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Review Article

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Overview of Marburg Viral Disease

Rameen Atique[1], Hafiza Arshi Saeed[1], Hafeez ur Rehman Ali Khera[2], Areesha Naveed[1], Javeria Sharif[1], Hafiza Rida Fatima[1], Ayesha Haidar[1], Aqsa Perveen[1] and Abdul Samad[3*]

[1]Department of Pathobiology and Biomedical Sciences, Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan
[2]Department of Clinical Sciences, Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan
[3]Division of Applied Life Science (BK21 Four), Gyeongsang National University, Jinju 52828, Korea

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***Corresponding Author:**
Abdul Samad
Division of Applied Life Science (BK21 Four), Gyeongsang National University, Jinju 52828, Korea
samad@gnu.ac.kr

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ABSTRACT

Marburg viral disease induced by the Marburg virus. It is a constituent of the Filovirus family, which also encloses the Ebola virus. The disease first came into light in 1967 during episodes of the virus in Marburg and Germany. After that, the infection caused high CFR in Angola, Uganda, and Congo. The disease includes the sudden outset of symptoms, including high fever, vomiting, intense headache, abdominal pain, and rash. In patients with severe infection, it leads to bleeding, jaundice, organ collapse, and eventually death. Fruit bats of genus Rousettus are considered to be the biological pool of the Marburg virus. This disease destroyed African countries with high death rates. The virus can be transferred from green African monkeys or fruit bats. It can be transmitted through human-to-human interactions via blood, body fluids of diseased people, and contaminated surfaces. MVD can be diagnosed by technical laboratory tests incorporating enzyme-linked immunosorbent assay (ELISA), reverse transcription-polymerase chain reaction (RT-PCR), and virus seclusion. Supportive maintenance has been done to demonstrate some efficacy in controlling the symptoms and improving the probability of survival. Adequate management and care have been taken to prevent the unusual spread of disease, such as the separateness of infected patients and suspected individuals, which should pertain to quarantine measures. Because of the high casualty rate and lack of a certified vaccine or any antiviral cure, the only way to keep MVD in check can be through prevention. This review briefly overviews the Marburg virus, including diagnosis, pathogenesis, transmission, and treatment.

INTRODUCTION

The Marburg virus causes Marburg viral disease. It is a member of the filoviridae family. It is a rod-like shape, as shown in Figure 1. This disease was first reported in 1967 when a hemorrhagic fever outbreak occurred in Germany. At that time, rephrase: thirty-one patients were prevalent, out of which seven patients developed severe disease with a fatal outcome. It has caused several outbreaks in sub-Saharan Africa and can cause illness with a high (88%) fatality rate [1]. The outbreak was reported initially in African countries like Kenya, Uganda, Angola, and South Africa. The primary sources of infection were African green monkeys (Chlorocebus aethiops) and various species of bats, which may include *Rousettus aegyptiacus* and *Hipposideros caffer*.The monkeys were imported from Uganda by scientists conducting experiments to produce polio vaccines [2]. The latest update of Marburg viral disease was reported from Ghana in 2022. This disease is highly associated with the destruction of the body organs, such as the liver, brain, and tissues of the renal system. The virus detected in the oral route and the fecal samples of bats proved that the Marburg virus can be transmitted from the infected bats to the in-contact bats. MARV is highly infectious; it can spread rapidly and cause death [3]. The infection can be transferred to humans and non-human primates (intermediate hosts) from the discharge of bats. The recent explosion of the Marburg virus was reported in

