Section A-Research paper

ISSN 2063-5346

ANTIVIRAL DRUG MOLECULES FOR HIV-RELATED ENTRY OR FUSION INHIBITION: COMPUTER-AIDED MOLECULAR DESIGNING (CAMD), DOCKING STUDIES AND DENOVO SYNTHESIS

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Abstract

Antiviral drug molecules are tiny organic molecules that have been designed in directive to target and inhibit viruses, like ***human immunodeficiency virus*** (HIV). HIV viral entry and fusion inhibition these two methods are complicated to achieve as HIV has a detailed mechanism of infection. It is difficult to design useful and safe molecules that can stop the virus from entering cells. Computer-aided molecular designing (CAMD) has created progress possible in the discovery of potential antiviral drug molecules. This basically acts by predicting the 3D structure of target molecules and the exchange between the drug molecules and proteins of viral entry or fusion techniques. This technique permits scientists to rapidly predict the molecular structure of a potential drug and determine potential inhibitors. The success of molecular docking studies depends on the use of accurate methods to achieve the interactions between target molecules and the drug. CAMD has also been utilized to design new and effective drugs via the de novo synthesis technique. This is the synthesizing process of new compounds or molecules from simple organic molecules like amino acids. The objective of this method is to design new

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compounds that can interact and attach to proteins of the virus to prevent viral entry or fusion. In overview, it has been discussed that antiviral drug molecules for HIV-related entry or fusion inhibition, have been created through the use of computer-aided molecular designing (CAMD) integrated with molecular docking studies and de novo synthesis. These techniques are crucial for the rapid development of unique and effective drugs against HIV infection.

Keywords: *Human immunodeficiency virus (HIV), CAMD, molecular docking, amino acids, de novo synthesis, entry or fusion inhibition)*

Introduction

This assignment has discussed a critical topic which is antiviral drug molecules for HIV-related entry or Fusion inhibition. For this research study, 3 important techniques are briefly discussed: computer aid molecular designing (CAMD), Docking studies and denovo synthesis. For discussing the result secondary research occurred. Data are collected from different pieces of literature, and journals. Here it has been provided with a critical section in the literature review portion where attached different authors' opinions on these techniques. After collecting the data the result is discussed from this it has to provide the idea about the following techniques. Here include the recommendation section, which is another important section that provides advice to improve the discussion techniques in the future.

Review of the literature

According to Gruevska, et al. (2021) in their research paper, stated that apoptosis of hepatocytes. In their literature they discussed Apoptosis, or programmed cell death, this is a cellular function that is critical for proper cell development and organ function. In their literature, they also discussed the potential impact of increased hepatocyte apoptosis in patients who are suffering from "***Human Immunodeficiency Virus"*** (HIV) and "***Acquired Immunodeficiency Syndrome"*** (AIDS). The enhancement of hepatocyte apoptosis may occur in liver dysfunction. HIV-infected patients receiving antiviral therapy are particularly susceptible to increased hepatocyte apoptosis. Their article suggests that this may adversely affect the health of these patients by interfering with the proper functioning of the liver. Also, the author suggested that hepatocyte apoptosis may be accountable for specific side effects of antiretroviral drugs, such as hepatotoxicity. Therefore, comprehending the significance of hepatocyte apoptosis and its possible causes may help develop better therapeutic options and correlate outcomes with treatment results. The result of the research study provides useful insight into the impact of increased hepatocyte apoptosis on HIV-infected patients. Further investigation is needed to understand the underlying mechanisms.
According to Cunha, et al. (2021) in their research paper, they discussed the novel antiretroviral therapeutic strategies described for HIV. Their research paper focus on overcoming antiviral resistance, modulation of the immune system and reduction of the viral reservoir. The first strategy used by the authors was to look at overcoming resistance, which includes the utilization

