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Exploring the Role of Host-Pathogen Interaction in Airborne Disease Susceptibility

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***Abstract* - The capacity of airborne infectious illnesses to generate broad epidemics and their high rates of transmission make them a constant concern to public health around the world. Serious morbidity and mortality can result from these illnesses, which are mostly transmitted by aerosols and respiratory droplets. To create efficient treatment and prevention plans, it is essential to comprehend the molecular mechanisms underpinning host-pathogen interactions. Four main airborne bacterial pathogens—Neisseria meningitidis, Yersinia pestis, Legionella pneumophila, and Streptococcus pneumoniae—and their interactions with host proteins are the subject of this study. We investigated the binding affinities of important virulence agents, including adhesins, toxins, and immune evasion proteins, with host receptors using molecular docking analyses. The docking results highlighted the molecular underpinnings of disease by revealing robust connections that promote bacterial adherence, immune system evasion, and intracellular survival. Human epithelial cell receptors and pneumococcal adhesins have high-affinity interactions, indicating possible targets for preventing bacterial colonization. Similar to this, Yersinia pestis uses its Type III Secretion System (T3SS) to control immunological responses, whereas Neisseria meningitidis uses host factor binding proteins to penetrate the blood-brain barrier. Legionella pneumophila demonstrates the pathogen's versatility in host invasion by taking advantage of the host's cellular machinery to establish a replicative niche.**

These discoveries open the door for innovative therapeutic approaches by offering vital insights into the molecular underpinnings of airborne illness susceptibility. Using monoclonal antibodies, small-molecule inhibitors, or vaccine-based strategies to target these interactions may prevent bacterial colonization and illness. Furthermore, improvements in ventilation, public health initiatives, and air filtration technology all contribute to the prevention of disease. Our capacity to create efficient antibacterial methods will be improved by combining computational docking research with experimental validation. This study advances our knowledge of the dynamics between airborne pathogens and hosts and encourages the creation of novel strategies to fight infectious diseases.

Keywords: Airborne, Docking, Interaction, Pathogen, Susceptibility, Transmission, Host.

I. INTRODUCTION

Because of their high rates of morbidity and mortality and ease of transmission, airborne infectious diseases continue to pose a serious threat to public health. These illnesses can infect people through inhalation or contact with infected surfaces, and they are mainly disseminated by respiratory droplets released when coughing, sneezing, or talking [1]. Several variables, such as the pathogen's virulence, the host's immune system, and the surrounding environment, affect how severe an airborne illness is [2]. The susceptibility and course of disease are largely determined by host-pathogen interactions. The pathogens that cause airborne illnesses have developed complex defense systems to get past the host's defenses and spread infection. These consist of immune evasion, virulence factor secretion, host cell attachment, and host signaling pathway modification [3]. A pathogen's capacity to infect and spread within a host is determined by its capacity to engage with particular host receptors. To attach to epithelial cells and avoid immune responses, *Streptococcus pneumoniae*, the causative agent of pneumonia, uses pneumolysin and choline-binding proteins [4], while Neisseria meningitidis, the causative agent of meningitis, uses adhesins such as NadA to interact with endothelial cells and gain access to the bloodstream and central nervous system. Creating successful treatment interventions requires an understanding of host-pathogen interactions. We may examine these interactions at the atomic level using molecular docking experiments, which give us information about the binding affinities of pathogenic proteins and host ligands [5]. Potential pharmacological targets to prevent pathogen colonization and infection can be investigated by identifying important residues implicated in these interactions. Drug discovery has made extensive use of computational docking, especially in the study of bacterial infections and the development of inhibitors for important virulence factors [6]. Pneumonia, scarlet fever,

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meningitis, Pneumonia, and Legionnaires' disease are the five main bacterial illnesses that are spread through the air, and they are being studied here. Bacterial pathogens with unique virulence mechanisms that interact with host proteins to promote infection are the cause of each of these illnesses. Our goal is to clarify how these interactions contribute to disease vulnerability by molecularly docking important bacterial proteins with their corresponding host ligands. In addition to improving our knowledge of host-pathogen dynamics, the results of this investigation will help identify new pharmaceutical targets for the treatment of these illnesses.

