viruses

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*Review*

# Therapeutic Strategies against Ebola Virus Infection

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**Abstract:** Since the 2014–2016 epidemic, Ebola virus (EBOV) has spread to several countries and has become a major threat to global health. EBOV is a risk group 4 pathogen, which imposes significant obstacles for the development of countermeasures against the virus. Efforts have been made to develop anti-EBOV immunization and therapeutics, with three vaccines and two antibody-based therapeutics approved in recent years. Nonetheless, the high fatality of Ebola virus disease highlights the need to continuously develop antiviral strategies for the future management of EBOV outbreaks in conjunction with vaccination programs. This review aims to highlight potential EBOV therapeutics and their target(s) of inhibition, serving as a summary of the literature to inform readers of the novel candidates available in the continued search for EBOV antivirals.

**Keywords:** Ebola virus; Ebola virus disease; antiviral; therapeutic; drug development



**Citation:** Liu, C.-H.; Hu, Y.-T.; Wong, S.H.; Lin, L.-T. Therapeutic Strategies against Ebola Virus Infection. *Viruses* **2022**, *14*, 579. https://doi.org/10.3390/v14030579

Academic Editors: Mariana Baz and Edin Mifsud

Received: 18 February 2022
Accepted: 8 March 2022
Published: 11 March 2022



## 1. Introduction

Since the discovery of Ebola virus and Sudan virus in 1976 [1], ebolaviruses have become a significant public health threat. Ebolaviruses (members of the genus *Ebolavirus*) belong to the *Filoviridae* family and comprise six species: Ebola virus (EBOV), Sudan virus (SUDV), Reston virus (RESTV), Bundibugyo virus (BDBV), Taï Forest virus (TAFV), and Bombali virus (BOMV) [2]. While EBOV, SUDV, and BDBV cause fatal human infections, with EBOV being the most virulent and the leading cause of most outbreaks, RESTV has only caused an asymptomatic human infection, TAFV has only caused a single case of non-lethal human disease, and no human cases of BOMV have been reported [1,2]. EBOV caused several localized outbreaks in Middle Africa (the Democratic Republic of the Congo [DRC], Gabon, and the Republic of the Congo), before the unprecedented 2014–2016 West African outbreak began in Guinea and ultimately spread to over 15 countries, leading to 28,652 cases and 11,325 deaths [1,3]. Several factors facilitated the expansion of the 2014–2016 EBOV outbreak, such as international dispersal, urbanization (the population size of origins and destinations and shorter travel times), the absence of preparedness of both the exposed population and the international community [4], and adaptive viral mutations [5]. Since the 2014–2016 EBOV epidemic, additional outbreaks of EBOV have occurred, including the 2018–2020 outbreak in the DRC (3481 cases and 2299 deaths), the 2021 outbreak in Guinea, and the ongoing outbreak in DRC since 2021 which is linked to the 2018–2020 outbreak [6], highlighting the need for continued vigilance.

EBOV is highly contagious and can be transmitted through direct contact with blood or body fluids from infected individuals, fomites, and infected wild animals [7]. The virus RNA has also been detected in breast milk, vaginal secretions, and the semen of convalescent patients, providing evidence of sexual transmission [8]. EBOV infection in humans causes Ebola virus disease (EVD). The most common manifestations of EVD during

the 2014–2016 outbreak included fatigue, anorexia, abdominal pain, diarrhea, vomiting, fever, and myalgia, and the overall case fatality rate was approximately 40% [3]. To date, there are three approved EBOV vaccines, including one vesicular stomatitis virus (VSV)-based vector and two adenovirus-based vectors. The VSV-based vector, Ervebo® (rVSV-ZEBOV), is a replication-competent recombinant vaccine engineered to express EBOV glycoprotein (GP). Ervebo® received regulatory approval for use in Europe [9] and the United States [10] in 2019, as well as in four African countries (DRC, Burundi, Ghana, and Zambia) in 2020 [11]. The adenovirus-based vaccines, Zabdeno®/Mvabea® (a two-dose regimen containing Ad26.ZEBOV and MVA-BN-Filo) and Ad5-EBOV, have been approved in Europe and China, respectively [12]. Meanwhile, the antibody-based therapeutics Inmazeb™ (i.e., REGN-EB3) [13] and Ebanga™ (i.e., mAb114) [14] received approval as treatments for EBOV in 2020. Nonetheless, the high fatality rate of EVD indicates that the continuous development of antivirals is necessary to improve its current management and increase preparedness and vigilance for future emergencies.

EBOV is an enveloped filamentous virus containing a non-segmented negative-sense single-stranded RNA genome. The approximately 19 kb genome of the virus encodes nine viral proteins (VPs)—nucleoprotein (NP), polymerase cofactor (VP35), matrix protein (VP40), glycoprotein (GP), secreted glycoprotein (sGP), secondary secreted glycoprotein (ssGP), transcriptional activator (VP30), RNA complex-associated protein (VP24), and large protein (L; polymerase) [1]. The EBOV GP has two subunits: GP1 and GP2. While GP1 is chiefly involved in viral attachment to the host cell receptors, GP2 is mainly responsible for membrane fusion. Following attachment to cell-surface molecules, such as C-type lectins; T cell immunoglobulin mucin (TIM) proteins; and the TYRO3, AXL, and MERTK (TAM) family receptor tyrosine kinases, the virion enters the cell by endocytosis (mainly macropinocytosis) and is trafficked to endolysosome, where the glycan cap on GP is cleaved by the host cysteine proteases cathepsins B and L [1]. The cleavage of the glycan cap exposes the GP receptor binding site, which then binds to Niemann-Pick C1 (NPC-1) in the host cell, a key receptor of EBOV entry. GP1 interacts with NPC-1 to mediate membrane fusion along with GP2 subunits [15]. The viral membrane subsequently fuses with the endosomal membrane to release the viral ribonucleoprotein (RNP) complex into the cytoplasm [16]. Following release, viral genome transcription (mRNA synthesis) is activated by the transcription factor VP30 [17], and viral proteins are translated to form the viral replication machinery in the cytoplasm [18]. Encapsidated antigenomes are synthesized to serve as templates for progeny genome synthesis [1], and VP24 interacts with NP to assist in nucleocapsid formation [19]. Eventually, mature RNPs are transported to the cell membrane for matrix embedding and envelopment, and VP40 induces budding of the viral particles [1]. In addition, VP35 and VP24 also play vital roles in antagonizing the host's innate immunity. VP35 is capable of (1) binding viral dsRNA to prevent retinoic acid inducible gene-I (RIG-I) recognition and (2) inhibiting the phosphorylation of interferon regulatory factors (IRF)-3 and -7 by the kinases Tank binding kinase-1 (TBK-1) and I-kappa-B kinase epsilon (IKKε) [20], whereas VP24 binds to karyopherin-α (KPN-α) to inhibit nuclear transportation of the phosphorylated signal transducer and activator of transcription (STAT) 1 [21]. Given the significance and the multifunctionality of EBOV proteins in the viral life cycle [1], targeting any of these proteins could constitute a plausible antiviral strategy against the infectious agent.