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Equatorial Guinea in January 2023, and the laboratory confirmed the victim of the Marburg virus in West Guinea on February 13, 2023. A total of 17 cases were reported, out of which 12 passed away (these cases were confirmed on 8 June 2023). Remove these lines or rephrase from an Indian point of view, the Marburg virus disease is a cue to prepare ourselves to tackle various infectious diseases because they have encountered the recent episode of the Nipah virus in 2018, which took several vitalities in the southern state of Kerala [4]. A virus becomes resistant as it can transform into different forms and has distinguishable effects in various areas. The highest CFR was recorded in Angola during the viral attack in 2005 because the Marburg viral Angola strain emerged as more pathogenic and invulnerable than other MARV strains when experimentation was done on non-human primates [5, 6]. Marburg virus is similar to the ebolaviruses in structure. It is an enveloped, non-segmented, single-stranded, and negative sense RNA virus that belongs to the *filovirus* family. One difference between the Marburg virus and the Ebola virus is that the Marburg virus is not immunosuppressive, grammatically wrong but the Ebola virus is. The Marburg virus has a single species, "Marburg Marburgvirus," which includes two viruses: Marburg (MARV) and Ravn virus (RAVV). There are two known variants of the Marburg virus: Marburg Musoke and Marburg Angola. The latter one is the most pathogenic and causes rapid illness in non-human primates. The glycoproteins on the cell surface are an essential feature of this virus and are the fundamental target for examining viral vaccines. The disease results in hemorrhagic fever along with the disability of organs like infection of the brain and spleen. The involvement of the central nervous system may result in confusion, excitability, and aggression in behavior [7]. It is a zoonotic disease transmissible to humans by bats, monkeys, and other intermediate hosts. Marburg virus can be transferred by direct contact with infected patients' blood and body fluids. The incubation period of the Marburg virus is two days to 3 weeks. The Ebola virus is also a member of the *et* family and resembles the Marburg virus's clinical features and transmission route. Presumably, the Marburg virus was thought to be less dangerous than the Ebola virus, which has caused two large explosions with high fatality rates. The first deadly outbreak happened in 1998-2000, which caused 128 deaths in the Democratic Republic of the Congo (DRC), and the case fatality rate was 83%. It was followed by the largest lethal population outbreak in Angola from 2004-2005, resulting in 329 deaths with a fatality rate of 88% [8, 9]. Different variants were associated with the spell of the Marburg virus infection in the DRC, but only one version caused disease in Angola [8, 10]. The investigation was done on miners who developed an infection after a visit to the Kitum Cave; the MARV was found in Egyptian fruit bats. Viral RNA was noticed in the liver, spleen, and lung tissue of a healthy female R. aegyptiacus (fruit bat) in July 2007. Phylogenetic variations of the viruses displayed that they were very different from the strains obtained from Kenya (Musoke and Ravn) but analogous to the cases unraveled in Europe in 1967. The strains of the Marburg virus isolated from bats and humans in 2007 belong to obscure lineages [11]. When histopathological inspection of the liver of the infected bats was done in the laboratory, there were no lesions that could cause the Marburg virus infection. On performing the immunohistochemical study, there were no traces of the Marburg virus. Diagnostics tests for evaluating the Marburg virus disease are reverse transcriptase polymerase chain reactions (RT-PCR) and enzyme-linked immunosorbent assay. Specific probes can be made for the sequencing of the MARV genome [12]. Indeed, the Marburg virus was unveiled about 50 years ago, but technicians have performed clinical trials to analyze it properly. Since there is no recent large-scale outbreak of MVD, less is known about it. The MARV outbreaks are unusual, which is why there is not enough information to evaluate and generate treatment options for MVD. Detailed disease studies and investigations may help in future medical trials and improve curative management of Marburg virus disease. Today, no authentic treatment is available for MARV infection. Therefore, supportive care can be done as a primary treatment for the patients of Marburg viral disease. Suspected patients of MVD can be managed by running their blood and urine tests. After confirmation of infection, patients must be quarantined. Proper precautionary measures should be taken to prevent infection (clean clothes and utensils). In poultry, several treatments have become successful with prolonged or increased survival rates on broiler chickens. The tested treatments may include cytokine inhibition and antibody transfer, but these treatments proved useless in the non-human primate (NHP) model. Drugs such as hydroxyzine and pentazocine are beneficial in monitoring. The treatment or therapy against the viral infection depends upon the host's immune response and the actions taken to control virus replication. Antibodies can be used for treatment because they target proteins of filovirus. An anti-EBOV convalescent serum with coordination of interferon and supportive care can be used for treating infection. However, the role of antibodies in serum for the patient's survival is anonymous [13]. Antibody-based treatment's success was first informed in 2012 when researchers used polyclonal immunoglobulin G. It was refined from the convalescent serum of NHPs,

