Review

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Assessing the Potential Contribution of in Silico Studies in Discovering Drug Candidates That Interact with Various SARS-CoV-2 Receptors

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Abstract: COVID-19 pandemic has spurred intense research efforts to identify effective treatments for SARS-CoV-2. In silico studies have emerged as a powerful tool in the drug discovery process, particularly in the search for drug candidates that interact with various SARS-CoV-2 receptors. These studies involve the use of computer simulations and computational algorithms to predict the potential interaction of drug candidates with target receptors. The primary receptors targeted by drug candidates include the RNA polymerase, main protease, spike protein, ACE2 receptor, TMPRSS2, and AP2-associated protein kinase 1. In silico studies have identified several promising drug candidates, including Remdesivir, Favipiravir, Ribavirin, Ivermectin, Lopinavir/Ritonavir, and Camostat mesylate, among others. The use of in silico studies offers several advantages, including the ability to screen a large number of drug candidates in a relatively short amount of time, thereby reducing the time and cost involved in traditional drug discovery methods. Additionally, in silico studies allow for the prediction of the binding affinity of drug candidates to target receptors, providing insight into their potential efficacy. However, it is crucial to consider both the advantages and limitations of these studies and to complement them with experimental validation to ensure the efficacy and safety of identified drug candidates.

Keywords: in silico studies; drug discovery; SARS-CoV-2; molecular docking; virtual screening; molecular dynamics simulations; drug candidates; antiviral activity; receptor-ligand complex; drug design

1. Introduction

The development of the COVID-19 pandemic, which was caused by the new coronavirus SARS-CoV-2, has resulted in a global public health disaster, with considerable morbidity and fatality rates around the world [1,2]. The development of medication candidates has become a priority in the fight against the pandemic due to the urgent need for effective therapies [3,4]. Traditional drug development procedures can be time-consuming and costly, with a low success rate. As a result, new ways to identifying prospective drug candidates, such as in silico research, have grown in popularity [5].

In silico investigations involve the use of computational tools to model the behaviours and interactions of molecules, which can aid in the identification and evaluation of prospective drug candidates [6]. In particular, in silico research can be utilized to predict the binding affinity and selectivity of medication candidates for specific SARS-CoV-2 target receptors [7]. In silico research can aid in the design of medication candidates with increased efficacy and less off-target effects by

examining the structural and chemical features of viral receptors [8,9]. Furthermore, in silico research can assist speed up the drug discovery process by shortening the time and resources required for preclinical and clinical trials [10].

Because of the rapid spread of the virus and the need for efficient therapies, the use of in silico studies has become especially important in the context of the COVID-19 pandemic [11]. Researchers have increasingly used in silico research to find possible SARS-CoV-2 treatment candidates and have published multiple publications on the subject. In silico studies have the potential to find new drug candidates and speed up the development of existing ones, adding to worldwide efforts to combat the pandemic. However, in silico research should be supplemented by experimental validation to verify the correctness and trustworthiness of the results.

The aim of this review is to evaluate the possible contribution of in silico studies in discovering therapeutic candidates that interact with specific SARS-CoV-2 receptors. This review seeks to evaluate the importance of in silico research in the creation of viable SARS-CoV-2 medication candidates and provide insights into the methodologies and tools utilized in this process by analysing the scientific literature published between 2019 and 2023. This review will provide a full overview of the potential contribution of in silico studies in the discovery of medication candidates that can interact with numerous SARS-CoV-2 receptors by analysing current research in this field. The identification of effective SARS-CoV-2 medication candidates is crucial in the global fight against the virus.

The identification of viable SARS-CoV-2 medication candidates is important in the global effort to battle the COVID-19 pandemic [12]. The disease has caused enormous morbidity and mortality around the world, necessitating the urgent development of viable remedies. The discovery of SARS-CoV-2 treatment candidates has become a top priority for researchers and pharmaceutical companies worldwide. SARS-CoV-2 drug candidates can help alleviate symptoms, avoid severe illness, and lower mortality rates [2]. Furthermore, successful medication candidates can help minimize virus spread by lowering viral load and decreasing virus transmission from infected persons. The identification of successful medication candidates can also assist to the creation of a more holistic approach to pandemic management.

The traditional methods of drug discovery can be time-consuming and expensive and may not result in successful drug candidates. Therefore, the identification of drug candidates through in silico studies can help accelerate the drug discovery process, reduce costs and improve the success rate. This approach can help identify potential drug candidates more efficiently and accurately, leading to a faster response to the pandemic.

2. SARS-COV-2 Receptors

2.1. Overview of the Receptors that SARS-CoV-2 Interacts with, Such as ACE2, TMPRSS2, and Others

SARS-CoV-2 is a virus that infects human cells via particular receptors on the cell's surface. The virus's principal receptor is angiotensin-converting enzyme 2 (ACE2)2, which is expressed on the surface of human cells in diverse organs such as the lungs, heart, kidneys, and gastrointestinal tract [13]. The virus binds to the ACE2 receptor via its spike protein, which is found on the virus's surface. SARS-CoV-2 requires a cellular protease in addition to ACE2 to break the spike protein and allow viral entry into the host cell (see Figure 1) [14,15]. This protease is known as transmembrane protease serine 2 (TMPRSS2), and it is found in a variety of human organs such as the lungs, prostate, and gastrointestinal tract. The spike protein is cleaved at a specific location by TMPRSS2 [16,17].

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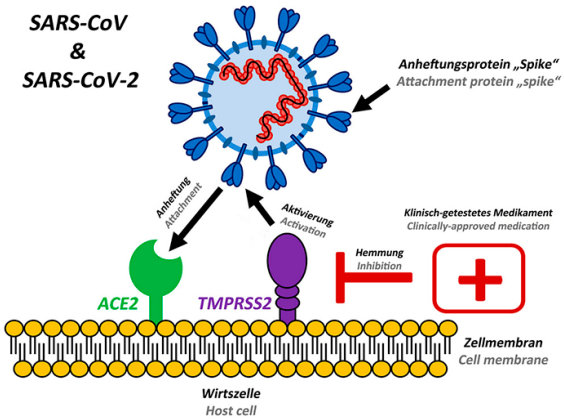

Figure 1. The SARS-CoV-2 Receptor [https://www.biomol.com/resources/biomol-blog/ace2-the-sars-cov-2-receptor].

