drugs and drug candidates

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Review

In Silico Therapeutic Study: The Next Frontier in the Fight against SARS-CoV-2 and Its Variants

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Abstract: COVID-19 has claimed around 7 million lives (from December 2019–November 2023) worldwide and continues to impact global health. SARS-CoV-2, the virus causing COVID-19 disease, is characterized by a high rate of mutations, which contributes to its rapid spread, virulence, and vaccine escape. While several vaccines have been produced to minimize the severity of the coronavirus, and diverse treatment regimens have been approved by the US FDA under Emergency Use Authorization (EUA), SARS-CoV-2 viral mutations continue to derail the efforts of scientists as the emerging variants evade the recommended therapies. Nonetheless, diverse computational models exist that offer an opportunity for the swift development of new drugs or the repurposing of old drugs. In this review, we focus on the use of various virtual screening techniques like homology modeling, molecular docking, molecular dynamics simulations, QSAR, pharmacophore modeling, etc., in repurposing SARS-CoV-2 therapeutics against major variants of SARS-CoV-2 (Alpha, Beta, Gamma, Delta, and Omicron). The results have been promising from the computer-aided drug design (CADD) studies in suggesting potential compounds for the treatment of COVID-19 variants. Hence, in silico therapeutic studies represent a transformative approach that holds great promise in advancing our fight against the ever-evolving landscape of SARS-CoV-2 and its variants.

Keywords: drug discovery; drug repurposing; SARS-CoV-2; COVID; molecular docking; QSAR; molecular dynamics; virtual screening

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1. Introduction

COVID-19 is a serious public health threat and has claimed many lives since 2019. Presently, the World Health Organization (WHO) coronavirus disease dashboard reports that the disease has resulted in more than 772 million infections and 6.9 million deaths (Data retrieved from https://covid19.who.int/; accessed on 27 November 2023). The highly mutated nature of the coronavirus (an RNA virus) means that SARS-CoV-2 changes at a rapid speed, thereby exacerbating the substantial threat that the disease poses globally [1]. Mutations in the virus have presented a formidable challenge to scientists, necessitating a constant adjustment of treatment guidelines for effective therapies. Consequently, extensive global studies were undertaken as researchers rushed against time to find appropriate therapeutic agents to treat COVID-19 as the world still fights to overcome the pandemic. The pandemic is over, but this highly contagious viral illness continues to derail the substantial progress in clinical research toward a better understanding of SARS-CoV-2, as many countries still witness outbreaks attributed to the emerging mutant variants of the virus.

To date, COVID-19 primary therapies are antivirals, anti-inflammatories, and respiratory treatments, with additional antibody therapies being an active and essential part of treating SARS-CoV-2 infection [2]. The first medication to be approved by the United States (US) Food and Drug Administration (FDA) for the treatment of COVID-19 was Remdesivir.

It was approved on 25 April 2022, for treating both adults and children [3]. This medication was identified as a potential therapeutic agent for COVID-19, owing to its inhibitory ability against SARS-CoV-2 in vitro [4]. Studies conducted on SARS-CoV-2-infected monkeys revealed that an early administration of remdesivir significantly reduced the viral load and pulmonary damage, while studies from the National Institute for Allergy and Infectious Diseases (NIAID) and SIMPLE studies reinforced the FDA's decision to issue an emergency use authorization (EUA) on 1 May 2022 for severely ill, hospitalized COVID-19 patients [5,6]. Other drugs approved by the FDA are the immune modulators baricitinib (Olumiant) and tocilizumab (Actemra) for certain adults hospitalized with COVID-19 and the oral antiviral pill Paxlovid (nirmatrelvir and ritonavir) (Figure 1) [7–9].

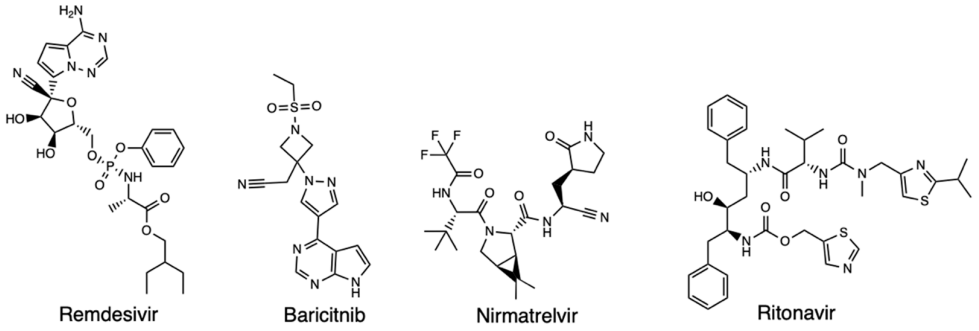

Figure 1. Structure of Remdesivir, Baricitnib, Nirmatrelvir, and Ritonavir.

