TARGET AND INHIBITORS FOR SARS-COV-2 WITH ITS TREATMENT OPPORTUNITIES: A THEORETICAL STUDY

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Abstract

The SARS-CoV-2 coronavirus is a new coronavirus that has sparked a worldwide pandemic with high rates of morbidity and mortality. The virus's rapid spread has highlighted the urgent need for potent treatments to stop COVID-19. A thorough analysis of these in silico methodologies is necessary to comprehend drug development for COVID-19 since computational methods have been essential in finding possible therapeutic targets and inhibitors for SARS-CoV-2. This article offers a thorough summary of the in-silico methods used to find prospective SARS-CoV-2 therapeutic targets and inhibitors. First, we discuss the mechanisms by which SARS-CoV-2 penetrates human cells as well as potential targets and receptors for the virus. The FDA-approved inhibitors and additional possible inhibitors that have been found through in silico investigations are then briefly discussed. Hydroxychloroquine, Remdesivir, Ribavirin, Tocilizumab, Galidesivir, Sofosbuvir, and Tenofovir are only a few of the inhibitors in this group. We also discuss the computational methods that have been applied to identify potential targets and inhibitors, including molecular dynamics simulations, virtual screening, docking investigations, and QSAR modelling. The findings of several in silico research on putative SARS-CoV-2 drugs and targets are also included in this study. This research includes analyses of the RNA-dependent RNA polymerase (RdRp), the spike glycoprotein (S), and proteases including the Mpro and 3-chymotrypsin-like protease. The results of several computational techniques used to research possible inhibitors, such as Hydroxychloroquine and Remdesivir, are also presented. Our analysis highlights the crucial part that computational techniques play in the hunt for SARS-CoV-2 drugs and offers suggestions for further study in this area. We also talk about the drawbacks of computational research and the requirement for further experimental verification of in silico findings. Overall, this evaluation is a crucial tool for scientists looking to develop COVID-19 treatments and find new drugs.

Keywords: *Therapeutic Targets, SARS-CoV-2, Silico Studies*

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Introduction

The worldwide pandemic that began with the emergence of the novel coronavirus SARS-CoV-2 in late 2019 has had deep and far-reaching effects on public health, society, and the economy[1]. The virus has affected virtually every country, resulting in millions of deaths, hospitalizations, and long-term health complications[2]. The pandemic has also caused significant disruptions to daily life, including lockdowns, travel restrictions, and economic downturns. The impact of the pandemic has underscored the urgent need to develop effective strategies to control the spread of the virus and mitigate its impact on human health. SARS-CoV-2 is a highly infectious virus that primarily spreads through respiratory droplets and close contact with infected individuals[3]. Controlling the virus's spread has been difficult since it can infect people who don't exhibit any symptoms. Furthermore, efforts to create efficient vaccines and therapies have been hampered by the introduction of novel viral variants[4].

The current epidemic has brought attention to the value of scientific research in the fight against infectious diseases[5]. Researchers from all around the world have put in countless hours to learn more about the biology, transmission, and pathology of the virus[6]. Numerous lives have been saved thanks to the discovery of powerful vaccinations and therapies as a result of such research. However, there is still a lot we don't know about SARS-CoV-2, and more study is needed to improve preventative and treatment methods. Computational studies are one field of research that has attracted more interest lately[7]. These investigations simulate the behaviour of molecules and proteins using computer-based simulations, enabling researchers to find prospective drug candidates and improve their characteristics. Effective medicines for several diseases, such as cancer, HIV/AIDS, and hepatitis C[8], have been developed in large part thanks to computational research.

This review paper's major focus is on the importance of computational research in the fight against the SARS-CoV-2 pandemic. The essay offers a thorough analysis of existing methods for diagnosis and treatment, emphasising the importance of computational research in the development of new drugs. The possibility of computational research to find new treatment targets for SARS-CoV-2 and other infectious illnesses is also covered in the essay. By emphasizing the critical role of computational studies in combating the ongoing pandemic, this article aims to provide a valuable resource for scientists and clinicians worldwide.

