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Research Article

In silico evaluation of compounds from *Hypericum perforetum* for anti-HIV activity

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ABSTRACT

Only a few medications are approved for the treatment of infected patients, despite the prevalence of HIV infection around the world and the absence of effective treatments for AIDS patients. The search for innovative anti-HIV medications with novel mechanisms of action and initiatives to lower attrition rates in the early stages of drug discovery is urgently needed. This study's goal is to assess *Hypericum perforetum* compounds for anti-HIV-1 activity after giving reported potential anti-HIV-1 leads priority. A series of recognised compounds from the medicinal plant *H. perforetum* were subjected to in silico HIV lead prioritisation. These molecules' energy-minimized architectures were docked with HIV-Protease. Using Autodock software, docking tests were conducted, and highly positive contacts between these compounds and the HIV-1 protease enzyme were found. With a higher docking score, occimene was discovered to be in the lead. Eight *H. perforetum* compounds were docked into HIV-1 protease in the current work, and one molecule, E-Beta-Ocimene, suggested that residues Asp29, Ile47, Val32, Leu76, and Pro79 might be crucial for the binding of these compounds. The findings indicated that there is room to increase the activity of occimene analogues in order to find an effective anti-HIV drug.

1. Introduction

The retrovirus known as the human immunodeficiency virus (HIV) is a member of the lentivirus family. HIV types 1 and 2 (HIV-1 and HIV-2) are the culprits behind AIDS (AIDS). Humans with AIDS experience immune system failure, which results in life-threatening opportunistic infections or cancers linked to the immune system's increasing failure (Rodriguez et al, 2016). The global HIV/AIDS epidemic is still an ongoing issue. 39 million persons with HIV/AIDS are estimated to be living in the world as of 2021. According to estimates, India has the third-highest number of HIV-positive individuals worldwide. The National AIDS Control Organization (NACO) report 2021 states that 24 lakh persons with HIV/AIDS were projected to have lived in India in 2017 (NAC, 2022). Those who are HIV-infected cannot currently be treated with specific vaccinations or medications. Presently, the anti-HIV class of medications being used worldwide includes nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) (Hunter et al, 2016; pappalardo et al, 2018); Swapna et al (2022). Protease enzyme aids in the integration of viral DNA into the genome of the host cell by moving viral DNA into the cell nucleus during the HIV life cycle (Passini et al, 2017; Brown et al, 2017). Medicines that disrupt crucial viral replication processes can halt this lethal process. Consequently, Protease activity can be inhibited in order to prevent the virus from infecting the host cell (Grandi et al, 2018; Gujjeti et al, 2013).

St. John's wort, also known as *Hypericum perforatum* L., is a popular medicinal herb that has been used for ten years (Parvinian et al, 2019; Jean et al, 2018). This plant, a member of the Hypericaceae family, has been shown to be effective in treating burns, bruising, swelling, anxiety, mild to moderate depression, wound healing, analgesia, hepatoprotection, antioxidant activity, and microbes (Fugimoto et al, 2018). Lately, numerous studies have shown that hypericum has antiviral and antidepressant characteristics (Parvinian et al, 2019; Pellizzer et al, 2018; Viceconti et al, 2019). Several plants have been utilised because of their biological functions. Due to the fact that these plants manufacture various chemicals. There is no research on the biological effects of *Hypericum perforatum* flower extracts on mastitis bacteria. In comparison to its other biological effects, the antioxidant capabilities of *H. perforatum* flower extracts have received less research. In our research, the non-enzymatic antioxidant, anti-mutagenic, and antibacterial properties of flower methanol extract were examined. The advantages of employing dietary or topically applied *H.*

perforatum preparations for the treatment or prevention of HIV sickness or infection, however, are not entirely well recognised. The potential of *H. perforatum* can still be used in the fight against HIV. The goal of the current investigation is to determine the function of *H. perforatum* in the treatment of HIV employing protease as a target receptor and to assess the lead molecule's binding effectiveness.