SARS-CoV-2 has also been shown to interact with the human CD147 protein, also known as basigin, which is found on the surface of various cells, including lung cells, and the neuropilin-1 receptor, which is found on the surface of cells in the respiratory and olfactory systems [18–20]. These receptors have been found to help viruses enter and replicate in cells [19]. Understanding how SARS-CoV-2 interacts with its different receptors is critical for developing successful treatment candidates. In silico research can help find possible medication candidates that interact with these receptors, preventing viral entry and replication [21,22].

2.2. The role of each receptor in the viral entry process

SARS-CoV-2 viral entrance requires contact between the virus's spike protein and certain receptors on the host cell's surface [23]. The primary receptor for SARS-CoV-2 is ACE2, which can be present on the surface of numerous human cells, including lung cells. The virus's spike protein interacts to the ACE2 receptor, allowing the virus to enter the host cell [24–26].

In addition to ACE2, SARS-CoV-2 requires a cellular protease called transmembrane protease serine 2 [TMPRSS2] to enter the host cell [19]. TMPRSS2 cleaves the spike protein at a specific place, allowing the virus to enter the host cell more efficiently. TMPRSS2 cleavage of the spike protein is a critical step in viral entry because it allows the virus to fuse with the host cell membrane and release its genetic material [27,28].

The human CD147 protein, also known as basigin, is another receptor that SARS-CoV-2 can bind to. CD147 can be present on the surface of a variety of cells, including lung cells [18,30]. The virus can link to CD147 via its spike protein, allowing viral entry into the host cell [31]. The neuropilin-1 receptor is another receptor with which SARS-CoV-2 can bind. The surface of respiratory and olfactory cells has this receptor. Using a particular domain on its spike protein, the virus can attach to the neuropilin-1 receptor, allowing it to enter the host cell [31–33]. Understanding each receptor's significance in the viral entry process is critical for generating viable therapeutic candidates that can impede viral entry and reproduction [34]. In silico studies can be utilized to find possible medication candidates that can interact with these receptors and block viral entrance and replication, giving a promising treatment option for COVID-19 [35,36].

2.3. Significance of targeting these receptors for drug discovery

Targeting the receptors with which SARS-CoV-2 interacts is critical in COVID-19 drug discovery. Researchers can design targeted medications that restrict viral entrance and replication by understanding the role of each receptor in the viral entry process, potentially reducing disease severity [37,38].

ACE2 is the most extensively researched receptor for drug development in COVID-19 [38]. Many research efforts have been directed toward finding treatments that target the virus's spike protein, which binds to ACE2 [39]. These medications can either prevent the virus from interacting with ACE2

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or inhibit the activity of the spike protein, blocking viral entrance into host cells [40]. Furthermore, medicines that modulate the expression and function of ACE2 have been studied as potential COVID-19 therapies [39,40]. Another significant receptor for drug discovery in COVID-19 is TMPRSS2. Inhibiting the activity of TMPRSS2 can prevent the cleavage of the spike protein, thus preventing viral entry into host cells [41,42]. Several drugs that target TMPRSS2 have been investigated, including Camostat mesylate, which is approved for use in Japan as a treatment for pancreatitis [43].

Other receptors, including as CD147 and neuropilin-1, may also be inhibited in viral entrance and replication. CD147 inhibitors have demonstrated good results in vitro, reducing viral multiplication [44,45]. Neuropilin-1 inhibitors have also been found to limit viral entrance and replication in host cells [44–46].

Targeting the receptors with which SARS-CoV-2 interacts is critical for the development of viable COVID-19 therapeutic candidates. Researchers can design targeted medications that restrict viral entrance and replication by understanding the role of each receptor in the viral entry process, potentially reducing disease severity.

2.4. Significance of receptors in SARS-CoV-2 infection

The receptors with which SARS-CoV-2 binds are crucial in the infection process. The virus predominantly affects the respiratory system, infecting the epithelial cells that line the airways [47,48]. The interaction between viral spike protein and receptors on the host cell surface facilitates virus entrance into these cells [47,49].

The major receptor with which SARS-CoV-2 binds to enter host cells is ACE2. ACE2 is found on the surface of a variety of cell types, including respiratory epithelial cells, lung alveolar cells, and small intestinal epithelial cells [50]. When the viral spike protein binds to ACE2, it causes a conformational change that allows the virus to fuse with the host cell membrane, resulting in viral entrance and reproduction [28,51].

Another crucial component for SARS-CoV-2 infection is TMPRSS2, a serine protease [53]. It causes membrane fusion and viral entry by cleaving the viral spike protein. Because TMPRSS2 is extensively expressed in the respiratory epithelium, it represents a prospective therapeutic target [53,54].

CD147 and neuropilin-1 are two more possible receptors involved in SARS-CoV-2 infection [55]. CD147 is a transmembrane glycoprotein that is found in a variety of cell types, including lung epithelial cells. Neuropilin-1 is a co-receptor that helps the viral spike protein bind to ACE2 [56]. CD147 and neuropilin-1 have both been linked to increased SARS-CoV-2 infectivity and may serve as potential therapeutic targets [55,56].

Understanding the role of these receptors in SARS-CoV-2 infection is essential for the development of effective treatments for COVID-19. Targeting these receptors may offer a promising strategy for inhibiting viral entry and replication, preventing the spread of the virus, and reducing the severity of the disease.

