clinical trials results revealed the vaccine to be generally well tolerated across all dose levels with higher immune responses in subjects. Eight phase Ⅰ and four phase Ⅱ/Ⅲ clinical trials including 17 000 subjects were conducted. Overall, the vaccine was found to be well-tolerated when given to healthy, non-pregnant adults[26].

Martinus *et al*. evaluated the stability and safety profile of heterologous prime-boost Janssen Ebola vaccine regimen in phase Ⅰ studies which included healthy adults. Potency of both components of Ad26.ZEBOV/MVA-BN-Filo regimen was assessed using qPCR-based potency assay and flow cytometry. The regimen included priming with a recombinant, live, non-replicating adenovirus vector Ad26 which could express Ebola Zaire glycoprotein. The potency of vaccine was assessed by agitation, temperature cycling, freeze-thawing. The frozen vaccine was found to maintain its potency for 36 months[27]. Wu *et al.* in 2019 designed recombinant baculoviruses (rBV) which expresses the Sudan virus matrix structural protein (VP40) (Rbv-vp40-vp40) or the SUDV-GP and SUDV virus like particles were produced by co-infection of Sf9 cells with Rbv-SUDV-VP40 and BV-SUDV-GP. The expression of SUDV VP40 and GP in SUDV VLPs was studied with the help of immunofluorescence assay (IFA) and western blot analysis. In insect cell, the expression of SUDV VLPs was evaluated by mice immunization. When they were vaccinated with SUDV VLPs, the frequency of antigen-specific cells secreting type 1 and 2 cytokines was markedly increased. The therapeutic effects of SUDV antibodies were studied in horses which were immunized with SUDV VLPs emulsified in Freunds complete adjuvant. The results showed SUDV VLPs possessed excellent immunogenicity and thus could be a promising approach for vaccine development against SUDV infection[28].

In 2019, Lehrer *et al.* developed a safe and efficacious formulation of insect-cell derived adjuvant protein vaccine to reduce the adverse reactions of available vaccines. The vaccine candidates containing EBOV glycoprotein with or without matrix protein were tested in guinea pigs for immunogenicity and efficacy against lethal EBOV. The developed vaccine was safe and immunogenic adjuvant subunit vaccine provided protection against EVD in guinea pigs[29]. Boum *et al.* in 2020 conducted a phase Ⅲ clinical trial. It was an open-label, non-randomized, single-arm immunogenicity evaluation of one dose of r VSVG-ZEBOV-GP among 1 172 frontline workers. Those who were not ready for treatment offered to act as control group. The blood (8 mL) was taken from the study participants after 14, 28 and 84 days post vaccination to assess total IgG Ab levels against ZEBOV GP using ELISA (used homologous Zaire-Kikwit strain) glycoprotein as antigen and plaque reduction neutralization (Nab) assay with ZEBOV as antigen. The results showed that the r VSVG/ZEBOV vaccine was able to produce an increase in IgG and neutralizing antibodies[30].

Tapia *et al.* in 2020 assessed the safety, reactogenicity and immunogenicity of one dose of monovalent, recombinant, chimpanzee adenovirus type-3 vectored ZEBOV glycoprotein vaccine (ChAd3-EBO-Z) in adults. Healthy adults were divided into two groups. The first group received ChAd3-EBO-Z vaccine while the other received saline placebo. No serious side effects were reported except mild headache. It was found that ChAd3-EBO-Z was immunogenic and well tolerated in adults[31]. Table 2 shows the vaccines being evaluated in clinical trials for the EVD.

3.2. Approved anti-Ebola therapy with monoclonal antibodies (mAb)

Two monoclonal antibodies namely Inmazeb™ (REGN-EB3) and Ansuvimab or Ebanga™ (mAB114) were the first antiviral antibody therapeutics approved for the treatment of ZEBOV infection in adults and children by the US FDA in late 2020 following the

Table 2. Some of the vaccines in development stage for Ebola[32-35].

Vaccines	Organizations
Chimp adenovirus 3 vectored glycoprotein (cAd3-EBOZ)	GSK and NIAID
Human adenovirus 5 vectored 2014 glycoprotein insect (Ad5-EBOV)	BIT and CanSino
Adenovirus 26 vectored glycoprotein/MVA- BN (Ad26. ZEBOV/MVA-BN)	Johnson and Johnson
HPIV-3 vectored glycoprotein	Ministry of Health (Russia)
Rabies vectored glycoprotein	Thomas Jefferson University
Purified glycoprotein	Protein Sciences
Ebola VP30 H_2O_2 treated	University of Wisconsin

outcome of PAmoja TuLinde Maisha (PALM) (or "Together Save Lives" in the Kiswahili language) clinical trial study[36]. These drugs target the viral entry process. A multicenter, open-label, randomized, and controlled PALM trial jointly sponsored by the WHO, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Health (NIH) and the Institut National de Recherche Biomédicale (INRB) was initiated in 2018 in the DRC. Its aim was to assess the safety and efficacy of four investigational therapies (ZMapp, remdesivir, mAb114 and REGN-EB3) in individuals of all age groups infected with ZEBOV. A total of 154 adults and 174 pediatric patients received Inmazeb™ and Ebanga™ while 168 subjects were given the ZMapp and remdesivir as investigational drugs. The study concluded that both mAb114 and REGN-EB3 were superior to ZMapp and remdesivir in reducing mortality from EVD[37–39].