II. HOST-PATHOGEN INTERACTIONS IN AIRBORNE DISEASE SUSCEPTIBILITY

A major global health burden is posed by airborne illnesses, which frequently result in pandemics and large outbreaks. Pathogens' capacity to cause infection is contingent upon their interactions with the host's immune system, the mode of transmission, and the host's physiological and genetic characteristics. Developing successful preventative and treatment plans requires an understanding of these host-pathogen interactions. [7].

Pathogen Strategies in Airborne Transmission: Mycobacterium tuberculosis, influenza viruses, and SARS-CoV-2 are examples of airborne pathogens that have developed several tactics to guarantee effective infection and transmission. These tactics include using host cellular machinery, adhering to the respiratory epithelium, evading the immune system, and aerosolization. [8]. To remain infectious during airborne transmission, pathogens must withstand environmental stress and desiccation. For instance, the waxy cell wall of tuberculosis bacteria allows for extended survival in aerosols and protects against dehydration.

Host Factors Influencing Susceptibility: Environmental, immune, and genetic variables all affect a host's vulnerability to airborne illnesses. A person's capacity to identify and eliminate infections may be impacted by genetic variations in immune response genes, such as those that encode major histocompatibility complex (MHC) molecules and Toll-like receptors (TLRs) [9].The first line of defense against airborne infections is mostly dependent on innate immunity. The respiratory epithelium traps and neutralizes infections by secreting mucus and antimicrobial peptides, functioning as a physical and immunological barrier. Smoking, air pollution, and long-term respiratory conditions, however, can weaken this barrier and make people more vulnerable. For long-term protection, adaptive immunity—specifically T-cell responses and antibody production—is crucial, as demonstrated by vaccine-induced immunity against COVID-19 and influenza. [10].

Immune Evasion and Pathogen Adaptation: Effective airborne infections have evolved complex defenses against the host's immune system. For example, influenza viruses can evade pre-existing immunity due to recurrent antigenic drift and shift. [11]. To inhibit antiviral responses, SARS-CoV-2 uses a variety of tactics, including inhibiting the expression of the major histocompatibility complex and interfering with interferon signaling. Certain bacteria, like Mycobacterium tuberculosis, can survive for a long time inside the host by preventing phagosome-lysosome fusion within macrophages. [12]. Treatment is made more difficult by this intracellular persistence, which also leads to latent infections that may reawaken in immune suppressed environments.

Implications for Public Health and Disease Control: Designing successful public health interventions requires an understanding of host-pathogen interactions in airborne illnesses. Disease transmission can be reduced by vaccination programs, better ventilation, and respiratory protection. Furthermore, new treatments that target host-pathogen interactions, like immune-modulating medications, may improve infection resistance. [13].The development of broad-spectrum vaccinations, the identification of genetic and molecular factors of vulnerability, and the enhancement of predictive models of airborne disease dissemination should be the main goals of future research. Preventing future pandemics will also require improved surveillance and early identification of new diseases. An important factor in establishing a person's susceptibility to airborne infections is host-pathogen interactions. Disease outcomes are influenced by host factors such as genetic diversity, immunological status, and environmental settings, whereas viruses use a variety of strategies to ensure transmission and immune evasion.

III. MECHANISTIC INSIGHTS AND SUSCEPTIBILITY

Examining the molecular connections in further detail demonstrates that pathogen virulence factors can modify host cellular responses, changing immunological signaling and airway epithelial integrity. In addition to influencing the initial infection, these interactions may trigger a series of immunological responses that worsen the severity of the illness. Novel treatment targets to lower susceptibility and transmission have been made possible by the discovery of the interactions between certain pathogen proteins and host receptors by the use of advanced imaging and genomic approaches. Designing interventions that strengthen host defences and lessen the burden of airborne illnesses on public health requires an understanding of mechanisms.

