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Original Article MEDICAL BIOLOGY

Repurposing antiviral drugs targeting RNA viruses: A focus on the fusion protein of human metapneumovirus

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ABSTRACT

OBJECTIVE: Human metapneumovirus (HMPV) is a clinically important respiratory pathogen causing severe lower respiratory tract infections, particularly in infants, elderly individuals, and immunocompromised patients. Despite its substantial disease burden and global circulation, no HMPV-specific antiviral therapy has been approved to date. This unmet clinical need underscores the importance of identifying rapidly translatable therapeutic strategies. The present study aimed to identify potential inhibitors of the HMPV fusion (F) protein through a structure-based drug repurposing approach, leveraging the advantages of existing safety and pharmacokinetic profiles of approved antivirals.

METHODS: Thirteen antiviral agents predicted to interact with the HMPV F protein were selected from the DrugBank database. Comprehensive in silico molecular docking analyses were conducted to evaluate ligand–protein interactions, with Ribavirin used as a reference compound and positive control. Binding affinity values were quantitatively compared, using the Ribavirin binding energy (–6.2 kcal/mol) as a benchmark for relative performance.

RESULTS: The docking analyses revealed that multiple approved antiviral agents—namely Ledipasvir, Velpatasvir, Paritaprevir, Elbasvir, Pibrentasvir, Glecaprevir, Voxilaprevir, Ombitasvir, Grazoprevir, Dasabuvir, and Sofosbuvir—exhibited significantly higher binding affinities to the HMPV F protein than Ribavirin. These findings highlight the unexpected and mechanistically relevant interaction potential of hepatitis C virus–targeting antivirals with the HMPV fusion machinery, suggesting a novel avenue for therapeutic intervention.

CONCLUSION: This study provides compelling in silico evidence that drug repurposing of clinically approved antiviral agents may accelerate the development of effective HMPV-specific therapies. By targeting the highly conserved and functionally critical HMPV F protein, the identified candidate compounds offer strong translational potential and justify prioritization for experimental validation and preclinical investigation. Collectively, these results contribute to filling a critical therapeutic gap and support drug repurposing as a viable and time-efficient strategy to address emerging and neglected viral respiratory infections.

Keywords: Antiviral drugs; drug repurposing; human metapneumovirus; molecular docking.

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Respiratory viruses have become a significant global health threat, particularly in the context of urbanization, environmental degradation, and climate change. In developed countries, deaths from respiratory virus infections are rare among healthy individuals. However, in less developed countries, child mortality remains high, with approximately 5 million children under the age of five dying from respiratory viral infections worldwide each year.

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The widespread prevalence of these infections renders people of all ages susceptible to respiratory viral diseases. Nevertheless, children are, on average, two to three times more likely to contract an infection than adults. Consequently, respiratory viruses pose a significant health threat to young children, the elderly, and individuals with weakened immune systems [1]. Most viruses spread through direct contact or respiratory droplets, but some can also be transmitted via aerosols. Viruses that primarily infect the respiratory tract include influenza viruses, adenoviruses, parainfluenza viruses, respiratory syncytial virus (RSV), coronaviruses, human metapneumovirus (hMPV), rhinoviruses, and enteroviruses. Influenza, parainfluenza, hMPV, and RSV typically cause epidemics, whereas adenoviruses, coronaviruses, and rhinoviruses are generally endemic. Other viruses that can cause respiratory tract diseases, particularly in immunocompromised individuals, include measles virus, varicella-zoster virus (VZV), herpes simplex virus (HSV), and cytomegalovirus (CMV) [2]. Especially after the COVID-19 pandemic that began in 2019, there is widespread concern about the emergence of new epidemics. The increasing number of human metapneumovirus (hMPV) cases since early 2025 has heightened public anxiety. First identified in 2001, hMPV has rapidly spread across continents, causing significant morbidity and mortality, particularly among young children, the elderly, and immuno-compromised individuals. In countries such as China, where densely populated urban areas and pollution exacerbate respiratory illnesses, the prevalence of hMPV is rising, making it an increasingly pressing global health concern [3]. hMPV belongs to the same virus family as respiratory syncytial virus (RSV), a seasonal virus that causes colds and lung infections [4]. Respiratory viruses, including influenza viruses, RSV, SARS-CoV-2, rhinoviruses, and adenoviruses, have a significant impact on global health. Currently, the only respiratory viruses with approved antiviral treatments for clinical use are RSV, influenza, and SARS-CoV-2. In contrast, other respiratory viruses lack specific antiviral therapies and rely solely on supportive care or investigational treatments, highlighting a critical gap in antiviral drug development.