Inmazeb™ or REGN-EB3 was developed by Regeneron Pharmaceuticals using VelocImmune® platform and associated VelociSuite® technologies. It is a cocktail of three murine derived, but fully glycoprotein-directed recombinant human monoclonal antibodies, consisting of atoltivimab (REGN3470), maftivimab (REGN3479), and odesivimab (REGN3471)[40]. A single shot IV infusion vial (sterile aqueous solution) of Inmazeb™ contains 241.7 mg each of atoltivimab, maftivimab, and odesivimab per 14.5 mL. Immunization of VelocImmune® mice with DNA encoding EBOV glycoprotein and purified EBOVGP followed by cloning the human variable regions onto human constant regions lead to the formation of fully human mAb[41]. This antiviral antibody drug targets glycoproteins and causes Ab-dependent cell cytotoxicity, phagocyte stimulation, and virus internalization inhibition of EBOV. The advantages of this drug are that it targets several different epitopes, given as a single shot and has a good half-life. Its dose is 150 mg/kg[37]. The common adverse effects associated with REGN-EB3 infusion are pyrexia, chills, tachycardia and polyuria[36].

Ebanga™ or mAb 114 is a recombinant, human Immunoglobulin G1 (IgG1) mAB to treat adults and pediatric population infected with ZEBOV. It is manufactured by Ridgeback Biotherapeutics and is administered (50 mg/kg) as a single 1-h IV infusion. It is available in lyophilized and frozen liquid form for injections. The drug is a single monoclonal antibody derived from the memory B-cell clone of the survivor of the 1995 EBOV outbreak. It binds to the glycan cap and the core of glycoprotein sub-unit 1. The mechanism of action is antibody-dependent cell cytotoxicity and high neutralizing activity[42,43]. General characteristics of the approved monoclonal antibody therapy for the treatment of EVD is presented in Table 3.

3.3. Recent development of synthetic medicinal compounds as anti–Ebola therapy

3.3.1. Antiviral and other repurposed drugs to treat EVD

Ebola in an example of a filovirus causes deadly infection with high mortality rates. Some of the currently used therapeutic agents have shown promising results against EVD. Some of the repurposed drugs found effective in EVD include amodiaquine **1**, adenosine nucleoside analogues and drug combinations such as toremifene-mefloquine-posaconazole **2–4**, toremifene-clarithromycin-posaconazole **5**, *etc*. acting as viral entry inhibitors[46]. The safety and efficacy of drug remdesivir (GS5734) **6** as anti-Ebola investigational agent was evaluated in the PALM trial. Due to the potent antiviral activity of favipiravir **7** and brincidofovir (3-hexadecyloxy-1-propanol lipid conjugate of acyclic nucleoside phosphonate cidofovir) **8**, these were also used prior to the PALM trial but in recent EBOV outbreaks, these have not been used because of their inconsistent results in

Table 3. Characteristics of approved anti-Ebola therapy[44,45].

Characteristic/feature	Inmazeb™	Ebanga™
Other names	Atoltivimab/maftivimab/odesivimab, REGN3470 (atoltivimab), REGN3479 (maftivimab), REGN3471 (odesivimab), REGN 3470/3471/3479, REGN3470-3471-3479	Ansuvimab-zykl; EboV mAb114; EVB114; mAb114; VRC EBOMAB092 00 AB
Composition	Cocktail of three recombinant monoclonal antibodies in equal ratio [atoltivimab (REGN3470), maftivimab (REGN3479), and odesivimab (REGN3471)]	Single human monoclonal antibody
Produced/developed by	Regeneron Pharmaceuticals	Ridgeback Biotherapeutics
Date of first approval	14 October 2020 in the USA	21 December 2020 in the USA
Mechanism of action	Antibody dependent cell cytotoxicity, neutralization, phagocyte stimulation, and virus internalization inhibition of EBOV	Glycoprotein inhibitor antibody-dependent cell cytotoxicity and high neutralizing activity
Available form	Aqueous sterile solution	Lyophilized and frozen liquid
Dose, route of administration and duration of therapy	150 mg/kg, single IV infusion over 2-4 h	50 mg/kg, single IV infusion over 30-60 min
Pharmacokinetics	Overall mean t½ values (27.3, 21.7 and 23.3 days) for odesivimab, atoltivimab and maftivimab, respectively	Cmax 1961.21 μg/mL; tmax 2.75 h; AUC0-28d 18588 μg·day/mL; beta phase t½ 23.6 days
Most frequent adverse events after administration	Pyrexia, chills, tachycardia	Pyrexia
Clinical trials conducted	NCT03719586, PALM, NCT03576690 and NCT02777151	PALM, NCT03719586, NCT03478891
Treatment population	Adult and pediatrics	Adult and pediatric patients, including neonates born to mothers with EVD

clinical studies[47]. Earlier ribavirin **9** was approved to treat EVD, but because of its toxicity, its use as anti-EVD has been discontinued. All these nucleoside analogues including favipiravir **7**, brincidofovir **8**, galidesivir **10**, and remdesivir **6** act as polymerase inhibitors and thus play a role in inhibiting viral RNA synthesis. The drug galidesivir **10** (BCX-4430) is a nucleoside analogue with broad spectrum activity against RNA virus and was found to be effective against the Marburg virus in non-human primate model and EBOV in mouse model. This drug inhibits viral RNA polymerase resulting in RNA chain termination[48]. With the right dose of BCX-4430, an improvement in survival rate and reduction of viral load was obtained[49]. The general mechanism of action of adenosine nucleoside analogues antiviral drugs is illustrated in Figure 2. The structure of the synthetic potent antiviral drugs against EBOV disease is shown in Supplementary Figure 1.