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IV. MOLECULAR DOCKING ANALYSIS

Selection of Pathogens and Proteins

This study involves four bacterial pathogens responsible for the given airborne diseases:

1. *Streptococcus pneumoniae*- Pneumonia
2. *Neisseria meningitidis*-Meningitis
3. *Yersinia pestis*- Pneumonic Plague
4. *Legionella pneumophila*-Legionnaires' Disease

For each pathogen, the primary virulence factor or surface protein involved in host interaction was selected for molecular docking. [14]

V. BIOINFORMATICS TOOLS AND TECHNIQUES

UniProt: The Universal Protein Resource, or UniProt, is a comprehensive database that provides comprehensive details on protein sequences and functional annotations. Researchers can access experimentally verified protein structures for a variety of purposes, including molecular docking studies, thanks to cross-references to structural databases such as the Protein Data Bank (PDB), even though UniProt does not directly host protein structure data. [15]. UniProt is used to get protein structures appropriate for docking experiments by doing the following:

Identify the Target Protein: To find the target protein, searching is performed on the UniProt website for the desired protein by name, gene identification, or UniProt accession number. Navigate to Structural Data: Navigate to the "Structure" section of the chosen protein's UniProt entry. In this case, UniProt offers cross-references to matching PDB entries that include protein structures that have been experimentally resolved.

Access PDB Entries: 3D coordinates of the protein structures can be downloaded in formats like PDB or mmCIF by clicking on the PDB links that are supplied. Docking simulations require these files to function.

Integrating UniProt Data with Docking Tools: Several molecular modeling and docking tools are made easier to use by UniProt's interaction with structural databases:

Homology Modelling: Tools such as SWISS-MODEL can use UniProt sequences to predict 3D structures based on homologous proteins in the absence of an experimental structure [16].

Molecular Dynamic Simulations: Protein dynamics can be studied by simulations using programs like GROMACS or AMBER that are informed by UniProt annotations, including post-translational changes [17].

Ligand Docking: With structural data obtained via UniProt, docking programs like AutoDock or Vina can predict how small molecules interact with the protein, aiding in drug discovery efforts. [18].

By connecting structural data from databases such as the PDB with protein sequences and functional information, UniProt acts as a crucial resource. For scientists performing molecular docking studies, this integration is crucial because it offers the structural templates and annotations required to accurately predict protein-ligand interactions.

PubChem: The National Center for Biotechnology Information (NCBI) is the maintainer of the publicly available chemical database PubChem [19]. It functions as an extensive collection of chemical molecules, encompassing ligands, bioactive molecules, and tiny compounds. To comprehend biological interactions at the molecular level, researchers use PubChem for cheminformatics, drug discovery, and molecular docking investigations.

Downloading Ligand Structures from PubChem: To research protein interactions in particular diseases, PubChem offers a comprehensive repository of ligand structures. Using PubChem's interface, researchers can look for ligands by molecular weight, chemical characteristics, and biological activity. [20]. Ligand structures are available for download in several forms that are compatible with molecular docking software and computational tools, such as **SDF (Structure Data File), SMILES (Simplified Molecular Input Line Entry System),** and **PDB (Protein Data Bank).**

Ligand Protein Interaction Studies: For the development of new drugs and treatments, an understanding of ligand-protein interactions is essential. **Researchers use computational tools like AutoDock, Schrödinger, or Molecular Operating Environment (MOE)** to undertake molecular docking experiments to retrieve protein structures of particular diseases from databases like the **Protein Data Bank (PDB)**[21]. Ligands retrieved from PubChem are examined for their binding affinity, molecular docking scores, and pharmacokinetic features.

Applications in Pathogen Research: PubChem ligands are widely used to identify potential inhibitors against viral, bacterial, and fungal proteins. For instance:

COVID-19 Research: To create antiviral medications, ligands that target the SARS-CoV-2 major protease (Mpro) have been investigated [22].

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Research on Tuberculosis: Ligands that interact with the enzymes of Mycobacterium tuberculosis are examined for potential novel antibiotics [23].

Malaria Research: Antimalarial medication development is aided by small compounds that target Plasmodium falciparum proteins [24].A priceless tool for obtaining ligand structures to investigate protein interactions in infections is PubChem. Researchers can speed up drug development and help create tailored treatments for infectious diseases by combining PubChem's data with computational modeling and docking studies.

CB Dock2: In structural biology and drug development, molecular docking is a crucial computational approach that enables scientists to forecast how ligands and proteins will interact. An extremely effective and user-friendly, sophisticated docking tool, CB-Dock2 automates cavity detection and docking. Because it can predict the affinities and patterns of binding of small molecules within protein active sites, protein-ligand docking is essential to structure-based drug design. [25]. Manual binding site selection is frequently necessary for traditional docking technologies, which can lead to bias and inefficiencies. [26]. By adding flexible docking techniques and automatic binding site recognition, CB-Dock2, an enhanced version of CB-Dock, gets around these issues. [27]. This online application improves docking prediction accuracy, making it appropriate for both inexperienced and seasoned users.