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of antiviral classes that do not have a resistance that is associated with them like entry inhibitors, maturation inhibitors, integrase inhibitors etc. The authors also explore the different drug combinations that basically help to keep viruses from mutating enhancing drug resistance forms. Their second strategy basically highlighted decreasing the viral reservoir. In the infected individual patient, the virus is hidden in the cells. The major component in this is the latency-reversing drugs that basically work to wake up the dormant viruses. Creating them immune-targetable and visible. Transplantation and gene therapy are used to decrease the reservoir of HIV. The third strategy focuses on the importance of modulating the immune system which basically helps to fight the virus. This possesses utilizing the adoptive transfer of immune cells like chimeric antigens carried by T cells, which have the potential to target and kill HIV. The vaccine helps to boost the individual's immune response to HIV. By using these three different strategies the author proposed novel therapeutic approaches that basically promote a combined antiviral treatment and as well as immunomodulation. The following strategies have the potential to decrease the resistance of antiretroviral treatment that reduce their reservoir of HIV.

Approved Drugs	Active Substances	References
Genvoya® Biktarvy®	150 mg elvitegravir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir 50 mg bictegravir/200 mg emtricitabine/25 mg tenofovir alafenamide	[38,39]
Atripla®	600 mg efavirenz/200 mg emtricitabine/245 mg tenofovir-DF	[40]
Rezolsta®	800 mg darunavir/150 mg cobicistat	[40]
Triumeq®	50 mg dolutegravir/600 mg abacavir/300 mg lamivudine	[41]
Evotaz®	300 mg atazanavir/150 mg cobicistat	[42]
Descovy®	200 mg emtricitabine/10 mg tenofovir alafenamide 200 mg emtricitabine/25 mg tenofovir alafenamide	[43]

Figure 1: Describe some approved drugs

(Source: Cunha, et al. 2021)

According to Andrianov, *et al*. (2019) in their research paper, they employed computational techniques to recognize novel aromatic compounds which could perform as potential HIV-1 entry inhibitors, mimicking the cellular receptor CD 4. In their research, they used a method that consisted in identifying putative compounds by taking into consideration the desirable physicochemical properties that are basically found in the molecule capable to penetrate the cellular membrane and attach to the CD4. The recognition pattern based on parameter selection was applied to the virtual library that includes several thousand previously reported aromatic compounds. This allowed for the recognition of several previously unknown molecules that showed activity against HIV-1 in silico. They tested a promising compound an in vitro antiviral assay that is based on the inhibition of the percentage of Env-Pseudotyped virus entry to the target cells. Their research study provides a great insight into their structural features of potential HIV-1 entry inhibitors. These in silico methods are effective when it dealing with large libraries and this applied in the future help to guide the improvement of novel antiviral agents.

The production of antiviral drugs can interact with areas on the surface of the HIV virus and block entry or inhibit the fusion of the HIV virus with the other cells which has been the aim of

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many research efforts. According to Rajkishan, *et al*. (2021) suggested that CAMD is an important tool in the development of drugs. This combines synthesis, design, and screening of the tiny molecule libraries with a medicinal chemistry approach to recognize a broad range of effective and novel HIV entry and fusion inhibitors. The author stated (Ejalonibu, *et al*. 2021) that CAMD is an analogue of potential drugs that have been recognized which binds to the target areas of the virus and inhibit fusion and entry processes. The author stated that docking studies are another procedure that is basically utilized for the potential interaction between drug molecules and the target areas of the HIV virus. The author stated that drug molecules show a good fit with the target protein and are subjected to further synthesis and analysis (Suat, 2020).

