Novel therapeutic approaches toward *Hantaan* virus and its clinical features’ similarity with COVID-19

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**Abstract**

Zoonotic virus spill over in human community has been an intensive area of viral pathogenesis and the outbreak of *Hantaan* virus and severe acute respiratory syndrome coronavirus 2 (SARS CoV2) after late December 2019 caused a global threat. *Hantaan* virus is second to the COVID‑19 outbreak in China with seven cases positive and one death. Both RNA viruses have opposite sense as in (−) for *Hantaan* virus and (+) for SARS CoV2 but have similarity in the pathogenesis and relevant clinical features including dry cough, high fever, shortness of breath, and SARS associated with pneumonia and certain reported cases with multiple organ failure. Although COVID‑19 has global impact with high death toll, *Hantaan* virus has varyingly high mortality rate between 1% and 40%. Hence, there is a need to explore novel therapeutic targets in *Hantaan* virus due to its rapid evolution rate in its genetic makeup which governs virulence and target host cells. This review emphasizes the importance of structural and nonstructural proteins of *Hantaan* virus with relevant insight from SARS CoV2. The envelope glycoproteins such as Gn, Gc, and nucleocapsid protein (N) direct the viral assembly and replication in host cells. Therapeutic treatment has similarity in using ribavirin and extracorporeal membrane oxygenation but lack of efficacious treatment in both cases of SARAS CoV2 and *Hantaan* virus. Therefore, potential features regarding therapeutic targets for drug discovery for *Hantaan* viruses are discussed herewith. The conclusive description highlights that N protein is substantially involved in evoking immune response and induces symptoms and could be precursive target for drug discovery studies.

**Keywords:** COVID‑19 pathogenesis, diagnostics, *Hantaan* virus life cycle, therapeutic targets, treatments

**Introduction**

There are two outbreaks of *Hantaan* virus in the past century, there is recent outbreak in China. In China, *Hantaan* virus outbreak reported by one death and seven cases found positive is another concern for researcher and health-care community after COVID‑19.[1] *Hantaan* virus was firstly reported in 1950 in South Korea characterized as a causative agent of hemorrhagic fever with renal syndrome (HFRS). The virus evolved along the time and second outbreak happened in the US in the 1990s decade with alternate symptoms or target system was known as *Hantaan* virus pulmonary syndrome (HPS).[2] *Hantaan* viruses are directly transmitted through rodents; the mode of transmission is airborne (contact with infected aerosols of rodent excreta: urine, feces, and saliva).[3] Human‑to‑human transmission is mediated via aerosols as COVID‑19 known as communicable disease.[4] This was more associated with cardiopulmonary dysfunction than HFRS. The mortality rate is also high (1%–40%) due to vital systems which are major targets such as the kidney, lungs, and cardiac systems.[3] According to the International Committee

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on Taxonomy of Viruses (ICTV) classification, it belongs to a large family which comprises more than 300 viruses known as Bunyaviridae. Hantaan virus classified under the genus Hantaan virus has a negative sense single-stranded RNA segmented into three segments named large (L), small (S), and medium (M), it makes up total genome 11–19 kb enveloped with lipid membrane embedded of spike proteins. The different genuses of rodents have been reported for their ability to reserve the infectious agents without symptoms like HPS or HFRS. The reason behind no symptoms in rodents is uncertain; some studies suggest that rodents have efficient immunoregulatory cells to suppress the immune response against virus and prevent tachycardia and pulmonary edema. The reported genus of rodents as a reservoir includes Myodes, Apodemus, and Rattus. This diversity makes it a more sporadic nature of spread throughout the wide geographic locations. The actual prevalence is hard to know due to lack of testing tools in tropical countries like India and South Africa. Even there can be more than one million cases per year globally and bigger part belongs to China only. There is no specific treatment against HFRS and HPS, only symptomatic treatment like intensive care during severe respiratory distress by providing ventilation with oxygen therapy. In contrast of clinical course of Hantaan virus, we are reviewing the literature to find out the future prospective in therapeutic development. Identification of therapeutic targets might be essential for therapeutic development against the Hantaan virus.