Since developing new drugs is time-consuming, expensive, and limited by other factors such as the lack of predictive ability of current animal models, the ability for drug repurposing and rediscovery provides a vital system in a health emergency such as the COVID-19 pandemic. Computer-Aided Drug Design (CADD) methods have seen significant advancements during the pandemic, with the integration of Artificial Intelligence (AI) playing a crucial role [10]. The urgency to find effective treatments and vaccines for COVID-19 prompted researchers to accelerate drug discovery processes, and AI emerged as a powerful tool in this endeavor. Leveraging computational software, AI, and Machine Learning (ML) models in the quest for more effective therapeutic methods has been instrumental in uncovering novel drugs and drug combinations [11]. Multiple multi-task deep learning models have been employed to identify existing drugs capable of targeting key viral proteins, particularly the main protease (3CLpro) and spike protein. For instance, Cyclica's PolypharmDB platform uncovered off-target applications of 30 existing drugs against the viral protein 3CLpro and the ACE2 binding site [12]. Additionally, other applications of DL-based virtual screening for the SARS-CoV-2 main protease, with open sharing of newly predicted chemical structures, have been published [13–15]. Atomwise, utilizing its AtomNet® deep convolutional neural network technology, focused on targeting conserved SARS-CoV-2 protein binding sites across various coronavirus species [12,16] and screened millions of virtual compounds against SARS-CoV-2 targets via 15 partnerships with academic researchers who conducted in vitro assays to test the predicted compounds.

The exploration of both structure–activity relationships (SARs) can help distinguish decoys from active compounds [17]. Sometimes, binding affinity is predicted for both active and inactive compounds, where virtual screening tools fail to detect activity. ML algorithms, coupled with quantitative structure–activity relationship (QSAR) models, can identify molecular descriptors associated with antiviral potency [18]. Decoys are used to train datasets for this purpose, using molecules that are structurally similar to the target of interest but lack the desired biological activity [19]. They are employed to enhance the accuracy of computational methods in identifying potential drug candidates by providing a reference set of non-binders [17] and help enhance the performance of docking algorithms. Metrics such as sensitivity, specificity, and receiver operating characteristic (ROC) curves are often employed to evaluate how well the model can discriminate between active compounds and decoys, aiding the predictive power of virtual screening [20,21]. The inclusion

of decoys in virtual screening libraries also helps strike a balance between sensitivity and specificity. Sensitivity ensures that true binders are not missed, while specificity reduces the chances of selecting false positives.

Docking has been applied in proposing the efficacy of statins, with molecular docking aiding in identifying remdesivir and proposing it as a potentially effective drug due to its ability to target the RNA-dependent RNA polymerase (RdRp) [22,23]. Potentially effective small molecules have been prioritized using techniques like molecular docking simulations and network-based repurposing [24,25]. Molecular docking, aided by ML, has been a prevalent approach for virtual screening against the various SARS-CoV-2 proteins essential for viral replication and infection, including 3CLpro, Spike Protein, RdRP, M^{pro}, ACE2 receptor, and TMPRSS2 protease [26,27], with deep learning-aided approaches gaining prominence for their automatic feature extraction, expediting discovery (Figure 2). Notably, protease has been a primary target due to its crucial role in viral replication and transcription [28]. Different datasets, such as the ZINC database, FDA-approved LOPAC library, SWEETLEAD library, or all purchasable drugs (Drugs-lib), have been utilized in these studies [29]. However, the blind application of docking approaches represents a notable constraint in drug discovery, with the potential to yield inactive molecules [30]. This limitation becomes particularly pronounced when considered within the context of energy-based scoring functions. The fundamental challenge lies in the precise prediction of the intricate interactions and dynamics inherent in a diverse range of molecular structures. The complexities of molecular recognition, binding, and specificity are not easily captured by universally applied scoring functions, underscoring the need for a more nuanced understanding of these interactions [31,32]. The recognition of this inherent challenge highlights the necessity for tailored and refined approaches in drug screening methodologies, emphasizing the importance of advancing computational tools to enhance accuracy and reliability in identifying pharmacologically relevant compounds.

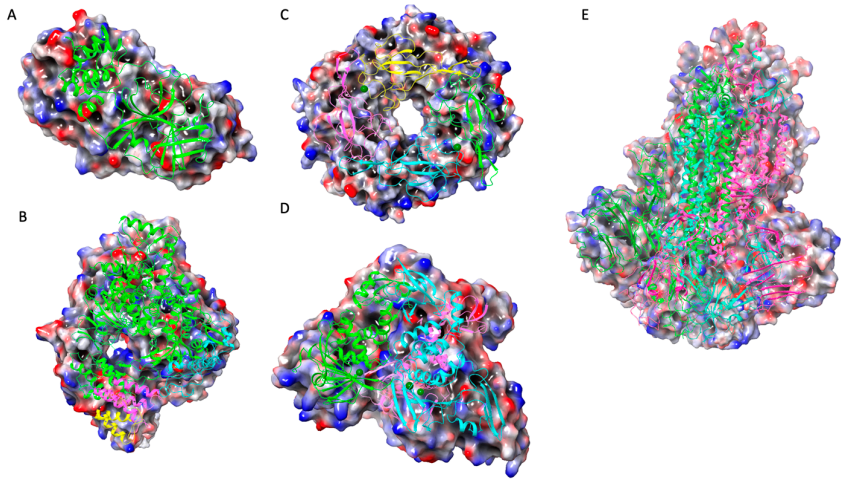

Figure 2. Protein structures of interest: (**A**) PDB 6Y2E, (**B**) PDB 6M71, (**C**) PDB 6VY0, (**D**) PDB 6W9C, and (**E**) PDB 6VXX.