2. Materials and Methods

2.1 **Data Set:**

The IMPPAT database (https://cb.imsc.res.in/imppat/home) was used to download phytoconstituents from the *H. perforatum* plant and common medicinal compounds (3D PDB). In table 1, the chosen compounds' chemical characteristics and structures (E-Beta-Formesene, 2,4-Dihydroxy cinnamic acid, E-Beta-Ocimene, Ferulic acid, Ethylene glycol dimethaceylate, Dillapiole, DHCeA, and 2-Methyl-1-butanol) were listed.

2.2 Bioactivity score prediction

Values assigned to a compound's drug score reveal its general potential as a drug candidate. The bioactivity score of synthesised compounds against common human receptors such GPCRs, ion channels, kinases, nuclear receptors, proteases, and enzymes can be predicted using a web-based tool called Mol Inspiration.

2.3 Evaluation of drug likeliness based on Lipinski's rule of five

For characterising the molecular characteristics of medicinal molecules needed for the calculation of significant pharmacokinetic parameters as absorption, distribution, metabolism, excretion, and toxicity, Lipinski's rule of five is useful (ADMET). The rule is useful for developing new drugs. Molsoft server (http://molsoft.com/mprop/) performed the drug-likeness and molecular property prediction.

2.4 Computational Docking Studies:

2.4.1 Preparation of Ligand and Protein:

The Protein Databank database provided the three-dimensional structure of the target HIV-1 Protease (1DMP), which was downloaded in PDB format (https://www.rcsb.org/structure/1dmp).

The protein's ligands and water molecules were taken out, the protein's chemistry was adjusted to account for the missing hydrogen, and then the protein's energy was minimised. Using Autodock technologies, it was possible to optimise drug molecules and phytoconstituents as well as add charges and hydrogen bonds.

2.4.2 Docking

Using Autodock 4, the HIV-1 Protease was docked with a few different phytochemical compounds. Docking server was used to validate the docking computations. To the ligand, Gasitier partial charges were added. Rotatable hydrogen bonds were defined and non-polar hydrogen atoms were combined. On receptor, docking calculations were performed. Affinity (grid) maps received the addition of necessary hydrogen atoms, kollaman charges, and salvation parameters. The auto-grid application generated 25 grid points and 0.500. The van der Waals and electrostatic terms were computed using the autodock parameters set and the distance dependent dielectric functions, respectively.

The Lamarckian algorithm (LGA) and the Solis and Wet local search methods were used to simulate docking. The drug molecules' initial orientation and torsion were set at random. During docking, all rotatable torsions were freed. A total of 10 separate runs, each of which was programmed to end after 250000 energy calculations, were used to create each docking experiment. The population was limited to 150 people. The quaternion and torsion step 5 as well as the translational step 0.2 were used during the search.

3. Results and Discussion

In the field of drug discovery research, computational docking is a crucial method for studying synthesised compounds and their interactions with biological therapeutic targets. The amino acids in the target proteins' active site area were predicted using the molecular docking programme.

3.1 Lipinski's parameters

To determine whether a chemical compound has the characteristics that would make it likely or potentially useful as a medicine in humans, Lipinski's rule of five (RO5) is utilised [29]. The oral activity of a medicinal compound is anticipated by computing certain molecular properties including log P (partition coefficient), polar surface area, number of hydrogen bond donors, number of hydrogen bond acceptors, and molecular weight. According to the rule, the majority of metal complexes with good membrane permeability have a log P value of 5, a number of hydrogen bond acceptors of 10, and a number of hydrogen bond donors of 5. A medication that is active when taken orally typically only violates the requirements once. The synthesised ligand and its complexes in the current investigation were found to be in good agreement with the specified criteria and are therefore considered to have good oral bioavailability.

Table 1 displays the evaluation of drug likelihood based on Lipinski's rule of five ligands. The Lipinski's rule of five is maintained for all ligands based on the drug likeliness evaluation.