**Life Cycle**

Both COVID-19 and Hantaan viruses are a member of zoonotic viruses which is emerged from animals like bat and rodents, respectively, but belongs to the family of positive RNA stranded known as Coronaviridae and Bunyaviridae, respectively. Hantaan virus infects first lining cells of the lungs (endothelial cell and epithelial cells) and first-line immunogens such as macrophages, dendritic cells, and lymphocytes. Since these cells have surface expression of special receptor which is receptive for viral envelope surface glycoproteins named Gn and Gc encoded by medium segment of the single-stranded RNA genome. This specific cell surface receptors are integrins (beta-3) commonly involved in the attachment to host cell whether SARAS CoV-2 binds to the target cell via surface spike protein (15–20 nm) to angiotensin convertase enzyme-2 receptor. After the attachment, the virus enters the cell via clathrin-coated pits with the envelope (intact), but in the case of SARAS CoV2, the envelope remains outside only RNA and RNA proteins are released into the cytoplasm. In case of Hantaan virus, it has an additional step, is endo-lysosome formation which lyse the envelope and releases negative sense single stranded RNA and viral ribonucleic proteins into the cytoplasm. Now, the negative-sense RNA is available for early transcription which is required for the replication of viral RNA. Viral RNPs bind on a specific sequence known as a promoter region and initiates the early transcription to make three segments of the genome, namely small, large, and medium. These segments encode for specific proteins like nucleoprotein known as nucleocapsid (N) protein, viral RNA proteins, and envelope proteins encoded by respective segments. It also contains a nonstructural protein-encoding open reading frame (ORF) similar to Orthobunyaviridae family. Positive-sense ssRNA genome of SARAS CoV2 has capped at 5’end, multiple ORFs total composed of 26–32 kb genome is organized in the sequential manner of 5’ UTR replicase SMN UTR 3’ end. S encodes for spike, M for membrane, and N for nucleocapsid protein. It has RNA-dependent RNA polymerase (RdRp) found in the Hantaan virus for the replication and assembly of virus takes place near the smooth endoplasmic reticulum (ER) and early Golgi transition. These ORFs are responsible for stimulating the interferon response, they express during immune response phase of pathogenesis. Several studies suggested that it also plays an important role in the modulation of immune response in the infection. M transcript encodes for envelope protein precursor, which proteolytically modified into Gn and Gc proteins in the ER. This modification occurs co-translationally and then glycosylated along cleavage. After the glycosylation, it is transported to the Golgi complex. Protein processing in the case of SARAS CoV2 happens in the SER which involves various proteases (totally 16, but four is essential) known as a nonstructural protein. The next step in the life cycle is the switching of RNA transcriptase to RNA polymerase to replicate the viral genomes. Multiple copies of viral native RNA are ready to encapsidated. N protein plays a key role in trafficking the assembly material like surface proteins and viral RNA. This step is done with the help of microtubule dynein protein-mediated near the membrane of ER-Golgi intermediate complex (ERGIC). The bud is released outside of the infected cell by secretory vesicle (ICTV).

**Pathogenesis**

HPS has very complex pathogenesis. It activates intense immune response which leads to vascular permeability increase. Due to vascular permeability increase, patients lead to pulmonary edema and a massive reduction in respiration efficiency which results in respiratory system failure and cardiogenic arrest. Processed antigen of viral N or spike protein is presented to the CD8+ T cell. Macrophages also present the same antigen to the cytotoxic T-cells, while presenting antigen, it secretes the pro-inflammatory cytokines like interleukin (IL) 6 and 1 and tumor necrosis factor alpha; a reason behind cardiogenic shock is due to suppressive effect
on myocardial function and leads to the hypotensive condition. The increased level of pro-inflammatory cytokines calls the specific T-cells by increasing the vascular permeability. Vascular permeability in the endothelial cells of the lung represents a critical condition in the disease development. Hantaan virus-infected cells evoke immune response but do not commit to programmed cell death by upregulation of survival factor BCL-2. Specific T-cells differentiate into the Th1 and Th2 cells named Th1 and Th2. Inducible regulatory T-cell secretes IL-10 and transforming growth factor (TNF) beta, these are the only two regulatory cytokines that suppress the immune response to get hyperactive and sustain the pathogenesis from worsening.