Numerous reviews have comprehensively addressed the landscape of computational drug discovery against SARS-CoV-2 [10,33–36], including AI- and ML-based screening [10,37–39]. Here, we sum up the computational drug discoveries against the SARS-CoV-2 variants (Table 1), displaying the status of variants-of-concerns (VOCs) at some time during the pandemic. They exhibited properties raising significant concerns due to their potential impact on the epidemiological situation, such as increased transmissibility or alterations in clinical disease presentation, raising substantial concerns about their potential impact on public health. Currently, they may be monitored, but the status has been downgraded from the VOC level. The findings represent a valuable pool of information that may be useful for future studies in similar or other viral pathogens responsible for infectious outbreaks.

Table 1. Variants considered for this review. They had a status of VOC at some time during the pandemic. There are currently no SARS-CoV-2 variants meeting the VOC criteria. VOI means variant of interest. VBM means the variant being monitored.

Serial No.	WHO Label	PANGO Lineage	Date of Designation
1	Alpha	B.1.1.7 and Q lineages	VOC: 29 December 2020 VBM: 21 September 2021
2	Beta	B.1.351 and descendent lineages	VOC: 29 December 2020 VBM: 21 September 2021
3	Gamma	P.1 and descendent lineages	VOC: 29 December 2020 VBM: 21 September 2021
4	Delta	B.1.617.2 and descendant lineages	VOC: 15 June 2021 VBM: 14 April 2022
5	Epsilon	B.1.427 and B.1.429	VOC: 19 March 2021 VOI: 26 February 2021 VOI: 29 June 2021 VBM: 21 September 2021
6	Omicron	B.1.1.529 and descendant lineages	VOC: 26 November 2021 VBM: 1 September 2023

2. Modeling for CADD with Small Molecules

Researchers have carried out intensive and extensive research on the coronavirus proteins and their mutants. Three-dimensional (3D) structures of the major SARS-CoV-2 proteins have been resolved and deposited in the Protein Data Bank (PDB). These structures provide a useful foundation for studying interaction with host receptors [40,41], discovering and designing drugs based on structure-based computations (structure-based drug design [SBDD]) [42], etc. Homology modeling studies have been important in discovering treatment options for SARS-CoV-2 entry receptors, such as transmembrane serine protease family member II (TMPRSS2) [43–45]. Rensi et al. created seven homology models representing an ensemble of structures with an average RMSD of 1.27 Å and a maximum RMSD of 1.675 Å [43]. Based on the findings, Argatroban, Otamixaban, Letaxaban, Edoxaban, Betrixaban, Darexaban, and Nafamostat all ranked highly across a majority of model structures and clustered with known active ligands (Figure 3). The known inhibitors confirmed results using a positive control. Ibrahim et al. used a custom DEKOIS 2.0 benchmark set for predicting SARS-CoV PLpro structure and was subsequently employed in a successful virtual screening of the DrugBank database [46].

Molecular dynamics (MD) simulations have been applied in combination with docking to validate the screened compounds against SARS-CoV-2. Mohammad et al. [47] modeled the spike protein of the Alpha variant (mutations: N501Y, A570D, P681H, D614G, T716I, S982A, and D1118H; deletions: H69, V70, and Y144). The mutant was docked with a human furin receptor and showed enhanced binding, responsible for increased infectivity. Similar findings were reported by Murugan and colleagues for the spike model with human ACE2 receptor [48]. Spike proteins of the Alpha, Beta, and Epsilon variants of SARS-CoV-2 were also modeled and tested for antigenicity, showing that the Alpha variant was the most antigenic compared to the Wuhan reference and other strains [49]. Kumar et al. [50] modeled the structures for Omicron and its variants (BA.1.1, BA.2, and BA.3), followed by a demonstration that they had higher infectivity due to increased binding interactions. They also had a higher affinity for the ACE2 receptor compared to the wild-type viral spike protein, shedding light on how variants affect viral entry into host cells. Ovchynnykova et al. [51] prepared mutant models of these variants and then screened traditional Chinese medicinal compounds against them. The compounds hesperidin, narirutin, and neohesperidin, which are flavanone glycosides found in citrus fruits, were identified as potential lead compounds for multitarget SARS-CoV-2 inhibition (Figure 4).

Eweas et al. [52] modeled docked, selected FDA-approved drugs against spike protein of several variants and identified Cefoperazone as having good affinity against all of them.