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immunized with exploratory MARV vaccines that endured subsequent filovirus infection [14].The term "viremia" refers to the presence of viruses in blood, and post-exposure treatments are evolved against filoviruses, among which monoclonal antibody-based strategies have appeared. It displays an elevated level of protection as these monoclonal antibodies target the virus's glycoproteins. The first outbreak of the Marburg viral disease was in two areas of West Germany; "Marburg a der Lahn" and "Frankfurt am Main" [2]. The virus was destroyed for the first time in August 1967 and ceased in November 1967. At first, 29 people were diagnosed with the infection, out of which seven patients grammatically wrong surrendered to the deadly virus. As we all know, the Marburg viral disease is caused by the Marburg virus, which belongs to the Filovirus family. Before developing the disorder, all suspects may have a direct connection with the sources of infection, which may be green African monkeys or various species of bats. The eruption of MVD took place among the laboratory manufacturers attempting to produce vaccines for poliomyelitis. Some past studies highlighted that infection first occurred when researchers sought to develop green monkey cell cultures using their tissues. The workers became infected with the Marburg virus while dealing with the tissues of infected green monkeys imported from Uganda. In addition to the two areas of West Germany, the Marburg virus also caused devastation in Belgrade and Yugoslavia (Serbia), and the carriers were the same Ugandan primates. The Marburg virus rendered devastation worldwide. The morbidity and mortality rates depended upon the intensity of the spell and virus strain, but the standard case fatality rate was about 50%. According to the World Health Organization (WHO) analyses, the Marburg virus causes a highly virulent disease and can develop hemorrhagic fever in humans and animals. In the first outbreak of 1967, laboratory staffers were exposed to the Marburg virus through the meat and organs of sick green African monkeys *(Chlorocebusaethiops).* A young man traveled from Zimbabwe to Johannesburg and contracted the virus in February 1975 and developed a primary infection. Kenya experienced an outbreak of the Marburg virus disease in 1980 when a doctor developed an infection in Nairobi, resulting in brutal haematemesis. In 1987, a 15-year-old boy fell prey to the infection and passed away. He reportedly confronted the Ravn virus (responsible for MVD) in a cave colonized by fruit bats. After that, the Marburg virus caused devastation from 1998-2000 in the Democratic Republic of Congo, 2004 to 2005 in Angola, 2012-2017 in Uganda, and recently in August 2021 in Guinea [15]. Marburg is a dangerous zoonotic virus that can spread disease in humans and non-human primates. Clinical indications are sudden fever, diarrhea, nausea, chills, vomiting, and headache. The disease is divided into three primary grades: You have stated different information above in introduction the initial phase may continue for four days; next is the organ phase, which longs for 5-13 days; and at the end, the recovery phase, which continues for 13 days [16]. This virus can deteriorate the organs and occasionally cause jaundice. It may lead to a rash of the pancreas and strenuous weight loss. A person with MVD can experience pain in the limbs, and the temperature of the body falls slowly. A patient can develop a rash on the face that can progress to the trunk and limbs. Some of the victims develop conjunctivitis and photophobia as well, and swelling of lymph nodes is also observed in the cervical and axillary regions. The disease usually lasts for 15-20 days. During this period, the patient may feel nausea, tumult, disturbance in the autonomic nervous system, fainting, and eventually die in a deep coma. Prophylactic and protective policies must be considered while dealing with the Marburg virus [17]. We should use personal protective equipment to prevent contamination and work in a biosafety cabinet to maintain hygiene and exposure to self-contamination. The particular epidemic can be controlled by proper laboratory equipment and awareness of the many risk factors. In areas of the outbreak, avoiding contact with non-human primates is appreciated. Humans should avoid frequent visits to mines and caves as fruit bats (carriers of the virus) live there. Adequate care should be taken to dissuade contact with the person having indications of MVD. Infected areas should be decontaminated with disinfectants, and the affected neighborhoods' public should be educated about the precautions, signs, and symptoms. Training hospital staff and front-line workers is essential to tackle the disease more efficiently. Proper care should be taken in the case of a pregnant woman because a fetus can contract a virus from the mother, and high fetal casualty rates highlight the need to concentrate on the treatment of the pregnant mother. The virus can also be excreted in breast milk, and the affected mother should avoid breastfeeding for at least 15 days [18]. Explain that till today, there is no approachable treatment available for the Marburg viral disease. However, possible trials and investigations are carried out in laboratories to determine the safe and protective therapies. Some are being tried out on nonhuman primates, while other trials were sampled on humans. Antiviral drugs (Galidesivir and Favipiravir), monoclonal antibodies, and interferons may be remedies. Considering vaccines, various laboratory practices are executed for the vaccine production of MARV. Currently, ongoing investigations focus on the recombinant vectors to produce genes that provide immunity against the