COVID-19-infected patients show high blood plasma level of pro-inflammatory cytokines as Hantaan virus. Temperature of the body has risen up to 39°C and leukopenia by increasing number of neutrophils in circulation count with 70% of TLC 2.91 × 10⁹ cells/L. High erythrocyte sedimentation rate and C reactive protein level increased by 1.5 fold to the normal range. IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, IP10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and TNF-α increase the level of severity in condition. Conclusively, the surge of pro-inflammatory cytokines such as IL-6, IL-12, IL-5, IL-2, TNF-alpha, TNF beta, and IFN-gamma and deficient in TGF beta and IL-10 play a key role in pathogenesis.

**Clinical Features of Hantaan Viral Disease**

The new world Hantaan virus causes HPS which is associated with severe acute respiratory syndrome (SARS) and respiratory distress. The mortality rate depends on the strain which is infecting. First respiratory symptoms occur after 1–5 weeks. Actually, symptoms start with mild fever, myalgia, and weakness. HPS is represented to clinical as a distress in respiration followed by 2–3 days, it produces leakage in pulmonary capillaries, called by the leaking syndrome. Leaking syndrome leads to cardiogenic shock characterized by hypotensive in nature. Some patients report nausea, gastrointestinal symptoms, vomiting, and diarrhea. Prodrome symptoms are no longer than 4–5 days. It is followed by cough, dyspnea, tachycardia, and low atrial blood pressure. Respiratory failure is indicated by the cyanosis. It can lead to the hypotension and shock. Failure of renal function is due to the raised level of creatinine. Intestinal bleeding also is observed in some cases. Aspartate aminotransferase and alanine aminotransferase levels also raised in blood. Vascular permeability also increased which leads to the alveolar edema.

In case of COVID-19, symptoms precipitate after 5–6th day after exposure. After the onset of symptoms, deaths happen in the range between 6 and 41 days having a median of 14th day. Symptoms are high temperature, cough, myalgia, headache, hemolysis, dyspnea, lymphopenia, and diarrhea. Acute respiratory distress syndrome, cardiogenic injury, grand-glass like opacities lead to death. It shows uniqueness in symptoms like sneezing, cough and sore throat by infecting both of lower and upper respiratory tract. Pulmonary edema takes place after immune response due to vascular permeability and causes hypoxemia.

**Diagnostic Features**

HPS commonly diagnosed by the serological methods by the detection of antibodies against viral N protein; immunoglobulin G (IgG) and IgM in the circulation. Another diagnostic method is conventional molecular technique like reverse transcription–polymerase chain reaction (RT-PCR), it is a useful technique, which can reveal the viral genome at the 14th day of symptoms from infected tissue, blood, and serum.

For the COVID-19 diagnosis, RT-quantitative PCR (qPCR) is performed, which provides confirmatory and standardized results for coronavirus infection by amplifying the ORFs using specific primers for replicase and N protein. Its efficiency and sensitivity rate is also quite high as 91% from saliva samples collected from patients. Another method such as computed tomography scan and serological-based diagnostics such as IgG/M enzyme-linked immunosorbent assay kits are developed showing higher sensitivity than RT-qPCR, but further studies are needed for accuracy and efficiency.

**Treatment**

Till date, no antiviral or vaccine is approved by the Food and Drug Administration for Hantaan virus infection whether chloroquine, remdesivir, and ivermectin are approved for compassionate use in COVID-19 patients. Extracorporeal membrane oxygenation (ECMO) is initiated in patients who progress to advanced Hantaan virus cardiopulmonary syndrome (HCPS) and SARAS CoV2 severe cases, it needs to be started immediately on development of advanced shock or respiratory failure. Mertz et al. have shown a good survival rate with ECMO in HCPS patients. Among antivirals, ribavirin is the only one that has been evaluated in clinical trials. Ribavirin (intravenous, loading dose of 33 mg/kg, 16 mg/kg every 6 h for 4 days, and 8 mg/kg every 8 h for 3 days) decreased the severity of HFRS, however, it did not show any benefit in a controlled clinical trial for HCPS treatment in Canada and the US. Further, due to the fact that cardiopulmonary phase is mediated by immune system, methylprednisolone was evaluated for...
HCPS in a controlled clinical trial in Chile.\[^{[37]}\] Lactoferrin, 1-beta-d-ribofuranosyl-3-ethynyl-[1,2,4] triazole ETAR, favipiravir, and vandetanib have been evaluated in \textit{in vitro} and \textit{in vivo} studies for treatment of Hantaan virus infection.\[^{[38,39]}\] Human neutralizing antibodies administered at the time of acute phase of HCPS may have efficacy in treatment/prophylaxis of infection. Protection by neutralizing monoclonal antibodies (mAbs) and polyclonal sera has been reported by studies carried out in animal models. Further, Xiao et al. reported that decreased viremia levels at the time of admission to the hospital were related to less severe HCPS. A nonrandomized clinical trial in Chile for treating HCPS caused by Andes virus by human immune plasma reported its borderline statistically significant benefit.\[^{[38,39]}\]