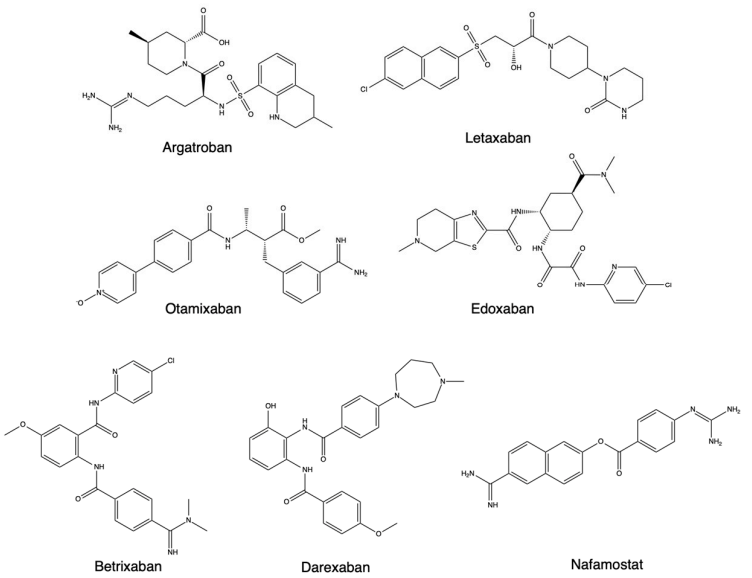

Figure 3. Structures of Argatroban, Otamixaban, Letaxaban, Edoxaban, Betrixaban, Darexaban, and Nafamostat.

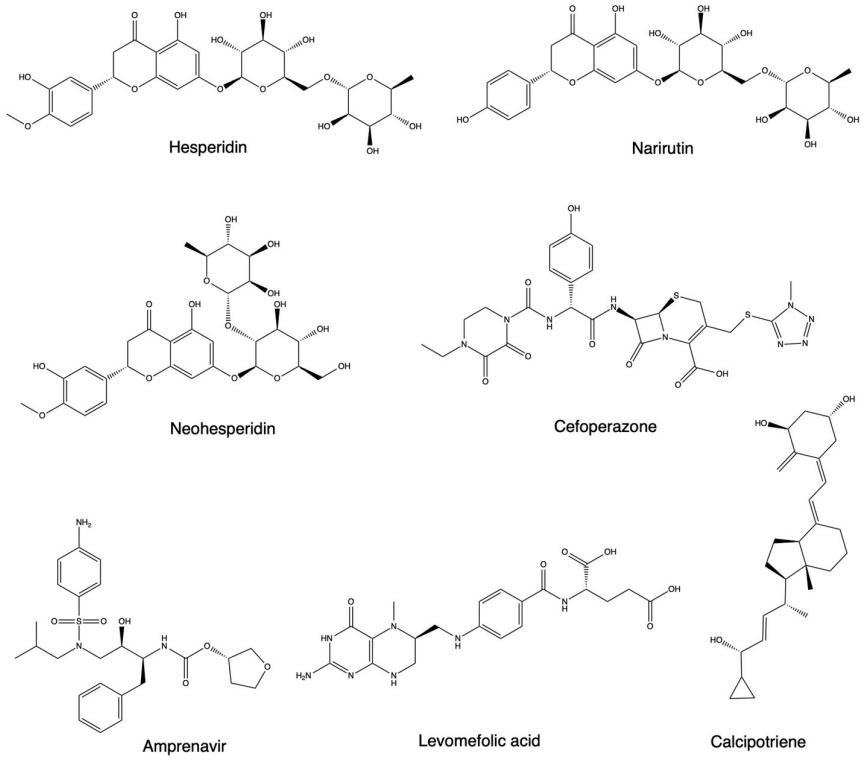

Figure 4. Structures of Hesperidin, Narirutin, Neohesperidin, Cefoperazone, Amprenavir, Levomefolic acid, and Calcipotriene.

Yang et al. [53] screened ZINC database compounds against spike proteins of ten variants of SARS-CoV-2 and docked antibodies against the RBD portion of the protein as well.

The SARS-CoV-2 protease M^{pro} was also identified as an important therapeutic target due to its essential nature for the processing of other viral proteins. The crystal structure availability of M^{pro} and inhibitors opened further opportunities to describe additional

compounds inhibiting these proteins. Molecular docking-based virtual screening (VS) was performed against SARS-CoV-2 variants using the S-217622 compound, and its pan-inhibition properties were confirmed via energy-based simulations [54]. Quan et al. [55] also identified a pan-ketamine inhibitor against the protease of SARS-CoV-2 variants. Guedes et al. [56] also screened FDA-approved and natural metabolites against several proteins of SARS-CoV-2 (including spike, RdRp, nucleocapsid, and M^{pro}) and their variants. Chan et al. used a drug–site pairing strategy to identify three drugs (amprenavir, levomefolic acid, and calcipotriol) binding to three different sites on the spike protein, nintedanib to the nucleocapsid, domperidone to Nsp3 domain, and avanafil to Nsp15 protein, from an FDA-approved drug library of more than 1200 compounds [57].