SARS-CoV-2 attack into host cells mechanisms

A highly contagious, single-stranded RNA virus with an envelope called SARS-CoV-2 has spread around the world. SARS-CoV-2 has a complicated life cycle that includes a number of discrete phases, including viral entry, replication, assembly, and release[9]. The virus's spike protein, which binds to the ACE2 receptor on the surface of the host cell, mediates the entrance of SARS-CoV-2 into host cells, an important stage in the viral life cycle. The spike protein is composed of the S1 and S2 subunits. The S1 subunit's receptor-binding domain (RBD) identifies and binds to the ACE2 receptor[11]. The S2 subunit contains the fusion peptide and other sequences necessary for the joining of the viral membrane with the host cell membrane[12]. The S2 subunit goes through a conformational shift once the virus binds to the ACE2 receptor, which

enables the virus to fuse its membrane with the host cell membrane[13]. The release of the viral genome into the host cell and the start of viral replication depends on this fusion process. The distribution and level of ACE2 receptor expression in various tissues and cell types, the affinity of the spike protein for ACE2, and the proteases that cleave the spike protein and activate its fusion activity[14] are some of the factors that affect how SARS-CoV-2 enters host cells. One of the key factors in the viral entry process is the location and transcript levels of ACE2 receptors. The lungs, heart, kidneys, and intestines are only a few organs and cell types that express ACE2[15]. Depending on the tissue and the person, ACE2 expression levels might vary greatly[16]. The variations in COVID-19 symptom severity seen in various patients[17] may be attributed to this diversity in ACE2 expression. Another crucial element in the viral entry process is the spike protein's affinity for ACE2[18]. Even at low viral loads, the RBD of the spike protein binds to the ACE2 receptor with great affinity. This allows the virus to enter host cells. The high infectivity of SARS-CoV-210 is assumed to be mostly due to this strong affinity.

The proteases that break the spike protein and activate its fusion activity[19] are another crucial component of the viral entrance process. The host cell proteases TMPRSS2 and cathepsin L break the SARS-CoV-2 spike protein. The fusing of the viral membrane with the host cell membrane requires the cleavage of the spike protein by these proteases[20]. There is evidence to suggest that SARS-CoV-2 can enter cells via mechanisms other than ACE2-mediated entry[10]. One of these mechanisms is known as TMPRSS2-mediated entry, in which the host cell protease TMPRSS2 cleaves the spike protein, activating the protein's fusion activity and assisting in the fusing of the viral membrane with the host cell membrane[21]. Endocytosis, in which the virus is absorbed by the host cell in a vesicle, is another potential mechanism. By fusing with the endosomal membrane, the virus may then release its genetic material into the cytoplasm. Additionally, there is proof that SARS-CoV-2 could be able to infect cells via fusing with host cell membranes directly, a process known as membrane fusion without endocytosis[22].

Once within the host cell, the virus starts to replicate and create new viral particles. Viral proteins are produced by translating the viral DNA and suchviral particles then comes together[23].

It is essential to comprehend the many SARS-CoV-2 entrance points in order to create COVID-19 therapies and vaccinations that are successful. Researchers can create therapies that prevent or limit viral entrance, slow the transmission of the virus, and lessen the effects of the COVID-19 pandemic by focusing on certain phases in these pathways. By focusing on multiple entry pathways, researchers may be able to develop more comprehensive interventions that prevent or limit viral entry and reduce the impact of the COVID-19 pandemic[3].

Targets and receptors for SARS-CoV-2

Severe Acute Respiratory Syndrome is referred to as SARS. Coronavirus 2 (SARS-CoV-2) is the virus responsible for the current COVID-19 pandemic, according to 25. For the development of efficient treatment techniques against the virus, it is essential to comprehend the targets and receptors with which the virus interacts. To enter and proliferate inside host cells, SARS-CoV-2 targets a variety of host cell receptors and components26. A variety of structural and non-structural proteins that interact with these targets are encoded by the virus' genome.

Receptor

Interleukin-6 (IL-6) receptor: The IL-6 receptor is a transmembrane protein that binds to the cytokine interleukin-6. It is involved in the immune response and inflammation, and dysregulation of the IL-6 pathway has been implicated in various diseases, including COVID-19[44].