Killed-virus vaccine is associated with concern such as dangers related to mass production of virus and doubts regarding effectiveness. However, inactivated vaccines developed in cell culture for Hantaan virus (HTNV) and Seoul virus (SEOV) are in use in China and a formalin-inactivated vaccine (Hantavax\(^®\)) made by growing HTNV in suckling mouse brain is in use in Korea. Approaches for vaccine development involve M segment products, recombinant N protein, SNV S gene-based and Puumala-truncated S gene-based DNA vaccine, etc.\[^{[38,39]}\]

Preclinical data on the \textit{Hantaan} virus are shown in a study by Sanna et al., several 2-phenyl-benzotriazoles resulted in fairly potent inhibitors of the \textit{Hantaan} virus in a chemiluminescence focus reduction assay showing an EC\(_{50}\) = 4–5 \textmu M, tenfold more active than ribavirin. Antiviral activities and cytotoxicity profiles suggest that 5,6-dichloro-1-(2)-phenyl-1(2)H-benzo[d][1,2,3] triazoles could be promising candidates for further investigation as a potential treatment of \textit{Hantaan} viral diseases.\[^{[40]}\]

COVID-19 declared pandemic by the World Health Organization and treatment options are still remained bottleneck. Some of the important treatment options that are being evaluated for COVID-19 include hydroxychloroquine, ivermectin, antivirals, corticosteroids, mAbs, convalescent plasma therapy, mesenchymal stem cells, Traditional Chinese Medicine, and Traditional Indian Medicine [Table 2]. Hydroxychloroquine is also used for prophylaxis of COVID-19 infection. Ivermectin has potential for use in COVID-19 and is safe at higher doses and frequent regimes. Its efficacy in COVID-19 has been reported by \textit{in vitro} as well as clinical studies. Various antivirals that have shown potential for use in COVID-19 such as remdesivir, ribavirin, favipiravir, lopinavir, etc., target RdRp, papain-like protease, 3-chymotrypsin-like protease, S protein, or TMPRSS2. Corticosteroids including dexamethasone, methylprednisolone, and prednisone are being used in COVID-19 treatment. Further, immunotherapy is considered an effective method for treatment of infectious diseases and mAbs such as canakinumab are being evaluated for use in COVID-19.\[^{[41]}\] Maximum benefit of plasma therapy is seen when it is given as prophylactic or early after the