VI. MATERIALS AND METHODS

CB-Dock2 functions through a streamlined workflow:

- **Structure Preparation:** Protein and ligand structures are uploaded by the user in PDB or MOL2 formats to prepare the structure.
- **Cavity Detection:** The program uses curvature-based cavity identification to automatically find possible binding pockets.
- **Docking Procedure:** To optimize the orientation and binding conformation of the ligand, CB-Dock2 uses AutoDock Vina for docking [28].
- **Result Analysis:** The tool offers rankings of possible binding sites, binding scores, and interaction visualizations.

A chosen ligand was docked to its target protein in a docking experiment utilizing CB-Dock2. In addition to providing docking scores that closely matched experimental data, the tool was successful in identifying the most likely binding site. Reliability was increased by the automated cavity detection method, which removed the need for prior knowledge of active locations. [27]. When it came to cavity detection and docking performance, CB-Dock2 outperformed other docking solutions like AutoDock and SwissDock in terms of efficiency and accuracy. [29]. CB-Dock2 improves the effectiveness of drug discovery processes by providing a simple and precise method for molecular docking. It is an effective tool for structural biology and computational chemistry researchers because of its automatic cavity detection and connection with AutoDock Vina.

VII. RESULTS

***Streptococcus pneumoniae* Docking Scores:**

Protein Name	Ligand Name	Docking Score
Serine/Threonine Protein Kinase	Staurosporine	-9.1
Protein Phosphatase PhpP	Okadaic acid	-9.2
Immunoglobulin A1 Protease	PMSF	-5.3
Pullulanase A	Acarbose	-9.1

- A docking score of -9.1 indicates that the Serine/Threonine Protein Kinase has a high binding affinity for Staurosporine. The association between staurosporine, a well-known kinase inhibitor, and this kinase suggests possible inhibition, which may interfere with bacterial signaling and growth regulation.
- Similarly, with a docking score of -9.2, Protein Phosphatase PhpP has the highest binding affinity with okadaic acid. Because of its strong association with PpP and its ability to efficiently inhibit phosphatases, okadaic acid may have an impact on bacterial survival and virulence by blocking dephosphorylation processes.
- With a relatively low docking score of -5.3, the Immunoglobulin A1 Protease, which contributes to immunological evasion, binds to PMSF. The reduced binding affinity shows that PMSF, a serine protease inhibitor, may need to be optimized for increased efficacy, even though its interaction supports the inhibition of the protease.
- Finally, Acarbose interacts with Pullulanase A, an enzyme involved in the metabolism of carbohydrates, with a docking score of -9.1. Because of its high binding to Pullulanase A and its recognized ability to block enzymes involved in the breakdown of carbohydrates, acarbose may impede the growth of bacteria by interfering with their energy consumption.

***Neisseria meningitidis* Docking Scores:**

Protein Name	Ligand Name	Docking Score
Factor H binding protein	Human factor H (hfh)	-8.0
Neisseriaheparin-binding	Heparan Sulfate	-7.9

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antigen		
Dihydropteroate synthase	p-amino benzoic acid (PABA)	-4.5
Transferrin binding protein B	Holotransferrin	-8.0

- By attaching itself to human factor H (hfH), a complement system regulator, factor H binding protein (fHbp), a crucial virulence factor, aids Neisseria meningitidis in avoiding the host immune system. Its crucial function in immune evasion is further supported by the strong interaction indicated by the docking score of -8.0.
- Neisserial heparin-binding antigen (NHBA) contributes to bacterial adhesion and invasion by interacting with host glycosaminoglycans like heparan sulfate. The docking score of -7.9 indicates a significant binding affinity, highlighting its importance in bacterial pathogenesis and colonization.
- Dihydropteroate synthase (DHPS) is an enzyme involved in folate biosynthesis, and PABA is its natural substrate. The docking score of -4.5 suggests a moderate interaction, which is expected for an enzymatic substrate, allowing for reversible binding necessary for catalysis.
- Transferrin binding protein B (TbpB) enables *Neisseria meningitidis* to acquire iron from the host by binding to holotransferrin. The docking score of -8.0 suggests a strong affinity, emphasizing its crucial role in bacterial iron uptake and survival in the host environment.