The initial step in the human metapneumovirus (hMPV) replication cycle involves attachment to host cells, specifically the epithelial cells of the respiratory tract, via the G glycoprotein. This G protein possesses an unprocessed signal peptide and a hydrophobic region that serves as a membrane anchor to facilitate attachment. However, recombinant viruses lacking the G protein are still capable of replicating both in vitro and in vivo, suggesting that G protein-mediated attachment is not essential for the progression of the replication cycle. Following attachment, the next critical step is the fusion of viral and host cell membranes, a process likely mediated by the F glycoprotein. While this fusion mechanism involves conformational changes in the F protein, similar to other members of the Paramyxoviridae family, hMPV fusion is not dependent on the G protein. This observation aligns with the notion that the G protein is dispensable for the downstream steps of the hMPV replication cycle [5]. The F protein of human metapneumovirus (hMPV) plays a critical role in antigenicity during viral entry. Members of the Pneumoviridae family possess fusion (F) proteins that, although sharing limited sequence identity, exhibit conserved structural features. These F proteins are synthesized as inactive precursors, designated as F0, which are subsequently cleaved by host cell proteases into two subunits: F1, constituting the C-terminal subunit, and F2, forming the N-terminal subunit. The resulting active fusion protein, in conjunction with the attachment glycoprotein, mediates the fusion of the viral envelope with the host cell membrane, facilitating viral entry.

Highlight key points

- Human metapneumovirus (HMPV) is a significant respiratory pathogen with no approved targeted antiviral therapy.
- Drug repurposing of 13 antiviral agents identified several candidates, including Ledipasvir and Sofosbuvir, with higher binding affinity to the HMPV F protein than Ribavirin.
- Repurposed antivirals with strong binding affinity represent promising candidates for further experimental and clinical evaluation against HMPV.

Drug repurposing is a branch of drug discovery that focuses on identifying alternative therapeutic applications for regulatory-approved drugs or compounds in clinical trials with established pharmacological and safety profiles. This approach significantly accelerates drug development timelines compared to novo drug design. In the context of pandemic situations, three primary strategies for drug repurposing have been identified: (1) investigating existing broad-spectrum antiviral agents; (2) screening molecular databases of approved or clinical-stage compounds for molecules with potential antiviral activity; and (3) utilizing artificial intelligence (AI) and network-based technologies to analyze virus-host

interactions and identify potential repurposing candidates that target these interactions [6]. Drug repurposing holds particular value in time-critical scenarios such as pandemics, where healthcare systems are burdened with patients who lack effective treatment options.

This study aims to provide effective, rapidly applicable, and evidence-based therapeutic options against human Metapneumovirus (hMPV), which has re-emerged with reported cases in 2025. In this context, the study focuses on repurposing FDA-approved antiviral agents to address a significant public health gap. By identifying potential therapeutic candidates, this study aims to enable early intervention against hMPV and prevent a recurrence of a global health crisis similar to the COVID-19 pandemic experienced in 2020.

MATERIALS AND METHODS

Ligand and Receptor Selection

From the DrugBank database [7], 13 drugs that have been approved by the FDA for use against RNA viruses and are used in the United States, European, and Canadian markets were identified from among 2182 antiviral drugs. These drugs are listed in Table 1.

This study will investigate the fusion (F) protein, which plays a critical role in the entry of hMPV into host cells. For this purpose, the three-dimensional structure with PDB ID 7SEJ, obtained from the Protein Data Bank (PDB), was utilized [8].

Molecular Docking Analysis

Water molecules were removed from the 7SEJ structure, and hydrogen atoms were added to prepare the protein for molecular docking studies. The finalized structure was saved in PDB format for subsequent analyses. The three-dimensional structures of 13 antiviral drugs, identified from the DrugBank database, were retrieved from the PubChem database. Molecular docking simulations and visualization were performed using UCSF Chimera [9]. Protein-ligand interaction analyses were conducted using Biovia Discovery Studio [10].

Druggability Prediction Analysis

Drugability prediction analysis is an analysis performed to determine which regions of a protein are druggable. This analysis was performed using the DoGSiteScorer algorithm of the ProteinPlus [11] web tool.