Jasenosky *et al*. in 2019 evaluated US FDA approved oral drug nitazoxanide (NTZ) **11** as inhibitor of EBOV replication. NTZ was found to enhance retinoic acid inducible protein 1 (RIG-1) like receptor, mitochondrial antiviral signalling protein, interferon regulatory factor 3 and interferon activity which induces transcription of antiviral phosphatise GADD34. By acting on RIG-1 and protein kinase, NTZ significantly inhibits Ebola replication in human cells. NTZ is used in oral therapy against EBOV by enhancing the RNA sensing and interferon axis that is triggered by foreign cytoplasmic RNA exposure. The tendency of NTZ to inhibit infections EBOV growth in human pulmonary epithelial A549 cells *in vitro* was tested. It was found that EBOV growth was inhibited completely at dose of 20 or 40 μM of NTZ[50].

In 2019, De Wald *et al*. evaluated the efficacy of amodiaquine (AQ) **1** in rhesus macaque model of EVD. Being a widely used antimalarial drug, it was chosen over other medications for the treatment of Ebola. According to multiple *in vitro* assays, AQ emerged as potent EBOV inhibitor. Earlier in 2014, a combination regimen of Artesunate and AQ was given to EBOV patients to block EBOV replication. For the pharmacokinetic study, rhesus monkeys were selected (2 groups of 2 males and 2 females). AQ inhibited EBOV replication in multiple cell types that included Huh7 and Vero E6 cells and primary human macrophages with IC_{50} value of 3.2-7.9 μM[51].

In 2020, Madelain *et al*. shed light on the importance of favipiravir **7** and ribavirin **9**, broad spectrum antiviral drugs and tested them against 15 female cynomolgus macaques. The results showed significant reduction of mortality and viral load. It was found that favipiravir, an RNA polymerase inhibitor, alone was more effective to treat EBOV infection rather than in combination[52]. In 2020, Lane *et al*. identified an antimalarial drug pyronaridine tetra phosphate **12** which showed good efficacy in mouse model infected with Ebola virus. Pyronaridine tetraphosphate is an approved drug in European Union which is active against three strains of EBOV and two strains of Marburg virus (MARV). This drug acts by blocking the entry stage of virus. The efficacy of drug was evaluated in guinea pig model of EBOV infection. Pyronaridine was found to be an effective drug for EBOV patients with survival of 40% at 300 mg/kg[53]. Lane *et al.* in 2020 developed a Bayesian machine learning (BML) approach which screened *in vitro* a set of 868 molecules for anti-Ebola activity. Out of all the compounds, three compounds were found to be active: Tilorone **13**, Quinacrine **14** and Pyronaridine tetraphosphate **12**. These molecules showed tendency to inhibit EBOV in HeLa cells and exhibited significant *in vivo* activity in the mouse adapted EBOV efficacy model. The combination of pyronaridine with tilorone was also tested in HeLa cells with the use of Bayesian Rule-Augmented Influence Diagram (BRAID) model which showed synergistic effect[54].

Ekins *et al.* in 2020 evaluated Tilorone **13** which is sold under trade names Amixin and Lavomax. Besides its use for several viral diseases, an effective agent against EBOV was also found. It is discovered by machine learning (ML) computational model. It acts by activating specific innate immune system pathways (RIG-I signalling pathway will sense intracellular viral RNA and activate cellular antiviral response) that suppresses the replication of virus. Tilorone **13** can be considered as broad-spectrum class of antiviral drug because it can be used to treat Marburg, chikungunya and MERS-CoV infections. Tilorone was found to have EC_{50} of 230 nM, with 100% survival rate at dose of 30 mg/kg once daily *i.p.*[55]. In 2020, Yoon *et al*. evaluated many compounds, out of which fifteen hit compounds were selected and further tested for antiviral activity targeting different types of G-protein coupled receptor (GPCRs). They tested GPCR modulator compounds for antiviral activity by dual luciferase assay and by immunoblotting or genetic analysis and by measuring cytotoxicity. Three compounds sertindole **15**, raloxifene **16** and ibutamoren **17** were found to be the most potent, showing antiviral efficacy against other human RNA viruses.

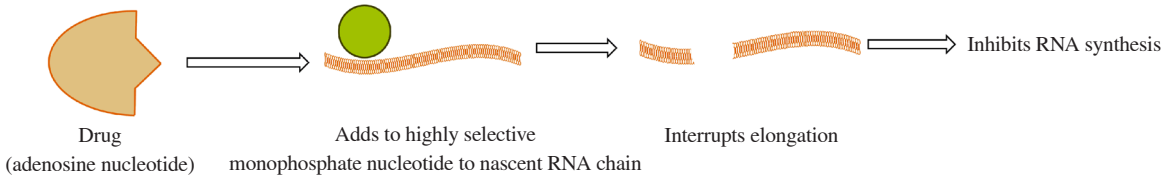

Figure 2. The general mechanism of adenosine nucleoside analogues antiviral drugs.

Among the selected compounds, ibutamoren showed the most potent inhibitory effect against EBOV with an EC_{50}: 0.2 μM, CC_{50}: 42.4 μM and SI: 22.8[56]. Pardo *et al.* in 2020 identified a potent compound remdesivir (GS-5734) **6** as a broad-spectrum antiviral drug to treat EVD. This drug has also been granted emergency use authorization by the USFDA to treat SARS-CoV-2 pandemic. Remdesivir is a monophosphoramidate prodrug of C-adenosine nucleoside analogue. This antiviral drug inhibits viral RNA synthesis. It has high potency against EBOV across multiple cell lines with EC_{50} of 0.08 μM in human macrophages[57]. Chemical structure of the repurposed drugs effective against EVD is shown in Supplementary Figure 2.

