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Advances in virtual screening techniques for anti-viral drug design: A computational perspective

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Abstract. With the outbreak of the novel coronavirus, which has been found to mutate almost once a week, future viruses may mutate faster than we think. To deal with the mutation of the virus as soon as possible, the development of new drugs should be accelerated. The traditional drug research and development cycle is long, the cost is high, and the human resource consumption is large. Virtual screening technology has gradually become an indispensable link in the research and development of new drugs because of its high efficiency and low cost. This paper introduces the discovery, structure, symptoms and pathogenesis of 5 viruses (HIV, HBV, HCV, Ebola Virus, Coronavirus), and summarizes the application cases of virtual screening technology in the research and development of new antiviral drugs in recent years, to provide a reference for researchers.

Keywords: anti-viral drug, virtual screening, drug discovery.

1. Introduction

The situation has been evolving rapidly since the outbreak of COVID-19 in early 2020. The pandemic has affected every aspect of society, from human life and health to the economy to work and lifestyle. By 2023, COVID-19 cases have been confirmed in more than 200 countries and regions in the world, except for several countries such as North Korea (World Health Organization, 2023b). This outbreak's rapid spread, wide range and high fatality rate is rare in a century. The pandemic is a global test.

To deal with its mutations as quickly as possible, research and development of new drugs should be accelerated. According to the literature, the development of each new drug is estimated to cost an average of US $1.3 billion, which will take about 12 years [1]. It can be seen that the traditional drug research and development cycle is long, the cost is high, and the human resource consumption is large.

Computer aided drug virtual screening uses computer artificial intelligence pattern recognition technology and computer technology and professional application software, the information of small molecules in the three-dimensional structure database was matched with the search criteria one by one to find small molecules conforming to specific properties or three-dimensional structure shape, and some promising compounds were selected from a large number of compounds for experimental activity evaluation, to find suitable drug molecules. Common databases for computer virtual drug screening include the Zinc Database [2]; Cambridge Structural Database (CSD) [3], Available Chemical Directory (ACD, MDL, San Leandro CA), National Cancer Institute Database (NCID), Chinese Natural Product

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Database (CNPD) [4], etc. The object of virtual screening is a compound database. This data is virtualized, which enlarges the scope of drug selection. Compared with traditional experimental screening, it saves the consumption of financial resources, energy and time, Narrows the cycle and investment of drug research and development, reduces the cost of drug development, and improves the efficiency of drug development [5]. The development of parallel algorithms has also enabled high-throughput virtual screening [6]. Virtual screening technology has become an important means of drug research and development. Computer-aided drug design has been widely used in the treatment of Alzheimer's disease [7], inflammation [8], neurodegenerative disorders and other diseases [9]. It is widely used in the research of anticancer drugs [10], antibacterial drugs [11], antiviral drugs and other drugs [12]. Now the main computer-aided screening softwares include AutoDock [13], DOCK-GOLD etc [14].

2. Computational Methods Against HIV Infection

Acquired immunodeficiency syndrome, or AIDS, describes a medical complication in that the host immune system is repaired, resulting in higher susceptibility to pathogen infection. AIDS is caused by infection with the Human immunodeficiency virus (HIV). In 2021, an estimated 38.4 million people were living with HIV worldwide, with 650,000 deaths that year [15].

The human immunodeficiency virus is about 120-140 nanometers in diameter and is roughly spherical [16]. In HIV, encodes a total of 17 known proteins, including six structural proteins, two envelope proteins, two regulatory proteins, three enzymes, and four helper proteins [17].

Strategically, drugs targeting HIV infection should interrupt the replication of virions in host cells. Therefore, every single step of its life cycle can be potentially utilised, including cell entry, replication of RNA, synthesis of proteins, genome integration, and virion release [18]. Scientists have developed several drugs that target different components of HIV's different life activities through virtual screening.

Against capsid protein, CAP-1 is a small molecule that has been identified as a capsid inhibitor of HIV-1. This compound was identified from computational screening of chemical libraries. This molecule binds to cracks in the CA-NTD domain and inhibits capsid protein synthesis [19].