TABLE 1. Antiviral drugs

Drug name	Pubchem CID
Ledipasvir	67505836
Velpatasvir	67683363
Paritaprevir	45110509
Elbasvir	71661251
Pibrentasvir	58031952
Glecaprevir	66828839
Voxilaprevir	89921642
Ombitasvir	54767916
Grazoprevir	44603531
Dasabuvir	56640146
Sofosbuvir	45375808
Ribavirin	37542
Rimantadine	5071

Pubchem CID: PubChem compound identifier.

RESULTS

This study commenced with a comprehensive drug repurposing investigation encompassing 2182 FDA-approved small-molecule drugs, with the human metapneumovirus (hMPV) fusion (F) protein selected as the therapeutic target. Using a filtering protocol based on the DrugBank database, we systematically screened the dataset to identify FDA-approved agents marketed in the United States, Europe, and Canada with reported activity against RNA viruses. This process yielded 13 candidate compounds, which were subsequently evaluated for their binding affinity toward the hMPV F protein through molecular docking analyses.

To establish a reference point, Ribavirin was employed as a positive control, producing a binding affinity score of –6.2 kcal/mol. A threshold was applied such that compounds exhibiting stronger binding affinities (≤–7.0 kcal/mol) were considered potential inhibitors of the fusion protein. Based on this criterion, 11 compounds were identified as promising candidates, ranked from highest to lowest binding affinity: Ledipasvir, Velpatasvir, Paritaprevir, Elbasvir, Pibrentasvir, Glecaprevir, Voxilaprevir, Ombitasvir, Grazoprevir, Dasabuvir, and Sofosbuvir (Fig. 1).

Drug-targetability predictions evaluate the capacity of specific protein binding sites to accommodate drug-

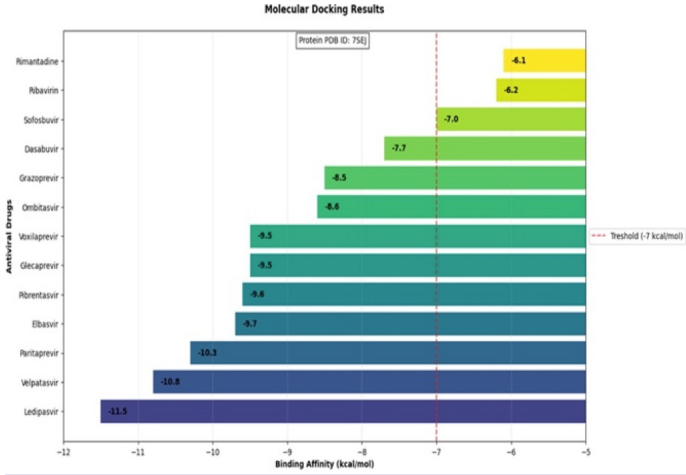


FIGURE 1. Molecular docking results.

like compounds. When integrated with knowledge of the target's role in disease pathology, such predictions can be applied to prioritize therapeutic targets for drug discovery. In recent years, substantial progress has been made in elucidating the molecular determinants of druggability, assembling datasets of targets with varying druggability profiles, and developing diverse computational approaches for predictive assessment. Collectively, these advances have enhanced the prospects of target-based therapeutic development.

In the present study, binding sites of the hMPV fusion protein with druggability scores exceeding 80% were identified (Fig. 2). Molecular docking visualizations further demonstrated that the binding regions of candidate compounds overlapped with protein sites scoring above the 80% druggability threshold (Fig. 3–5).

DISCUSSION

Acute lower respiratory tract infections (ALRTIs) remain the leading cause of morbidity and mortality attributable to infectious diseases worldwide. Both bacterial and viral pathogens play a predominant role in these infections, with viral etiologies frequently manifesting as pneumonia, bronchitis, or bronchiolitis. However, identification of the causative agent in respiratory tract infections often presents a challenge; studies indicate that no pathogen can be detected in approximately 40–50% of ALRTI cases. In recent years, intensified research into the microbial etiology of respiratory infections has led to the discovery of novel viruses beyond the spectrum of classical respiratory pathogens. Among these, human metapneumovirus (hMPV), first identified in 2001, has

