Establishing Veranoside-A2 as a Potential Antiretroviral Agent for the Treatment of HIV-AIDS: A Computational Analysis

Ayan Agrawal
M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University)
Isha Rani
M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University)
Kamal Shah
GLA University
Somdutt Mujwar (somduttmujwar@gmail.com)
M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University)

Research Article

Keywords: HIV-AIDS, Immunity, Antivirals, Anti-HIV, Herbal, Drugs, etc.

Posted Date: August 17th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1952015/v1

Abstract

Immunocompromised human ailment commonly acknowledged as acquired immunodeficiency syndrome (AIDS) is instigated on by human immunodeficiency virus (HIV). HIV infection spreads through the exchange of bodily fluids including blood, sperm, vaginal fluid, and breast milk because these fluids include both free virus particles and virus that has already infected immune cells. It has been one of the most widely communicable human diseases by sexual transmission. HIV directly affects the human immune system resulting in the gradual loss of immunity in response to the pathogenic invasion responsible for life-threatening infections and malignancies to proliferate. HIV infect vital immune cells like CD4 T-cells and macrophages in the human body in a number of ways, including by pyroptosizing infected T-cells, which causes a slow decline in their population. Herbal plants are used for the therapy of HIV infection since the traditional time. Some of the commonly used herbs for the treatment of HIV infection are *Vernonia amygdalina, Rheum officinale, Hypoxis hemerocallidea, Rheum palmatum, Cinnamomum tamala, Cassia abbreviata, Cinnamomum zeylanicum, Sutherlandia frutescens, Artemisia annua, Calendula officinalis*, etc. These plants are supposed to be investigated further for isolation of anti-viral agents against HIV.

Introduction

Human immunodeficiency virus (HIV) is a retroviral that specifically affecting CD4 immune T-cells which regulates the human immune system to fight off against various infectious diseases. HIV lower the count of CD4 cells within the human body resulting in their compromised immunity, making it difficult to fight against infections and person become more prone to other communicable diseases[1–3]. HIV damage so many cells that body is unable to fight against pathogens and ultimately results in acquired immunodeficiency syndrome (AIDS)[4, 5, 1]. HIV/AIDS remains a major worldwide health concern for the humans. In 2020, there were an estimated 37.7 million HIV-positive individuals worldwide, with prevalence rate of 0.7% for adults. Around 16% of these persons (6.1 million) are unaware that they are infected with the virus[6]. Since the AIDS epidemic's start, an estimated 79.3 million individuals have been infected with HIV, and 36.3 million have passed away from AIDS-related diseases. AIDS-related illnesses claimed the lives of 680,000 persons in 2020. Since a high of 1.9 million in 2004 and a low of 1.3 million in 2010, this number has dropped by roughly 64%. Most HIV-positive individuals inhabit in low- and middle-income countries. East and Southern Africa are the most HIV-affected regions in the world, with 20.6 million individuals living with the disease[7–9]. The therapy i.e., given to HIV patients is called as anti-retroviral therapy (ART) [10–12]. Various anti-retroviral drugs such as Zidovudine (NRTI), Nevirapine (NNRTI), Lopinavir (Protease Inhibitor), Raltegravir (Integrase Inhibitor) are available in the market[13, 14]. However, in the administration of long-term HIV control, undesirable side effects and convivence/adherence are the main issues. Patients who take numerous pills repeatedly are at risk for a variety of serious side effects, including drug-drug and drug-food interactions, central nervous system symptoms, and the formation of a drug-resistant virus[15]. Since, virus is resistant to anti-retroviral drugs and also, they have side effects so, the discovery of new ART agents is required to control the epidemic condition. HIV is a retrovirus having RNA as a main genetic material confirmed by the presence of the enzymes like ribonuclease-H (RNase H), RNA-dependent DNA polymerase (RDDP) and reverse transcriptase (RT) which converts HIV-RNA into proviral DNA[16–19]. Traditional drug discovery approaches rely on random screening, which has a number of drawbacks, like time-consuming, expensive etc. In the last decade, computer-aided drug development (CADD) approaches have emerged to overcome these drawbacks. These technologies are less expensive to implement and provide a realistic option for screening potential medication candidates.

Material And Methods

i. Design of Ligand Library

A ligand library of 50 herbal leads from *Vernonia amygdalina*, *Rheum officinale, Rheum palmatum, Hypoxis hemercallidea, Sutherlandia frutescens, Artemisia annua, Calendula officinalis, Cinnamomum tamala, Cassia abbreviata, Cinnamomum zeylanicum*, etc. was prepared by exploring the literatures from various sources. The above-mentioned plants have reported for the presence of alkaloids, terpenoids, saponins, steroids, glycosides, etc.[20–22] Thus, 50 ligands of the plant belonging to the diverse chemical classes were included in the ligand library with intent to identify the most prominent lead molecule responsible for the treatment of HIV in humans and also try to identify the most probable mechanism of action involved in anti-HIV activity of that particular active constituent of the plant.

ii. Target Identification

The macromolecular target molecules involved in pathophysiological management as well as for the treatment of HIV in the humans were explored through available literatures. It has been observed that certain macromolecular targets were actively involved in the treatment of HIV.