3.3.2. Small molecule drugs as anti–Ebola therapy

Aman *et al.* in 2009 identified a novel broad spectrum small antiviral molecule FGI-106: **18**. It showed inhibitory activity against multiple and genetically distinct viruses including Ebola, Rift valley and dengue fever viruses. It has also shown promising results against HIV and hepatitis C virus (HCV). The antiviral activity of FGI-106 was evaluated in mouse model (C57BL/6 mice) infected with ZEBOV strain. Mice were treated with different doses of FGI-106. FGI-106 injections were administered at 24 h and 72 h post infection. This decreased the mortality in a dose dependent manner. Results of cell-based assay proved the antiviral efficacy and overall toxicity of drug-EC_{50}: 100 nM, CC_{50}: 10 μM against host cell Vero E6 with selectivity index (SI) of 100[58]. Hodge *et al.* in 2016 showed ranpirnase (a low molecular weight endoribonuclease enzyme) from oocytes of frog, *Rana pipiens* reduced viral levels in infected mice. Results of *in vitro* activity of ranpirnase tested against kikwit-95 strain of EBOV showed it was effective in inhibiting Ebola infection at EC_{50}: 0.50-0.73 g/mL. It was also found that ranpirnase protected mice adapted EBOV stroke CDC-808012 prophylactically from the effects of EBOV infection. It was proposed to act by degrading the RNA. Furthermore, it was well tolerated and showed low toxicity[59].

In 2016, Dowell *et al*. evaluated *in vitro* antiviral activity of eighteen randomly selected compounds that act by disrupting EBOV entry, replication and exit from cells. The *in vitro* screening was done on MRC-5 (human foetal lung) and Vero E6 (African green monkey kidney) cells. *In vivo* screening was done on guinea pig models. Out of all, three compounds namely 17-DMAG **19**, BGBB 324: **20** and NCK-8 were found to be the most promising[60]. Luthra *et al.* in 2017 reported the use of antiviral derivatives and benzoquinolines to identify potential lead-based inhibitors of EBOV and RNA synthesis. A library of compounds was screened against EBOV minigenome assay. An angelicin (angular furanocoumarin) derivative which is an analogue of antiviral compound GSK983 (a tetrahydrocarbazole) and benzoquinolines was screened. SW456: **21** (IC_{50}: 1 μM and CC_{50}: 32 μM), a benzoquinoline derivative was found to be the most active[61]. Luthra *et al.* in 2018 designed compound SW835: **22** which is a racemic version of GSK983 and acts as a DHODH inhibitor. It potentially inhibits EBOV replication in stomatitis virus and zika virus. SW835 acts by targeting the RNA synthetic machinery and inhibits host cell nucleotide synthetic pathways[62].

In 2017, Sun *et al.* screened 795 unique three-drug combinations in an EBOV entry assay and their ability to inhibit live virus infection in cells was validated. A targeted drug combination approach was used and each drug was selected based on its mechanism of action. The results showed that three sets of three-drug combinations block more than 90% Ebola VLP entry. The two sets of three-drug combinations show synergistic effect by functionally inhibiting NPC1 protein, ASM activity and NAADO-stimulated lysosomal calcium release. The two sets of drug combinations toremifene-mefloquine-posaconazole and toremifene-clarithromycin-posaconazole were found to be effective. These two sets of drug combinations were proposed to block EBOV entry and to show synergistic effect[63].

A few coumarin based antihistamine like small molecules as potent inhibitors of filovirus entry were identified from a pool of 1 220 small molecules designed using ligand-based approach by Cheng *et al*. in 2017. The coumarin derivatives were reported to target a late stage of EBOV entry and found to exhibit promising inhibitory activity against both pseudo (p) typed EBOV and Marburg virus in A549 human cancer cell lines as well as in human primary cells. The most potent coumarin derivative was CBS1129 (**23**) with an IC_{50} value of 2.4 μM against pEBOV. In EBOV infection, IC_{50} value was slightly higher (3.7 μM) with CC_{50} of 71 μM and an SI of 19. Further structure activity relationship (SAR) studies suggested that coumarin scaffold with hydrophobic substituents at 3rd or 4th positions interacts with hydrophobic pocket between the GP1 and GP2 subunits on the target and thus it is vital for exhibiting anti-filovirus activity. The coumarin scaffold could be explored to develop useful anti-Ebola therapeutics[64].

Cui *et al*. in 2018 screened a small library of 92 bedaquiline derivatives and identified several diaryl-quinoline derivatives as potential EBOV specific entry inhibitors using a pseudotyped (HIV-1/EBOV) entry assay. SYL1712 (**24**) was noted to be the most potent entry inhibitor of EBOV displaying an IC_{50} of 1 μM and 2 μM against pEBOV and infectious EBOV, respectively. SAR studies indicated that quinoline ring with aryl substituents either on 3 or 4 position is essential for EBOV inhibitory activity. Further molecular docking and time-of-addition studies demonstrated it blocked the GP-mediated entry like toremifene and other small molecule inhibitors[65]. Chemical structures of nitrogen containing anti-Ebola compounds (**18–24**) are presented in Supplementary Figure 3.

Sakurai *et al*. in 2018 synthesised a series of 4-aminoquinolines which are structurally like drug amodiaquine and evaluated their ability to act against Ebola virus infection. Amodiaquine has been used as oral therapy to treat malaria for more than 66 years. The synthesized derivatives were found to be more active than amodiaquine itself. SAR studies indicated that alkyl chain and halogen bonded to quinoline ring are responsible for activity with no toxicity. The most potent derivatives act by blocking entry of Ebola virus into the host cells. The antiviral activity was evaluated using replication competent EBOV encoding green fluorescent protein (GFP) as the infection reporter. Human liver cells (Huh-7) were chosen as the major target for EBOV infection. Compound **25–28** showed highest activity with IC_{50}: 0.73, 0.64, 0.29 and 0.72 μM, respectively[66].