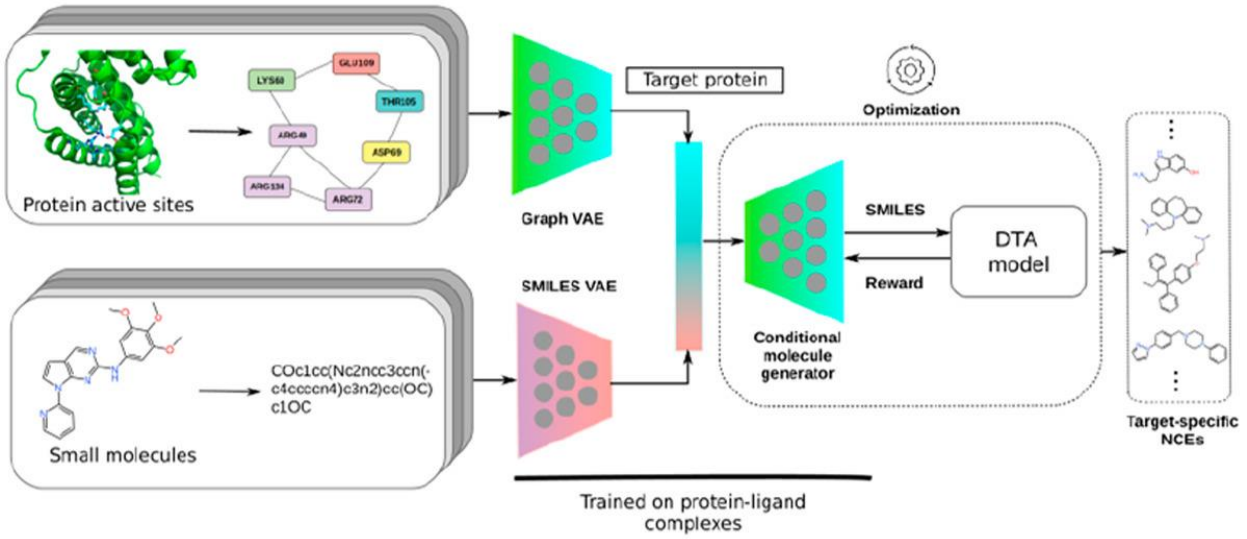

Figure 2: De novo structure-based drug design

(Source: https://pubs.acs.org)

De novo synthesis is utilized for the production of new antiviral drug molecules for HIV fusion or entry inhibition. The author stated that this technique involves the design of the molecule into a tiny form with desired properties. Their aim is to develop the compound with a structure closer to that of the target protein than the other drugs.

ISSN 2063-5346

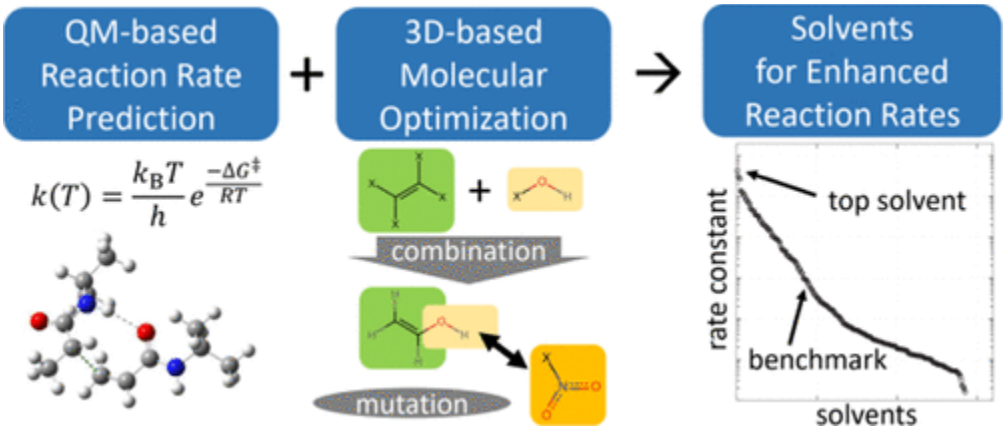

Figure 3: CAMD design of reaction solvent

(Source: https://pubs.acs.org)

Materials and Methodology

For conducting this research secondary analysis has occurred. The data are collected from the different pieces of literature, journals, news articles etc. For collecting the data initially abstract screening has occurred of the selected literature based on the keywords. The data are collected based on the keywords. The pieces of literature are very essential for this study that provide effective information about the research topic. Searching the different information it helps to get knowledge of the different author's opinions about the research topic. The secondary research technique is very effective for this research because it helps to provide different authors' opinions about the research topic. From this, it helps to take a decision about the research topic.