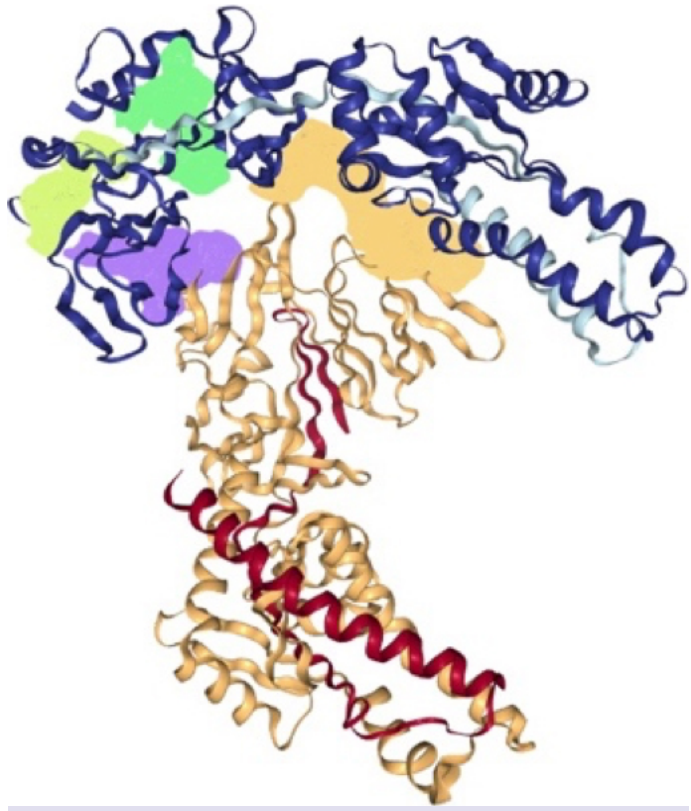


FIGURE 2. Druggability prediction result.

emerged as a clinically significant pathogen. hMPV is now recognized as a major cause of respiratory disease worldwide, particularly in children, the elderly, and immunocompromised individuals, and its seasonal circulation, potential for severe disease, and lack of targeted antiviral therapies highlight its importance as a global public health concern [3, 12].

Human metapneumovirus (HMPV) is a major respiratory pathogen that predominantly affects children, the elderly, and immunocompromised individuals. Despite its considerable clinical burden, no antiviral therapy specifically targeting HMPV has been approved to date. The virus's seasonal re-emergence, potential to cause severe lower respiratory tract disease, and ability to evade host immune responses have elevated it from a seasonal pathogen to a pressing global public health threat requiring urgent intervention. The HMPV fusion (F) protein represents a particularly attractive target for antiviral drug development due to its essential role in multiple stages of the viral life cycle. As a key determinant of viral entry, the F protein mediates (i) recognition of host cell surface receptors, (ii) fusion of the viral envelope with host cell membranes, and (iii) cell–cell fusion leading to syncytium formation. Inhibition of these F protein–