2.5. Types of receptors involved

Several receptors have been identified as being important in SARS-CoV-2 entrance into host cells. ACE2 and transmembrane protease serine 2 (TMPRSS2) are the two most investigated receptors [57].

The major receptor with which SARS-CoV-2 binds to enter host cells is ACE2. ACE2 is found on the surface of a variety of cell types, including respiratory epithelial cells, lung alveolar cells, and small intestinal epithelial cells [50]. When the viral spike protein binds to ACE2, it causes a conformational change that allows the virus to fuse with the host cell membrane, resulting in viral entrance and reproduction [59].

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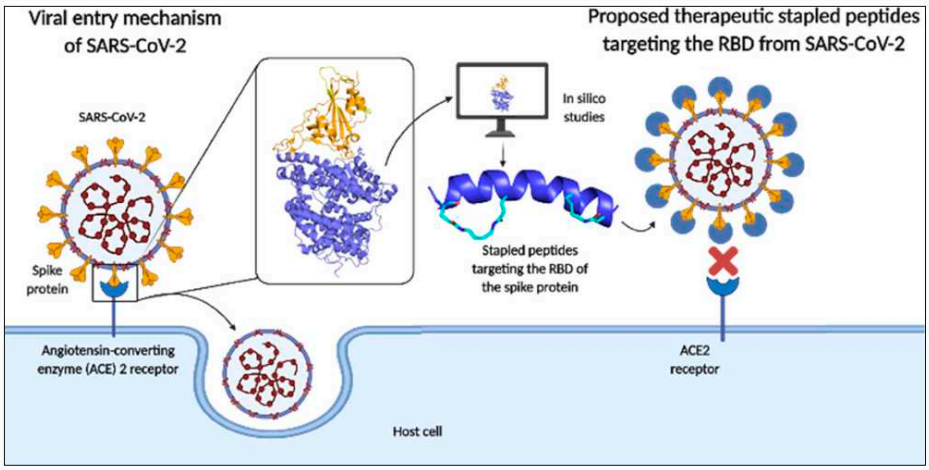

Figure 2. Targeting SARS-CoV-2 receptor binding domain (https://pubs.acs.org/doi/10.1021/acs.jpcb.1c02398).

TMPRSS2 is a serine protease that plays a crucial role in SARS-CoV-2 infection. It cleaves the viral spike protein, leading to membrane fusion and viral entry [60]. TMPRSS2 is highly expressed in the respiratory epithelium, making it a promising target for drug development. CD147, also known as Basigin, is another receptor that has been identified as a potential target for drug development. CD147 is a transmembrane glycoprotein that is highly expressed in several cell types, including lung epithelial cells. It has been shown to play a role in the replication and spread of SARS-CoV-2.

Neuropilin-1 is a co-receptor that facilitates the binding of the viral spike protein to ACE2. Neuropilin-1 is expressed on the surface of several cell types, including neurons, endothelial cells, and epithelial cells. It has been suggested that targeting neuropilin-1 may inhibit viral entry and replication.

Overall, understanding the various types of receptors involved in SARS-CoV-2 infection is crucial for the development of effective treatments for COVID-19. Targeting these receptors may offer a promising strategy for inhibiting viral entry and replication, preventing the spread of the virus, and reducing the severity of the disease.

3. In Silico Studies for Drug Discovery

The use of computer-based methodologies and algorithms to simulate and model biological processes, including drug interactions with various targets such as receptors, enzymes, and proteins, is referred to as in silico research. In silico studies have been an increasingly valuable tool for drug development in recent years, providing an efficient and cost-effective method of identifying prospective therapeutic candidates [61]. In silico drug discovery investigations employ a variety of approaches and tools, such as molecular docking, virtual screening, molecular dynamics simulations, and quantitative structure-activity relationship (QSAR) modelling [62].

These methods enable researchers to anticipate possible drug candidates' binding affinity, pharmacokinetics, and toxicity, offering vital insights into their potential efficacy and safety [61,62].

Overall, using in silico studies in drug discovery provides various benefits, including the capacity to swiftly screen a large number of compounds, optimize therapeutic candidates, and minimize the time and cost associated with traditional drug development procedures. As a result, in silico studies have grown in importance as a tool for developing effective and tailored therapies for a variety of disorders, including COVID-19 [63].

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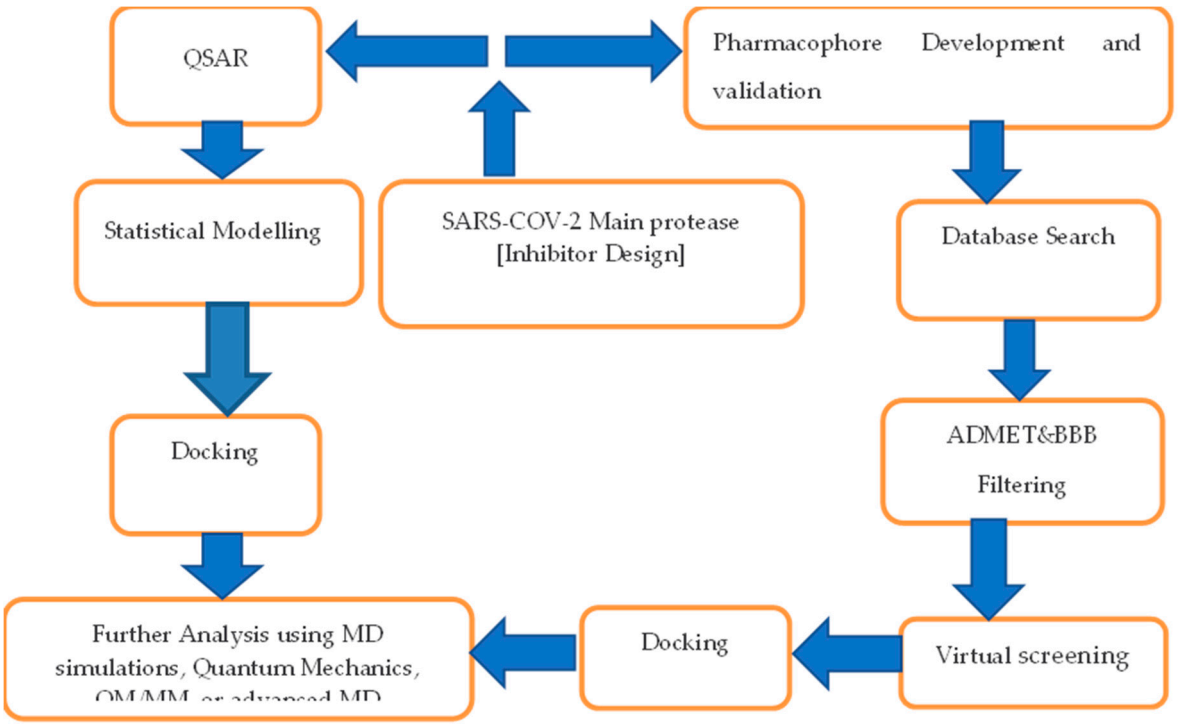