Results and Discussion

For conducting this research the antiviral drug molecules for HIV-related entry and fusion inhibition can be studied extensively by using a combination of 3 different techniques that are CAMD, novo synthesis and docking studies. CAMD is an automated technique that is basically free energy-driven technology. This technology is basically allowed for synthesis and design, and the evaluation of novel drug molecules (Tarasova, *et al*. 2020). Docking studies will enable the quantitatively analyzed the binding energy of the drug molecules as well as their potential target also. Another important technique of de novo synthesis involves combining the various chemical binding that basically assembles the newly synthesized drugs from scratch. Using the CAMD technique, virtual drug synthesis can be performed on a huge number of potential drug molecules. By this process molecules of low binding energy can be recognized that are more likely to interact with the target protein. Also, CAMD can be supplemented with a ligand-based strategy that helps to narrow down the list of effective molecules. This process of virtual drug design eliminates the requirement for costly synthesis and testing of the candidates and confirms that only the most promising molecules are sent for experimental testing.

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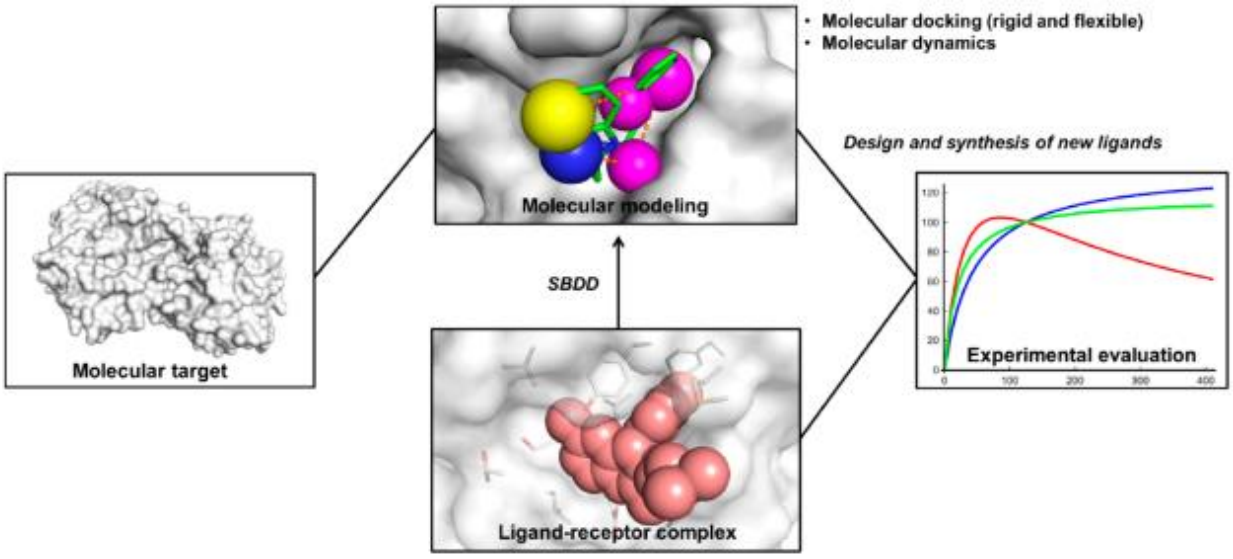

Figure 4: Molecular docking process

(Source: https://www.mdpi.org)

By using docking studies it has been found that researchers will achieve an understanding of the precise interactions between the candidate drug molecules and target protein. These studies measure the relative binding energies of a set of drug candidates and their targets and can help to recognize inverse agonists (Crisa and Bora, 2021). This basically helps to guide the selection of substances that are most likely to interact with the target protein. The other technique de novo synthesis is very powerful for drug design. This approach entails the combination of various chemical building blocks to form a novel compound that is not found in nature. The synthesized molecules can be then tested for their capability to completely or partially block the HIV entry point or fusion process.