The existing pharmacological data confirms the involvement of reverse transcriptase[23], HIV protease[24], and α-glucosidase[25] in the disease progression of HIV. Therefore, in the current study we are targeting viral reverse transcriptase enzyme which is responsible for the transformation of viral RNA into DNA, HIV protease which is involved in the processing of the GAG and GAG-POL polyproteins during viral maturation, and viral α-glucosidase, which is responsible to prevent the fusion of HIV with the host cell.

iii. Molecular Docking Studies

Macromolecular drug targets which were having active involvement in the HIV-viral lifecycle were shortlisted to proceed further with molecular docking studies. The three-dimensional structural models of all the shortlisted macromolecular drug targets viz reverse transcriptase (pdb id: 1ep4), protease (pdb id: 7doz), and α-glucosidase (pdb id: 7kb6) were procured from protein databank and prepared for docking simulation[26]. Complexed ligand was separated from the downloaded macromolecular and both the nascent target protein as well as separated ligand was saved in default Autodock format to proceed further with their redocking for validating the utilized docking parameters. Validated docking protocols for each of the macromolecular target were further employed for computational screening of the ligand library against each of the macromolecular drug targets used in the current study[27–32].

iv. Pharmacokinetic and Toxicological Evaluation

The pkCSM-pharmacokinetics server was used to anticipate the evaluation of the physicochemical, pharmacokinetics, and toxicological characteristics of the lead compounds acquired following the docking-based screening. Lead molecules were screened by the online server for predicting their smooth kinetics throughout the human body for its physiological expression without any associated side effects[33–38].

Molecular weight (MW), topological polar surface area (TPSA), partition coefficient (LogP), rotatable bonds count, hydrogen bond acceptor/donor (HBA/HBD), and solubility (LogS) of the lead compounds were calculated. These variables control the lead candidates' ADME-T profile. The leads' druggability was further determined by their gastrointestinal absorption, permeability across blood brain barrier (BBB), and the inhibitory potential of the cytochrome P450 isoenzymes[38, 39, 34, 35, 40, 41]. Lipinski's rules of five, Veber's rule, and druggability were used to standardize these characteristics.

v. Molecular Dynamic Simulation

Desmond module of Schrödinger was used to run molecular dynamic (MD) simulations for 100 ns for the macromolecular complex of vernonioside-A2 against viral reverse transcriptase enzyme acquired after virtual screening in order to examine their binding stability and binding patterns. TIP3P explicit water model was utilized to generate a orthorhombic shaped simulation box having a 10 Å gap among ligand-protein complex with the wall of the box[36, 42–45, 27, 46]. Isosmotic environment within the simulation box was formed by neutralizing the existing charge through the addition of counter ions with 0.15 M NaCl. Energy minimization of the system was performed by executing 2000 iterations with a merging criterion of 1 kcal/mol. MD simulations lasting 100 ns was performed by using energy minimized complex system. Throughout the simulation, a constant 300K temperature and 1.013 bars of air pressure were maintained. The trajectory path was set to 9.6 and the energy interval to 1.2 ps and at the trajectories were used to create simulation interaction diagrams at the end of the simulation[47, 48, 33, 41, 36, 37].

Result And Discussion

i. Design of Ligand Library

Based upon the available literature ligands like Vernonioside-A, B, A1, A2, A3, B2, B3, A4, luteolin, stigmasterol, β-sitosterol, rhein, aloe-emodin etc. were shortlisted for generating a ligand library. The two-dimensional structure of these ligands was generated by obtaining isomeric SMILES from PubChem and converting them into two-dimensional structure using ChemDraw 8.0[49]. These two-dimensional structures of all the shortlisted ligands were utilized for generation of their three-dimensional structure followed by energy minimization process.