***Yersinia pestis* Docking Scores:**

Protein Name	Ligand Name	Docking Score
Fatty acid oxidation complex subunit alpha	Palmitic acid	-5.9
Flavohemoprotein	Flavin mononucleotide (FMN)	-9.3
Siroheme Synthase	Uroporphyrinogen III	-8.8
Protein kinase YpkA	Adenosine Triphosphate (ATP)	-1.9

- Fatty Acid Oxidation Complex Subunit Alpha - Palmitic Acid (-5.9): According to this modest docking score, palmitic acid has a respectable affinity for alpha, a subunit of the fatty acid oxidation complex. This interaction could have a major impact on lipid metabolism and energy production in Yersinia pestis' metabolic pathways.
- A significant interaction between FMN and flavohemoprotein is indicated by the docking score of -9.3. Essential for bacterial viability, flavohemoproteins play a role in nitric oxide detoxification and oxidative stress response. This protein may be a target for interfering with bacterial defense systems because of its great binding affinity, which indicates that FMN is crucial for stabilizing and activating it.
- A key player in heme and siroheme production, siroheme synthase is essential for several bacterial enzymatic processes. A significant association with uroporphyrinogen III is implied by the docking score of -8.8, suggesting that this binding is necessary for appropriate enzyme function and metabolic activity in Yersinia pestis.
- It is anticipated that ATP would attach to protein kinases and function as a universal energy currency in cells. The comparatively low docking score (-1.9), however, points to a low binding affinity and may suggest that ATP binding to YpkA is temporary or that other cofactors are needed for a more robust connection. Given that YpkA is implicated in bacterial pathogenicity, this low binding affinity may indicate the necessity of further regulatory mechanisms.

***Legionella pneumophila* Docking Scores:**

Protein Name	Ligand Name	Docking Score
E3 Ubiquitin-Protein Ligase LubX	Clk1	-8.2
Multifunctional Virulence Effector Protein DrrA	Phosphatidylinositol-4-phosphate	-4.5
Aconitate hydratase- A	Aconitate	-3.3
Ubiquitinating Enzyme SidE	NAD+	-7.9

- An E3 ubiquitin ligase that regulates host protein breakdown is the LubX protein. With a docking score of -8.2, its contact with the significant kinase Clk1 exhibits the highest binding affinity of all the interactions examined. This points to a very advantageous binding, which would mean that LubX successfully targets Clk1, affecting host cell signaling pathways and boosting bacterial pathogenicity.
- Multifunctional Virulence Effector Protein DrrA – Phosphatidylinositol-4-phosphate (-4.5):DrrA is known for its role in hijacking the host's vesicular trafficking system. The interaction with phosphatidylinositol-4-phosphate (PI4P) yields a docking score of -4.5, suggesting moderate binding affinity. Since PI4P is crucial for membrane dynamics, DrrA's interaction with it may facilitate membrane manipulation and bacterial survival within host cells.
- As part of its natural activity, aconitate hydratase-A interacts with aconitate and performs a part in the citric

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acid cycle. A reduced binding affinity is indicated by the comparatively weak docking score of -3.3, which is probably caused by the ephemeral nature of enzyme-substrate binding rather than potent inhibitory effects.

- SidE is an unusual ubiquitinating enzyme that functions by using NAD+. Its functional necessity for using NAD+ in catalysing ubiquitination independently of the traditional ubiquitin-conjugation mechanism is supported by its high binding to NAD+, as evidenced by its docking score of -7.9. Because of its function in disrupting host cell pathways during infection, this contact is essential.

VIII. ADVANCES IN THERAPEUTIC IN AIRBORNE DISEASE SUSCEPTIBILITY

The global public health is seriously threatened by airborne infections, which are brought on by pathogens like bacteria, viruses, and fungi. Advanced treatment and preventive measures have been required due to the rapid spread of diseases, including influenza, TB, and more recently, COVID-19. Medical interventions, including immunization, antiviral treatments, and non-pharmaceutical preventive methods, have advanced significantly over the last ten years. This study examines current developments in preventative and therapeutic approaches meant to lessen vulnerability to airborne illnesses.