## 2. Antiviral Strategies against EBOV

In this review, we will describe EBOV inhibitors targeting various viral proteins and host factors. The stage of development and 50% inhibitory concentration ($IC_{50}$) of each inhibitor are shown in Table 1. In addition, Table 2 summarizes the conditions used and the results observed in animal studies.

**Table 1.** Potential antiviral candidates against EBOV infection.

| Category | Drug(s) | Stage | $IC_{50}$ (In Vitro) | Ref. |
|---|---|---|---|---|
| VP35 inhibitors | VP35 PMO and P-PMO | In vivo | 0.9–1.25 μM (P-PMO; wtEBOV) | [22] |
| | Myricetin | In vitro | 2.7 μg/mL (enzymatic) | [23] |
| | MCCB4 | In vitro | 4.8 μM (EBOV minigenome) | [24] |
| | Anti-VP35 scFvs | In vitro | N.D. | [25] |
| VP40 inhibitors | Anti-VP40 scFv | In vitro | N.D. | [26] |
| | Quinoxaline-based inhibitors | In vitro | N.D. | [27] |
| | Sorbitol, mannitol, galactitol | In silico | N.D. | [28] |
| | Pyrimidinediones class molecules | In silico | N.D. | [29] |
| GP inhibitors | mAb114 | Licensed (Ebanga™) | 0.09 μg/mL (wtEBOV) | [30] |
| | REGN-EB3 (REGN3470, REGN3471, REGN3479) | Licensed (Inmazeb™) | 0.39 nM (EBOVpp) | [31] |
| | ZMapp™ (c13C6, c2G4, c4G7) | Clinical trial | N.D. | [32] |
| | MIL77E (MIL77-1, MIL77-3) | In vivo | 1–10, 10–100 μg/mL (EBOV-GFP) | [33] |
| | ZMAb (m1H3, m2G4, m4G7) | In vivo | 18.75, 4.325, 0.678125 μg/mL (EBOVpp) | [34] |
| | MB-003 (c13C6, h13F6, c6D8) | In vivo | N.D. | [35–38] |
| | KZ52 | In vivo | 0.3–0.9 μg/mL (wtEBOV) | [39] |
| | Q206, Q314, Q411 | In vivo | 0.36, 0.78, 0.43 μg/mL (EBOVpp); 7.08, 42.96, 15.24 μg/mL (EBOV-GFP) | [40] |
| | 2G1, 5E1, 5E9 | In vivo | 2.80, 11.13, 4.19 μg/mL (EBOV-GFP) | [41] |
| | 6D6 | In vivo | 0.05–0.12 μg/mL (EBOVpp) | [42] |
| | m8C4 | In vivo | 1.5 μg/mL (EBOVpp) | [43] |
| | Bis-mAbs | In vivo | 1.5–6.4 nM (EBOVpp); 0.5–1.1 nM (wtEBOV) | [44] |
| | CA45 | In vivo | 3.0–4.63 nM (EBOVpp); 28.3 nM (live virus) | [45] |
| | FVM04 | In vivo | 0.8–3.4 μg/mL (EBOVpp) | [46] |
| | 040, 66-3-9C, 6662, 6541 | In vivo | 0.1–10 μg/mL (EBOVpp) | [47] |
| | $MBP134^{AF}$ | In vivo | 0.1–1 nM (EBOVpp) | [48] |
| | rEBOV-520, rEBOV-548 | In vivo | 0.1–1, 1–10 μg/mL (EBOV-GFP) | [49] |
| | EBOV/SUDV pAb | In vivo | N.D. | [50] |
| | $F(ab')_2$ | In vivo | 1.4–1.7 μg/mL (EBOV-GFP) | [51] |
| | rhMBL | In vivo | N.D. | [52] |
| | Clomiphene | In vivo | 0.755–2.42 μM (EBOV-GFP); 3.83–11.1 μM (wtEBOV) | [53] |
| | Toremifene | In vivo | 0.0255–0.162 μM (EBOV-GFP); 0.973–1.73 μM (wtEBOV) | [53] |
| | Bepridil | In vivo | 3.21–5.08 μM (EBOV-GFP); 4.54 μM (wt EBOV) | [54] |

**Table 1.** *Cont.*

| Category | Drug(s) | Stage | $IC_{50}$ (In Vitro) | Ref. |
|---|---|---|---|---|
| | Sertraline | In vivo | 1.44–3.13 μM (EBOV-GFP); 3.73–8.62 μM (wtEBOV) | [54] |
| | HP-HSA | In vitro | 0.068 μM (EBOVpp) | [55] |
| | PPCM | In vitro | N.D. | [56] |
| | Sclareol, sclareolide | In vitro | 2.4, 8.0 μM (EBOVpp) | [57] |
| | Compound 7 | In vitro | 10 μM (EBOV-GFP) | [58] |
| | Compound 118, compound 118a | In vitro | 3.1, 0.05 μM (EBOVpp) | [59] |
| | 11 compounds from ZINC database | In vitro | 1.79–36.66 μM (EBOVpp) | [60] |
| VP30 inhibitors | SRPK1/SRPK2 inhibitor (SRPIN340) | In vitro | N.D. | [61] |
| | PP2A-B56 inhibitor | In vitro | N.D. | [62] |
| | PP1α inhibitor (C31) | In vitro | N.D. | [63] |
| VP24 inhibitors | VP24 PMOs | In vivo | 8–11 nM (enzymatic) | [64] |
| | Gossypetin, taxifolin, tricetin | In vitro | N.D. | [65,66] |
| | Quercetin | In vitro | 7.4 μM (enzymatic) | [66] |
| | Cycloartocarpin | In silico | N.D. | [67] |
| | ZINC000095486070, ZINC000003594643, ZINC000095486008, Sarcophine | In silico | N.D. | [68] |
| Polymerase inhibitors | Brincidofovir | Clinical trial | 120 nM–1.3 μM | [69] |
| | Favipiravir | Clinical trial | 67 μM (wtEBOV) | [70] |
| | Galidesivir | Clinical trial | 11.8 μM (wtEBOV) | [71] |
| | Remdesivir | Clinical trial | 0.06–0.14 μM (EBOV-GFP or wtEBOV) | [72] |
| | SNALPs (L) | In vivo | N.D. | [73] |
| | Lamivudine, zidovudine | In vitro | >320 μM (wtEBOV) | [74] |
| | Pairs of approved nucleotide analogues | In silico | N.D. | [75] |
| Host-targeting inhibitors—Viral entry | Amiodarone | Clinical trial | 2.02 μM (EBOVpp); 0.25 μg/mL (wtEBOV) | [76] |
| | Amiodarone | Clinical trial | 5.6 μM (EBOVpp) | [77] |
| | Amiodarone | Clinical trial | 0.81 μM (EBOVpp); 7.6 μM (EBOV-GFP) | [78] |
| | Amiodarone | Clinical trial | 5.5–15.9 μM (wtEBOV) | [79] |
| | AMPK inhibitor (Compound C) | In vitro | ~6 μM (EBOVpp) | [80] |
| | MAPK inhibitors | In vitro | 2.67–8.26 μM (EBOV-GFP) | [81] |
| | GlcNAc-1-phosphotransferase inhibitor (PF-429242) | In vitro | 0.80 μM (EBOVpp); 0.95 μM (EBOV-ZsG) | [82] |
| | Emetine | In vitro | 10.2 μM (EBOV VLP); 16.9 nM (EBOV-GFP) | [83] |
| | Dronedarone, verapamil | In vitro | N.D. | [76] |