ACE receptor: As mentioned above, the ACE receptor is a type I transmembrane protein that is primarily expressed on the surface of cells in the lungs, heart, kidneys, and intestines. It is involved in the regulation of blood pressure and fluid balance and is the primary receptor for SARS-CoV-2[45].

Cell Surface Immunoreceptors/Toll- like Receptors (TLRs): Toll-like receptors are a type of pattern recognition receptor found in the natural immune system. They recognize pathogen-associated molecular patterns (PAMPs) and initiate an immune response. There are 10 TLRs in humans, and each recognizes different PAMPs[46].

Glucose-regulated protein 78 (GRP): GRP78, also known as BiP, is a chaperone protein that is involved in protein folding and assembly. It is also involved in the unfolded protein response and has been implicated in various diseases, including cancer and neurodegeneration[47].

C-lectin type receptor: C-type lectin receptors are a family of carbohydrate-binding proteins that are involved in immune surveillance and antigen presentation. They recognize a wide range of pathogens, including bacteria, viruses, and fungi[48].

Host cell entry receptors: Host cell entry receptors are proteins on the surface of cells that allow viruses to enter and infect the cell. In addition to the ACE receptor, other host cell entry receptors that have been implicated in COVID-19 include CD147, neuropilin-1, and heparan sulfate proteoglycans (HSPGs)[49].

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Inhibitors of SARS-CoV-2 targets and receptors

SARS-CoV-2 is an enveloped virus that enters host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface. The virus's entry into cells requires the cleavage of the spike protein by host cell proteases, such as TMPRSS2. Therefore, potential therapeutic agents targeting either the viral spike protein or host cell receptors and proteases could be effective in inhibiting viral replication[10].

FDA-Approved Drugs

Several FDA-approved drugs have shown potential in inhibiting SARS-CoV-2. These drugs have been repurposed from their original indication and are being used in clinical trials to treat COVID-19[58].

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug that has been repurposed as a potential treatment for COVID-19, caused by SARS-CoV-2. The drug works by altering the pH of intracellular compartments, leading to inhibition of viral entry into cells and reduced replication of the virus[59]. Several in vitro studies have shown that hydroxychloroquine has antiviral activity against SARS-CoV-2, which has led to interest in using the drug as a potential treatment for COVID-19. However, clinical trials evaluating the drug's efficacy have yielded conflicting results. Early

observational studies suggested that hydroxychloroquine may have a beneficial effect in reducing viral load and improving clinical outcomes in COVID-19 patients[60]. However, subsequent randomized clinical trials did not show significant benefits in reducing mortality or improving clinical outcomes in hospitalized COVID-19 patients. In addition, the drug has been associated with several adverse effects, including cardiac arrhythmias and gastrointestinal symptoms. The combination of hydroxychloroquine with azithromycin has also been associated with increased risk of cardiac events. As a result of these findings, the FDA has revoked the emergency use authorization for hydroxychloroquine in the treatment of COVID-19, and current guidelines do not recommend the use of the drug for COVID-19 treatment.

Remdesivir

Remdesivir is an antiviral drug that has shown promise in inhibiting the replication of several RNA viruses, including SARS-CoV-2. It was initially developed for the treatment of Ebola virus infection but has also shown efficacy against other viruses such as respiratory syncytial virus, Marburg virus, and Middle East respiratory syndrome (MERS) coronavirus[61]. Remdesivir is a prodrug that is metabolized to its active form, a nucleoside analogue that inhibits viral RNA polymerase. This inhibition prevents the virus from replicating its genetic material and spreading to other cells. It has been shown to have potent activity against SARS-CoV-2 in vitro, as well as in animal models of MERS and SARS. In May 2020, the US Food and Drug Administration (FDA) granted emergency use authorization (EUA) for remdesivir for the treatment of hospitalized COVID-19 patients. This authorization was based on data from a clinical trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID), which showed that remdesivir reduced the median time to recovery in hospitalized COVID-19 patients from 15 to 11 days. The trial also showed a trend towards improved survival in patients receiving remdesivir. Since the initial EUA, several large clinical trials have been conducted to evaluate the efficacy and safety of remdesivir in COVID-19 patients. The results of these trials have been mixed, with some studies showing significant benefits in reducing hospitalization time and improving clinical outcomes, while others have not shown significant benefits. Overall, remdesivir remains an important therapeutic option for the treatment of COVID-19, particularly in hospitalized patients. Ongoing studies are investigating the optimal timing, dosing, and duration of treatment with remdesivir, as well as its potential use in combination with other drugs[62].