2.1. Computational Peptide Inhibition Studies

Peptides, although often limited by systemic bioavailability, offer promise for combating SARS-CoV-2 as the oral, nasal, and pulmonary delivery of peptides directly to the site of infection, namely the upper and lower airways. The optimization of peptides for bioavailability, potency, stability, safety, and size is crucial for large-scale manufacturing and successful clinical translation. The prophylactic and therapeutic potential of peptide-based interventions, especially in short-term applications, could significantly contribute to controlling the COVID-19 pandemic, even alongside vaccination efforts. Initially, the peptide design strategies against SARS-CoV-2 were primarily focused on extracting candidates from the ligand-binding motif of the ACE2 receptor and optimizing their sequences to create potent inhibitors targeting the RBD. The computational workflow employed in these designs typically includes established techniques such as homology modeling, computational mutagenesis, docking protocols, re-scoring methods, and MD simulations. Han and Kral designed inhibitors in silico, composed of two consecutive, self-supporting α-helices (a bundle) derived from the protease domain ACE2. MD simulations demonstrated that the α-helical peptides maintain their secondary structure and exhibit highly specific and stable binding, effectively blocking the interaction with SARS-CoV-2. Ling et al. also designed HR1- and HR2-based antiviral peptides, indicating a stronger interaction compared to the natural stage of the fusion core and having the capability to competitively bind with HR1, preventing the formation of the fusion core. In another study, antimicrobial peptides caerin 1.6 and caerin 1.10 from amphibians were identified as having an affinity for the spike protein residue Arg995, situated in the S2 subunit [58]. Another study reported conjugated TAT-peptide docked with drugs (lopinavir, ritonavir, favipiravir, and hydroxychloroquine) repurposed against M^{pro} of SARS-CoV-2 by using PatchDock. The study offered crucial information for the development of cost-effective and biocompatible TP-conjugated anti-SARS-CoV-2 therapeutics [59]. In another study, docking revealed RdRp, 3CL, spike, and nucleocapsid, demonstrated high affinities for binding glycocin F from *Lactococcus lactis* and lactococcine G from *Lactobacillus plantarum* [60]. Marine polypeptides from the Pacific oyster also showed good docking with M^{pro} [61]. Fusion inhibitors based on EK1 pan-CoV inhibitors against variants of the SARS-CoV-2 HR1 domain have also been reported [62]. Fruit bromelain-derived peptide DYGAVNEVK has also shown inhibition of RBD (spike protein) [63].

Rajpoot et al. [64] designed peptide inhibitor Mod13AApi (YADKYQKQYKDAY) with wild-type spike and Alpha, beta, gamma, and delta lineages to hinder ACE2 and spike binding. Physicochemical and computational ADMET analyses indicated favorable properties for the inhibitory peptide. Singh et al. [65] identified five antiviral peptides, AVP1056, AVP1059, AVP1225, AVP1801, and HIP755, targeting RBD of spike protein to hinder its binding with ACE2.

2.2. Quantitative Structure–Activity Relationships (QSAR) Mapping

QSAR is used to predict and interpret the biological activity of molecules based on their structural features. This method involves the mathematical modeling of the relationship between physicochemical properties or molecular descriptors of compounds

and their biological activities. Studies have been carried out using QSAR methods to develop phosphorus-based drugs, which have good inhibitory activity against SARS-CoV-2 proteins and their non-synonymous variants [66–68]. A QSAR study based on the simplified molecular-input line-entry system (SMILES) strings of 32 bicycloproline derivatives has also been applied in the discovery of COVID-19 therapeutics, with the strings applied in calculating 0D, 1D, and 2D molecular descriptors [69]. Similar SMILES notation has been used to reveal new compounds with a potential 3C-like protease and RdRp inhibition activity in rediscovering and repurposing SARS-CoV-2 drugs. QSAR-based virtual screening of 26,467 food compounds and 360 heterocyclic variants identified promising hits against M^{pro} [70]. Apart from this, QSAR analysis on a dataset of sixty-two peptides against the M^{pro} was attempted [71]. The developed QSAR models pinpointed specific features such as the number of sp2 hybridized Oxygen atoms within seven bonds from aromatic Carbon atoms, the presence of Carbon and Nitrogen atoms at a topological distance of 3, and other atom pair interrelations as crucial pharmacophoric elements. The analysis yielded statistically robust and highly predictive models, with R2 = 0.80–0.82, Q2loo = 0.74–0.77, and Q2LMO = 0.66–0.67. These could be utilized for guiding future modifications of peptide-type compounds for anti-SARS-CoV activity. QSAR model of carbon nanoparticles and a SARS-CoV-2 RNA fragment has also been attempted [72]. Models for 17 carbon nanoparticle types revealed strong predictive capabilities, with molecular weight, surface area, and carbon atom degrees sum identified as key descriptors influencing interactions. The affinity between carbon nanoparticles and the virus RNA increased in the order of fullerenes < graphenes < carbon nanotubes.

2.3. Antibody Docking

SARS-CoV-2-neutralizing antibodies primarily target conformational epitopes, and, using docking simulations, researchers have inferred that the CR3022neutralizing antibody from humans and mouse antibodies F26G19 and D12 displayed high affinity for the spike protein of SARS-CoV-2 [73]. Utilizing in silico all-atom MD simulations and deep learning approaches, Zhang et al. revealed that delta variant mutations significantly diminished the binding affinity between spike protein and the LY-CoV555 antibody (also known as Bamlanivimab), which has demonstrated efficacy in neutralizing the wild-type SARS-CoV-2. Previous research has also highlighted the significant impact of a single mutation in the receptor-binding domain (RBD), with some antibodies being notably affected by individual mutations, e.g., K417N reduces the neutralizing activity of Etesevimab, and Bamlanivimab is notably weakened by E484A. Certain antibodies are influenced by multiple mutations, and the combined effect of these mutations can only be estimated based on the individual impact of each mutation. Regdanvimab may experience reduced effectiveness due to the combined presence of K417N, E484A, Q493R, and Y505H in Omicron. The neutralization effectiveness of antibodies may be variably diminished due to the extensive mutations present in the variant proteins. Antibody and nanobody interaction modeling with variant spike proteins to study the evasion of variants by comparing binding scores has also been attempted [74]. Mutations in the variants altered the conformation of the spike protein epitope, making it less recognizable to specific antibodies, including REGN10933, LYCoV555, B38, C105, or H11-H4. This shows how variants may accumulate escape mutations that confer a selective advantage by avoiding neutralization. However, Nb20 showed distinct behavior by recognizing a less variable epitope on the spike protein, enabling it to maintain neutralizing activity against the Delta variant. Antibody–variant interactions have implications for vaccine development. This information regarding interactions with neutralizing antibodies is crucial for designing vaccines that provide broad protection. Das et al. identified that tixagevimab, regdanvimab, and cilgavimab exhibit effective neutralization against a majority of SARS-CoV-2 Alpha strains, while tixagevimab, bamlanivimab, and sotrovimab form a robust complex with the Delta variants. They leveraged this information to design a chimeric antibody by combining the CDRH3 region of regdanivimab with the framework of sotrovimab. The aim was to address variants that might have the potential to