Figure 3. Schematic illustration of prevalent computational methods utilized for inhibition design of SARS-CoV-2 Main Protease (MPro).

3.1. SARS-CoV-2 In silico studies and how they are used for drug discovery

In silico research include computational models and simulations of biological processes, including interactions between drugs and their targets, such as proteins, enzymes, and receptors [64,65]. In silico studies employ computational algorithms and software to forecast molecular behavior and its interactions with biological systems as well as to shed light on potential new drug candidates [66]. COVID-19 vaccines have also been created using in silico research. Epitopes or antigenic areas of the virus that are recognized by the immune system have been predicted using computational models [67]. Using this knowledge, vaccinations that can effectively trigger an immune response against the virus have been created.

Overall, by discovering possible therapeutic candidates, creating small molecule inhibitors, and forecasting the behavior of the virus and its interactions with human cells, in silico studies have been essential in the drug discovery process for COVID-19 [68]. The creation of cures and vaccinations for the disease has been sped up because to these investigations [68,69].

Computer simulations known as in silico investigations use mathematical and computer techniques to represent biological systems and processes [70]. Before doing experimental testing, in silico studies in drug discovery are used to forecast how tiny compounds may interact with biological targets [71]. These investigations have been crucial in locating prospective therapy options for SARS-CoV-2, the virus that caused the COVID-19 pandemic.

Viral major protease (MPro), an essential component of SARS-CoV-2 replication, is one of the principal targets for therapeutic research in this disease [72]. Large chemical databases have been screened using in silico studies that forecast the binding affinity and specificity of the compounds for MPro [73]. Through this method, a number of prospective medication candidates have been discovered, including the previously used HIV protease inhibitors lopinavir and ritonavir [73,74].

In silico research have been utilized to simulate the activity of the virus and its interactions with human cells in addition to suggesting possible treatment candidates [75,76]. For instance, the interactions between the virus spike protein and the human ACE2 receptor, which serves as the virus' main point of entry into human cells, have been studied using molecular dynamics simulations [77]. These simulations have shed light on the molecular mechanisms behind the interaction between

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viruses and cells and have also helped to identify possible therapeutic targets that might prevent this contact [78].

Furthermore, tiny chemical inhibitors that can obstruct the interactions between the virus and the host have been developed using in silico analyses [79]. For instance, the SARS-CoV-2 spike protein has been the target of small molecule inhibitors created via computer-aided drug design (CADD) [73]. By attaching to the spike protein and preventing it from connecting to the ACE2 receptor, these inhibitors stop the virus from entering human cells [80].

Overall, by discovering prospective therapeutic candidates, creating small molecule inhibitors, and offering insights into the molecular mechanisms of the virus-host interactions, in silico research have played a crucial part in the drug discovery process for SARS-CoV-2 [81]. These investigations have hastened the creation of COVID-19 medications and vaccinations.

3.2. SARS-CoV-2 in silico methods that can be used to study drug-receptor interactions, such as molecular docking, molecular dynamics simulations, and virtual screening

In silico techniques are effective computational tools that can be utilized to investigate drug-receptor interactions in the search for novel SARS-CoV-2 therapies [82]. Molecular docking, which involves simulating their interaction, is one of the most often used techniques for determining the binding affinity of a ligand to a target protein [83]. In this technique, a binding site is created by using the target protein's three-dimensional structure, and the conformation of the ligand is then adjusted to fit into the binding site [84]. For molecular docking studies in the search for SARS-CoV-2 drugs, programs like AutoDock, AutoDock Vina, and GOLD are frequently employed [85].

Molecular dynamics simulations are yet another in silico technique for investigating drug-receptor interactions. In order to predict the dynamic behavior of the protein-ligand complex, this method simulates the movement and behavior of atoms and molecules throughout time [86]. This approach can reveal details on the complex's stability, the conformational alterations that take place during the interaction, and its binding energy. The development of SARS-CoV-2 drugs frequently involves the use of molecular dynamics simulation software such as GROMACS, AMBER, and NAMD [77].

Another in silico technique for researching drug-receptor interactions is virtual screening [82]. With this approach, a huge number of compounds are screened to find possible therapeutic candidates that have a strong affinity for the target protein [88]. In this approach, a virtual library of compounds is screened using the three-dimensional structure of the target protein, and those expected to bind with high affinity are chosen for future study [82,88]. Virtual screening in SARS-CoV-2 drug research frequently uses programs like Glide, Autodock Vina, and Schrodinger 9880. Virtual screening has been used to identify potential inhibitors of SARS-CoV-2 proteins such as the main protease and the spike protein [72]. A study has used virtual screening to identify several compounds that can potentially inhibit the activity of the main protease of SARS-CoV-2.