Against transmembrane protein gp41, the gp41 transmembrane protein plays a key role in the complex fusion process of HIV. Gp41 is usually embedded in the envelope. When gp120 binds to CD4 molecules, it has a conformational change, exposing the binding site of the HIV co-receptor. After binding with the co-receptor, gp41 mediates the fusion of HIV and CD4 cells, thus HIV enters the cell. Through virtual screening, someone selected theaflavin gallate (TF3) for similarity search and finally proposed three small molecules as possible gp41 inhibitors. The experimental results show that the carboxylic acid part of these compounds is used for electrostatic interaction, which is the same as the TF3 hydroxyl group. The Root means square deviation (RMSD), root mean square fluctuation (RMSF) and radius of gyration (Rg) changes generated in the simulation process confirmed the binding stability of the three compounds and the complex of TF3 and gp41 [20].

Against reverse transcriptase, 5 different docking platforms were used to predict the relative biological activity of 111 known 1,2,4-triazole and 76 other azole type HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). The results show that some molecular docking procedures can help predict the relative biological activity of azole NNRTI after optimisation and proper validation [21].

Against protease, darunavir is the most potent HIV PR inhibitor that is known. A series of darunavir derivatives were evaluated with 3D-QSAR (quantitative structure–activity relationship) and docking methods, demonstrating that the ligand-based and receptor-based results were in agreement with the experimental results. The evaluation was conducted by 3D-QSAR study. This set of information can be used to design highly effective drug candidates against wild and mutated forms of the virus [22].

Against integrase, 38 compounds were selected from an in-house library containing 1,430 natural products and their derivatives, via structure-based virtual screening, with one of them, named NPD170, showing the highest anti-viral activity [23].

In addition to viral proteins, CCR5 and CXCR4 are also being studied as drug targets, which could potentially inhibit the entry of viruses into host cells. Receptor - and ligand-based virtual screening

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pipelines prove to be promising tools for finding antagonists for selected targets. The compounds screened by computer simulation can inhibit the CCR5 and CXCR4 receptors [24].

3. Computational Methods Against HBV Infection

Hepatitis is the inflammation of the liver tissue. It can be asymptotic or develop yellow discolouration of the skin and whites of the eyes (jaundice), poor appetite, vomiting, tiredness, abdominal pain, and diarrhoea [25]. Virus infection is one of the most common causes of hepatitis, which can be classified into hepatitis A, B, C, D, E and G [26].

So far 6 viruses have been identified which are exclusively associated with hepatitis, and they were named according to their order of discovery: hepatitis A virus (HAV) to hepatitis G virus (HGV). Neither similarity in genome organisation nor nucleotide sequence homology is evident among these six hepatitis viruses [27]. Clinically, HBV and HCV have drawn more concern due to their high fatality rates. As estimated by the CDC, in the US there were 14,000 new HBV cases and 66,700 new HCV cases in the year 2020. The yearly deaths of HBV and HCV are 0.45 and 3.45 (per 100,000 population), respectively [28].

HBV is a kind of hepadnavirus, which contains dsDNA as genetic materials but requires reverse transcription to replicate (class VII). The genome of HBV is in a unique partially double-stranded manner, and it is repaired to be an intact double-stranded circular DNA in the host cells before transcription [29]. Drugs are also available for chronic hepatitis B treatment: interferon α as a broad-spectrum antiviral cytokine was approved by the FDA[30]; nucleoside analogues are also effective e.g. entecavir and tenofovir [31].

In addition to existing treatments for HBV infection, people are also working to develop novel anti-HBV drugs via computational methods. Current drugs used to treat hepatitis B are effective in inhibiting viral replication, but they also have some potential side effects and limitations. Resistance to nucleoside drugs is a limitation of this class of drugs. Long-term use of these drugs can cause the virus to mutate and become resistant to the drugs. Interferon drugs need to be injected and used for long periods, and not all patients can voluntarily finish the entire treatment. Interferon drugs may also cause adverse effects such as autoimmune diseases and psychiatric problems [32].

As the key enzyme for genome replication, DNA polymerase is a major drug target. For example, a recent study acquired the HBV polymerase structure via homology modelling from the reverse transcriptase of HIV, which was then used for molecular docking of 56 phytochemicals. As a result, a compound known as frangulosid was identified to possess high affinity to the active site of HBV DNA polymerase [33].