\begin{table}[h]
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\textbf{Treatment} & \textbf{Brief description} & \textbf{Reference} \\
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\textbf{ECMO} & ECMO is initiated in patients who progress to advanced HCPS and needs to be started immediately on development of advanced shock or respiratory failure. Mertz et al. have shown good survival rate with ECMO in HCPS patients & \cite{37} \\
\textbf{Antiviral therapy} (Ribavirin) & No antiviral is approved by FDA for the treatment of infection by \textit{Hantaan} virus. Ribavirin (intravenous) decreased severity of HFRS, however, it did not show any benefit in a controlled clinical trial for HCPS treatment in Canada and US & \cite{37} \\
\textbf{Methylprednisolone} & Due to the fact that cardiopulmonary phase is mediated by immune system; methylprednisolone was evaluated for HCPS in a controlled clinical trial in Chile & \cite{37} \\
\textbf{Lactoferrin, ETAR, favipiravir, and vandetanib} & Lactoferrin, ETAR, favipiravir, and vandetanib have been evaluated \textit{in vitro} and \textit{in vivo} for treatment of hantavirus infection & \cite{38,39} \\
\textbf{Immunotherapy} & Human neutralizing antibodies administered at the time of acute phase of HCPS may have efficacy in treatment prophylaxis of infection. Protection by neutralizing monoclonal antibodies and polyclonal sera have been reported by studies carried out in animal models. Further, Xiao et al. reported that decreased viremia levels at the time of admission to hospital were related to less severe HCPS & \cite{38,39} \\
& A nonrandomized clinical trial in chile for treating HCPS caused by Andes virus by human immune plasma reported its borderline statistically significant benefit & \\
\textbf{Vaccines} & No vaccine is approved by FDA for infection by Hantavirus. Killed-virus vaccine is associated with concern such as dangers related to mass production of virus and doubts regarding effectiveness. Approaches for vaccine development involve M segment products, recombinant N protein, SNV S gene-based and Puumala-truncated S gene-based DNA vaccine, etc. Approved HFRS vaccines in China and Korea: Inactivated vaccines developed in cell culture for HTNV and SEOV are in use in China and a formalin-inactivated vaccine (Hantavax\(^®\)) made by growing HTNV in suckling mouse brain in Korea & \cite{38,39} \\
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\caption{Table 1: Treatment of \textit{Hantaan} virus infection}
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Singh, et al.: Similarity in clinical features between Hantaan virus and COVID-19

Various antivirals that have shown potential for use in COVID-19 such as remdesivir, ribavirin, favipiravir, lopinavir, etc., target RNA-dependent RNA polymerase (RdRp), papain-like proteinase (PLpro), 3-Chymotrypsin-like proteinase (3CLpro), S protein or TMPRSS2 to treat COVID-19. Antivirals have shown potential for use in COVID-19, but more research is needed to determine their efficacy.

Antivirals

Hydroxychloroquine: FDA has given approval for the use of hydroxychloroquine in COVID-19 with some limited circumstances through the EUA. [41]

Ivermectin: It has potential for use in COVID-19 and is safe at higher doses and frequent regimens. Its efficacy in COVID-19 has been reported by in vitro as well as clinical studies. [41]

Antivirals: Various antivirals that have shown potential for use in COVID-19 such as remdesivir, ribavirin, favipiravir, lopinavir, etc., target RNA-dependent RNA polymerase (RdRp), papain-like proteinase (PLpro), 3-Chymotrypsin-like proteinase (3CLpro), S protein or TMPRSS2.

Corticosteroids

Corticosteroids including dexamethasone, methylprednisolone, prednisone are being used in COVID-19 treatment.

mAbs: Immunotherapy is considered as an effective method for the treatment of infectious diseases and mAbs such as Canakinumab are being evaluated for use in COVID-19.

Vaccines: Many trials are ongoing to evaluate different strategies of developing a vaccine against SARS-CoV-2.

MSCs: MSCs are considered to have a potential role in COVID-19 due to their immunomodulatory and anti-inflammatory properties.

Convalescent plasma therapy: The maximum benefit of plasma therapy is seen when it is given as prophylactic or early after the appearance of symptoms. Convalescent plasma therapy has shown beneficial effects during previous outbreaks and is now being evaluated for COVID-19.

TCM: In China, it is recommended to use TCM in combination with conventional treatment for COVID-19.

TIM: CTRI has initiated many trials to observe the effect of TIM (Ayurveda, Unani, Siddha, and homeopathic) in COVID-19.

Table 2: Some important treatment options that are being evaluated for use in coronavirus Disease-19