evade neutralization mediated by monoclonal antibodies [75]. Tang et al. docked antibodies against the RBD portion of the protein as well.

2.4. ML for Inhibitor Screening

Researchers have used different AI methods for generating drug-like molecules and then screened them against SARS-CoV-2 proteins. Elend et al. [76] used an evolutionary algorithm and a neural network model coupled with MD simulations to design and assess potential drug candidates. The study illustrates this workflow by applying it to the design of drugs targeting the M^{pro}. Out of approximately 140,000 molecules generated via AI methods, MD analysis identifies 2 molecules as promising drug candidates. A Bayesian ML model identified lumefantrine, an antimalarial, as a potential candidate against spike protein from FDA-approved compounds, and its binding was confirmed via in vitro analysis [77]. Nguyen et al. [78] used algebraic topology and deep learning (MathDL) to accurately rank the binding affinities of 137 SARS-CoV-2 M^{pro} inhibitor structures. Haneckzok and Delijewski [79] employed various supervised ML models utilizing different approaches (including shallow learning methods with fixed molecular fingerprints, Graph Convolutional Neural Networks utilizing self-learned molecular representations, and a combination of fixed and Graph-CNN learned representations) to the molecular representation of FDA-approved compounds against 3CLpro. The antimicrobial drug Sulfadiazine was ranked as the top inhibitor. Qu et al. [80] employed a de novo design method, integrating a recurrent neural network, reinforcement learning, and molecular docking to generate inhibitors for the SARS-CoV-2 main protease. Around 30,000 molecules were generated and subjected to physicochemical filters and molecular docking scores, resulting in the selection of five drug candidates. Yao et al. [81] assessed 2635 FDA-approved drugs and 1062 active ingredients from Traditional Chinese Medicine herbs using docking coupled with ML and identified Fostamatinib, Linagliptin, Lysergol, and Sophoridine as potent inhibitors after validation with experimental assays (Figure 5). ML has also been used to explore scaffold diversity and identify potential COVID-19 drugs, such as Tizanidine HCl and Raltegravir, against the main protease, helicase, papain-like protease, and replicase polyprotein 1ab [82]. Analyzing fragments and breaking down molecular structures revealed that pyrrolidine and indole molecular scaffolds were potent inhibitors of SARS-CoV-2. Jukic et al. [83] used virtual screening coupled with ML to maximize enrichment and incorporate structural data on known 3CLpro inhibitors into focused libraries. Decoys were used in data training, and compounds were prioritized against Alpha, beta, gamma, and delta variant proteases. Ghosh et al. [84] used a random forest approach to target spike-human protein interaction for the Alpha, Beta, Delta, Gamma, and Omicron variants. A list of 40 unique drugs, including eicosapentaenoic acid, doxercalciferol, ciclesonide, dexamethasone, methylprednisolone, among others, was prioritized based on data from DrugBank and ChEMBL.

2.5. ML for Antibody Screening

Magar et al. [85] employed various ML models to predict potential synthetic antibodies for SARS-CoV-2 neutralization. Utilizing 1933 virus–antibody sequences with patient neutralization responses, an ML model was trained. Employing graph featurization with ML methods such as XGBoost, Random Forest, Multilayered Perceptron, Support Vector Machine, and Logistic Regression, thousands of hypothetical antibody sequences were screened. Nine stable antibodies with potential SARS-CoV-2 inhibition were identified, and their stability was verified using a combination of bioinformatics, structural biology, and MD simulations. Desautels et al. [86] generated neutralizing antibody structures for SARS-CoV-2 based on SARS-CoV-1 neutralizing antibodies using ML. These were predicted to interact with the SARS-CoV-2 RBD, exhibiting improved interaction with free energies as low as −82.0 kcal/mol. In a study by Frei et al. [87], a deep learning-guided approach was employed to identify antibodies with enhanced resistance to SARS-CoV-2 evolution. Deep Mutational Learning, an ML-guided protein engineering method, was

utilized to explore a vast sequence space of combinatorial Spike protein receptor binding domain mutations, predicting their impact on ACE2 binding and antibody escape. A high mutational distance library was constructed using the full-length RBD of Omicron BA.1 and experimentally screened for ACE2 binding or neutralizing antibodies, followed by deep sequencing. Ensemble deep learning models were trained on the resulting data, accurately predicting binding or escape for therapeutic antibody candidates targeting diverse RBD epitopes. The approach was extended to assess antibody breadth by predicting binding or escape to synthetic lineages representing millions of sequences generated via in silico evolution. This deep learning strategy holds promise for designing next-generation antibody therapies effective against future SARS-CoV-2 variants.