Moreover, some other protein targets are also exploited. For instance, HBx is a functional protein of HBV that is mainly involved in protein-protein interaction. A study used the predicted structure of HBx to screen out a few rutin (a phytochemical) derivatives with anti-HBx activity [34]. Interestingly, the secondary structure of RNA may also be a drug target. A recent study revealed Daclatasvir to be an effective compound to inhibit the ε domain of the pre-genomic RNA of HBV. Since Daclatasvir is also an FDA-approved drug for HCV infection, it may have the potential to treat complex virus-linked liver infections or cancer [35].

4. Computational Methods Against HCV Infection

HCV is a kind of flavivirus, which belongs to class IV, with (+) ssRNA that is used directly as mRNA. HCV is coated by an E1-E2 envelope[36]. Unlike HBV infections in adults, the vast majority of HCV infections are not self-resolved and can progress to a chronic infection. The high chronicity is an outstanding feature of an HCV infection [37].

The HCV virus contains nucleic acid and protein components, and the virus is surrounded by a membrane. Key proteins in the capsid of HCV include ribosomal key proteins, antigenic viruses (E1, E2), dihydroenzymes, snake venom phosphodiesterase, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. E1 and E2 are two structural proteins of HCV, which are located on the surface of the virus and are mainly responsible for binding to host cells. NS3-NS5B is several non-structural proteins of HCV, including a

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protease, an RNA-independent RNA polymerase, an RNA-dependent RNA polymerase/spirase, and a regulatory factor [38].

Traditionally the combination therapy of IFN and ribavirin is used for the treatment of a chronic HCV infection. Recently serine protease inhibitors have been developed to specifically block the action of HCV [39].

A study targeting NS5B polymerase of HCV identified a rhodanine analogue with decent potency [40]. Here the Glide's High Throughput Virtual Screening (HTVS) workflow was employed. 4 compounds were screened out with promising affinity, with their IC50 and their binding kinetics analysed. In another study, 227 compounds were obtained based on pharmacophore research from a library containing 37,447 chemicals and further molecular docking screened out 103 of these showing high affinity against the RNA polymerase of HCV. Then the top 40 compounds with the highest scores were selected for a cell-based assay. Among them, T29 exhibited the highest affinity to the hydrophobic pore at the aryl binding site, and compound T29 showed the most effective antiviral effect as assessed by the cell-based assay [41].

Another study used NS3/NS4A serine protease as the target, which is essential in HCV maturation and attenuating host immunity. Through this work, 16 hits were identified from 203k compounds, and two of the strongest molecules with lower cytotoxicity were successfully screened [42].

5. Computational Methods Against Ebola Virus

Ebola virus disease (EVD) is a severe and frequently lethal disease caused by the ebola virus (EBOV). It was first discovered in 1976 in Sudan and the Democratic Republic of Congo [43]. Signature symptoms of EVD include high fever, diarrhoea, organ dysfunction, and internal and external haemorrhage. EVD is notorious for its high case-fatality rate (CFR). The accumulated death toll of EVD has exceeded 30,000 around the world, of which more than 11,000 are from the 2014-2016 outbreak [44].

The nucleic acid of EBOV encodes seven genes. Apart from GP, each gene only encodes one protein [45]:

Table 1. List of Genes and Proteins of Ebola Virus.

No.	Gene	Protein
1	NP	nucleoprotein for RNA encapsulation
2	L	RNA polymerase
3	VP35	for RNA synthesis regulation and other functions
4	VP40	for cellular trafficking and other functions
5	GP	glycoprotein for viral entry, receptor-binding, fusion etc.
6	VP30	contains zinc-binding site, for transcription regulation
7	VP24	multifunctional, including IFN inhibition

As of March 2023, there are two treatments approved by the FDA to treat EVD. The first drug approved in October 2020, Inmazeb™, is a combination of three monoclonal antibodies [46]. The second drug, Ebanga™, is a single monoclonal antibody and was approved in December 2020 [47].

There have been a few studies using virtual screening to find pharmacological inhibitors of Ebola virus proteins. Common drug targets include VP40, VP35 and glycoprotein (GP). The 3D structures of such proteins have been available for virtual screening studies:

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Table 2. List of Proteins Available for Virtual Screening of Ebola Virus.