In 2019, Pessi *et al.* reported the use of inhibitory activity of peptides c-terminal heptad repeat (HR-2) domains of class Ⅰ fusion proteins against Ebola infection. To allow daily dosing, the serum half-life of peptides was elongated by conjugation with cholesterol.

Further, to increase the potency, the peptides were restricted to stabilize a helical structure. Lead peptides were tested on an EBOV lethal mouse model to determine the efficacy. The results showed that engineered peptides conjugated to cholesterol and inhibited viral production thereby it was protective against lethal EBOV infection[67].

Penny *et al*. in 2019, reported several FDA approved drugs as two pore channels blockers. Two pore channels are emerging as potential drug targets due to their effects of regulating trafficking of various cargoes including viruses. They are Ca^{2+} permeable ion channels localised on the endo-lysosomal system. Virtually, a database of 1 500 approved drugs was screened. High-throughput anti-Ebola screen identified approved drugs which target dopamine and estrogen receptor. Trifluoperazine **29** (IC_{50}: 4.48 μM) was found to target dopamine receptor while Raloxifene **30** (IC_{50}: 1.84 μM) was identified to target estrogenic receptor (Supplementary Figure 4)[68].

Gaisina *et al.* in 2020 designed, synthesized and optimized some newer and highly potent 4-(aminomethyl) benzamide derivatives as filovirus entry inhibitors. Various libraries of target compounds prepared by incorporating indoline, substituted phenyl ring and heterocyclic derivatives in the 4-(aminomethyl) benzamide pharmacophore were found to be effective against both infectious EBOV (Mayinga) and Marburg (Angola) virus (MARV). One of the 4-potent (aminomethyl) benzamide derivatives (**CBS1118: 31**) against both EBOV and MARV (EC_{50}: <10 μM) was identified as a hit compound and was further structurally modified to obtain anti-filovirus entry agents demonstrating good pharmacokinetic profile, high selectivity and potency. Replacing the acetate group on phenyl ring connected to amide functionality with adamantyl ring yielded the most potent and a broad-spectrum compound of the series namely *N*-(4-((1*R*,3*R*,5*S*)-adamantan-1-yl) phenyl)-4-(piperidin-1-ylmethyl) benzamide (**32**) which displayed EC_{50} of 0.11 and 0.31 μM against EBOV and MARV. Compound **32** showed low cytotoxicity *i.e.*, high selectivity (SI >100), favorable pharmacokinetic profile and good metabolic stability in plasma and liver microsomes. Additionally, molecular docking studies on to the EBOV GP (PDB: 5JQ7) further provided an insight into its mechanism of action. The docking results revealed that compound **32** binds to GP in the toremifene hydrophobic binding site mainly through carbonyl group and adamantyl ring confirming that like toremifene, it also inhibits viral entry by binding directly to EBOV-GP. The authors suggested that compound **32** bearing 4-(aminomethyl) benzamide scaffold is a promising and suitable candidate to develop new therapeutics to treat EVD and thus should be further optimized[69].

EBOV replication inhibitory activity of quinoline nucleus containing antimalarial drugs such as chloroquine, amodiaquine and 36 quinoline derivatives was tested by Goyal *et al.* in an *in vitro* model of Ebola infection using a transcription-competent virus-like particle (trVLP) assay. The most potent quinoline derivative **33** bearing a propylene amino side chain at the 2nd position exhibited a low toxicity but the highest inhibitory activity against Ebola trVLP replication (IC_{50}: 4.66 μM). It was argued that presence of an -NH_2 group at the end of the propylene chain in compound **33** resulted in a better cell viability (81%) than -OH group. Compound **33**, because of its promising activity, chemical stability, besides its simple structure that can be easily synthesized, modified and optimized to obtain a good pharmacokinetic profile could be a starting point to develop potent anti-Ebola agents[70].

Bessières and co-workers in 2021 reported the synthesis and anti-Ebola activity of some new benzimidazole-piperidine hybrids. Molecular mechanistic studies showed that synthesized 2-substituted-6-[(4-substituted-1-piperidyl) methyl]-1H-benzimidazole derivatives inhibit viral entry at the level of Niemann-Pick 1 (NPC1) protein. Two position isomeric compounds namely diethyl ({3-[2-({1-[(2-phenyl-1H-1,3-benzodiazol-6-yl) methyl] piperidin-4-yl} methyl) phenoxymethyl]-phenyl}methyl) phosphonate **34** (EC_{50}: 0.93 μM, SI: 10) and diethyl ({4-[2-({1-[(2-phenyl-1H-1,3-benzodiazol-6-yl) methyl] piperidin-4-yl}methyl) phenoxy-methyl] phenyl}-methyl) phosphonate **35** (EC_{50}: 0.64 μM, SI: 20) were noted to be 2-3 times more selective and almost as potent as a standard drug toremifene (EC_{50}: 0.38 μM, SI: 7) against cell line. Compounds **34** and **35** with EC_{50} and CC_{50} values comparable to those observed with infectious EBOV, blocked the EBOV GP-mediated entrance of these particles into Huh7 cells. Molecular docking of **34** and **35** into the active site of induced fit optimized NPC1 crystallized structure (PDB id: 5U73) confirmed that both the compounds bind to the NPC1 amino acids that participate in binding to GP *via* hydrogen bond and π-π stacking interactions[71]. Chemical structures of compounds **31–35** are presented in Supplementary Figure 5.

Lasala *et al.* used a host target-based approach to identify potential viral entry inhibitors of protein-protein interaction to combat EBOV infections. After the virtual screening, docking scores and chemical diversity, a total of 34 small molecules were identified which effectively blocked interactions between EBOV-GP and domain C of the late endosomes protein NPC1 resulting in the failure of the delivery of genetic viral material inside the host cells and eventually stopping of EBOV infection. The most promising hit compound was a carbazole derivative (SC816) **36** which was observed to interfere with the intracellular cholesterol transport receptor NPC1. Structurally, it was characterized by the presence of a carbazole ring connected through a hydrazide with a lateral chain bearing a (1-benzylpiperidin-4-yl)-ethylamine and showed an IC_{50} of 0.37 μM against pEBOV with SIc (pEBOV) (CC_{50}/IC_{50}) value of 19[72].