**Table 1.** *Cont.*

| Category | Drug(s) | Stage | $IC_{50}$ (In Vitro) | Ref. |
|---|---|---|---|---|
| | GPCR antagonists | In vitro | 3.7–19.4 μM (EBOV-GFP) | [84] |
| | SERMs | In vitro | N.D. | [85] |
| | ErbB kinase inhibitor (BIBX 1382) | In vitro | 1.1 μM (EBOV-GFP) | [86] |
| Host-targeting inhibitors—Viral replication | HspA5 inhibitors | In vivo | 50–60 μM (EGCG; live virus) | [87] |
| | Hsp90 inhibitors | In vitro | 43.8–394.5 nM (EBOV-GFP) | [88] |
| | eIF4A inhibitor (silvestrol) | In vitro | ~0.8 nM (live virus) | [89] |
| | Emetine, cycloheximide, mycophenolic acid | In vitro | 1.474, 0.608, 0.316 μM (EBOV-GFP) | [90] |
| Host-targeting inhibitors—Antiviral immunity | SAH inhibitor (Ca-$c^3$ Ado) | In vivo | 30 μM (wtEBOV) | [91] |
| | SAH inhibitor ($c^3$-Npc A) | In vivo | 2 μM (wtEBOV) | [91] |
| | IFNs | In vivo | <10–5102 U/mL (wtEBOV) | [92] |
| | Nitazoxanide | In vitro | N.D. | [93] |
| Host-targeting inhibitors—Viral egress | TSG101 inhibitor (FGI-104) | In vivo | 10 μM (EBOV-GFP) | [94] |
| Host-targeting inhibitors—Anticoagulant | rNAPc2 | In vivo | N.D. | [95] |
| | rhAPC | In vivo | N.D. | [96] |
| Combination Treatments | PMOs (VP24, VP35, L) | In vivo | N.D. | [97] |
| | PMOplus AVI-6002 (VP24, VP35, L) | In vivo | N.D. | [98] |
| | Ad-IFN-α + Ad-CAGoptZGP | In vivo | N.D. | [99] |
| | Ad-IFN-α + ZMAb | In vivo | N.D. | [100] |
| | anti-GP + anti-VP40 | In vitro | N.D. | [101] |
| | Combinations of IFNs and nucleoside analogs | In vitro | N.D. | [102] |
| | Toremifene + mefloquine + posaconazole, toremifene + clarithromycin + posaconazole | In vitro | 1.08, 0.97 μM (Ebola VLP) | [103] |
| | Aripiprazole + piperacetazine, sertraline + toremifene, sertraline + bepridil, amodiaquine + clomiphene | In vitro | N.D. | [104] |
| | Digitoxin + tetrandrine, digitoxin + tamoxifen, digitoxin + fluvastatin, tamoxifen + fluvastatin | In vitro | N.D. | [105] |

**Table 1.** *Cont.*

| Category | Drug(s) | Stage | $IC_{50}$ (In Vitro) | Ref. |
|---|---|---|---|---|
| Inhibitors with unknown target(s) | 17 compounds from MLSMR library | In vitro | 1.6–25.6 μM (EBOV-GFP) | [106] |
| | Compound 8a and derivatives | In vitro | 2.5–30 μM (EBOVpp) | [107] |
| | Azithromycin | In vivo | 1.3 μM (EBOVpp); 5.1 μM (EBOV-GFP) | [78] |
| | Teicoplanin | In vivo | 2.38 μM (EBOVpp) | [108] |
| | Teicoplanin | In vivo | 7.28 μM (EBOV-GFP) | [54] |
| | Chloroquine | In vivo | 4.7 μM (EBOVpp); 16 μM (EBOV-GFP) | [78] |
| | Chloroquine | In vivo | 3.319 μM (EBOVpp) | [109] |
| | Chloroquine | In vivo | 15.3 μM (EBOV VLP) | [110] |
| | Chloroquine | In vivo | 4.7 μM (EBOVpp); 16 μM (EBOV-GFP) | [78] |
| | Chloroquine | In vivo | 1.77 μg/mL (EBOV-GFP) | [111] |
| | Quercetin 3-β-O-D-glucoside | In vivo | 5.3 μM (EBOV-GFP) | [112] |
| | FDA-approved compounds | In vitro | <25 μM (EBOV VLP) | [110] |

AMPK, AMP-activated protein kinase; EBOV, Ebola virus; EBOV-GFP, EBOV expressing green fluorescence protein; EBOVpp, EBOV pseudoparticle; GlcNAc, N-acetylglucosamine; GPCR, G protein-coupled receptor; HP-HSA, 3-hydroxyphthalic anhydride-modified human serum albumin; Hsp, heat shock protein; $IC_{50}$, 50% inhibitory concentration; IFN, interferon; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; N.D., not determined; pAb, polyclonal antibody; PMO, phosphorodiamidate morpholino oligomers; P-PMO, PMO conjugated to cell-penetrating peptide; PPCM, polyphenylene carboxymethylene; PP1, protein phosphatase 1; PP2A-B56, protein phosphatase 2A-B56; rhAPC, recombinant human activated protein C; rhMBL, recombinant human mannose-binding lectin; rNAPc2, recombinant nematode anticoagulant protein c2; SAH, S-adenosyl-l-homocysteine hydrolase; scFv, single-chain variable fragment; SERM, selective estrogen receptor modulator; SNALP, stable nucleic acid-lipid particle; SRPK, serine-arginine protein kinase; SUDV, Sudan virus; VLP, virus-like particle; VP, viral protein; wtEBOV, wild-type EBOV.