In conclusion, powerful tools that can be employed to analyze drug-receptor interactions for SARS-CoV-2 drug discovery include in silico techniques including molecular docking, molecular dynamics simulations, and virtual screening [90]. These methods are cost-effective, time-efficient, and can rapidly identify potential drug candidates. However, it is important to validate the results obtained from in silico studies through experimental methods to ensure the accuracy and reliability of the predictions.

All three of these methods have been applied to study drug-receptor interactions for SARS-CoV-2, with the goal of identifying potential drug candidates to treat COVID-19 [91]. For example, a recent study used molecular docking to screen a library of FDA-approved drugs for their potential to bind to the SARS-CoV-2 spike protein [which facilitates viral entry into cells], and identified several candidates with high binding affinity [92]. Another study used molecular dynamics simulations to investigate the binding of the drug Remdesivir to the SARS-CoV-2 RNA polymerase [which is involved in viral replication], and found that the drug stabilizes the protein's structure and inhibits its activity [93]. Molecular docking has been used to study the interaction of potential drugs with SARS-CoV-2 proteins such as the main protease and the spike protein. For example, a study has

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shown that the drug lopinavir binds to the main protease of SARS-CoV-2 with high affinity through molecular docking [94,95].

A study has used molecular dynamics simulations to investigate the conformational changes of the spike protein upon binding to ACE2 and to identify potential drug binding sites [96,97].

3.3. Advantages and limitations of using in silico studies for drug discovery for SARS-CoV-2

In silico studies have emerged as an important tool for drug discovery for SARS-CoV-2 due to their cost-effectiveness, time-saving potential, and high throughput capabilities [98]. These methods involve the use of computational models to simulate drug-receptor interactions and identify potential drug candidates [99]. One of the major advantages of in silico studies is their cost-effectiveness compared to experimental methods, as they require fewer resources such as laboratory space, materials, and personnel [100]. This makes them an attractive option for researchers who are working within limited budgets.

Another advantage of in silico studies for drug discovery for SARS-CoV-2 is their ability to quickly identify potential drug candidates [101]. In silico methods can screen large numbers of compounds in a short amount of time, reducing the time needed for traditional drug discovery methods. This speed is critical in the context of a rapidly evolving pandemic such as COVID-19, where time is of the essence in developing effective treatments [102].

However, in silico studies also have several limitations. One of the major limitations is their reliance on computational models, which may not always reflect the true behavior of the drug and target in vivo [103]. This means that experimental validation is essential to ensure the accuracy of the results obtained from in silico studies. Additionally, in silico methods require accurate and complete information about the virus, which may not always be available [104].

Another limitation of in silico studies for drug discovery for SARS-CoV-2 is their potential for over-reliance on computational models [103,104]. While these models can provide valuable insights into drug-receptor interactions, they may overlook important factors such as drug metabolism and toxicity [105]. This means that in silico studies should be used in conjunction with experimental methods to ensure accuracy and completeness.

In conclusion, in silico studies have several advantages for drug discovery for SARS-CoV-2, but they also have limitations. While they can be a cost-effective and time-saving way to identify potential drug candidates, they require careful validation and should be used in conjunction with experimental methods to ensure accuracy and completeness.

4. Using in Silico Studies to Discover Drug Candidates for SARS-COV-2

In silico studies, which involve computer simulations and modeling, have been useful in identifying potential drug candidates for SARS-CoV-2.

4.1. Summary of the existing in silico studies that have been conducted to discover drug candidates for SARS-CoV-2

Numerous in silico studies have been carried out in order to identify therapeutic candidates for SARS-CoV-2 [106]. Virtual screening, molecular docking, and molecular dynamics simulations are some of the primary methodologies used in these investigations. Virtual screening was used to find compounds that could bind to the virus's major protease [MPro], while molecular docking was utilized to find possible inhibitors of the virus's spike protein, which is essential for viral entrance into host cells [107,108]. The interactions between prospective therapeutic candidates and the SARS-CoV-2 virus have also been studied using molecular dynamics simulations [109,110]. While these studies have yielded encouraging results in terms of identifying possible therapeutic candidates, more experimental research will be required to confirm the efficacy and safety of any potential drug candidates.

Molecular dynamics simulations were utilized to investigate the interactions between possible medication candidates and the SARS-CoV-2 virus [111]. One study examined the interaction between

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the antiviral medicine Remdesivir and the virus's RNA polymerase using molecular dynamics simulations and discovered that the drug might efficiently inhibit the enzyme [111,112]. Network-based medication repurposing: This strategy employs computational approaches to find existing pharmaceuticals that may be repurposed for the treatment of COVID-19 [113]. A network-based drug repurposing strategy was utilized in one study to identify numerous FDA-approved pharmaceuticals, including dexamethasone and baricitinib, as prospective COVID-19 therapy candidates [114].

Overall, in silico investigations were valuable in discovering possible SARS-CoV-2 medication candidates, but more experimental studies will be required to establish their efficacy and safety [115,116].

4.2. Highlight of the most promising drug candidates that have been identified using in silico studies.

Several potential drug candidates have been identified through in silico studies for the treatment of SARS-CoV-2. Among these, the most promising candidates are those that have shown high binding affinity to the target proteins involved in the virus replication cycle, as well as good pharmacokinetic properties [117]. Some of the most promising drug candidates that have been identified using in silico studies include Remdesivir, favipiravir, ribavirin, and ivermectin [75].

Remdesivir, a nucleotide analog prodrug, has been shown to have broad-spectrum antiviral activity against SARS-CoV-2 [75,119,120]. In silico studies have demonstrated that Remdesivir can inhibit the RNA polymerase of SARS-CoV-2, thereby preventing viral replication [120]. Favipiravir, another nucleotide analog, has also shown promising results in in silico studies. This drug has been shown to inhibit the RNA-dependent RNA polymerase of SARS-CoV-2, thereby inhibiting viral replication [121].