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expression proteins of the Filovirus. The vaccine trials have been done on the Marburg virus by using inactivated Marburg virus particles, growing them in a Petri plate, and killing them with warmth or chemicals. So, several methods have been investigated to use a live-attenuated version of the Marburg virus as a vaccine. Protein-based vaccines that appear to be effective in the case of MVD and mRNA-1,360 have been formulated and produce adequate viral protein utilizing mRNA technology. In various in-vitro and in-vivo studies, black seeds *(Nigella sativa)* have proved to be antiviral, antioxidant, and immunomodulatory in treating patients infected with the Marburg virus disease. The anti-viral effects of N. sativa help to reduce the viral load in MARV patients, and it is also effective against other viral diseases such as HIV, HCV, HBV, and EBV. Primary prevention and management measures are essential to regulate the Marburg viral disease. Sanitation and hygienic steps should be followed to avoid contact with blood and other body saps. Wildlife animals should be carefully supervised with protective gloves [19]. Several plasma treatments have been experimented on clonal antibodies and demonstrated more promising results. In the future, MVD can be deterred and governed by influential diagnostic techniques, training of healthcare workers, and supplying helpful control criteria for infection. Scientists or researchers from all over the world should share information to enhance public awareness of the virus in public to control death rates in outbreaks. To recover from the harmful virus, supportive care is essential because people living in shallow areas cannot afford high-quality treatments and diagnoses. It usually includes maintenance of the body hydration, medication, physio-social consent, and nutrition. Drugs taken orally are beneficial to degrade the symptoms of infection, like nausea, fever, confusion, and headache. Patients can intake intravenous fluids to keep the body hydrated and vitamins to meet the body's nutritional requirements.

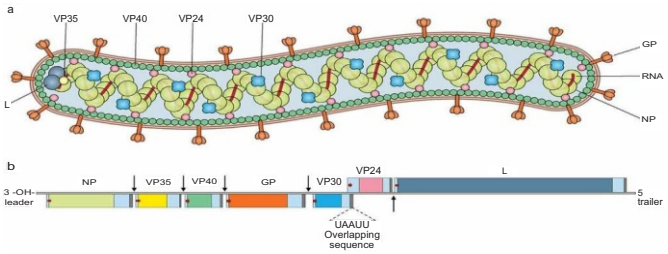

Figure 1: Virion Structure and Genome Organization of Marburg Virus

The Marburg virus structure, along with depicting the structural proteins. Bottom, an illustration of the genome organization of the Marburg virus. This seven-gene strain of the Marburg virus has been drawn roughly to scale. The light blue boxes indicate noncoding areas, and the colored box code regions for genes. The red arrows demonstrate the position of the transcriptional start signals, while the pale brown bars highlight conserved transcriptional stop signals. Intergenic regions segregate the genes, indicated using black arrows, except the overlapping sequence (black triangle) between VP24 and VP30. At the extreme ends, the 3' and 5' trailer sequence is shown in Figure 2 [20].

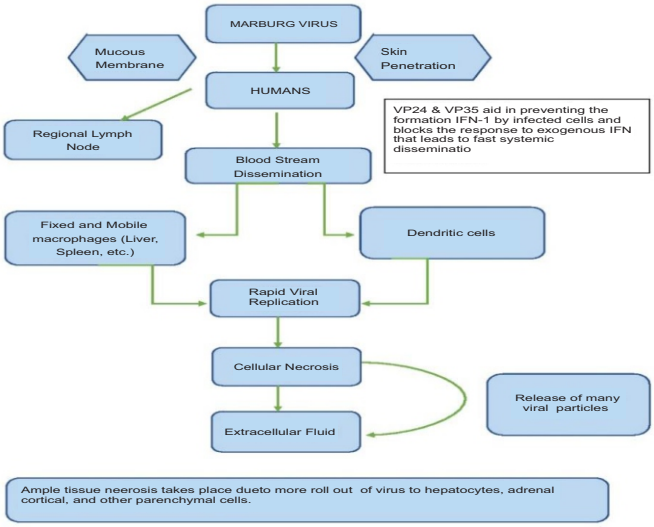

Figure 2: Pathogenesis is of Marburg Virus

Marburg virus can be transmitted from human to human and animal to human as well because it is a zoonotic disease, as shown in Figure 3.