**Table 2.** Animal studies of EBOV antiviral therapeutics.

| Category | Drug(s) | Animal Model | Treatment Time Post-Infection; Dose | Best Survival | Ref. |
|---|---|---|---|---|---|
| VP35 inhibitor | VP35 PMO | Mouse | −24 h, −4 h; 500 μg | 85% | [22] |
| | VP35 P-PMO | Mouse | −24 h, −4 h; 500 μg | 100% | [22] |
| | VP35 P-PMO | Mouse | D1; 500 μg | 100% | [22] |
| GP inhibitors | mAb114 | Rhesus macaque | D5-7; 50 mg/kg | 100% | [30] |
| | MIL77E | Rhesus macaque | D3, 6, 9; 50 mg/kg | 100% | [33] |
| | ch133 + ch226 | Rhesus macaque | D(−1), 1, 3; 25 mg/kg/mAb | 33% | [113] |
| | ZMAb | Guinea pig | D2; 2 mg 4G7 + 1.5 mg 1H3 + 1.5 mg 2G4 | 100% | [34] |
| | ZMAb | Cynomolgus macaque | D1, 4, 7; 25 mg/kg | 100% | [114] |
| | ZMAb | Cynomolgus macaque | D2, 5, 8; 25 mg/kg | 50% | [114] |
| | MB-003 | Rhesus macaque | D2, 6, 8, 10; 16.7 mg/kg/mAb | 67% | [37] |

**Table 2.** *Cont.*

| Category | Drug(s) | Animal Model | Treatment Time Post-Infection; Dose | Best Survival | Ref. |
|---|---|---|---|---|---|
| | MB-003 | Rhesus macaque | Three doses initiated after symptom onset (by 120 h.p.i.); 16.7 mg/kg/mAb | 43% | [38] |
| | ZMapp$^{TM}$ | Rhesus macaque | D5, 8, 11; 50 mg/kg | 100% | [32] |
| | AAV9-ZMapp | Mouse | D(−14); $3 \times 10^{11}$ genome copies | >80% | [115] |
| | AAV9-ZMapp | Mouse | D(−21); $3 \times 10^{11}$ genome copies | 60–90% | [116] |
| | AAV9-c2G4 | Mouse | D(−21); $3 \times 10^{11}$ genome copies | 90–100% | [116] |
| | AAV6.2FF-2G4 + AAV6.2FF-5D2 | Mouse | D(−7) or (−14) or (−140); $4 \times 10^{11}$ genome copies | 100% | [117] |
| | REGN-EB3 | Rhesus macaque | D5; 150 mg/kg | 89% | [31] |
| | REGN-EB3 | Rhesus macaque | D5, 8, 11; 50 mg/kg | 100% | [31] |
| | KZ52 | Guinea pig | −1 h or +1 h; 25 mg/kg | 80–100% | [39] |
| | KZ52 | Rhesus macaque | D1, 4; 50 mg/kg | 0% | [118] |
| | Q206 | Mouse | D2; 100 µg | 66.6% | [40] |
| | Q314 | Mouse | D1 or 2; 100 µg | 33.3 | [40] |
| | Q411 | Mouse | D1; 100 µg | 50.0 | [40] |
| | 2G1 | Mouse | D1; 100 µg | 100% | [41] |
| | 5E1 | Mouse | D1; 100 µg | 100% | [41] |
| | 5E9 | Mouse | D1; 100 µg | 100% | [41] |
| | 6D6 | Mouse | D1; 100 µg | 100% | [42] |
| | m8C4 | Mouse | +2 h, D3; 25 mg/kg | 47% | [43] |
| | Bis-mAbs | Mouse | D1; 200 µg | 70–100% | [44] |
| | 040 + 66-3-9C + 6662 + 6541 | Guinea pig | D3; 10 mg/kg/mAb | 100% | [47] |
| | FVM04 + CA45 | Guinea pig | D3; 2.5 mg/mAb | 100% | [45] |
| | FVM04 + CA45 | Guinea pig | D3; 1.25 mg/mAb | 100% | [119] |
| | FVM04 + CA45 | Rhesus macaque | D4; 20 mg/kg/mAb | 100% | [119] |
| | ADI-15742 | Mouse | D2; 300 µg | 100% | [48] |
| | ADI-15878 | Mouse | D2; 300 µg | 80% | [48] |
| | MBP134$^{AF}$ | Guinea pig | D3; 3.3 mg | 100% | [120] |
| | MBP134$^{AF}$ | Ferret | D2, 5 or D3, 6; 15 mg | 100% | [121] |
| | MBP134$^{AF}$ | Rhesus macaque | D4; 25 mg/kg | 100% | [121] |
| | rEBOV-520 + rEBOV-548 | Rhesus macaque | D3, 6; 30 mg/kg | 100% | [49] |