3.2 Bioactivity score prediction

The term "pharmacological activity" refers to how medications help living things. The medication is meant to attach to a biological target. The most popular proteins, including enzymes, ion channels, and receptors, are considered biological targets. Drug target is another name for the biological target. The bioactivity scores of the produced complexes were determined based on a variety of characteristics, including binding to nuclear and G protein-coupled receptor (GPCR) ligands, ion channel modulation, kinase and protease inhibition, and enzyme activity inhibition. With the use of the online calculator Molinspiration (www.molinspiration.com), all the parameters were computed and the synthesised complexes were predicted to have moderate biological activity. In Table 2, the bioactivity rating is shown. It is well established that for metal complexes, the bioactivity score should be greater than 0.0 to indicate activity; between 5.0 and 0.0 indicates moderate activity; and less than 5.0 indicates inactivity. Bioactivity scores for the ligand and the four complexes, which ranged from 5.0 to 0.0, clearly show that they have the qualities

Table-1. Evaluation of drug likeliness based on Lipinski's rule of five of ligands

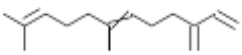
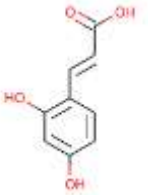
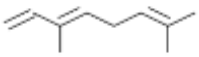
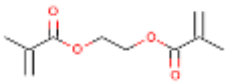
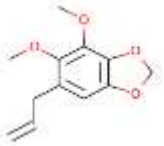
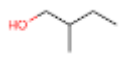
Sl.No	Compound name	Molecular structure	Molecular formula	Molecular weight	No. of H bond acceptors	No. of H bond donors	LogP	molPSA
1.	E-Beta-Formesene		$C_{15}H_{24}$	204.19	0	0	5.20	0.00 A^2
2.	2,4-Dihydroxy cinnamic acid		$C_9H_8O_4$	180.04	4	3	1.30	62.79 A^2
3.	E-Beta-Ocimene		$C_{10}H_{16}$	136.13	0	0	3.48	0.00 A^2
4.	Ferulic acid		$C_{10}H_{10}O_4$	194.06	4	2	1.50	52.80 A^2
5.	Ethylene glycol dimethaceylate		$C_{10}H_{14}O_4$	198.09	4	0	1.23	42.61 A^2
6.	Dillapiole		$C_{12}H_{14}O_4$	222.09	4	0	2.16	32.47 A^2
7.	DHCeA		$C_{10}H_{11}N_5O_2$	233.09	5	4	-0.76	83.81 A^2
8.	2-Methyl-1-butanol		$C_5H_{12}O$	88.09	1	1	1.02	17.63 A^2

Table-2. Bioactivity score of the ligand

S. No.	Compound	Parameters of Bioactivity score					
		GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	E-Beta-Formesene	-0.44	-0.05	-0.77	0.07	-0.68	0.27
2	2,4-Dihydroxy cinnamic acid	-0.50	-0.29	-0.77	-0.02	-0.79	-011
3	E-Beta Ocimine	-0.98	-0.29	-0.77	-0.02	-0.79	-0.11
4	Ferulic acid	-0.47	-0.30	-0.72	-0.14	-0.81	-0.12
5	Ethylene glycol dimethaceylate	-0.78	-0.24	-1.02	-0.33	-0.89	-0.35
6	Dillapiole	-0.51	-0.34	-0.91	-0.68	-0.92	-0.32
7	DHCeA	0.56	0.41	0.71	-1.15	-0.11	1.32
8	2-Methyl-1-butanol	-3.59	-3.66	-3.76	-3.61	-3.55	-3.45