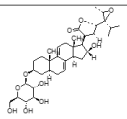
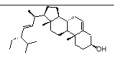
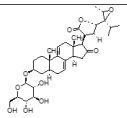
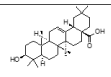
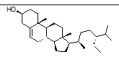
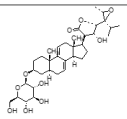
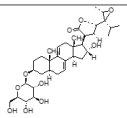
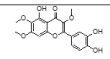
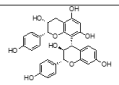
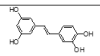
ii. Target Identification

Reverse transcriptase, HIV-protease, and α-glucosidase are the viral enzymes that plays an important role in the viral lifecycle of HIV virus within human body and by inhibiting these enzymes we can interrupt the further maturation of HIV virus within the human body. The three-dimensional structure model of reverse transcriptase, HIV protease, and α-glucosidase for executing the docking studies were procured from protein databank. The crystallized structure model of viral reverse transcriptase (pdb id: 1ep4) was revealed by X-ray diffraction technique at a resolution of 2.50 Å by using *E. coli* as an expression system. Structural model of viral reverse transcriptase consists of two macromolecular chains of 560 amino acids complex with a carbamate-based inhibitor molecule S-1153. The crystallized structure model of viral protease enzyme (pdb id: 7doz) was revealed by X-ray diffraction technique at a resolution of 1.91 Å by using *E. coli* as an expression system. Structural model of viral protease consists of a single macromolecular chain of 203 amino acids complex with an inhibitor molecule nelfinavir. The crystallized structure model of viral α-glucosidase (pdb id: 7kb6) was revealed by X-ray diffraction technique at a resolution of 2.20 Å by using *H. sapiens* as an expression system. Structural model of viral α-glucosidase consists of four macromolecular chains out of which chain A and C consists of 977 amino acids, chain B and D consists of 554 amino acids and complex with valiolamine derivatives as a potent inhibitor.

iii. Molecular Docking Studies

Three-dimensional structural model of all the separated macromolecular targets used in the current study were redocked against their reference ligand which were complexed in their crystallized structure for the validation of the utilized docking protocol. After successful validation the prepared molecular ligand library was computationally screened against each of the macromolecular targets used in the current study. After completion of the virtual screening of the ligand library the best lead molecule is selected based upon the minimum binding energy within the predefined range of -5 to -15 kcal/mol[41, 36, 50, 44–46, 51]. The binding score of each of the ligand of the ligand library against each macromolecular target is tabulated in Table I.

Table I. Binding score obtained for each of the ligand of the designed ligand library against each of the shortlisted macromolecular target involved in the treatment of HIV.

Sr. No.	Name	Structure	A.G.	Protease	R.T.
1.	Vernonioside A2		-8.83	-10.92	-11.17
2.	Stigmasterol		-8.78	-10.32	-11.00
3.	Vernonioside A3		-8.56	-9.93	-9.76
4.	Oleanolic Acid		-8.34	-10.49	-8.61
5.	βsitosterol		-8.12	-9.27	-10.83
6.	Vernonioside B1		-7.73	-9.66	-9.40
7.	Vernonioside A1		-7.40	-10.48	-11.29
8.	Chrysosplenol D		-7.36	-7.41	-7.99
9.	Cassiabrevone		-7.21	-8.00	-7.64
10.	Piceatannol		-7.15	-6.34	-7.38

Analyzing the docking score obtained after the computational screening of designed library clearly showing that the vernonioside-A2 and Stigmasterol is showing best binding affinity against all the macromolecular targets used in the current study.

iv. Pharmacokinetic and Toxicological Evaluation

Physicochemical and pharmacokinetic factors control drug transport within the human body. These regulatory characteristics are critical for a drug molecule's pharmacological expression via pharmacodynamics and toxicological qualities. As per to the Lipinski's rule of five, compound Vernonioside-A2 is having the considered parameters within the desired range, i.e., MW < 500, <10 HBA, < 5 HBD, TPSA 20–130 $Å^2$, < 5.0 LogP. The reported physicochemical features imply that Vernonioside-A2 has a drug-like candidature with optimized pharmacokinetics. P-glycoprotein acts as a physiological barrier for xenobiotics, drugs, and toxins, has not shown substrate-like expression for the ligand Vernonioside-A2.

Vernonioside-A2 has not demonstrated substrate-like expression for the majority of cytochrome P450 isoenzymes. AMES, hERG-I inhibition, skin sensitization, Tetrahymena Pyriformis toxicity, hepatotoxicity, and minnow toxicity are only a few of the toxicity pathways that the ligand constantly demonstrates a high inclination for elimination from the body with a very few expressions. Overall, the expected pharmacokinetics, and toxicological profile of Vernonioside-A2 based upon physicochemical parameters fits well in the prescribed range, indicating its promising future as a candidate for therapeutic development. Table II lists the pharmacokinetics, and toxicological features of the shortlisted compounds.

Table II. Pharmacokinetic and toxicological analysis of screened leads against viral reverse transcriptase enzyme.