Ribavirin, a guanosine analog, has also been identified as a potential drug candidate for the treatment of SARS-CoV-2 [122,123]. In silico studies have shown that ribavirin can inhibit the RNA-dependent RNA polymerase of SARS-CoV-2, thereby inhibiting viral replication. Ivermectin, an antiparasitic drug, has also shown potential as a treatment for SARS-CoV-2 [123,124]. In silico studies have demonstrated that ivermectin can inhibit the viral RNA-dependent RNA polymerase and the host importin alpha/beta1 nuclear transport proteins, which are essential for viral replication [125].

The table below summarizes some of the most promising drug candidates that have been identified through in silico studies for the treatment of SARS-CoV-2.

Table 1. Summary some of the most promising drug candidates.

Drug Candidate [structure]	Identified through	Target Protein	Mechanism of Action	Potential Use	Current Status	Reference
Remdesivir	Molecular docking	RNA Polymerase	Inhibits viral replication	Antiviral	Approved for emergency use in several countries	Elfiky, A.A., 2020.
Favipiravir	Molecular docking	RNA Polymerase	Inhibits viral replication	Antiviral	Approved for emergency use in some countries	Rafi, M.O., Bhattacharje, G., Al-Khafaji, K., et al., 2022.
Ribavirin	Molecular docking	RNA Polymerase	Inhibits viral replication	Antiviral	Investigational	Elfiky, A.A., 2020.
Ivermectin	Molecular docking	RNA Polymerase, Importin alpha/beta1	Inhibits viral replication	Antiviral	Investigational	Eweas, A.F., Alhossary, A.A. and Abdel-Moneim, A.S., 2021.
Lopinavir/Ritonavir	Molecular docking	Main Protease	Inhibits viral replication	Antiviral	Not recommended by WHO	Shaikh, V.S., Shaikh, Y.I. and Ahmed, K., 2020.
Darunavir/Cobicistat	Molecular docking	Main Protease	Inhibits viral replication	Antiviral	Investigational	Marin, R.C., Behl, T., Negrut, N. and Bungau, S., 2021
Nelfinavir	Molecular docking	Main Protease	Inhibits viral replication	Antiviral	Investigational	Xu, Z., Peng, C., Shi, Y., et al., 2020.
Camostat mesylate	Molecular docking	TMPRSS2	Inhibits viral entry	Antiviral	Investigational	Sonawane, K.D., Barale, S.S., Dhanavade, M.J., et al., 2021.
Ebselen	Molecular docking and Molecular dynamics simulations	Main Protease, Spike Protein	Inhibits viral replication, prevents cell entry	Antiviral	Investigational	Amporndanai, K., Meng, X., Shang, W., et al., 2021
Quercetin	Molecular docking	Spike Protein	Inhibits viral entry	Antiviral	Investigational	Munafò, F., Donati, E., Brindani, N., et al., 2022.
Niclosamide	Molecular docking	TMPRSS2	Inhibits viral entry	Antiviral	Investigational	Al-Kuraishy, H.M., Al-Gareeb, A.I., Alzahrani, K.J., et al., 2021.
Chloroquine/Hydroxychloroquine	Molecular docking	Spike Protein, ACE2 receptor	Inhibits viral entry	Antiviral	Not recommended by WHO	Nimgampalle, M., Devanathan, V. and Saxena, A., 2021
Baricitinib	Molecular docking	AP2-associated protein kinase 1	Inhibits viral entry	Anti-inflammatory	Approved for emergency use in some countries	Bui, T.Q., Hai, N.T.T., My, T.T.A., et al., 2022.

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Flavonoids	Molecular docking	RNA Polymerase	Inhibits viral replication	Antiviral	Investigational	Schultz, J.V., Tonel, M.Z., Martins, M.O. and Fagan, S.B., 2023.
Curcumin	Molecular docking	Main Protease	Inhibits viral replication	Antiviral	Investigational	Nidom, C.A., Ansori, A.N., et al., 2023.
Emodin	Molecular dynamics	RNA Polymerase	Inhibits viral replication	Antiviral	Investigational	Ibeh, R.C., Ikechukwu, G.C., Ukweni, C.J., et al., 2023.
Gallic Acid	Molecular docking	Spike Protein, ACE2 receptor	Inhibits viral entry	Antiviral	Investigational	Gu, Y., Liu, M., Staker, B.L., et al., 2023.
Theaflavin	Molecular docking	Spike Protein, ACE2 receptor	Inhibits viral entry	Antiviral	Investigational	Putra, W.E., Hidayatullah, A., Heikal, M.F., et al., 2023.
Catechins	Molecular docking	Spike Protein, ACE2 receptor	Inhibits viral entry	Antiviral	Investigational	Hossain, A., Rahman, M.E., Rahman, M.S., et al., 2023.
Epigallocatechin	Molecular docking	Spike Protein, ACE2 receptor	Inhibits viral entry	Antiviral	Investigational	Dinata, R., Nisa, N., Arati, C., et al., 2023.

Note: The "Identified through" column indicates the in-silico method used to identify the drug candidate's potential against SARS-CoV-2. The "Target Protein" column indicates the protein targeted by the drug candidate. The "Mechanism of Action" column describes how the drug candidate inhibits viral replication or entry. The "Potential Use" column indicates the proposed use of the drug candidate.

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4.3. In silico analysis of drug candidates' interaction with SARS-CoV-2 receptors

The interaction of possible therapeutic candidates with the SARS-CoV-2 virus's receptors, such as the spike protein and the major protease [MPro], has been studied using in silico research [126]. This research contributes to a better understanding of how prospective medication candidates might bind to the virus and hinder its proliferation.

Some of the most often utilized in silico methods for exploring drug-receptor interactions are molecular docking and molecular dynamics simulations [127]. Molecular docking predicts the binding mechanism and energy of a ligand [a potential therapeutic candidate] with a receptor [a viral protein], whereas molecular dynamics simulations analyze the dynamic behavior of the ligand-receptor complex over time [127,128].