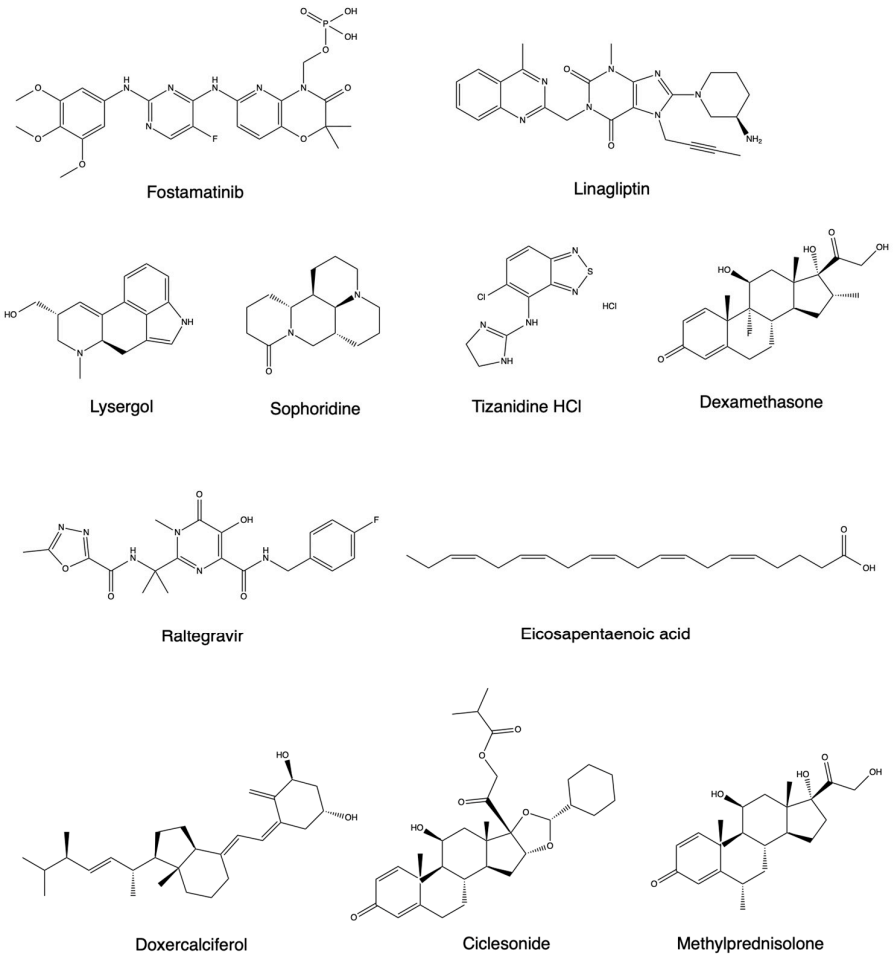

Figure 5. Structures of Fostamatinib, Linagliptin, Lysergol, Sophoridine, Tizanidine HCl, Dexamethasone, Raltegravir, Eicosapentaenoic acid, Doxercalciferol, Ciclesonide, and Methylprednisolone.

2.6. Nanoinformatics for SARS-CoV-2 Inhibition

In a docking study, Fe_2O_3 and Fe_3O_4 iron oxide nanoparticles (FDA-approved for anemia) were explored for their interaction with the domain of SARS-CoV-2 spike protein [88]. Efficient binding was observed, suggesting potential viral inactivation by inducing conformational changes. Research by Zhang et al. [72] also provided theoretical insights into the potential applications of engineered carbon nanoparticles for the adsorption, separation, and inactivation of SARS-CoV-2 RNA. Carbon nanotubes showed better binding than fullerene and graphene nanoparticles. ZnO nanoparticles docking with COVID-19 targets, including the ACE2 receptor, RdRp, and main protease, have shown favorable binding with hydrogen bond formation [89]. Skariyachan et al. [90] predicted the binding potential of carbon nanotubes and nano-fullerene to multiple targets of SARS-CoV-2, including the spike glycoprotein, RNA-dependent RNA polymerase, main protease, papain-like protease,

and RNA binding domain of the nucleocapsid proteins. Docking and simulation suggested significant binding of carbon nanotubes and fullerene to the prioritized multi-targets of SARS-CoV-2, with carbon nanotubes showing better interaction. Aallaei et al. [91] used docking and MD simulation to study the cytotoxicity of various copper nanoparticle shapes and their impact on inactivating the coronavirus by binding spike and protease of the virus. The results revealed that interactions with cylindrical and conical copper NP ligands were more efficient than spherical copper NPs in controlling coronavirus replication. Al-Sanea et al. [92] also demonstrated the potential of green synthesized silver nanoparticles against SARS-CoV-2 NSP16.