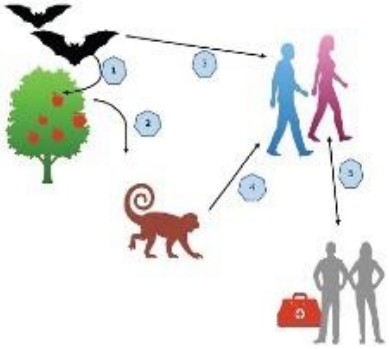

Figure 3: Mode of Transmission of Marburg Virus [19]

When a person gets infected by the Marburg virus, the manifestations are unclear and complicated to diagnose clinically. With time, the progression of the disease occurs. This information is wrong or wrongly written It becomes an epidemic with distinctive signs and symptoms [21]. At the onset of the infection, the patient feels severe headaches and bother in the lumber region. Besides this, the eyes of many patients become prudent, painful, and pressurized. Proper diagnosis and the isolation of patients are necessary because the virus can be transmitted easily from one person to another, like in healthcare workers and doctors. The headache and fever are pursued by chest pain,

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fatigue, puking, and diarrhea. The doctors may doubt Marburg's infection because the patient displays a papular rash and instantaneous cachexia, but the commencement of hemorrhagic fever confirms the disease. All these signs lead to considering Lassa fever, which includes sore throat and facial edema in the late stage of illness. The blood of infected individuals is examined, and it depicts malarial parasites associated with chills and headaches [22]. Patients also develop secondary infections like bacterial infections, typhoid fever, hepatitis, and yellow turmoil. Samples for diagnosis of the viruses are taken from the acute and convalescent phase of the incubation period and by performing liver biopsy and throat washing. After sampling, they are sent to a laboratory for serological and virological testing. The serum is collected from the infected person, and complement fixation tests are conducted for viral confirmation as an antigen. Immunohistochemical techniques are also used for the detection and identification of viral particles. In the diagnosis process, virus isolation is a sensitive method, and the Marburg virus shows enhanced growth in Vero cells and Vero E6 cells. Remove this One technique of RT-PCR formulated by researchers uses the dye SYBR green with a set of primers Filo-A (5`-ATCGGAATTTTTCTTTCTCATT-3`) and Filo-B (5`-ATGTGGTGGGTTATAATAATCACTGACATG-3`). They are concocted to intensify the L genes of the MARV virus. Another method of using real-time quantitative RT-PCR was evolved by investigators in which a fluorogenic TaqMan probe is tagged with dye 6-carboxyfluorescein at the 5` end of DNA and quencher tag at the 3` end. Transmission electron microscopy can be manipulated to detect the Marburg virus in tissues and body fluids. Viral antigens can also be diagnosed with the help of immunochemistry by examining tissue lacerations and determining vision configuration. Operators deduce by performing these techniques that viruses reside in pancreatic cells and hepatocytes. MARV is aimed at macrophages as fibroblasts, vital replication sites for the Marburg virus [23]. Although no known treatment is present for the Marburg virus disease, some therapies are considered to increase the survival rate of infected persons. Filoviruses are deadly viruses and have caused destruction worldwide. As we discussed earlier, the Angola strain of the Marburg virus causes 85% of death rates [24]. Viral infections resulting in hemorrhagic fever can be dealt with with various therapeutic schemes comprised of immunization, management of antibodies, and use of antiviral medications for therapy. Different classes of antivirals are used based on the molecule they target, specific proteins that destroy virus particles, interferon, and immunomodulatory substances [25]. In case of a proper remedy for MVD, the disease is overseen by diverse pharmacological aspects and supportive measures to prevent organ failure and prolong a patient's life. The cases of the Marburg virus disease can be regulated by strict guidance of preventive techniques and isolation. Rephrase or remove When a patient experiences septic shock, he/she is divulged to the ICU to get the intrusive antidote for prevention and surveillance of ailment. Sometimes, the patient can be treated with decent supportive maintenance and administering a distinct antiviral cure. In filoviruses, clinical strategies can be split into three grades, i.e., incubation of virus, pre-coagulopathy, and coagulopathy [26, 27]. In the foremost phage, the organism is exposed to a viral particle until it shows symptoms, and at this stage, the infected patient gets a vaccination and an antiviral treatment [28]. Next, in the second step, the virus begins to replicate and provoke diseases, and in this phase, virostatics are influential. The final and last phase is portrayed by coagulation irregularities caused by defects in the cytokine grid. At this set, interfering and proinflammatory cytokines are the only choices left to evaluate the infection. Non-human primates can be dealt with by using disease-modifying mechanisms such as human recombinant protein C (rhAAPC), d chemotherapeutic procedures are used to cope with coagulation disabilities and nematode dicoumarol protein c2 (rNAPc2) are clotting substances [29, 30]. It is valuable to obstruct the activity of tissue factor VIIa (a protein complex). PMOs (phosphorodiamidate morpholino oligomers) are inhibitory molecules that prevent the replication of filovirus particles. Positively charged PMOs and short interfering RNA (siRNA) can be used as a victorious vaccine to be administrated in non-human primates for persuasive restorative of filoviruses [31, 32]. siRNA marks specific genes through RNA machinery and inhibits viruses that induce hemorrhagic fever, such as MARV. Mannose is a sugar present in cells that has a receptor CD206 present on the exterior of dendritic cells and macrophages. siRNA combines with CD206, resulting in GalNAc-siRNA and mannose forming a complex with siRNA that is mannose-siRNA [33, 34]. These two complexes are studied in non-human mod that target the MARV proteins and provide security [35, 36].