Table-3. Phytochemical compounds docked against HIV-1 Protease

Sl. No	Compound Name	Binding energy	Inhibition constant	Intermolecular energy	Residue involving interaction
1	E-B-Formesene	-1.64	63.08	-3.73	VAL-82,32; LEU-23; PRO-81; THR-80; ASP-29,30; ALA-28; ILE-47,84; GLY-48
2	2,4-Dihydroxy cinnamic acid	-2.60	12.46	-4.09	PRO-81,79; GLY-78 VAL-56,32; THR-80 ILE-84,47; ALA-28; ASP-29,30
3	E-Beta-Ocimene	-3.68	2.01	-4.57	HIS69, GLY68, THR12, ILU66, GLU65
4	Ferulic acid	-0.93	207.18	-2.42	LEU-23; VAL-82; THR-80; PRO-81; ILE-47,84; ALA-23 GLY-48; ASP-29,30
5	Ethylene glycol dimethaceylate	-2.9	7.53	-4.98	ASP-29,30; ALA-28 GLY-48; ILE-47,84; LEU-76 PRO-79,81; VAL-56; THR-80
6	Dillapiole	-2.85	8.21	-4.04	THR-80; VAL-32,82; PRO-81 ILE-47,84; ALA-28; ASP-29,30
7	DHCeA	-2.65	11.45	-3.84	ASP-29,30; LEU-76 VAL-32,56,82; ILE-47,84; THR-80 PRO-81; GLY-48; ALA-28
8	2-Methyl-1-butanol	-2.21	23.93	-3.11	VAL-32,56,82; PRO-79,81 ILE-47,84; THR-80

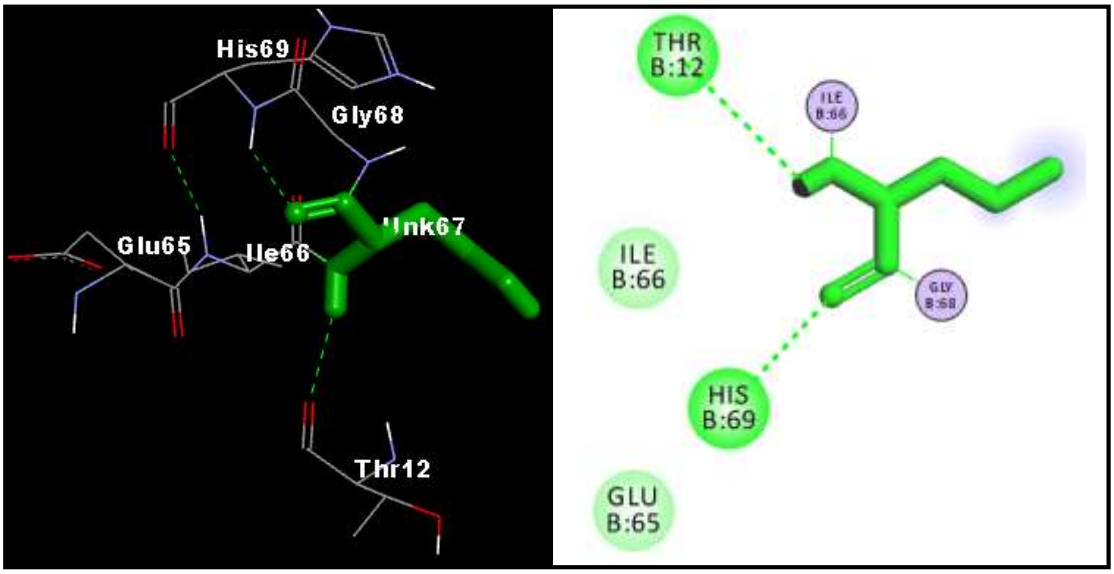


Figure-1. Docking simulation of E-Beta-Ocimene with HIV-1 protease (PDB: 1DMP);
a-3D interactions; b-2D interactions. Green colour dot lines shows hydrogen bond interactions

needed for the complexes to act as possible medications with some alterations to their chemical structure (Table-2).

3.3 Docking interactions

The physicochemical characteristics of *H. perforatum* compounds were investigated, and docking results were tallied. The chemical E-B-Ocimene had better binding affinity to the enzyme when docked against HIV-1 PT, and it obtained a best ligand pose energy of -3.68. The residues involved in the interaction are HIS69, GLY68, THR12, ILU66, and GLU65 (Figure-1).

Hence, among the seve ral chemicals that can inhibit Protease function and prevent the virus from becoming contagious, the former compound is an efficient inhibitor. To confirm their biological potential, additional in vitro and in vivo studies of specific phytoconstituents are nonetheless required. Figure 1 depicts a 3d and 2d structures of the corresponding drug molecule and phytoconstituents interacting with the active site.