3. Future Prospects of Computational Therapeutic Study for SARS-CoV-2

The future prospects of computational therapeutic studies for SARS-CoV-2 are highly promising considering the challenges inherent in traditional drug discovery methods. Traditional approaches encounter significant obstacles, such as time-consuming processes that often span years from target identification to clinical trials [93]. This prolonged timeline becomes a critical limitation, especially during pandemics, where swift therapeutic solutions are imperative. Additionally, the high cost and resource intensity associated with traditional drug discovery exacerbate the challenge, making it financially burdensome and limiting the exploration of multiple drug candidates [94]. Identifying suitable drug targets further adds to the bottleneck, relying on laborious experimental methods that may not keep pace with the urgent demand for innovative therapies. In response to these challenges, recent advances in in silico therapeutic studies have emerged as a beacon of progress. Computational methods, particularly CADD, have the potential to revolutionize the traditional drug discovery process [95,96]. Techniques like docking and simulation have proven instrumental in identifying specific regions on viral proteins crucial for interactions with host cells, enabling the targeted design of inhibitory peptides [97,98]. This approach allows for designing inhibitors with increased potency, reduced adverse effects, and long-lasting activity. Moreover, the adaptability of CADD models facilitates the rapid assessment of how emerging viral variants might impact drug efficacy, providing anticipatory capabilities essential for designing drugs effective against evolving strains of SARS-CoV-2 [99]. CADD also leveraged big data to generate comprehensive insights into the interactions between drugs and viral proteins. The analysis of large datasets enhances researchers' understanding of the complex dynamics involved in viral infections and drug responses.

QSAR models contribute to predicting the biological activities of chemical compounds based on their structural features, enhancing the screening process for potential drug candidates [100]. Computational approaches extend to antibody interactions with the virus at a molecular level, aiding in the design and optimization of antibodies for maximum efficacy in neutralizing the virus [101]. ML has also been in practice for accelerating the drug discovery process by identifying novel compounds with anti-SARS-CoV-2 activity. ML algorithms play a crucial role in accelerating the drug discovery process [77]. Methods using ML have been effective in identifying novel compounds with anti-SARS-CoV-2 activity and predicting the impact of viral mutations on drug efficacy [84]. As ML algorithms continuously learn from updated datasets and real-time information, they enhance their predictive accuracy, providing valuable insights for the development of targeted and adaptable therapeutic interventions. New computational methods also enable a more personalized approach to drug design, considering individual variations in viral strains and host responses. This tailoring of therapeutics can improve treatment outcomes and reduce adverse effects [102,103]. In essence, the integration of ML into SARS-CoV-2 research not only expedited drug discovery during the pandemic but has established a foundation for intelligent, data-driven responses to the challenges posed by viral variants. Looking ahead, these recent advances in in silico therapeutic studies offer significant potential for shaping the future landscape of drug discovery and pandemic preparedness. The integration of computational methodologies provides a foundation for more intelligent,

data-driven responses to the challenges posed by viral variants, laying the groundwork for a more efficient and adaptable approach to combat future pandemics.

Keeping these developments in mind, the post-COVID vision for CADD involves several transformative trends based on both the merits and limitations experienced during the pandemic. One notable shift is the increased integration of AI and machine learning into CADD methodologies, leveraging these technologies for enhanced predictive modeling and efficient analysis of large datasets. Collaborative open data platforms are anticipated to become more prevalent, encouraging global cooperation by facilitating the sharing of diverse datasets in drug discovery research. Adaptive virtual screening protocols are likely to evolve, incorporating real-time data and dynamic simulations to improve hit identification accuracy. CADD strategies are expected to focus on polypharmacology and drug repurposing, exploring broader drug interactions and repurposing opportunities. Advanced molecular dynamics simulations will play a more significant role in capturing dynamic biomolecular interactions over extended timescales. Future vision also includes the development of virtual patient models, integrating genomics and clinical data for personalized medicine in drug discovery. Ethical considerations and responsible AI practices are likely to be incorporated into CADD approaches to address biases and ensure fairness. Real-time monitoring and early warning systems are envisioned for proactive measures in drug discovery against potential future pandemics. Virtual collaboration platforms will facilitate remote collaboration among interdisciplinary drug discovery teams, and the continued emphasis on experimental validation will maintain a balance between computational predictions and robust biological understanding. Overall, these trends aim to shape a more innovative, collaborative, and ethically grounded future for CADD in drug discovery.

4. Conclusions

The existing computational drug repurposing and redesign models offer an opportunity for developing new drug candidates for treating SARS-CoV-2. Compounds that act on various viral proteins necessary for infection or replication have been screened using CADD, and there is evidence that there are potent candidates for further analysis in vitro and in vivo. The future implications of CADD for SARS-CoV-2 drug discovery are transformative, offering innovative solutions to overcome the challenges posed by viral infections. As technology continues to advance, the integration of computational approaches such as ML with docking, simulation, and other assays, including experimental methodologies, will likely become a cornerstone in the development of effective antiviral therapeutics. The consolidated in silico approach has the potential to catalyze advancements in drug discovery, contribute to our understanding of viral infections, and enhance preparedness for future infectious outbreaks, along with the opportunity to combat mutating strains of circulating viruses and infectious agents.

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