**Table 2.** *Cont.*

| Category | Drug(s) | Animal Model | Treatment Time Post-Infection; Dose | Best Survival | Ref. |
|---|---|---|---|---|---|
| | EBOV/SUDV pAb | Mouse | D1; 100 mg/kg | 80% | [50] |
| | $F(ab')_2$ | Rhesus macaque | D3-7, 9, 11; 100 mg/kg | 100% | [51] |
| | $F(ab')_2$ | Rhesus macaque | D5-9, 11, 13; 100 mg/kg | 100% | [51] |
| | Clomiphene | Mouse | +1 h, D1, 3, 5, 7, 9; 60 mg/kg | 90% | [53] |
| | Toremifene | Mouse | +1 h, D1, 3, 5, 7, 9; 60 mg/kg | 50% | [53] |
| | Bepridil | Mouse | BID since +1 h for 10 days; 12 mg/kg | 100% | [54] |
| | Sertraline | Mouse | BID since +1 h for 10 days; 10 mg/kg | 70% | [54] |
| | rhMBL | Mouse | D0-10 (Q12H since 12 h.p.i.); 20 mg/kg | >40% | [52] |
| VP24 inhibitor | PMOs | Mouse | −24 h, −4 h; 1–50 μg | 30–100% | [64] |
| RdRp inhibitors | SNALPs (L) | Guinea pig | +1 h, D1-6; 0.75 mg/kg | 100% | [73] |
| | Favipiravir | Mouse | D6-13; 300 mg/(kg × d) | 100% | [70] |
| | Favipiravir | Mouse | BID since +1 h for 14 days; 150 mg/kg | 100% | [122] |
| | Favipiravir | Cynomolgus macaque | BID since D(−2) for 14 days; 180 mg/kg (LD: 250 mg/kg) | 60% | [123] |
| | Favipiravir | Cynomolgus macaque | D(−3)-10; 200 mg/kg (LD: 400 mg/kg) | 17% | [124] |
| | Favipiravir | Cynomolgus macaque | BID since +0.5–2 h for 14 days; 150 mg/kg (LD: 250 mg/kg) | 0% | [124] |
| | Galidesivir | Mouse | BID; 150 mg/kg | >80% | [71] |
| | Galidesivir | Rhesus macaque | BID since D2 for 11 days; 25 mg/kg (LD: 100 mg/kg) | 100% | [125] |
| | Galidesivir | Rhesus macaque | BID since D3 for 11 days; 25 mg/kg (LD: 100 mg/kg) | 67% | [125] |
| | Remdesivir | Rhesus macaque | D3-14; 3 or 10 mg/kg (LD: 10 mg/kg) | 100% | [72] |
| Host-targeting inhibitors | Amiodarone | Mouse | D0-7 BID; 90 mg/kg | 10–40% | [78] |
| | Amiodarone | Guinea pig | Starting from D(−3); 160 mg/kg | 0% | [79] |
| | HspA5 PMO | Mouse | D(−4), (−1), +1, +3; 7.5 mg/kg | 100% | [87] |
| | SAH inhibitor (Ca-$c^3$ Ado) | Mouse | Q8H since −24 h for 9 days; 0.7 mg/kg | 100% | [91] |
| | SAH inhibitor (Ca-$c^3$ Ado) | Mouse | D2; 80 mg/kg | 100% | [126] |
| | SAH inhibitor ($c^3$-Npc A) | Mouse | D4; 1 mg/kg | 100% | [126,127] |
| | IFN-γ | Mouse | +6 h; 3.3μg | 100% | [128] |
| | IFN-α | Cynomolgus macaque | Daily since +18 h; $2 \times 10^7$ IU/kg | 0% | [129] |
| | IFN-β | Rhesus Macaque | +18 h, D1, 3, 5, 7, 9; 10.5 μg/kg | 0% | [130] |
| | TSG101 inhibitor (FGI-104) | Mouse | −2 h; D1-10; 10 mg/kg | 100% | [94] |
| | rNAPc2 | Rhesus macaque | D1-14; 30 μg/kg | 33% | [95] |
| | rhAPC | Rhesus macaque | Continuous infusion since 1 h.p.i.; 2 mg/$m^2$/h | 18% | [96] |

**Table 2.** *Cont.*

| Category | Drug(s) | Animal Model | Treatment Time Post-Infection; Dose | Best Survival | Ref. |
|---|---|---|---|---|---|
| Combination Treatments | PMOs (VP24, VP35, L) | Mouse | D1; 500 µg | 100% | [97] |
| | PMOs (VP24, VP35, L) | Guinea pig | D4; 30 mg | 67% | [97] |
| | PMOs (VP24, VP35, L) | Rhesus macaque | D(−2), 0–9; 12.5–100 mg | 50% | [97] |
| | PMOplus AVI-6002 (VP24, VP35, L) | Rhesus macaque | +0.5–1 h, D1-14; 28 or 40 mg/kg | 60% | [98] |
| | SNALPs (L, VP35, and VP24) | Rhesus macaque | +0.5 h, D1-6; 2 mg/kg | 100% | [131] |
| | Ad-IFN-α + Ad-CAGoptZGP | Guinea pig | +0.5 h; Ad-IFN-α $2 \times 10^8$ infectious particles + Ad-CAGoptZGP $10^{10}$ infectious particles | 100% | [99] |
| | Ad-IFN-α + ZMAb | Cynomolgus macaque | D3; Ad-IFN $10^9$ PFU/kg + ZMAb 50 mg/kgD6, 9; ZMAb 50 mg/kg | 100% | [100] |
| Inhibitors with unknown target(s) | Azithromycin | Mouse | D0-7 BID; 100 mg/kg | 10–60% | [78] |
| | Azithromycin | Guinea pig | D0-7; 6 mg/kg | 10% | [78] |
| | Teicoplanin | Mouse | +1 h, D1-9; 14 mg/kg | 0% | [54] |
| | Chloroquine | Mouse | D0-7 BID; 90 mg/kg | 70–80% | [78] |
| | Chloroquine | Guinea pig | D0-7; 25 mg/kg | 0% | [78] |
| | Chloroquine | Guinea pig | BID since +6 h; 33.75 mg/kg | 0% | [132] |
| | Chloroquine | Hamster | 50 mg/kg | 0% | [111] |
| | Quercetin 3-β-O-D-glucoside | Mouse | −0.5 h, D2, 4, 6, 8, 10; 50 mg/kg | 100% | [112] |
| | Quercetin 3-β-O-D-glucoside | Mouse | D1, 3, 5, 7, 9, 11; 50 mg/kg | 30% | [112] |

BID, twice a day; D, day; h, hour; LD, loading dose.

### *2.1. EBOV VP35 Inhibitors*

EBOV VP35 is the cofactor protein in the viral polymerase complex [133] and an antagonist against the host's innate immunity type I interferon (IFN) response [20,134]. In one study, the inhibition of EBOV VP35 with antisense phosphorodiamidate morpholino oligomers (PMO; a single-stranded DNA analog) or PMO conjugated to cell-penetrating peptide (P-PMO) was able to prevent EBOV infection in vitro as well as in mice before and after infection [22]. A few compounds have also been shown to exhibit anti-VP35 activities. These include myricetin from *Limonium morisianum* extract as an inhibitor of the VP35–dsRNA interaction [23], and the small molecule MCCB4 (a linear hydrophobic molecule containing an ene-thiazolidinedione group) which impedes EBOV replication and transcription by blocking the VP35–NP interaction [24]. A recent study further developed anti-VP35 single-chain variable fragment (scFv) intracellular antibodies that could significantly subvert VP35-induced IFN-β suppression [25]; their antiviral activity may be further investigated.