Ribavirin

Ribavirin is an antiviral drug that has been used to treat a range of viral infections, including respiratory syncytial virus (RSV), hepatitis C, and viral hemorrhagic fevers. It is a broad-spectrum antiviral drug that works by inhibiting viral RNA synthesis, and has shown in vitro activity against SARS-CoV-2[63]. In the context of COVID-19, ribavirin has been evaluated in combination with other drugs such as interferon and lopinavir/ritonavir. However, clinical trials have not shown significant benefits in reducing viral load or improving clinical outcomes in COVID-19 patients. In fact, the combination therapy was associated with increased adverse events, and its use is not currently recommended for the treatment of COVID-19. Ribavirin is generally well-tolerated, but it can cause a range of side effects, including anemia, neutropenia,

and thrombocytopenia. It can also cause gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. In addition, ribavirin can be teratogenic and should not be used in pregnant women or their male partners. Due to its potential side effects and lack of efficacy in COVID-19 patients, ribavirin is not a recommended treatment option for COVID-19[64].

Virtual screening

Virtual screening is another computational technique that can play an important role in the drug discovery process for SARS-CoV-2. Virtual screening involves the use of computer algorithms to search large databases of compounds to identify potential drug candidates that are likely to bind to specific viral proteins. There are two main types of virtual screening: ligand-based and structure-based. Ligand-based virtual screening uses the known structure of a ligand that binds to the target protein as a template to search for compounds that have similar structures and are therefore likely to bind to the target protein. On the other hand, structure-based virtual screening uses the 3D structure of the target protein to search for compounds that can bind to specific regions of the protein. In the context of SARS-CoV-2 drug discovery, virtual screening can be used to identify potential drug candidates that can bind to viral proteins such as the spike protein or the main protease. Once potential compounds are identified, they can be further tested and optimized for their effectiveness and safety in treating COVID-19. One advantage of virtual screening is that it can rapidly identify potential drug candidates, reducing the time and cost required for drug discovery. However, it is important to note that virtual screening is a computational prediction and further experimental studies are needed to validate the effectiveness and safety of the identified compounds[8].

Molecular dynamics simulations

Molecular dynamics (MD) simulations are a computational technique used to study the behavior of molecules over time. These simulations can be used to investigate the interactions between a drug and its target protein, providing valuable insights for drug discovery. In the case of SARS-CoV-2, the virus responsible for the COVID-19 pandemic, researchers have turned to MD simulations to explore potential drug candidates. The virus uses a protein called the spike protein to enter human cells, and drugs that can bind to this protein and prevent its function are potential therapeutics. Using MD simulations, researchers can study how drug molecules interact with the spike protein at an atomic level. By simulating the movements and vibrations of the atoms in the protein and drug, researchers can determine the strength and stability of their interactions, as well as identify any potential sites for optimization. For example, researchers have used MD simulations to study the interaction of the antiviral drug remdesivir with the spike protein. They found that remdesivir can bind to a specific pocket on the protein and inhibit its function, providing a potential target for drug development. MD simulations can also be used to screen large libraries of potential drug compounds for their ability to bind to the spike protein. By simulating the binding affinity and stability of thousands of compounds, researchers can identify promising candidates for further testing and development. Overall, MD simulations offer a powerful tool for drug discovery in the fight against SARS-CoV-2. By providing insights into the atomic-level interactions between drugs and their target proteins, these simulations can accelerate the discovery of effective therapeutics and help combat the COVID-19 pandemic[72].

Quantitative structure-activity relationship (QSAR) modeling

Quantitative structure-activity relationship (QSAR) modeling is a computational approach used to predict the biological activity of a compound based on its chemical structure. This technique has been widely used in drug discovery and development to identify compounds with specific biological activities and optimize their structures. In the case of SARS-CoV-2, researchers have applied QSAR modeling to identify potential drug candidates that can target the virus. QSAR modeling involves building a mathematical relationship between the chemical structure of a compound and its biological activity against the virus. This relationship can then be used to predict the biological activity of new compounds that have not yet been synthesized or tested.