No.	Protein	Method	Resolution (Å)	Reference
1	VP40	X-ray crystallography	1.60	[48]
2	VP35	X-ray crystallography	1.75	[49]
3	GP	cryo-EM	4.30	[50]

In 2016, a group in Hong Kong selected the RNA-binding site of VP40 as the docking target. iScreen server was used, which is a compact web server for TCM docking and virtual screening. Following validation by molecular dynamics simulation (MSD), emodin-8-beta-D-glucoside was identified as a novel VP40 inhibitor [51].

In another study, A virtual screening method combining a pharmacophore model, 3D QSAR model and docking study was used for screening. 144 inhibitors of VP35 collected from literature were charaterised by 3D-QSAR analysis. A common pharmacophore called HypoA was selected for the test. The pharmacophore model HypoA was further optimized to produce a new pharmacophore model HypoB. A common pharmacophore named HypoA was chosen for the test. A subsequent virtual screening further selected seven potentially active compounds for use as VP35 inhibitors [52].

A more recent study utilised a larger chemical library, the Mcule database, which consists of around 36 million compounds for a high-throughput virtual screening against the GP protein of Ebola. Following the molecular docking using AutoDock Vina and post-optimisation using FlexX, three compounds showing high drug-likeness were identified [53].

6. Computational Methods against Coronavirus Infection

Since the 21st century, people have experienced three waves of coronavirus outbreaks, including SARS, MERS and Covid-19.

The causative reagents of SARS, MERS, and COVID-19, namely SARS-CoV, MERS-CoV, and SARS-CoV-2, are all (+) ssRNA viruses (class IV) and are enveloped, spherical, and about 120 nm in diameter and possess a single strand RNA genome of approximately 30 kb. The key genes that encode important proteins, including outer membrane protein (S protein), envelope protein (E protein), small membrane protein (M protein) and core protein (N protein), line on the genome from 5’ end to 3’ end [54].

For SARS and MERS, there haven’t been any FDA-approved targeted drugs. Corticosteroid, nonetheless, was used to treat SARS infection during its outbreak and improved the survival rate [55]. For COVID-19, remdesivir, a re-purposed nucleoside analogue originally used for the Ebola virus, is used to inhibit the replication of viruses [12]. Immune modulators such as Olumiant and Actemra are also used for certain hospitalised adults [56]. Since the identification of SARS, MERS and SARS-CoV-2, there have been extensive studies to reveal the 3D structures of the viruses [57].

In 2021, use pharmacophore-based virtual screening to identify potential inhibitors of S1 protein. Before the virtual screening, 11,295 natural compounds were searched for pharmacophore, which figured out 4 leading compounds. Pharmacokinetics and toxicity assays were also performed for these selected compounds [58].

In the past three years, there have been dozens of virtual screening attempts trying to figure out novel drugs against SARS-CoV-2. Notable examples include:

In 2021, according to the NSP12-NSP7-NSP8 complex structure of SARS-CoV-2 and NSP12-NSP7-NSP8 complex structure of SARS-CoV, the NSP12-NSP7 interface model and NSP12-NSP8 interface model were established respectively for virtual screening. Based on virtual screening and docking scores, 8 compounds were selected to calculate the binding free energy. These 8 compounds can be well combined with NSP12-NSP7-NSP8 in crystal structure and provide candidate drugs for the treatment and prevention of SARS-CoV-2 and SARS [59].

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Most virtual screening studies against SARS-CoV-2 have, more or less, guided future directions of drug discovery. However, there is also criticism of the quality of such studies, as many of them are contradictory, and lack necessary validation [60].
Systematic revisions and validations of existing virtual screening against SARS-CoV-2 are needed. The opportunity for future coronavirus diseases, either novel or evolved, has been prospected [61].

7. Conclusion

In this paper, we collate some pieces of literature on the design of antiviral drugs for 5 kinds of viruses by using virtual screening technology and fully show that virtual screening technology can help people screen antiviral drugs in the database. Virtual screening technology has become increasingly prominent in the field of drug design and drug development.

While sorting out the literature, it is found that virtual screening is usually faced with a database containing a large number of compounds, so the calculation amount is very huge. At the same time, various ideas of computer drug design are constantly innovating and improving, and corresponding programs and algorithms should also be improved and developed. The design and development of personalized medicine requires the common development of the basic disciplines of life science, and the integration and penetration of biological and medical data.

Virtual screening in the field of drug design has a lot of application cases, with the further improvement of computer technology and artificial intelligence, virtual screening is expected to play a more important role in drug development.

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