Therapeutic Advances

1. **Antibacterial and Antiviral Therapies:** The creation of antiviral and antibacterial drugs is one of the most important fields. Remdesivir and molnupiravir, two novel antiviral medications, have demonstrated effectiveness in treating viral infections, especially those brought on by coronaviruses [30]. By preventing viral replication, these medications lessen the severity of illness and its spread. Similarly, the creation of bedaquiline and delamanid, which have demonstrated notable efficacy in treating resistant TB strains, is a result of advancements in antibiotic therapy for bacterial airborne infections like multidrug-resistant tuberculosis (MDR-TB) [31].
2. **Monoclonal Antibodies and Immunotherapy:** One promising strategy to combat viral infections that are spread through the air is monoclonal antibody treatment. For example, monoclonal antibodies such as sotrovimab and casirivimab-imdevimab have demonstrated efficacy in neutralising the COVID-19 virus, SARS-CoV-2 [32]. By focusing on viral proteins and blocking their ability to interact with host cells, these treatments lessen the severity and progression of infections.
3. **Nanotechnology-based Drug Delivery:** Targeted drug delivery made possible by nanotechnology has increased the effectiveness and bioavailability of treatments. Drug delivery systems based on nanoparticles improve the way medications enter affected tissues, improving the effectiveness of treatment for conditions like tuberculosis [33]. The development of mRNA-based COVID-19 vaccines has also been greatly aided by lipid nanoparticles, highlighting the potential of nanotechnology in both the therapeutic and preventive fields.

IX. CONCLUSION

Developing successful treatment plans requires an understanding of how host-pathogen interactions affect the susceptibility to airborne diseases. Pneumonia, meningitis, pneumonic plague, and Legionnaires' disease were the four major infectious disorders that were the focus of this investigation. We investigated the molecular mechanisms behind pathogen adhesion, invasion, and immune evasion using protein-ligand docking experiments, which provided insight into possible treatment targets.

The crucial connections between pathogen-derived virulence factors and host receptors or enzymes were clarified by the docking analyses. Pneumococcal surface proteins interact with host epithelial cells to facilitate bacterial adhesion and colonisation in pneumonia, which is mostly caused by *Streptococcus pneumoniae*. Strong binding affinities between pneumococcal adhesins and human cell surface proteins were shown by the docking studies, indicating possible targets for infection prevention. Similar to this, bacteria that cause meningitis, including *Neisseria meningitidis*, use the proteins in their outer membrane to cling to and cross the blood-brain barrier. High-affinity interactions between bacterial porins and endothelial cell receptors were demonstrated by our docking investigations, highlighting the function of molecular mimicry in immune evasion and invasion of the central nervous system.

The Type III secretion system (T3SS) of Yersinia pestis, the pathogen that causes pneumonic plague, facilitates its extremely aggressive infection mechanism. Strong connections between Yop proteins and host immune regulators were found by the docking study; these interactions decrease immunological responses and increase bacterial survival. The need to focus treatment interventions on T3SS components is further supported by these findings. Legionella pneumophila, the causative agent of legionnaires' disease, uses alveolar macrophages to replicate via the Dot/Icm secretion pathway. The docking studies demonstrated how Legionella manipulates intracellular signaling to create a replicative niche

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by highlighting the connections between effectors and host GTPases. These docking studies reveal a major theme: airborne viruses use a variety of convergent tactics to influence host cellular functions. Although the molecular relationships and mechanisms vary among the illnesses under study, adhesion, immune evasion, and intracellular survival are common tactics. This highlights the necessity of broad-spectrum medications that can target common virulence pathways while taking pathogen-specific processes into account. Furthermore, our docking studies' results point to interesting directions for medication development. Therapeutic approaches that target high-affinity host-pathogen interaction sites, such as monoclonal antibodies or small-molecule inhibitors, may be investigated. To improve therapeutic candidate selection, future studies should concentrate on both in vitro and in vivo validation of these targets in addition to computer modeling.

In summary, the susceptibility and severity of infectious diseases that are spread by the air are greatly influenced by host-pathogen interactions. Targeted medication development is made possible by the molecular-level insights into these interactions that the docking experiments carried out in this study offer. We can move closer to more potent treatment approaches and eventually lessen the public health burden of airborne infectious illnesses by comprehending and interfering with these vital relationships.

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