4. Conclusion

The pharmaceutical and functional food businesses depend on an understanding of how proteins and ligands interact. The development of bioinformatics has provided a platform for employing computational techniques to investigate diseases at the molecular level. An important factor in the design of drugs with a structure-based approach is the protein-ligand interaction. Eventually, our investigation revealed that E-Beta-Ocimene, out of all the compounds, effectively inhibits HIV-1 Protease, and this plant's phytochemicals can function as HIV-1 Protease inhibitors. This study stresses the value of using small molecules derived from various plant sources to improve *in silico* studies of protein-ligand interactions. Our *in silico* approach can be further investigated in order to develop more potent and effective HIV-1 Protease inhibitors using ligand-based drug development techniques.

Conflicting Interests

The authors have declared that no conflicting interests exist.

References

[1] Brown, R. Qiang, P.J. Stadnik, L.J. Stotts, J.A. Von Arx. Virtual humans for implantable device safety assessment in MRI: mitigating magnetic resonance imaging hazards for implanted medical devices. IEEE Pulse, 8 (4) (2017), pp. 50-53.

[2] Fujimoto, L.M. Angelone, E. Lucano, S.S. Rajan, M.I. Iacono. Radio-frequency safety assessment of stents in blood vessels during magnetic resonance imaging Front. Physiol., 9 (2018), p. 1439.

[3] Grandi, S. Morotti, E. Pueyo, B. Rodriguez. Editorial: safety pharmacology - risk assessment QT interval prolongation and beyond. Front. Physiol., 9 (2018), p. 678.

[4] Gujjeti, R. P., & Mamidala, E. (2014). Anti-HIV activity and cytotoxic effects of Aerva lanata root extracts. American Journal of Phytomedicine and Clinical Therapeutics, 2(7), 894-900.

[5] http://molsoft.com/mprop/

[6] https://cb.imsc.res.in/imppat/home

[7] https://www.rcsb.org/structure/1dmp

[8] Hunter, N.P. Smith The cardiac physiome project J. Physiol. (Lond.), 594 (23) (2016), pp. 6815-6816.

[9] Jean-Quartier, F. Jeanquartier, I. Jurisica, A. Holzinger. In silico cancer research towards 3R. BMC Cancer, 18 (1) (2018), p. 408.

[10] NACO. India HIV Estimates 2021. Fact Sheet. MoHFW, GoI, 2022.

[11] Pappalardo, G. Russo, F.M. Tshinanu, M. Viceconti. In silico clinical trials: concepts and early adoptions. Brief. Bioinformatics (2018).

[12] Parvinian, et al. Credibility evidence for computational patient models used in the development of physiological closed-loop controlled devices for critical care medicine. Front. Physiol., 10 (2019), p. 220.

[13] Passini, et al. Human in silico drug trials demonstrate higher accuracy than animal models in predicting clinical pro-arrhythmic cardiotoxicity. Front. Physiol., 8 (2017), p. 668.

[14] Pellizzer, C.A.A. Lemos, D.A.F. Almeida, V.E. de Souza Batista, J.F. Santiago Júnior, F.R. Verri. Biomechanical analysis of different implant-abutments interfaces in different bone types: an in silico analysis. Mater. Sci. Eng. C Mater. Biol. Appl., 90 (2018), pp. 645-650.

[15] Rodriguez, et al. Human-based approaches to pharmacology and cardiology: an interdisciplinary and intersectorial workshop Europace, 18 (9) (2016), pp. 1287-1298.

[16] Swapna, K., Srujana, M., & Estari, M. (2022). Inhibitory effect against reverse transcriptase of HIV-1 of the extract of selected medicinal plants. International Journal of Health Sciences, 6(S5), 10623–10633. https://doi.org/10.53730/ijhs.v6nS5.10841

[17] Viceconti, E. Dall'Ara. From bed to bench: How in silico medicine can help ageing research. Mech. Ageing Dev., 177 (2019), pp. 103-108.