Despite being identified more than five decades ago, Marburg viral disease (MVD) remains relatively underexplored compared to other filoviral infections such as Ebola. The sporadic nature of outbreaks and their geographic concentration in sub-Saharan Africa have limited large-scale clinical investigations and therapeutic trials. Furthermore, gaps persist in understanding reservoir dynamics, viral evolution, effective antiviral

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therapies, and vaccine development. Therefore, a comprehensive and updated synthesis of available evidence is essential to highlight current knowledge, identify research deficiencies, and support improved preparedness and response strategies against MVD.

DISCUSSION

Appropriate knowledge of each aspect of the deadly virus is essential as the published articles from pioneer writers are followed. The MARV infection has been disregarded for many years, but it has recently gained the interest of scientists and researchers because controlling it has become a challenge for them. The highest number of cases was monitored between 2004 and 2005 in Angola, where the case fatality rate was 90%. Different episodes of the Marburg viral disease were reported in Uganda from 2007 to 2017, where 100% CFR was recorded in 2014. Recently, this deadly virus played a game of demise in West Guinea in 2023. Disease-modifying narcotics and inhibitors of viral proteins have shown more promising consequences in patients [37, 38]. Viral RNA and IgG antibodies in vectors (bats) are detected by serological data and screening of bats by RT-PCR. The broad-spectrum drug "favipiravir" is beneficial as an intervention for filovirus conditions. Designation of the reservoir host should permit the development of risk-lessening parameters to mitigate the possibility of coming disease outbreaks. Control and proper management are necessary to prevent infection [39]. Formal governance and supportive therapies can treat some cases with fewer viral loads. Kalonji (black seeds) is beneficial in the treatment of the Marburg virus disorder because of its anti-inflammatory efficiency as a MARV attacks lymphocytes and macrophages, and these contaminated cells facilitate the synthesis of human necrotic factor and Nigella sativa (kalonji) destroy alpha-tumor necrotic factor [40].

This review is limited by reliance on previously published literature and available outbreak reports, which may not fully capture unpublished data or evolving epidemiological trends. The rarity and unpredictability of outbreaks restrict large-scale clinical trials and comprehensive therapeutic validation. Future research should focus on strengthening surveillance systems, advancing rapid diagnostic tools, accelerating vaccine and antiviral development, and promoting One Health approaches to better understand zoonotic transmission. International collaboration, data sharing, and investment in outbreak preparedness will be critical to mitigating the global threat posed by Marburg viral disease.

CONCLUSIONS

After worldwide devastation caused by COVID-19, the Marburg virus appears to be a rising challenge in front of the world. Because of the high case fatality rates, MVD was confirmed to be a deadly infection challenges to manage due to the undersupply of vaccines and insufficient cures. Endeavors are made globally by researchers, healthcare professionals, and epidemiologists so that humanity can tackle the Marburg viral disease more effectively. Although Africa has been specified as the prospective source of the MARV, most outbreaks have been caused by animal spillage to the human population. Vaccine studies have been continuous for the past few years, and the virus is being investigated on various animal models, including NHPs, hamsters, poultry, and mouse samples. N. sativa is a spice used traditionally to treat different ailments. The discourses learned from the past outbreaks emphasized the significance of preparedness and creation to address the threat of MVD to public health. The explicitness and sensitivity of these diagnostics are beneficial in epidemiological analysis and examination of filovirus infections.

Authors' Contribution

Conceptualization: RA, HAS, HURAK, AN, JS, HR, F, AH, AP, AS
Methodology: RA, HAS, HURAK, AN, JS, HR, F, AH, AP, AS
Formal analysis: RA, HAS, HURAK, AN, JS, HR, F, AH, AP, AS
Writing and Drafting: RA, HAS, HURAK, AN, JS, HR, F, AH, AP, AS
Review and Editing: RA, HAS, HURAK, AN, JS, HR, F, AH, AP, AS

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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