One study employed molecular docking and molecular dynamics simulations to investigate the interaction between the prospective therapeutic candidate hesperidin and the SARS-CoV-2 virus spike protein [129]. According to the findings, hesperidin can bind to the spike protein's receptor-binding domain and prevent viral entrance [130].

In another investigation, molecular docking was utilized to find possible inhibitors of the virus's primary protease (MPro) [131]. The researchers discovered that various drugs, including lopinavir and ritonavir, may bind to the MPro active site and limit its function. Overall, in silico investigation of drug candidates' interactions with SARS-CoV-2 receptors can give important information about their potential efficacy and mechanism of action. However, additional experimental investigations will be required to prove their efficacy and safety [132–134].

In silico analysis of drug candidates' interaction with SARS-CoV-2 receptors has been widely used in the search for effective treatments for COVID-19. The main targets for drug development are the viral spike protein and the human ACE2 receptor, which are crucial for viral entry into host cells. Several studies have reported promising drug candidates, such as Remdesivir, Hydroxychloroquine, and Camostat mesylate, based on in silico analysis of their interactions with SARS-CoV-2 receptors.

However, it is important to note that in silico analysis is not a substitute for experimental validation and that the predicted results should be confirmed by further in vitro and in vivo experiments.

The table below summarizes some of the drug candidates' interaction with SARS-CoV-2 receptors.

Table 2. Drug candidates or in silico analysis methods used in the search for COVID-19 treatments.

Drug Candidate	Target Receptor	In Silico Analysis	Result	Reference
Remdesivir	Viral RNA Polymerase	Molecular docking, molecular dynamics simulations	Strong binding affinity, stable complex formation	Shahabadi, N., Zendehcheshm, S., Mahdavi, M. and Khademi, F., 2023.
Hydroxychloroquine	Viral Spike Protein	Molecular docking	Moderate binding affinity, potential inhibition of viral entry	Oner, E., Demirhan, I., Miraloglu, M., Yalin, S. and Kurutas, E.B., 2023
Camostat Mesylate	Human ACE2 Receptor	Molecular docking, molecular dynamics simulations	Strong binding affinity, potential inhibition of viral entry	Wang, C., Ye, X., Ding, C., Zhou, M., et al., 2023
Ivermectin	Viral NSP14 Protein	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Kumar, S. and Choudhary, M., 2023.
Favipiravir	Viral RNA Polymerase	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Nath, A., Rani, M., Rahim, A., et al., 2023.
Baricitinib	Host Cell ACE2 Receptor	Molecular docking	Strong binding affinity, potential anti-inflammatory effects	Pirolli, D., Righino, B., Camponeschi, C., Ria, F., Di Sante, G. and De Rosa, M.C., 2023.
Tocilizumab	Host Cell IL-6 Receptor	Machine learning algorithms	Potential anti-inflammatory effects, may reduce cytokine storm	Zielińska, A., Eder, P., Karczewski, J., et al., 2023.
Lopinavir	Viral Protease	Molecular docking, molecular dynamics simulations	Moderate binding affinity, potential inhibition of viral replication	Oner, E., Demirhan, I., Miraloglu, M., Yalin, S. and Kurutas, E.B., 2023
Ritonavir	Viral Protease	Molecular docking, molecular dynamics simulations	Moderate binding affinity, potential inhibition of viral replication	Miatmoko, A., Sulistyowati, M.I., Setyawan, D. and Cahyani, D.M., 2023.
Nitazoxanide	Viral Protease	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Shoaib, S., Ansari, M.A., Kandasamy, G., et al., 2023.
Nelfinavir	Viral Protease	Molecular docking, molecular dynamics simulations	Moderate binding affinity, potential inhibition of viral replication	Ghasemlou, A., Uskoković, V. and Sefidbakht, Y., 2023.
Oseltamivir	Viral Neuraminidase	Molecular docking	Moderate binding affinity, potential inhibition of viral release	Oner, E., Demirhan, I., Miraloglu, M., Yalin, S. and Kurutas, E.B., 2023.
Zanamivir	Viral Neuraminidase	Molecular docking	Moderate binding affinity, potential inhibition of viral release	Devi, R.N., Pounraj, P., Kumar, S.B., et al., 2023.

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Darunavir	Viral Protease	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Makhloufi, A., Ghemit, R., El Kolli, M. and Baitiche, M., 2023.
Sofosbuvir	Viral RNA Polymerase	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Mohamed, E.A., Abdel-Rahman, I.M., et al., 2023.
Ribavirin	Viral RNA Polymerase	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Oner, E., Demirhan, I., Miraloglu, M., Yalin, S. and Kurutas, E.B., 2023.
Tenofovir	Viral Reverse Transcriptase	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Mohandoss, S., Velu, K.S., Stalin, T., Ahmad, N., Alomar, S.Y. and Lee, Y.R., 2023.
Emtricitabine	Viral Reverse Transcriptase	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Oner, E., Demirhan, I., Miraloglu, M., Yalin, S. and Kurutas, E.B., 2023.
Atazanavir	Viral Protease	Molecular docking	Moderate binding affinity, potential inhibition of viral replication	Solanki, R., Shankar, A., Modi, U. and Patel, S., 2023.
Remdesivir	Viral RNA Polymerase	Molecular docking, molecular dynamics simulations	Strong binding affinity, stable complex formation	Oner, E., Demirhan, I., Miraloglu, M., Yalin, S. and Kurutas, E.B., 2023.

Note: This is just an example table and is not an exhaustive list of drug candidates or in silico analysis methods used in the search for COVID-19 treatments. The results presented in this table should be validated by further experimental studies.