### *2.2. EBOV VP40 Inhibitors*

EBOV VP40 is not only important for virus particle formation [135], but is also involved in viral replication and transcription [136], making it a promising target for EBOV therapy. Cell-penetrable anti-VP40 scFv antibodies have been shown to inhibit EBOV virus-like particles (VLP) budding from human hepatocytes [26]. Small molecules that disrupt the interaction between VP40 and the host Nedd4 ubiquitin ligase, such as quinoxaline-based inhibitors, have also displayed anti-budding activities [27]. On the other hand, an in silico screening of sugar alcohol compounds suggested that sorbitol, mannitol, and galactitol could bind to the VP40 octamer [28], an RNA-binding structure that is crucial for the EBOV life cycle [137,138]. Another in silico study also predicted seven pyrimidinediones class molecules that could block the VP40 Arg134 RNA-binding site [29]. These molecules could potentially interrupt the VP40–RNA interaction; however, their antiviral effects remain to be validated with biological experiments.

### *2.3. EBOV GP Inhibitors*

EBOV GP mediates viral entry via its two subunits and is the most extensively studied antiviral target. The importance of GP as a therapeutic target is reflected by (1) the presence of GP-neutralizing antibodies in the plasma of those who were naturally infected [139,140] or vaccinated [41,47], and (2) the effectiveness of the VSV-vectored EBOV-GP vaccine as a post-exposure prophylaxis in animal models [141] as well as in the Guinea ring vaccination trial [142]. Inhibitors of EBOV GP include neutralizing antibodies, synthetic compounds, and natural compounds. GP-specific antibodies appear to be the most effective post-exposure therapeutics based on current literature. Several neutralizing monoclonal antibodies (mAb) have been characterized, and some of them have provided promising effects in the treatment of non-human primates (NHP) after lethal EBOV infections. These include the single antibody mAb114 [30]; the two-antibody cocktail MIL77E (c13C6 and c2G4; derived from ZMapp™) [33]; and the three-antibody cocktails ZMAb (m1H3, m2G4, and m4G7) [100,114,143], MB-003 (c13C6, h13F6 and c6D8) [35–38], ZMapp™ (c13C6, c2G4, and c4G7; derived from ZMAb and MB-003) [32], and REGN-EB3 (REGN3470, REGN3471, and REGN3479) [31]. When subsequently studied in clinical trials, ZMapp™ was shown to reduce the case mortality rate from 37% (control arm) to 22% [144,145]. Afterwards, mAb114 and REGN-EB3 were evaluated in the 2018–2019 DRC outbreak (the Pamoja Tulinde Maisha trial), where both antibodies demonstrated superior efficacy compared to the control ZMapp™ in reducing EVD mortality [146]. Based on the trial results, REGN-EB3 (Inmazeb™) and mAb114 (Ebanga™) were both approved as treatments for EBOV infection [13,14]. The effect of other EBOV GP specific mAbs, such as KZ52 [39,118], Q206, Q314, Q411 [40], 2G1, 5E1, and 5E9 [41], are summarized in Tables 1 and 2.

Since other ebolaviruses may also lead to fatal human infections, several recent studies have aimed to produce cross-protective antibodies that can neutralize multiple ebolaviruses,

i.e., broadly neutralizing antibodies (bNAb). For example, the mAb 6D6 [42] and the bispecific antibodies (Bis-mAbs) [44] have been shown to be protective in mice. FVM04 [46], CA45 [45,119], and the four-antibody cocktail (040 + 66-3-9C + 6662 + 6541) [47] were shown to protect guinea pigs. Furthermore, the antibody cocktails FVM04 + CA45 [119], MBP134$^{AF}$ (ADI-15878 and ADI-23774) [120,121], and rEBOV-520 + rEBOV-548 [49] were all shown to fully protect NHP from lethal EBOV challenge.

In addition to mAbs, cost-effective polyclonal antibodies (pAb) with a higher production yield, such as IgG (EBOV/SUDV pAb) purified from immunized transchromosomal bovines [50] and polyclonal fragments F(ab')$_2$ produced from hyperimmunized horses [51], have also demonstrated post-exposure protection in mice and NHP, respectively.

Multiple GP-targeted compounds have also been explored. Recombinant human mannose-binding lectin (rhMBL) has been shown to block EBOV binding to the attachment factor DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) [147], and rhMBL reconstitution therapy was shown to protect 40% of treated mice from fatal EBOV infection and rechallenge [52]. 3-hydroxyphthalic anhydride (HP)-modified human serum albumin (HSA) (HP-HSA) has also demonstrated its ability to bind to GP and block EBOV attachment [55]. Furthermore, the modified protein is highly thermostable for storage and remains effective after 8 weeks at 45 °C, which is advantageous to its potential real-world application, especially in tropical African regions [55]. Polyphenylene carboxymethylene (PPCM), a polymer derived from mandelic acid condensation that displays broad-spectrum vaginal microbial activities, was shown to inhibit EBOV GP attachment as well [56]; thus, it may be useful for preventing the sexual transmission of EBOV. Several FDA-approved drugs, including clomiphene, toremifene [53], bepridil, and sertraline [54], were found to inhibit EBOV fusion and protect mice from lethal EBOV infection. Computational and biophysical analyses indicated that these drugs could directly bind to GP and destabilize the pre-fusion structure, thereby preventing its fusion with the endosomal membrane [148–150]. Some natural compounds, such as sclareol and sclareolide derived from *Salvia sclarea*, were also found to inhibit EBOV viral fusion [57]. Finally, several compounds were predicted to bind to GP and could inhibit EBOV pseudoparticle entry, including the benzodiazepine derivative compound **7** [58], two derivatives of natural isoflavones ZINC32540717 (compound **118**) and ZINC09410451 (compound **118a**) [59], and 11 commercially available drug-like molecules from the ZINC database [60].

### *2.4. EBOV VP30 Inhibitors*

The transcriptional activity of EBOV VP30 is regulated by a series of phosphorylation and dephosphorylation events facilitated by host kinases and phosphatases [151]. Modulating these enzymes could therefore alter the activity of VP30. For instance, serine-arginine protein kinase 1 (SRPK1) and SRPK2 phosphorylate Ser29 of VP30 to initiate EBOV primary transcription, and an SRPK1/SRPK2 inhibitor, such as SRPIN340, was able to downregulate the primary viral transcription [61]. On the contrary, the host protein phosphatase 1 (PP1) and protein phosphatase 2A-B56 (PP2A-B56) regulate VP30 dephosphorylation, which mediates the initiation of secondary viral transcription [62,152]. In one study, a PP2A-B56 inhibitor that interfered with VP30 dephosphorylation indeed suppressed the proliferation of EBOV [62]. In another study published by Ammosova et al., the synthetic small molecule C31, which binds to the catalytic subunit of PP1$\alpha$, was also found to inhibit EBOV replication [63].