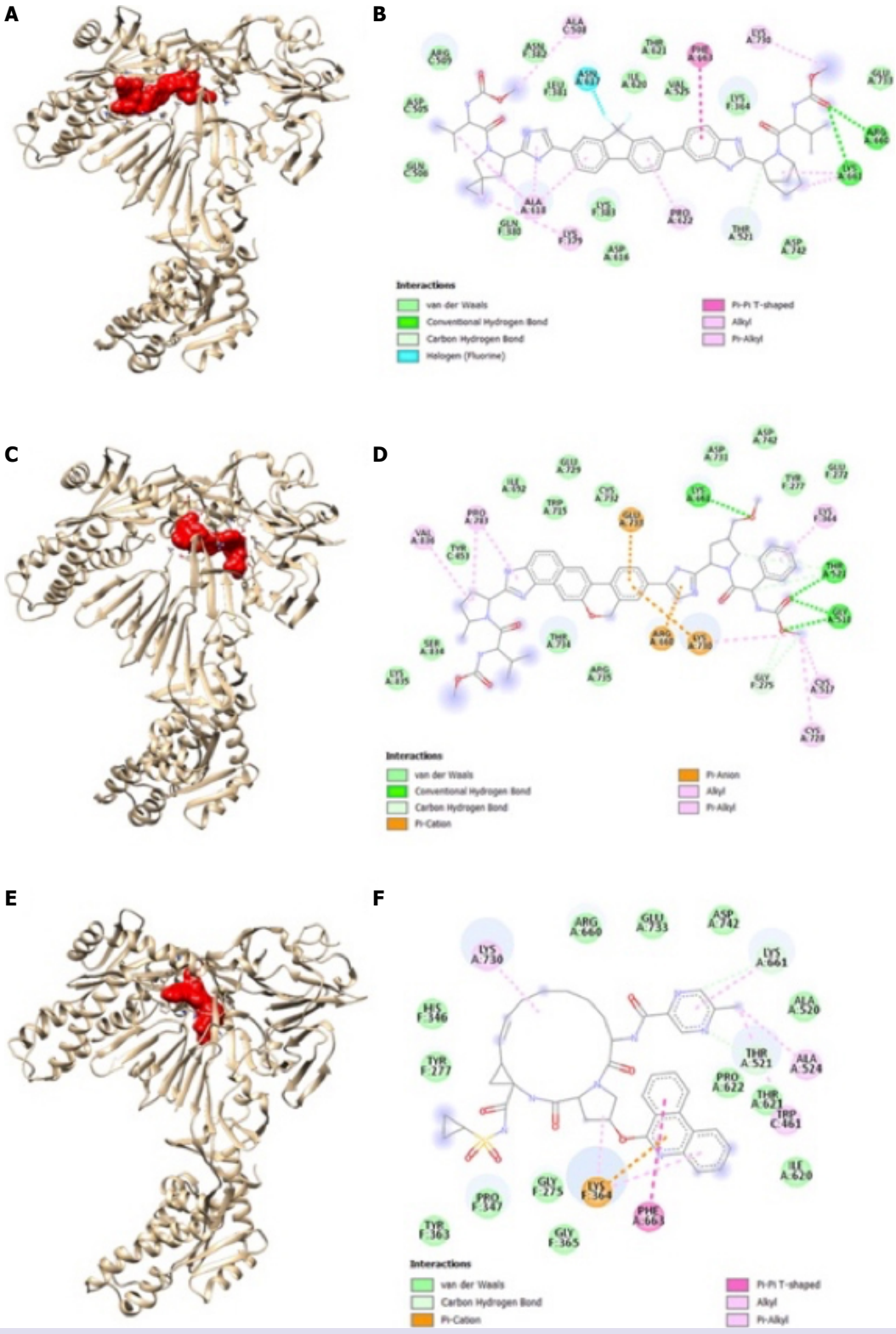


FIGURE 3. The interaction of Ledipasvir **(A, B)**, Velpatasvir **(C, D)**, Paritaprevir **(E, F)** drugs with HMPV fusion protein.

mediated processes is expected to impair viral entry and spread, thereby reducing HMPV infection and improving clinical outcomes [13].

Like other viruses, HMPV is a simple entity composed of nucleic acid (RNA) enclosed within a protein coat and lacks the machinery required for independent replication.