Han *et al*. in 2022 used a high-throughput screening to discover (*3S,4aS,8aS*)-2-(3-amino-2-hydroxypropyl) decahydroisoquinoline-3-carboxamide scaffold as promising Ebola entry inhibitors. The optimization of a hit compound **37** (IC_{50}: 0.79 μM and SI: 24 against EBOV-GP) led to identification of a 3 times more potent and almost twice more selective anti-Ebola compound **38** (IC_{50}: 0.05 μM, SI: 98) than the reference viral entry inhibitor toremifene (IC_{50}: 0.17 μM, SI : 55)[73].

Plescia *et al.* in 2022 synthesized a new library of phenol-substituted derivatives of the natural product scaffold diphyllin (**39**) in a hope to obtain compounds capable of inhibiting EBOV cell entry *via* selective inhibition of vacuolar (V)-ATPase. Diphyllin derivatives were found to prevent viral entrance in cells challenged with the EBOV; however, their effects were reliant on structural changes and many of them showed potency in low nanomolar range. The most potent compound was **40** with an IC_{50} value of 4.02 nM for V-ATPase inhibition[74].

In continuation of their work to discover and develop potent anti-EBOV agents, a previously identified viral entry process inhibitor, a carbazole derivative SC816 (**36**) as a hit compound, was optimized by Garcia-Rubia *et al.* in 2023 in a hope to obtain lead molecules with enhanced pharmacotherapeutic profile. A library of *N′*-Phenylacetohydrazide derivatives showed significant improvement in both potency and selectivity against viral pseudotypes in comparison to the hit compound SC816 (**36**). Compounds 3-((2-(1-Benzylpiperidin-4-yl) ethyl) amino)-*N′*, *N′*-diphenylpropanehydrazide (**41**) and 3-((2-(4-Benzylpiperazin-1-yl) ethyl) amino)-*N′*, *N′*-diphenylpropanehydrazide (**42**) were found to be the most promising lead compounds for the development of anti-EVD drugs. Both compounds exhibited good penetration into the brain, improved pharmacokinetic profile, good microsomal stability, low binding to hERG channel in mice upon oral and ip administration to mice. The therapeutic window was also improved as both showed high potency (EC_{50}: 0.05 and 0.58 μM against pEBOV; 0.30 and 2.70 μM against ZEBOV) along with low toxicity *i.e.*, high selectivity (SI: 115 and CC_{50}/EC_{50}: 93 against pEBOV).

Docking and molecular dynamics simulation studies revealed that these compounds inhibit viral entry to stop virus infection by preventing the attachment of EBOV-GP to the NPC1 receptor[75]. Chemical structures of anti-Ebola compounds **36–42** are presented in Supplementary Figure 6.

3.3.3. Natural products as anti–Ebola therapy

Natural products have been used as therapeutics since a long time. Haikal *et al*. in 2019 docked 527 natural products present in medicinal plants of Indonesian origin to identify potential inhibitors of Hsp90 protein. 1-O-galloyl-6-O-lutenoyl-α-D-glucose **43**, euphorbianin **44** and scutellarein-7-neohesperidoside **45** were found to be the best natural products to treat EVD when compared with Herbimycin as standard ligand[76].

In 2020, Yu *et al.* reported the use of antimicrobial peptides (AMPs, also known as host defence peptides). Two engineered LL-37 variants human cathelicidin antimicrobial peptide (AMP) LL037 and engineered LL-37 AMP inhibited the infection of recombinant virus pseudo typed with EBOV glycoprotein and wild type EBOV. Engineered AMPs were found to be potent inhibitor of EBOV entry as they impaired Cat B-mediated cleavage of EBOV-GP[77].

Biedenkopf *et al*. in 2016 analyzed the inhibitory effects of silverstrol **46** upon EBOV infected Huh-7 cells and primary human macrophages. Silverstrol is a natural compound which is isolated from the plant *Aglaia foveolate*. It acts as specific inhibitor of elF4A which is a part of heterotrimeric translation initiation complex in eukaryotes. Silverstrol when tested on Huh-7 cells and human macrophages by BSL4 assay, it was found to be a promising first line drug to treat acute EBOV and other infections[78].

In 2019, Lane *et al*. evaluated some products from natural origin for antiviral activity. Seven small natural compounds were tested for anti-EBOV activity. Out of seven compounds, eugenol **47** and *p*-anisaldehyde **48** were found to be the most potent with EC_{50} of 1.3 μM and 2.8 μM. Eugenol **47** is an essential oil obtained from cloves, cinnamon, basil and bay having diverse pharmacological actions and p-anisaldehyde **48** is present in fragrances[79]. Kwofie *et al.* screened a number of compounds from the chemical data base out of which four natural compounds ZINC000095486070: **49**, ZINC000003594643: *50*, ZINC000095486008: **51** and sarcopine exhibited significant EBOV.VP 24 inhibitory activity. VP24 protein found in EBOV helps it to replicate, hence was selected as viable target. It also interferes with host immune response and promotes nucleocapsid formation. Molecular docking study performed utilising AutoDock Vina (PDBID: 4MOQ) showed that ZINC000095486070 had high binding affinity of -9.7 K cal/mol[80].