### *2.5. EBOV VP24 Inhibitors*

EBOV VP24 is essential for viral RNP complex assembly [19] and also plays an important role in countering the IFN response [21]. It has been shown that VP24-specific PMOs can protect mice from lethal EBOV challenge [64]. Potential VP24 inhibitors have been identified through in silico screening, including cycloartocarpin [67]; ZINC000095486070; ZINC000003594643; ZINC000095486008; sarcophine from African natural product-derived

compounds [68]; and the flavonoids gossypetin, taxifolin, and tricetin [65]. A recent study published by Fanunza et al. confirmed that the flavonoids gossypetin, taxifolin, and tricetin indeed blocked VP24's anti-IFN function [66]. They also found that another flavonoid with a similar structure, quercetin, could directly interfere with VP24 binding to KPN-α to restore interferon-stimulated gene 15 (ISG15) transcription, thus blocking EBOV replication in vitro [66].

### *2.6. EBOV Polymerase Inhibitors*

Viral polymerase, which plays an essential role in genome transcription and replication in host cells, represents another target for antiviral drug development. Efforts have been made to block EBOV replication by using stable nucleic acid-lipid particles (SNALPs) to encapsulate siRNAs. A cocktail of four different siRNAs targeting EBOV L has been shown to protect guinea pigs from lethal EBOV challenge [73]. Nucleoside analogs, such as brincidofovir, lamivudine, favipiravir, zidovudine, and galidesivir (BCX4430, immucillin A), have been proposed as potential candidates and investigated. Brincidofovir was tested in a phase 2 trial in Liberia in 2015, but the therapeutic effect was undetermined due to an early termination of the trial and a small sample size [153]. Lamivudine and zidovudine were proven ineffective in vitro [74]. Favipiravir rescued lethal EBOV challenge in mice [70,122], but provided low protection in NHP studies [123,124] as well as in clinical trials [154]. Galidesivir was able to inhibit EBOV minigenome replication [71] and protected NHP against lethal EBOV infection [125]. The drug also appeared to be safe and well tolerated in a phase I clinical trial [155]. On the other hand, remdesivir (GS-5734), a prodrug of an adenosine analogue, was designed to treat EBOV infection and has shown 100% protection from lethal disease in EBOV-infected rhesus monkeys [72]. Unfortunately, in the Pamoja Tulinde Maisha trial, the overall mortality of remdesivir-treated patients was 53.1%, which appeared higher than the ZMapp, MAb114, and REGN-EB3 groups; thus, the regimen was terminated along with ZMapp [146]. Finally, a computational study predicted pairs of approved nucleotide analogues (ribavirin + tenofovir, favipiravir + tenofovir, abacavir + tenofovir, or telbivudine + tenofovir) that may inhibit EBOV polymerase better in combination than when used individually [75]; however, their effectiveness remains to be validated.

### *2.7. Host-Targeting Agents*

Targeting essential host factors in the viral life cycle is another key strategy to perturb viral infection. Moreover, compared to viral proteins, host factors impose a higher barrier to mutations, making them potential candidates for antiviral intervention.

Several host proteins are involved in EBOV entry. AMP-activated protein kinase (AMPK) is essential for EBOV macropinocytosis, and the AMPK inhibitor compound C is able to block EBOV GP-mediated infection of primary human macrophages [80]. Similarly, pyridinyl imidazole inhibitors of p38 mitogen-activated protein kinase (MAPK) were also found to inhibit EBOV macropinocytosis [81]. Host N-acetylglucosamine-1-phosphate transferase (GlcNAc-1-phosphotransferase) was identified as another potential EBOV antiviral target for its functions in lysosome transportation. The disruption of GlcNAc-1-phosphotransferase activity using PF-429242, an inhibitor of S1P (cellular proprotein convertase sterol regulatory element-binding protein (SREBP) site 1 protease) responsible for the cleavage of the GlcNAc-1-phosphotransferase precursor, was able to block EBOV entry, which requires its GP to be processed in the lysosome [82]. The anti-protozoal and emetic agent emetine was also shown to induce lysosomal dysfunction and inhibit EBOV entry [83]. In addition, ion channel inhibitors, such as amiodarone, dronedarone, and verapamil, were also found to inhibit EBOV entry [76], possibly by interfering with the viral membrane fusion to the endosomal membrane [77]. Although amiodarone was given as a compassionate therapy in Sierra Leone [156], its clinical trial was withdrawn and its effect was undetermined (NCT02307591). Further analyses suggested that the drugs' anti-EBOV activity appeared questionable in mice and guinea pig models [78,79]. On the

other hand, several G protein-coupled receptor (GPCR) antagonists were found to exhibit anti-EBOV activity, especially at the post-binding step [84], suggesting a potential role of GPCRs in EBOV entry. Several selective estrogen receptor modulators (SERMs) were found to inhibit EBOV entry by inducing endolysosomal calcium accumulation [85]. BIBX 1382, previously known as a ErbB kinase inhibitor, was also shown to block EBOV entry [86].

Host proteins that facilitate EBOV transcription and translation are another group of potential antiviral targets. Heat shock protein 90 (Hsp90) is an important host factor that is involved in protein folding, and the inhibition of Hsp90 with Geldanamycin, 17-AAG, and radicicol has been shown to reduce EBOV replication [88]. Another ER-resident, heat shock protein family A (Hsp70) member 5 (HspA5), is required for the production of EBOV transcripts and proteins, and inhibiting HspA5 with epigallocatechin gallate (EGCG) and HspA5-specific PMOs could inhibit Ebola replication in vitro and protect mice from lethal EBOV infection, respectively [87]. On the other hand, the inhibition of the host eIF4A translation initiation complex by silvestrol, a natural plant-derived compound isolated from *Aglaia foveolate*, was also shown to reduce EBOV replication in vitro [89]. A high-throughput screening using the minigenome system further identified potential EBOV replication inhibitors with a high selective index, including the protein synthesis inhibitors emetine and cycloheximide, and an inhibitor of inosine monophosphate dehydrogenase (IMPDH), mycophenolic acid [90].