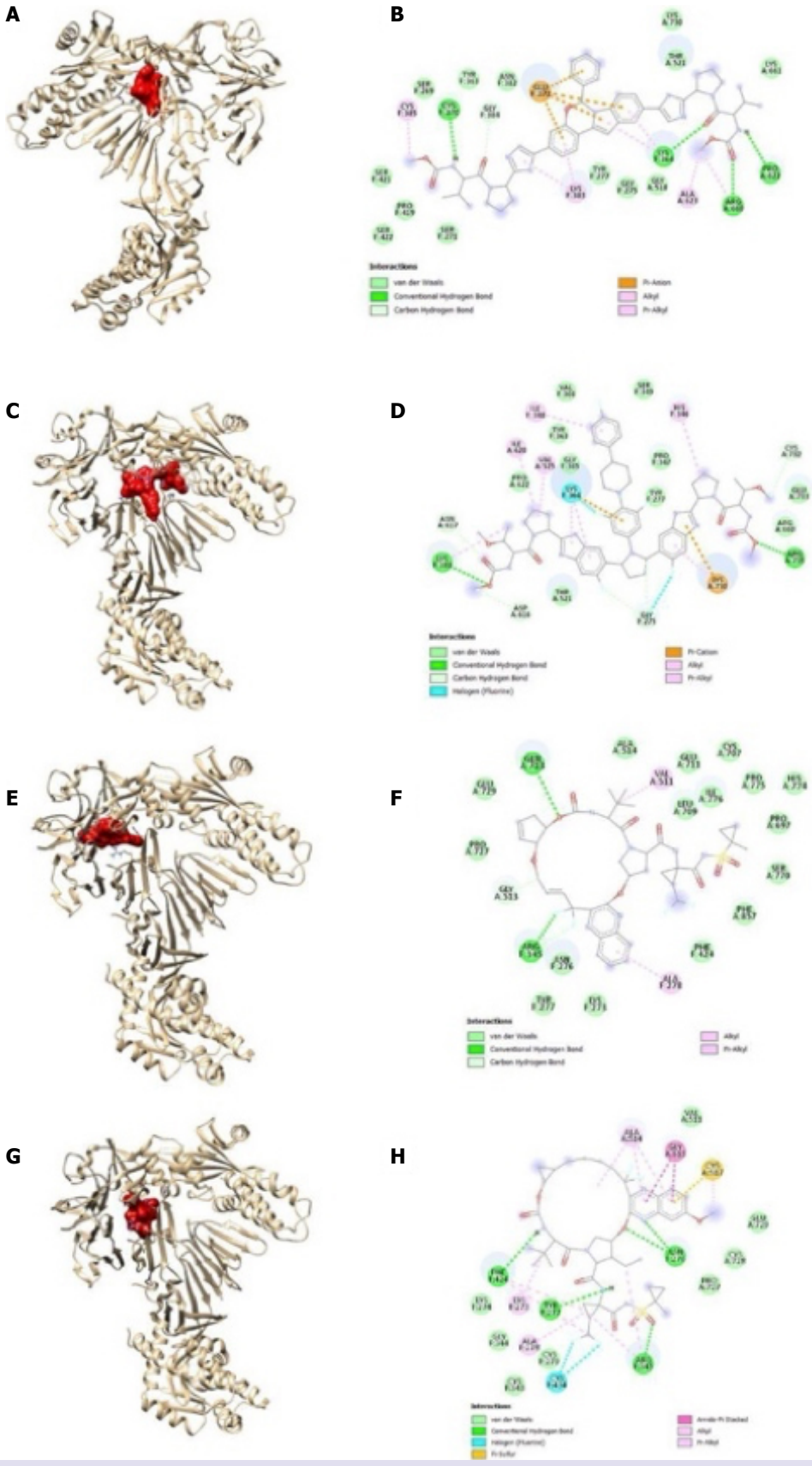


Figure 4. The interaction of Elbasvir **(A, B)**, Pibrentasvir **(C, D)**, Glecaprevir **(E, F)**, Voxilaprevir **(G, H)** drugs with HMPV fusion protein.