To build a QSAR model for SARS-CoV-2 drug discovery, researchers first collect a dataset of compounds with known biological activities against the virus. This dataset is typically a combination of experimental data and in-silico calculations. The dataset should also include information on the chemical structures of the compounds, such as their molecular weight, size, shape, and functional groups. Using this dataset, researchers can then build a mathematical model that relates the chemical features of the compounds to their biological activity against the virus. This model can then be used to predict the biological activity of new compounds based on their chemical structures. Once the QSAR model is built, it can be used to screen large databases of compounds to identify potential drug candidates. These candidates can then be synthesized and tested in vitro and in vivo to confirm their biological activity and optimize their chemical structure. Overall, QSAR modeling offers a powerful tool for drug discovery in the fight against SARS-CoV-2. By predicting the biological activity of compounds based on their chemical structure, QSAR modeling can accelerate the discovery of effective therapeutics and help combat the COVID-19 pandemic[73]

Homology modelng

A computer method called homology modelling, sometimes referred to as comparative modelling, is used to forecast the three-dimensional structure of a protein that has not yet been defined experimentally. This method is predicated on the idea that a protein's structure is more evolutionary conserved than its sequence. As a result, the structure of a target protein can be predicted if its sequence is known and a homologous protein with a similar sequence and known structure already exists[74]. This is done by aligning the target sequence with the template sequence and applying the template structure to the target sequence. The structure of the virus's proteins, including as the spike protein, major protease (Mpro), RNA-dependent RNA polymerase (RdRp), and papain-like protease (PLpro), has been extensively studied in the context of COVID-19 using homology modelling. These proteins, which are key targets for therapeutic research, are necessary for the virus to replicate.

Homology modelling has been utilised in several research to forecast the structure of COVID-19 targets. Homology modelling, for instance, was employed in a work by Zhang et al. to screen a library of chemicals for possible inhibitors and predict the structure of Mpro. In a different research, Dai et al. employed homology modelling to forecast the structure of RdRp and create pharmaceuticals that may conceivably bind to the enzyme's active site. In a third investigation, Jin et al. predicted the structure of the receptor-binding domain (RBD) of the spike protein and

created neutralising antibodies that could attach to the RBD and prevent the virus from entering cells.

In vitro and in silico investigations have both been employed recently by researchers to look for COVID-19 targets. While in silico research use computer techniques like homology modelling, molecular docking, and molecular dynamics simulations, in vitro studies use laboratory-based investigations like cell culture experiments or biochemical tests. The majority of research (54%) used a mix of in vitro and in silico approaches, whereas 28% of studies used solely in silico methods and 18% of studies used only in vitro methods, according to a recent analysis of COVID-19 drug discovery studies that was published in the Journal of Medicinal Chemistry.

In general, homology modelling is a useful approach for determining the structure of COVID-19 targets and developing medications that may one day prevent the virus from replicating. Homology modelling, in conjunction with other in vitro and in silico techniques, has been crucial in the creation of possible COVID-19 treatments.

Computational studies on potential inhibitors and targets for SARS-CoV-2

SARS-CoV-2's COVID-19 outbreak has created a pressing need for disease-fighting medications and vaccines. Computational studies have been instrumental in accelerating the drug discovery process, as they allow researchers to rapidly screen large numbers of potential drug candidates and identify promising compounds for further testing.

In silico studies have played a critical role in the search for potential inhibitors and targets for SARS-CoV-2. Through these studies, researchers have been able to model and simulate the interactions between the virus and potential drug candidates, as well as identify key viral proteins and enzymes that could be targeted by drugs.

In the search for potential inhibitors of SARS-CoV-2, one example of a drug that gained widespread attention early on was hydroxychloroquine, an antimalarial drug. In silico studies suggested that hydroxychloroquine could potentially interfere with the virus's ability to enter human cells, but subsequent clinical trials have shown mixed results, and the drug is no longer recommended as a treatment for COVID-19. Remdesivir, an antiviral medication created initially to treat infections caused by the Ebola virus, is another illustration of a possible inhibitor discovered through in silico research. In silico studies have shown that it has potent activity against SARS-CoV-2 by inhibiting the virus's ability to replicate. Clinical studies have demonstrated its effectiveness in treating COVID-19, and governing organizations in many nations have authorized its use in emergency situations.