Tsang *et al*. in 2022 discovered *Maesa perlarius* as an anti-EBOV plant lead after having tested over 500 extracts of medicinal plants against infection with Ebola-virus-pseudotyped particles (EBOVpp). The methanol extract of the stems of *Maesa perlarius* showed a powerful inhibitory action against EBOVpp (IC_{50}: 0.52 μg/mL). This extract on further fractionation led to isolation of three proanthocyanidins and two flavon-3-ols which exhibited an IC_{50} value ranging from 0.83 μM to 36.00 μM against pEBOV-GP. Procyanidin B2 (**52**), the most potent compound, on molecular docking analysis and binding affinity studies was found to target EBOV-GP. These identified flavan-3-ol monomers and oligomers as lead molecules can be used as motifs to develop target-oriented anti-EBOV agents with improved potency[81]. Chemical structures of natural products identified to be active against EVD are presented in Supplementary Figure 7.

3.4. Nutritional care for Ebola patients

Adequate nutrition is very important in management of critical illnesses. Ververs and Arya in 2000 have comprehensively discussed and advocated the importance of good nutrition as an integral part of supportive care for Ebola patients. The minimum recommended daily allowance of nutrients should be through fortified food or micronutrient powders. Vitamin A is important for maintaining an immune response to infectious diseases. The published data provide evidence that by maintaining an optimal nutrition can improve the treatment response[82]. Lamontagne *et al*. discussed the importance of hydration to support and maintain electrolyte balance in EVD patients[83].

Aluisio *et al.* described the use of oral vitamin A supplementation in 424 patients. Mortality rate was less among patients who received vitamin A. A dose of 200000-400000 IU was sufficient to decrease the mortality rate. Avoidance of trans fatty acid was also recommended to avoid GI irritations[84]. In 2015, Chaiyasit *et al*. reviewed the nutritional management for EVD patients. It is prerogative that physician should ensure that the adequate range of energy, protein, fat and micronutrient is provided to the patient along with proper medicine[85]. Henwood *et al.* in 2020 analysed a data of Ebola positive women. Out of 729 reproductive aged women, 44 reported pregnancies among which 13 were tested Ebola positive and 6 out of 13 later died. Symptoms were anorexia, asthenia, diarrhoea, fever, myalgias, nausea and vomiting. Two neonates born by vaginal deliveries died after 8 days. It was found that there is increased risk of death from EVD in pregnant women as compared to non-pregnant reproductive aged women[86]. Black *et al.* in 2015 reported the issues related to pregnant women during an Ebola outbreak. Supportive

treatment was given to pregnant women suffering from EVD, such as replacement of electrolytes and fluids and management of distressing symptoms. Supplementation of iron is recommended for pregnant women. There is no proven cure for EVD, but some therapies based on symptoms and vaccinations are available for clinical trials. Pregnant women are at higher risk of catching the infection[87].

3.4.1. Food and energy

Management of protein energy malnutrition is an important factor for patients suffering from chronic illness. The required amount of protein is 1.2 g/kg of ideal body weight (source: meat-based protein). Along with proper food, liquid food supplementation such as NaCl and dextrose is needed to overcome the problem of energy depletion[88].

Carbohydrate: The major source of energy obtained from daily diet is carbohydrate. But foods having high glycaemic index and low fibre such as sweets and desserts may cause dysfunction of immune system and could lead to inflammation. Consequently, those with Ebola should refrain from eating foods high in carbohydrates[89].

Fat: Consumption of trans fatty acid might result in inflammation by destroying macrophage function and eventually reducing body's immunity. Ebola patients should think about consuming more omega-3 fatty acids and consuming less saturated fats in order to maintain good health[90].

Micronutrients: Some studies have suggested supplementation with intravenous vitamin C or high dose of vitamin C in the infected Ebola patients. It is known that vitamin C strengthens the immune system and reduces the inflammation. For the patients infected with Ebola, the combination of vitamin C and calcium intravenously with blood transfusion is given to reduce the chance of infection[91,92].

3.4.2. Supportive care

Survival is increased by rehydrating with oral or intravenous fluids and treating particular symptoms. Currently being assessed are a number of potential treatments, such as immunological therapies, medication therapies, and blood products[93].

4. Patent applications filed/granted for Ebola treatment

A thorough search on USPTO/ESPACENET and google patents website was done to retrieve information on filed/granted patent applications for the EVD. Some selected and relevant patent applications are summarized in Table 4.

5. Conclusions

EVD remains a rare and a serious health threat, necessitating continuous advancements in therapeutic strategies. Initially limited to repurposing clinically used drugs and supportive care, recent breakthroughs include the development of vaccines, notably Ervebo and the Zabdeno/Mvabea combination, providing critical protection against Zaire Ebolavirus. While Inmazeb™ and Ebanga™ stand as the sole US FDA-approved drugs for EVD, there persists an urgent need to develop diversified antiviral approaches to enhance future outbreak management.

This article reviewed the pharmacotherapeutic landscape of currently approved therapies and vaccines effective against EVD, recognizing their vital role in mitigating the disease's impact. Given the persistently high mortality rates among Ebola patients, ongoing collaborative efforts within the scientific community seems to be promising avenues, focusing on the development of small synthetic molecules and novel technology-based vaccines. Recognizing the time-intensive nature of new drug development, researchers are encouraged to explore and repurpose existing drugs for potential efficacy against EBOV. While vaccines remain a cornerstone in the cost-effective control of EVD outbreaks, challenges such as viral mutations underscore the need for targeted antiviral agents with minimal toxicity. This review emphasizes the significance of ongoing studies to unlock the full potential of existing drugs and advance the development of novel antiviral strategies.