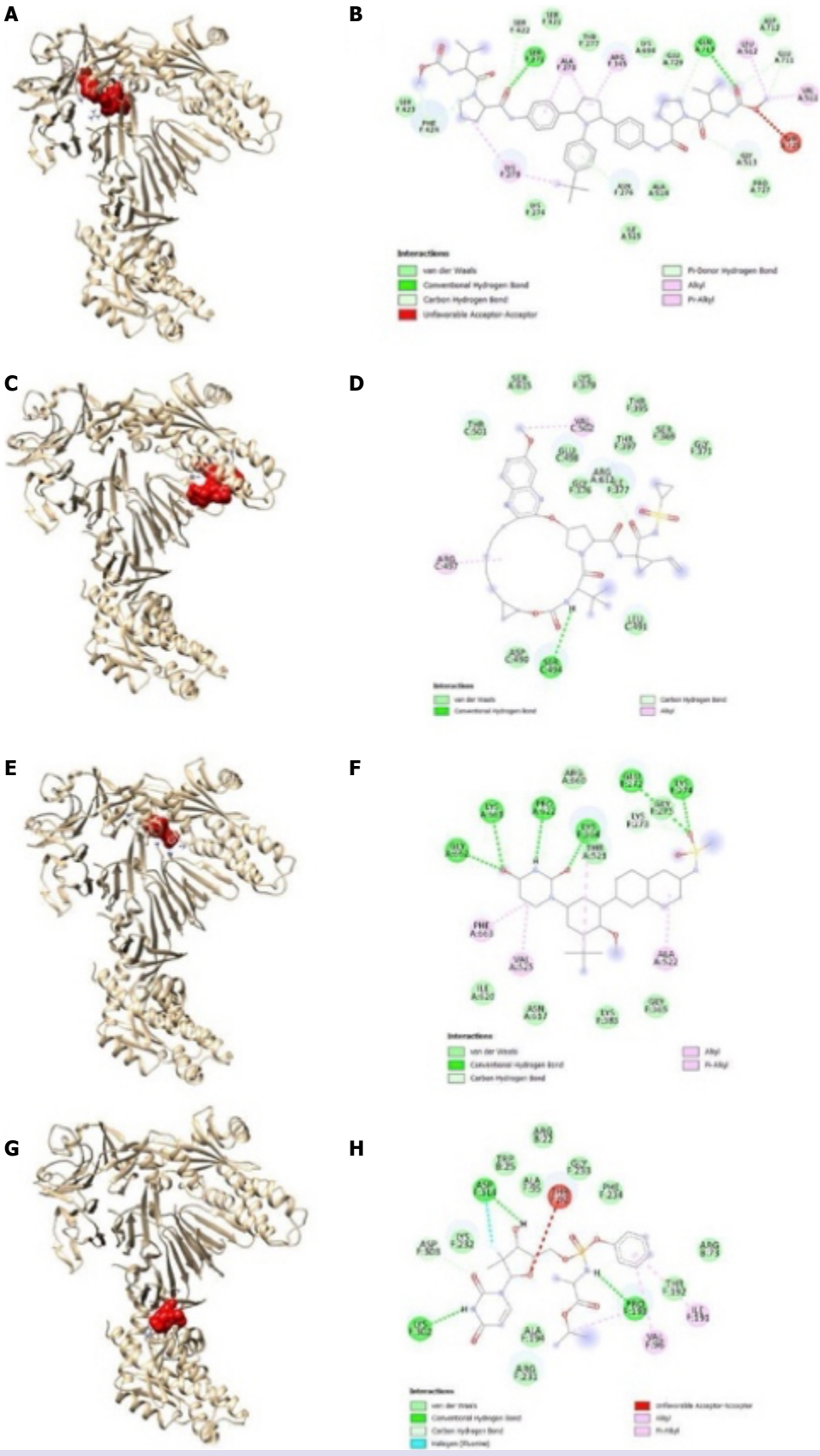


FIGURE 5. Interaction of Ombitasvir **(A, B)**, Grazoprevir **(C, D)**, Dasabuvir **(E, F)**, Sofosbuvir **(G, H)** drugs with HMPV fusion protein.

Viral propagation depends on hijacking host cellular processes to generate progeny virions, often culminating in host cell death. Viruses are estimated to outnumber bacteria by an order of magnitude in nature and can only complete their replication cycle within living cells. Owing to their dependence on host cellular machinery, viruses do not produce the enzymes required for replication, making them refractory to antibiotics; only antiviral drugs can be employed as therapeutic agents. The development of new antiviral drugs, however, is an arduous and resource-intensive process, typically requiring more than a decade and investment in the range of 1–2 billion USD. Moreover, most available antivirals are designed to target specific viral proteins, a strategy that is increasingly challenged by high development costs and the emergence of drug resistance [14].

Drug repurposing, defined as the application of an approved drug to a novel disease indication, has emerged as a widely adopted strategy to reduce the cost and time associated with drug development while offering therapeutic solutions for conditions with limited or no treatment options. In the context of viral diseases, drug repurposing often involves systematic screening of small-molecule libraries coupled with computer-aided approaches to evaluate the potential efficacy of existing compounds against viral targets. The primary advantage of this strategy lies in its ability to accelerate translation into clinical research, as repurposed agents already possess established safety and pharmacokinetic profiles, thereby facilitating rapid deployment in clinical settings or for humanitarian use during public health emergencies. Candidate drugs are typically identified by screening libraries of molecules with well-characterized biological activity, including FDA-approved or investigational compounds as well as naturally occurring bioactive agents [15].