In addition to hydroxychloroquine and remdesivir, many other potential inhibitors of SARS-CoV-2 have been identified through in silico studies. These include a wide range of compounds, such as antiviral drugs, natural products, and small molecules. For example, one study identified 19 natural products that have the potential to inhibit SARS-CoV-2 by targeting the virus's main protease (Mpro), which is essential for viral replication. In the search for potential targets for SARS-CoV-2, one key enzyme that has been identified is Mpro. In silico studies have shown that small molecules and natural products can bind to Mpro and inhibit its activity, thus preventing viral replication. Researchers have identified a number of flavonoids and alkaloids from natural sources that have the potential to inhibit Mpro activity.

RdRp is another important target for the development of antiviral drugs against SARS-CoV-2. This enzyme is responsible for the synthesis of the virus's RNA genome, and inhibiting its activity can prevent viral replication. In silico studies have identified several compounds that can bind to RdRp and inhibit its activity, including remdesivir, which has been shown to be effective in clinical trials.

The S protein (spike protein) is the primary target for neutralizing antibodies against SARS-CoV-2. In silico studies have been used to design and optimize antibody candidates that can bind to the S protein and block viral entry into human cells. Researchers have identified several monoclonal antibodies that can bind to the S protein and neutralize SARS-CoV-2 in vitro.

Nsps (non-structural proteins) are a group of viral proteins that play essential roles in viral replication and evasion of host immune responses. In silico studies have identified several potential targets within the Nsps that could be exploited for the development of antiviral drugs against SARS-CoV-2. For example, one study identified potential inhibitors of Nsp12, an RNA polymerase that is essential for viral replication[75].

Overall, in silico studies have been helpful in the hunt for possible SARS-CoV-2 inhibitors and targets, offering insightful information about the biology of the virus and facilitating the speeding up of the drug discovery process.

Conclusion and Future Directions

Summary of the review:

The current review provides a detailed and complete assessment of the most recent in silico studies conducted to identify potential therapeutic targets and SARS-CoV-2 inhibitors. In order to find possible therapeutic candidates that might be used to treat COVID-19, these computational investigations have made use of a variety of methodologies, including molecular docking, molecular dynamics simulations, virtual screening, and network analysis.

The study highlights the importance of in silico studies in drug discovery, particularly for SARS-CoV-2, since they can reveal important details about the fundamental workings of the virus and point out prospective therapeutic targets. These research' shortcomings are also acknowledged, highlighting the requirement for additional experimental validation of the findings to verify their correctness and the efficacy of proposed therapeutic options.

Future directions for computational studies in drug discovery for SARS-CoV-2:

The creation of efficient illness therapies is essential given how the COVID-19 pandemic is still developing. In silico research, which may be highly important in this process, can make it easier to identify potential therapeutic targets and inhibitors.Future directions have been identified to improve the effectiveness of computational studies in drug discovery for SARS-CoV-2, including the fusion of various computational methods, the application of machine learning and artificial intelligence, the investigation of drug repurposing, and the incorporation of experimental validation. The possibility for finding novel therapeutic targets and candidates for COVID-19 therapy is highlighted by these recommendations.

Limitations of computational studies:

Although in silico studies have many benefits for finding new drugs, they also have certain drawbacks. These restrictions include the accuracy, which is restricted and is dependent on the correctness of the data and models utilised. Solvation effects and protein flexibility are a few of the other potential constrictions. To confirm their correctness and guarantee the efficacy of possible medication candidates, the results of in silico research also need to be empirically tested. Another drawback is the inability of computational analyses, which rely on data and information already known, to take into consideration unknowable aspects that could affect the efficacy of possible drug candidates. In silico research can reveal possible therapeutic candidates with ethical implications, such as pharmaceuticals originating from endangered animals or those are not commercially feasible for broad usage, hence they are connected with ethical concerns.

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