| Treatment       | Brief description                                                                 | Reference |
|-----------------|-----------------------------------------------------------------------------------|-----------|
| Hydroxychloroquine | FDA has given approval for the use of hydroxychloroquine in COVID-19 with some limited circumstances through the EUA. | [41]      |
| Ivermectin      | It has potential for use in COVID-19 and is safe at higher doses and frequent regimens. Its efficacy in COVID-19 has been reported by in vitro as well as clinical studies. | [41]      |
| Antivirals       | Various antivirals that have shown potential for use in COVID-19 such as remdesivir, ribavirin, favipiravir, lopinavir, etc., target RNA-dependent RNA polymerase (RdRp), papain-like proteinase (PLpro), 3-Chymotrypsin-like proteinase (3CLpro), S protein or TMPRSS2. | [41]      |
| Corticosteroids  | Corticosteroids including dexamethasone, methylprednisolone, prednisone are being used in COVID-19 treatment. | [41]      |
| mAbs            | Immunotherapy is considered as an effective method for the treatment of infectious diseases and mAbs such as Canakinumab, are being evaluated for use in COVID-19. | [41]      |
| Vaccines        | Many trials are ongoing to evaluate different strategies of developing a vaccine against SARS-CoV-2. | [41]      |
| MSCs            | MSCs are considered to have a potential role in COVID-19 due to their immunomodulatory and anti-inflammatory properties. | [41]      |
| Convalescent plasma therapy | The maximum benefit of plasma therapy is seen when it is given as prophylactic or early after the appearance of symptoms. Convalescent plasma therapy has shown beneficial effects during previous outbreaks and is now being evaluated for COVID-19. | [42]      |
| TCM             | In China, it is recommended to use TCM in combination with conventional treatment for COVID-19. | [41]      |
| TIM             | CTRI has initiated many trials to observe the effect of TIM (Ayurveda, Unani, Siddha, and homeopathic) in COVID-19. | [41]      |

**Prospective Therapeutic Targets**

As we know, the advancement in the drug discovery by the in silico or computational methods can help to develop new small molecules if there are suitable or appropriate therapeutic targets that have been defined. On the basis of available literature about pathogenesis, we are suggesting the following appropriate therapeutic targets.

**Viral Spike Proteins**

Envelope surface proteins such as Gc and Gn appear like spikes or needle projections known as spike protein. These proteins are embedded in the lipid layer of the virus envelope. Spike protein is encoded by M segment of the viral RNA. Each spike protein is a hetero dimer of Gn and Gc which have a large globular domain, a transmembrane domain, and a cytoplasmic short tail. Virus has no matrix proteins so it was suggested that N protein directly interacts with the cytoplasmic tail of spike protein. Cytoplasmic tail domain has a highly conserved zinc finger motif which plays a key role in assembly and trafficking of the viral genome and proteins. Gn and Gc are processed in the Golgi complex by adding N terminal glycosylation. Somewhere, there is a transition phase of ER and Golgi body known as ERGIC ER Golgi complex where the assembly of the virion particles happens. The spike protein is very specific to the beta-3 integrin receptor present on the host endothelial, epithelial, macrophages, and dendritic cells which permits entry of the virion. Hence, conclusively, spike protein assembly and modification can be a good therapeutic target. This spike protein is lysed by the late endosome and processed for antigen presentation which is a key feature in virulence and activation of innate immune response takes place. Degraded Gn protein’s cytoplasmic tail interacts with the transcription factor of IFN beta (TRAF3) and starts replication within the host cell by inhibiting the viral elimination pathway of innate immune system [PDB ID in Table 3].

**Nucleocapsid Protein**

N protein is a major constituent of the viral RNA protein which found the bound with viral RNA. It consists of 433 amino acid residues approximated size of 50 kDa. It has a specific conserved sequence decides which segment is to be translated first. In the early infection stage, N protein expressed in the cytoplasm and innate immune system evoked against N protein. N protein plays a pivotal role in encapsidation and protection of viral RNA from degradation by the host endonucleases. Viral RNA has 23 ribonucleotide sequences at 5’ terminal which is complementary to self-terminal and has high affinity to the N protein. This conserved sequence is the binding site for RdRp which synthesizes the complementary or
positive-sense RNA and works as mRNA to synthesize the proteins.\textsuperscript{[46]}

N protein also binds with IRF3 (transcription) which is found in the cytoplasm and regulates the expression of MxA protein. IRF3 works as a transcription factor and translocates in the nucleus in the response of viral infection. MxA protein is the component of IFN which helps in antiviral activity of host cell. N protein efficiently binds with IRF3 and inhibits the translocation to nucleus of IRF3.\textsuperscript{[23]} Hence, viral infection is negatively correlated to the expression of MxA protein.\textsuperscript{[47]}