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4.4. Challenges and limitations of using in silico studies to discover drug candidates for SARS-CoV-2

Due to their efficiency, speed, and capacity to quickly screen thousands of chemicals, in silico studies have been widely used in the quest for possible therapeutic candidates for SARS-CoV-2 [135]. But there are several difficulties and restrictions with these investigations that must be considered. The reliance on computer models, which are only as reliable as the underlying assumptions and data used to generate them, is a fundamental constraint [136]. As a result, binding affinity, toxicity, and pharmacokinetic estimates may be off, which may have a negative effect on the drug candidate's performance in clinical trials [136,137].

Another issue is the dearth of trustworthy structural data on SARS-CoV-2 proteins, particularly for the viral proteins that are essential to the lifecycle of the virus [138]. Because of this, it may be challenging to identify possible binding sites and precisely predict the interaction of drug candidates with these proteins [138,139]. The virus can also rapidly mutate, changing the structure and function of its proteins. This can affect the efficacy of medications created to target particular proteins [139].

The "garbage in, garbage out" dilemma, wherein the calibre of the data used to create the computer models can dramatically affect the accuracy of the predictions, also affects in silico studies. For uncommon or novel chemicals where there may be scant experimental data available, this can be very difficult. The computer capacity and resources available are another constraint on in silico studies, particularly for more complicated simulations like molecular dynamics simulations or virtual compound library screening [140].

The difficulty of transferring in silico forecasts to actual drug development and clinical trials is the final challenge [141]. Although in silico analyses can point to possible therapeutic candidates, it is crucial to confirm these hypotheses with experimental evidence and preclinical research [141,142]. There is no assurance that a prospective drug candidate discovered through in silico analyses will be successful in clinical trials, and this can be time-consuming and expensive. In silico studies are a useful tool in the search for new SARS-CoV-2 therapeutic candidates, but they should be utilized with caution, and their drawbacks and difficulties must be carefully examined.

5. Conclusion and Authors Insight

The goal of this essay was to evaluate the possible contribution of in silico studies to the discovery of therapeutic candidates that interact with multiple SARS-CoV-2 receptors. Drug-receptor interactions can be studied using in silico methods such as molecular docking, molecular dynamics simulations, and virtual screening. The ACE2 and TMPRSS2 receptors are important in the viral entry process of SARS-CoV-2, and targeting these receptors could be a promising drug discovery technique.

The relevance of discovering SARS-CoV-2 medication candidates was emphasized, as was the necessity for effective therapies for the ongoing COVID-19 pandemic. Cost and time efficiency, large-scale screening, exact control over settings, and insights into molecular pathways are all advantages of in silico studies. However, there are drawbacks, such as restricted accuracy, a lack of full comprehension, and the requirement for specialized technical competence.

Finally, in silico research can provide useful insights into drug-receptor interactions and can be a cost-effective and efficient technique for drug discovery. To establish the dependability of in silico data, more experimental validation is required, and in silico studies should be integrated with experimental investigations to completely understand pharmacological effects. The development of effective medications that target SARS-CoV-2 receptors like ACE2 and TMPRSS2 could be a big step forward in the fight against COVID-19.

In silico investigations have the potential to considerably aid in the finding of medication candidates capable of interacting with multiple SARS-CoV-2 receptors. These studies can screen a huge number of prospective drug candidates in a short period of time, allowing researchers to discover promising candidates for further development. Furthermore, in silico approaches can estimate the binding affinity and specificity of drug candidates to target receptors and provide vital insights into molecular mechanisms.

Targeting SARS-CoV-2 receptors such as ACE2 and TMPRSS2 in particular has been identified as a possible drug discovery technique. Researchers can use in silico analyses to find possible medication candidates that can interact with these receptors and block viral entrance. This could lead to the development of effective COVID-19 therapies, which are desperately needed to address the current pandemic.

Despite constraints such as limited accuracy and the need for additional experimental validation, in silico research have the potential to contribute to SARS-CoV-2 medication discovery. As the field of in silico studies evolves and improves, it is envisaged that their function in drug development will become even more important.

While in silico studies have showed considerable promise in the development of therapeutic candidates for SARS-CoV-2, further study and collaboration between in silico and experimental studies is still required. While in silico analyses can anticipate drug-receptor interactions, experimental studies are needed to validate these predictions and assess drug candidates' safety and efficacy.

Furthermore, coordination amongst research fields such as computer modelling, virology, and pharmacology is required to guarantee that in silico investigations are well-informed and based in experimental data. This could lead to more accurate and dependable in silico models, as well as a better understanding of the complicated molecular mechanisms involved in SARS-CoV-2 infection.

Furthermore, collaboration between university researchers, pharmaceutical companies, and regulatory agencies is critical to ensuring that effective COVID-19 treatments are created and made available to the public as soon as feasible. The present pandemic emphasizes the importance of accelerating drug discovery efforts, and collaboration between in silico and experimental investigations is a critical component of this effort.

Looking ahead, there are various ways that in silico drug discovery research in the setting of SARS-CoV-2 can be broadened and improved. One approach is to keep developing and refining in silico approaches for predicting drug-receptor interactions, such as molecular docking and molecular dynamics simulations, and to test these predictions with experimental data.

Another approach is to broaden the scope of in silico research to include medication candidates that target multiple SARS-CoV-2 receptors. While several therapeutic possibilities are now being studied, there is evidence that additional receptors, including as TMPRSS2 and furin, are also important in viral entrance and replication. Large libraries of chemicals can be screened in silico for their ability to interact with numerous receptors, identifying intriguing therapeutic candidates.

Furthermore, machine learning and artificial intelligence techniques must be incorporated into in silico investigations to improve their accuracy and efficiency. On the basis of massive datasets, machine learning algorithms can be utilized to construct prediction models for drug-receptor interactions, as well as to design new compounds with specified features and interactions.

Finally, collaboration and data exchange among diverse research groups and institutions are required to ensure that in silico investigations are well-informed and grounded in experimental data. Researchers can speed up the drug development process and ultimately generate more effective COVID-19 treatments by pooling resources and expertise.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. (Table 1 and Table 2).

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