Highlighting various treatment modalities, including nutritional care, antiviral therapies, repurposed drugs, and small molecules in the preclinical studies, this review serves as a comprehensive guide for researchers working to develop therapeutic interventions against EBOV. It is anticipated that this information will stimulate and guide more research projects that will improve our capacity to fight against EVD outbreaks in the future. Safeguarding global public health continues to depend critically on our ability to find safe, affordable, and effective therapeutic modalities as we navigate the complicated landscape of EVD.

Although the current review offers valuable insights into the management of Ebola virus infections, it has certain limitations. Firstly, due to the rapidly evolving nature of Ebola virus research, the scope of the review may not encompass all recent advancements or emerging trends in the field. Additionally, the inclusion criteria used to select studies and the methods employed for data synthesis might introduce bias and restrict the generalizability of the findings. Furthermore, there is a possibility that the review does not adequately address regional variations in epidemiology, pathogenesis, and therapeutic development, potentially overlooking crucial nuances in disease management strategies. Nevertheless, despite these limitations, the review remains a valuable resource for comprehending the current state of research and steering future directions in Ebola virus therapeutics.

Conflict of interest statement

The authors declare that there are no conflicts of interests.

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Table 4. Patents on Ebola virus disease.

S. No	Patent No., title	Patent date	Inventors	Description
1	US7267823B2 Ebola peptides and immunogenic compositions containing same	11 September 2007	Mary K. Hart, Julie A. Wilson, Gene Garrard Olinger Jr., Michael A. Bailey	A method and composition for use in inducing an immune response which is protective against infection with EBOV.
2	US8017130B2 Method of accelerated vaccination against Ebola viruses	13 September 2011	Gary J. Nabel, Nancy J. Sullivan, Thomas W. Geisbert, Peter B. Jahrling	It relates to genetic vaccines for stimulating cellular and humoral immune responses in humans and other hosts.
3	US2012/0251502A1 Human Ebola virus species and compositions and methods thereof	4 October 2012	Jonathan S. Towner, Stuart T. Nichol, James A. Comer, Thomas G. Ksiazek, Pierre E. Rollin	It provides details related to detection and treatment of the Ebola Bundibugyo virus.
4	WO2016057909A1 Immune-modifying particles for the treatment of Ebola virus	14 April 2016	Daniel R. Getts	It discloses a method to reduce filovirus infection induced inflammatory response by administering these same negatively charged particles.
5	WO2017015457A1 Ebola vaccine	26 January 2017	Giuseppe Ciaramella	This invention describes composition and preparation of EBOV RNA vaccine.
6	US20170233742A1 Compositions comprising small interfering RNA Molecules for prevention and treatment of Ebola virus disease	17 August 2017	Yibin Cai, Patrick Y. Lu, John J. Xu	It discloses composition and method of developing siRNA molecules to inhibit EBOV gene expression in Ebola patients.
7	US9676763-B2 Method of treating Ebola	13 June 2017	James Cunningham, Kyungae Lee Tao Ren Chandran Kartik	It describes synthesis of heterocyclic compounds developed to target EbOV- envelope GP.
8	EP2350270A4 Human Ebola virus species and compositions and methods thereof	7 March 2018	Jonathan S Towner, Stuart T. Nichol, James A Comer, Thomas G Ksiazek, Pierre E Rollin	It relates to the composition and methods of preparation of molecule to treat human EBOV infection.
9	US10155947B2 Method for inhibiting Ebola virus *via* miRNA	18 December 2018	Chenyu Zhang, Hongwei Liang, Zhen Zhou, Ke Zeng, Xi Chen	It discloses a method and application of microRNA for inhibiting EBOV.
10	Publication of US20180362620A1 Humanized anti-Ebola virus glycoprotein antibodies and methods of use	20 Decemebr 2018	Mark Dennis, Mary Mathieu	It describes diagnostic, prophylactic and therapeutic use of anti-EBOV GP antibodies.
11	US10266584B2 Antibodies specific to glycoprotein (GP) of Ebola virus and uses for the treatment and diagnosis of Ebola virus infection	23 April 2019	Olivier Reynard, Viktor Volchkov	It describes use of glycoprotein (GP) specific binding in diagnosis and treatment of EVD.
12	US10369166B2 Pharmaceutical compositions for treating Ebola virus disease	6 August 2019	Susan E. Vecht-Lifshitz	This invention describes compounds pharmaceutical compositions to inhibit the formation of S-adenosyl methionine (SAM) in the virus.
13	US10829544B2 Monoclonal antibodies that bind to viral glycoproteins	10 November 2020	Christos Kyratsous, William Olson, Peter Mason, Neil Stahl	The present invention relates to antibodies that bind to Ebola virus glycoprotein, pharmaceutical compositions comprising these antibodies and methods of use thereof.
14	EP3204426B1 Compositions for use in treating viral hemorrhagic fever	25 November 2020	Laurence Corash	It describes beneficial uses of various supportive methods such as immune plasma and convalescent plasma in the treatment of hemorrhagic fever due to virus infections.
15	US11090325B2 Compositions for treating Ebola virus infection	17 August 2021	Reza Fathi, Dror Ben-Asher, Guy Goldberg	It discloses composition of a formulation containing clarithromycin and [3(4-chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-yl) methyl) amide to treat EBOV infection.
16	JP6845574B2 Monoclonal antibody that neutralizes the infectivity of all Ebola virus species	17 March 2021	Taka R. Yoshida, Reiko Yoshida, Wakako Koyama, Yoko Miyamoto, Shun Maruyama, Shigeru Iida, Shinya Ogawa	It describes a monoclonal antibody that can recognize and neutralize EBOV.

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Authors' contributions

SAK and NS conceived and designed the study; NS, SAK and MJA collected and summarized the data; AA and AH reviewed the data; SAK, NS and MJA contributed equally to the writing of the manuscript; SAK and AH supervised the project and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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