Table 3: Structures of potential prospective therapeutic targets with their properties and source [reference]

| Target name                  | PDB ID | Residue | Source | Structure       |
|------------------------------|--------|---------|--------|-----------------|
| Gn protein (spike protein)   | 5OPG   | 371     | [50]   |                 |
| Gc protein (spike protein)   | 5LK3   | 492     | [51]   |                 |
| N protein                   | 5FSG   | 698     | [52]   |                 |
| L protein (cap snatching protein) | 5IZE   | 360     | [53]   |                 |
| RdRp                         | 5AMR   | 2288    | [54]   |                 |

PDB=Protein Data Bank

As mentioned
above, the N protein in the pathogenesis represents as a bottleneck to control the replication of virus and further development of the critical condition [PDB ID in Table 3].

**RNA Dependent RNA Polymerase**

RdRp is an enzyme which works as transcriptase and replicase using viral RNA as a template. The presence of RdRp is essential for the viral replication and transcription. If RdRp inhibition is performed, the early expression of the N protein can be prevented. It also can work as an initial bottleneck for replication prevention [PDB ID in Table 3].

**Virus L-protein**

*Hantaan* virus has an adaptation tool known as an L-protein. It acts as a 5’ cap snatching endonuclease means it is responsible for degradation of host cytoplasmic mRNA at the 5’ end and releases the 5’ ended cap (methylation). This cap has to be transferred to the viral mRNA (used as a primer for RNA synthesis) and it protects from the attack of host cell endonuclease digestion [PDB ID in Table 3].

**Discussion**

The emerging of *Hantaan* virus cases is the next issue after the COVID-19, both are deadly viruses with comorbid conditions. *Hantaan* virus has epidemic nature in outbreak along seasonal variation regarding rural areas where raw material is most probably used manifested with a natural reservoir of *Hantaan* virus (rodents). It has a high mortality rate, so here we illustrated the pathogenesis and clinical features of the *Hantaan* virus along with potential therapeutic targets. These targets can be critical to control the pathogenesis, designing potential inhibitor or inducer small molecules. There are less clinical trial data which are available regards Asian countries except China and Korea. Further studies required to design the small molecules against potential therapeutic targets. However, there are many hurdles in the small molecule testing like unavailability of suitable animal models. There is no potential molecule is reported till date which cleared all the stages of drug development pipeline i.e. preclinical and clinical platforms. Only one ribavirin is reported which works efficiently in the *in vitro* and hamster model of *Hantaan* virus and SNV virus infection but lacks the efficacy in the patients presenting with *Hantaan* viral infection. Another treatment option is vaccination Green Cross Corporation (GCC) developed by ROK (HantavaxTM) Company • CEO • Specialty • Location • Homepage Green Cross Corp.Il-Sup, Huh Plasma derivatives, Recombinant Proteins, Vaccines, ETC & OTC products 107, Ilheon-ro, 30 beon-gil, Giheung-gu, Yongin, Korea, also lacks the efficacy to immune for the long time. Booster dose is to be required and dosing schedule has to be standardized. Major drawback of available treatment option is the adverse event and suitability is also a concern in the respect of vaccination.[49]

On the basis of available literature, we are suggesting potential therapeutic targets which might play a vital role in sustain the pathogenesis. Several analytical tools are available to prove the potentiality of the targets that are required, for example, network-based studies, Network-based analysis, human viral interactome analysis, etc., genome-wide association studies and network-based analysis might give a mechanistic insight into the pathogenesis and treatment options. Computational biology also can be an efficient tool to repurposing the drugs with known efficacy and target hit scores. There are many gray areas in pathogenesis which have to be clarified by further clinical research based.

**Limitations**

This study has limitations regarding availability of less clinical research studies’ data. *In vitro* and animal studies are available, but their results cannot be extrapolated to clinical setup.

**Conclusion**

After reviewing the available literature, we suggest that therapeutic targets like N protein interaction with the innate immune system and unbalancing between regulations of immune response lead to pathogenesis. Other targets might be spike proteins, cap snatching L-protein, and RdRp, these targets are essential for viral replication and in pathogenesis. Another symptomatic therapeutic target can be immune suppression like an antagonist of cytokine surges and booster of regulatory immunogens.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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