In summary, it has been discussed that a combination of the CAMD technique, de novo synthesis and docking studies of antiviral drug molecules for HIV-related entry or fusion inhibition can be effectively studied (Kovač and Časar, 2020). To perform virtual drug synthesis, mapping the binding selectivity of designing novel molecule and drug candidates with the correct affinity, and reactivity. The researchers can expedite the drug discovery process and recognize novel antivirals capable of inhibiting HIV entry or fusion.

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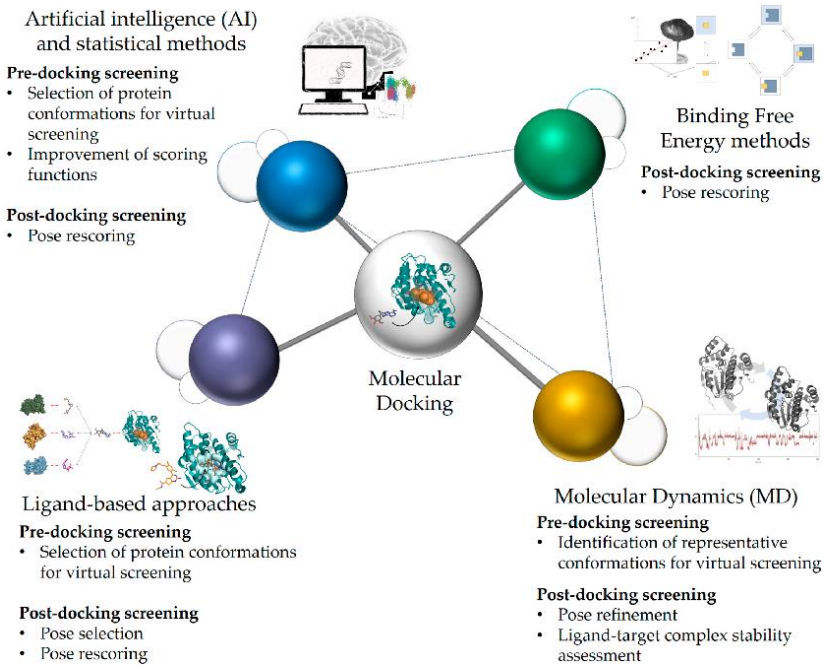

Figure 5: Molecular docking process for drug discovery
(Source: https://d3i71xaburhd42.cloudfront.net)

Conclusion and future scope

After doing this research it has concluded that CAMD, docking studies, and de novo synthesis are crucial procedures that have been used to development of antiviral drugs for HIV fusion and entry inhibition. These efforts have broad application in the development of a drug that could importantly improve HIV control in the patient and helps to save lives.

Future Scope

For conducting this research study there include 3 different techniques that are CAMD, docking studies and Denovo synthesis. These are very effective procedures for antiviral drug molecule entry or fusion inhibition. In the future focus on this different technique and use advanced technology to improve the technique, so that people who are suffering from HIV get accurate medicine at the proper time. This study will help in the overall well-being of society.

Recommendations

This research study includes 3 different techniques that are CAMD is an effective approach for the design and discovery of the drug. It integrates the utilization of computational tools and chemical methods in order to combine chemically diverse compounds into a single entity with high bioactivity. The molecules are designed in a way that they particularly interact with a target site, thereby decreasing the chance of adverse drug-to-drug interaction. Various docking studies such as Virtual docker, and Glide are employed in CAMD to access the potential of compounds

ISSN 2063-5346

to attach with HIV viral protein, the use of denovo synthesis is a series of molecules with the desired activity that can be tested for HIV inhibition.

Successful anti-HIV drugs have been developed by using these procedures in an accurate way. Fusion inhibitors for example maraviroc, enfuvirtide interact with the HIV protein and this hinders the interaction with the host cell thus limiting HIV virus entry into the cells. Protease inhibitors named ritonavir and atazanavir work on the HIV protease enzyme thereby preventing the appropriation maturation of the viral enzyme and this hinders the virus replication. So these approaches are very effective for antiviral drugs for HIV-related entry or fusion.