Drug repurposing is a strategic approach that aims to evaluate approved pharmaceutical agents for new therapeutic purposes against different pathogens. It saves time and resources compared to traditional drug discovery processes, especially for rapidly evolving pathogens such as RNA viruses. In this study, the therapeutic potential of direct-acting antivirals (DAAs) and nucleoside analogues used in Hepatitis C virus (HCV) treatment was investigated in Human Metapneumovirus (hMPV) infections. Drug selection was performed by screening the DrugBank database for molecules reported to be effective against RNA viruses, and Ledipasvir, Velpatasvir, Pibrentasvir, Glecaprevir, Voxilaprevir, Ombitasvir, Grazoprevir, Elbasvir, Paritaprevir, Dasabuvir, Sofosbuvir, Ribavirin, and Rimantadine were included in the study. The primary pharmacological targets of these antiviral agents are viral proteins within the hepatitis C virus (HCV) replication complex, including NS3 protease, NS5A, and NS5B RNA polymerase. However, silico docking analyses suggest that these compounds may also exhibit binding affinity for the human metapneumovirus (hMPV) fusion (F) protein, a key mediator of viral entry into host cells. Although these predicted molecular interactions do not establish a direct inhibitory mechanism, they provide a theoretical rationale for further investigation of these agents in the context of hMPV infection. Ribavirin, a broad-spectrum antiviral that has been evaluated both clinically and experimentally against various RNA viruses, including hMPV, was used as positive control in this study. In a previous experimental model, BALB/c mice infected with hMPV received intraperitoneal Ribavirin at 40 mg/kg twice daily, corticosterone at 0.2 mg/mL (aqueous solution), or a combination of both agents. Ribavirin treatment significantly suppressed viral replication in the lungs and reduced pulmonary inflammation by the fifth day post-infection, whereas glucocorticoid administration resulted only in modest reductions in alveolar and interstitial inflammation relative to untreated controls. Studies employing various animal models have demonstrated that Ribavirin possesses a broad-spectrum antiviral activity against paramyxoviruses, including human respiratory syncytial virus (hRSV), mouse pneumonia virus, and measles virus. In addition, in vitro experiments using LLC-MK2 cell lines have shown that Ribavirin exhibits comparable antiviral efficacy against both hRSV and human metapneumovirus (hMPV). Beyond Ribavirin, there is currently no published evidence regarding the antiviral activity of Ledipasvir, Velpatasvir, Pibrentasvir, Glecaprevir, Voxilaprevir, Ombitasvir, Grazoprevir, Elbasvir, Paritaprevir, Dasabuvir, and Sofosbuvir against hMPV. Consequently, further in vitro investigations are warranted to evaluate the potential of these RNA virus-targeting drugs against hMPV [16, 17].

Conclusion

Ribavirin has previously been investigated for its inhibitory activity against hMPV and was employed as a positive control in the present study.

- All 13 antiviral compounds included in the molecular docking analysis demonstrated binding to druggable sites on the hMPV fusion protein.
- Molecular docking of Ribavirin yielded a binding affinity of –6.2 kcal/mol. Eleven antiviral agents exhibiting higher binding affinity than Ribavirin—namely, Ledi-

pasvir, Velpatasvir, Pibrentasvir, Glecaprevir, Voxilaprevir, Ombitasvir, Grazoprevir, Elbasvir, Paritaprevir, Dasabuvir, and Sofosbuvir—may represent promising candidates for inhibition of the fusion protein.

- To date, no in vitro studies have investigated the inhibitory potential of these compounds against the hMPV fusion protein. Consequently, further experimental studies, including both in vitro and in vivo evaluations, are warranted to address this knowledge gap.

In summary, human metapneumovirus (hMPV) represents a significant global health concern due to its high morbidity, particularly among children, the elderly, and immunocompromised individuals, and the absence of approved antiviral therapies. The hMPV fusion (F) protein plays a central role in viral entry and propagation, making it a promising target for therapeutic intervention. Drug repurposing approaches, combined with silico molecular docking analyses, provide an efficient strategy to identify potential antiviral agents capable of inhibiting the F protein. This study highlights several FDA-approved antivirals with predicted high binding affinity to the F protein, offering a foundation for future experimental validation. The findings underscore the importance of further in vitro and in vivo investigations to assess the therapeutic potential of these compounds and to advance the development of effective interventions against hMPV infection.

Ethics Committee Approval: The study did not require ethical approval.

Informed Consent: This study is entirely in silico and does not involve human participants, patient samples, or animal experiments. Therefore, ethics committee approval and informed consent were not required.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Authorship Contributions: Concept – MA; Design – MA; Supervision – OTY; Data collection and/or processing – MA, OTY; Analysis and/or interpretation – MA, OTY; Literature search – MA, OTY; Writing – MA, OTY; Critical review –OTY.

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