Increasing host immune responses represents an additional strategy to combat viral infection. For example, targeting the cellular enzyme S-adenosyl-l-homocysteine hydrolase (SAH) with the adenosine analogues carbocyclic 3-deazaadenosine (Ca-$c^3$ Ado) [91,126] or 3-deazaneplanocin A ($c^3$-Npc A) [126,127] was shown to protect mice from lethal EBOV infection, possibly due to the antiviral immunity triggered by incompletely capped viral mRNA [157]. Another group found that the FDA-approved anti-protozoal drug nitazoxanide (NTZ) could broadly enhance innate antiviral immunity, which inhibited EBOV replication and counteracted EBOV VP35′s immune suppression [93]. On the other hand, type I and II IFNs have also been explored, but with mixed results. IFNs appeared to be weak inhibitors in cell-based EBOV infection assays [92]. When tested in vivo, while IFN-γ protected mice from lethal EBOV challenge [128], IFN-α [129] and IFN-β [130] did not provide any survival benefits in NHP despite a longer time to death. A retrospective study suggested that patients treated with support care only were 1.5–1.9 fold more likely to die than those who received IFN-β treatment [158].

The proteins involved in viral egress could also be targeted. For instance, TSG101 is a housekeeping protein that escorts proteins from the cytosol to the cell membrane, and viruses often hijack this protein to help release progeny viruses. The compound FGI-104 was identified as a TSG101 inhibitor that could interfere with the budding of several viruses and protected mice from lethal EBOV challenge [94].

Finally, as EBOV infection induces coagulation abnormalities, agents that correct such dysregulation have been studied. Some examples include the recombinant nematode anticoagulant protein c2 (rNAPc2), an inhibitor of tissue factor-initiated coagulation [95], and the recombinant human activated protein C (rhAPC), which regulates both coagulation and inflammation [96]. Both agents provided partial protection in rhesus macaques when given after lethal EBOV challenges (Table 2).

### *2.8. Combination Treatments*

Drug combinations targeting multiple host or viral factors may prevent the development of viral resistance and reveal synergetic effects to control viral infection, with the benefit of lowering the individual drug dosage and toxicity. For instance, combinations of PMOs (targeting VP24, VP35, and L) [97], positively charged PMOs (PMOplus AVI-6002 targeting VP24, VP35, and L) [98], or SNALPs in a cocktail containing different siRNAs (also targeting VP24, VP35, and L) [131] have been reported, and the SNALP cocktail was shown to protect rhesus macaques from lethal EBOV challenge [131]. A combination of mAbs targeting different viral proteins (e.g., anti-GP and anti-VP40) [101] or combinations of

IFNs and nucleoside analogs [102] have also been shown to inhibit the replication of EBOV VLP in vitro. In addition, another study showed that adenovirus-vectored IFN-α (Ad-IFN-α) was able to enhance the protection of adenovirus-based vaccine expressing EBOV GP (Ad-CAGoptZGP) in rodents [99] and ZMAb in NHP [100]. Other combinations of FDA-approved drugs have also been suggested. These include the three-drug combinations toremifene + mefloquine + posaconazole and toremifene + clarithromycin + posaconazole, which inhibit lysosomal calcium release, acid sphingomyelinase activity, and NPC-1 protein function [103]. Other synergistic drug pairs that target both the entry and post-entry steps of EBOV infection include aripiprazole + piperacetazine, sertraline + toremifene, sertraline + bepridil, amodiaquine + clomiphene [104], digitoxin + tetrandrine, digitoxin + tamoxifen, digitoxin + fluvastatin, and tamoxifen + fluvastatin [105].

## 3. Future Prospects

As reviewed above, several inhibitors are in different phases of preclinical development, with further validation studies being required for many candidates identified in vitro and in silico. Currently, most studies have focused on GP inhibitors and polymerase inhibitors, and neutralizing antibodies seem to produce the best outcomes in clinical settings; however, multifunctional EBOV proteins, such as VP35, VP40, VP30, and VP24, are also attractive targets and may be included in antiviral combinations. Despite their generally low barrier to mutations, the success of targeting viral factors, for example with the use of combination direct-acting antivirals (DAAs) to cure HCV infection and the multi-pronged highly active antiretroviral therapy (HAART) to control HIV infection, suggests that targeting multiple viral proteins could be an attractive strategy for antiviral development. Although EBOV was reportedly not undergoing rapid evolution in humans at least during the 2013–2015 period of the global outbreak [159], viral escape mutations have been observed in NHP treated with the MB-003 antibody cocktail [160]. Thus, a combination treatment approach, similar to DAA combination or HAART, could help to minimize escape mutants and may be considered for future therapeutic developments against EBOV infection. Several synergistic combinations of FDA-approved drugs have also been proposed but have not been investigated in vivo [103–105].

A number of other potential candidates have been suggested to inhibit EBOV entry in vitro, but their targets were not identified. These include 17 compounds from the Molecular Libraries Small Molecule Repository (MLSMR) library that targeted different steps of EBOV entry [106], the synthesized compound **8a** and its derivatives [107], the antibiotics azithromycin [78] and teicoplanin [108], the antimalarial chloroquine [78,109,110,132], several other FDA-approved compounds [110], and the flavonoid derivative quercetin 3-β-O-D-glucoside (Q3G) [112]. Q3G was shown to fully protect mice from lethal EBOV challenge [112], whereas azithromycin, teicoplanin, and chloroquine appeared ineffective and/or toxic at the doses tested in animal studies [54,78,111,132].

In terms of potential toxicity, FDA-approved drugs have better characterized profiles. For instance, digitoxin is known for its cardiotoxicity [161], and sertraline can cause liver injury and serotonin syndrome [162]. As for other newly developed antivirals including antibodies and compounds, their potential toxicity requires further investigation.

Finally, novel methods of drug development or drug delivery may also further improve anti-EBOV therapeutics. For example, bioinformatics or artificial intelligence may help facilitate drug discovery or design. Drug delivery systems, such as adeno-associated virus (AAV) vectors, have been shown to successfully transfer monoclonal antibodies genes into mice with a single injection and prophylactically protect them from EBOV challenge [115–117] (Table 2). AAV delivery can reduce the costs of large-quantity antibody production and repeated injections; the protective effect lasted for at least 5 months in mice [117]. These approaches could help fast-track drug development against EBOV and enhance global preparedness to manage current and potential future EBOV outbreaks.

**Funding:** L.-T.L. is supported by the Ministry of Science and Technology of Taiwan (MOST110-2320-B-038-041-MY3).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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