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Reference list

Journals

Andrianov, A.M., Nikolaev, G.I., Kornoushenko, Y.V., Xu, W., Jiang, S. and Tuzikov, A.V., 2019. In silico identification of novel aromatic compounds as potential HIV-1 entry inhibitors mimicking cellular receptor CD4. *Viruses*, *11*(8), p.746.

Crisan, L. and Bora, A., 2021. Small molecules of natural origin as potential anti-HIV agents: A computational approach. *Life*, *11*(7), p.722.

Cunha, R.F., Simões, S., Carvalheiro, M., Pereira, J.M.A., Costa, Q. and Ascenso, A., 2021. Novel antiretroviral therapeutic strategies for HIV. *Molecules*, *26*(17), p.5305.

Ejalonibu, M.A., Ogundare, S.A., Elrashedy, A.A., Ejalonibu, M.A., Lawal, M.M., Mhlongo, N.N. and Kumalo, H.M., 2021. Drug discovery for Mycobacterium tuberculosis using structure-based computer-aided drug design approach. *International Journal of Molecular Sciences*, *22*(24), p.13259.

Gruevska, A., Moragrega, Á.B., Cossarizza, A., Esplugues, J.V., Blas-García, A. and Apostolova, N., 2021. Apoptosis of hepatocytes: relevance for HIV-infected patients under treatment. *Cells*, *10*(2), p.410.

Gruevska, A., Moragrega, Á.B., Cossarizza, A., Esplugues, J.V., Blas-García, A. and Apostolova, N., 2021. Apoptosis of Hepatocytes: Relevance for HIV-Infected Patients under Treatment. Cells 2021, 10, 410.

Khoury, Z.H. and Meeks, V., 2021. The influence of antiretroviral therapy on HIV-related oral manifestations. *Journal of the National Medical Association*, *113*(4), pp.449-456.

Kovač, L. and Časar, Z., 2020. A literature review of the patent application publications on cabotegravir–an HIV integrase strand transfer inhibitor. *Expert Opinion on Therapeutic Patents*, *30*(3), pp.195-208.

Ma, Y., Frutos-Beltrán, E., Kang, D., Pannecouque, C., De Clercq, E., Menéndez-Arias, L., Liu, X. and Zhan, P., 2021. Medicinal chemistry strategies for discovering antivirals effective against drug-resistant viruses. *Chemical Society Reviews*, *50*(7), pp.4514-4540.

MALLICK, T., MOLECULAR BIOLOGY AND TREATMENTS OF HIV1/AIDS AND NATURAL PHYTOCHEMICALS AS POTENT SOURCE FOR NEW DRUG DEVELOPMENT.

Rajkishan, T., Rachana, A., Shruti, S., Bhumi, P. and Patel, D., 2021. Computer-Aided Drug Designing. *Advances in Bioinformatics*, pp.151-182.

Sharma, D., Sharma, N., Manchanda, N., Prasad, S.K., Sharma, P.C., Thakur, V.K., Rahman, M.M. and Dhobi, M., 2022. Bioactivity and In Silico Studies of Isoquinoline and Related Alkaloids as Promising Antiviral Agents: An Insight. *Biomolecules*, *13*(1), p.17.

Suat, S.A.R.I., 2020. Molecular Modelling and Computer Aided Drug Design: The Skill Set Every Scientist in Drug Research Needs and Can Easily Get. *Hacettepe University Journal of the Faculty of Pharmacy*, *40*(1), pp.34-47.

Tarasova, O., Ivanov, S., Filimonov, D.A. and Poroikov, V., 2020. Data and text mining help identify key proteins involved in the molecular mechanisms shared by SARS-CoV-2 and HIV-1. *Molecules*, *25*(12), p.2944.

Wittine, K., Saftić, L., Peršurić, Ž. and Kraljević Pavelić, S., 2019. Novel antiretroviral structures from marine organisms. *Molecules*, *24*(19), p.3486.