Property	Descriptor	Vernonioside A2	Stigmasterol	Vernonioside A3	Oleanolic acid	β-sitosterol	Vernonioside B1	Vernonioside A1	Chrysosplenol D
MW	(g/mol)	632.791	412.702	630.775	456.711	414.718	632.791	632.791	360.318
LogP	-	2.3866	7.8008	2.5948	7.2336	8.0248	2.3866	2.3866	2.6026
Rotatable bond	-	6	5	6	1	6	6	6	4
HBA	-	10	1	10	2	1	10	10	8
HBD	-	5	1	4	2	1	5	5	3
TPSA	$(Å)^2$	265.314	186.349	264.681	201.354	187.039	265.314	265.314	146.955
Absorption	Water solubility (mol/L)	-4.208	-6.781	-4.033	-3.493	-6.871	-3.831	-4.208	-3.505
Absorption	Caco2 permeability	-0.359	1.218	-0.428	1.305	1.205	-0.48	-0.359	1.053
Absorption	Intestinal absorption (%) (human)	53.934	95.372	61.921	100	94.866	46.152	59.934	74.86
Absorption	Skin Permeability (Log Kp)	-2.741	-2.794	-2.74	-2.723	-2.794	-2.737	-2.741	-2.735
Absorption	P-glycoprotein substrate	Yes	No	Yes	No	No	Yes	Yes	Yes
Absorption	P-glycoprotein I inhibitor	Yes	Yes	Yes	No	No	Yes	Yes	No
Absorption	P-glycoprotein II inhibitor	No	Yes	No	Yes	Yes	No	No	No
Distribution	VDss (human)	-0.368	0.224	-0.391	-1.062	0.24	-0.626	-0.368	0.365
Distribution	Fraction unbound (human)	0.324	0	0.32	0	0	0.336	0.324	0.145
Distribution	BBB permeability	-1.405	0.787	-1.416	-0.351	0.797	-1.259	-1.405	-1.489
Distribution	CNS permeability	-3.797	-1.701	-3.827	-1.047	-1.754	-3.884	-3.797	-3.453
Metabolism	CYP2D6 substrate	No	No	No	No	No	No	No	No
Metabolism	CYP3A4 substrate	No	Yes	Yes	Yes	Yes	No	No	No
Metabolism	CYP1A2 inhibitor	No	No	No	No	No	No	No	Yes
Metabolism	CYP2C19 inhibitor	No	No	No	No	No	No	No	No
Metabolism	CYP2C9 inhibitor	No	No	No	No	No	No	No	No
Metabolism	CYP2D6 inhibitor	No	No	No	No	No	No	No	No
Metabolism	CYP3A4 inhibitor	No	No	No	No	No	No	No	No
Excretion	Total Clearance (log ml/min/kg)	0.385	0.618	0.316	-0.081	0.628	0.383	0.385	0.72
Excretion	Renal OCT2 substrate	No	No	No	No	No	No	No	No
Toxicity	AMES toxicity	No	No	No	No	No	No	No	Yes
Toxicity	Max. tolerated dose (human) (log mg/kg/day)	-2.352	-0.6	-1.719	0.612	-0.555	-1.861	-2.352	1.085

Property	Descriptor	Vernonioside A2	Stigmasterol	Vernonioside A3	Oleanolic acid	β-sitosterol	Vernonioside B1	Vernonioside A1	Chrysosplenol D
Toxicity	hERG I inhibitor	No	No	No	No	No	No	No	No
Toxicity	hERG II inhibitor	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Toxicity	Oral Rat Acute Toxicity (LD50) (mol/kg)	4.146	2.313	3.858	2.764	2.326	3.724	4.146	2.267
Toxicity	Oral Rat Chronic Toxicity (LOAEL) (mg/kg/day)	2.671	0.846	2.817	2.177	0.829	2.836	2.671	2.349
Toxicity	Hepatotoxicity	No	No	No	No	No	No	No	No
Toxicity	Skin Sensitisation	No	No	No	No	No	No	No	No
Toxicity	T. Pyriformis toxicity (mg/L)	0.285	0.458	0.285	0.285	0.454	0.285	0.285	0.289
Toxicity	Minnow toxicity	1.819	-1.993	0.85	-1.872	-2.12	1.051	1.819	0.168

v. Molecular Dynamic Simulation

Vernonioside-A2 was revealed as one of the most stabilized ligands after running MD simulation for a brief period of time. Thus, in order to determine the stability of the complex ligand Vernonioside-A2 within the macromolecular target, the same technique has been amplified for a longer length of 100 ns. The protein backbone's stability and structural shifts are measured using the RMSD during the simulation period. Trajectories obtained after performing the MD simulation of the macromolecular complex Vernonioside-A2 has revealed their stability throughout the 100 ns simulation with an average RMSD value ranging from 3–7 Å for macromolecular backbone and 6–8 Å for the complex ligand. RMSD of the complex ligand Vernonioside-A2 as well as the macromolecule was demonstrated stable behavior with a very little fluctuation as shown in Figure I.

RMSF value of the macromolecule was calculated by considering the fluctuation of the macromolecular Cα atoms to identify the movement of the amino acids with respect to their initial position. The movement of amino acids in the active site is inversely correlated with variations, and vice versa. The amino acid residues are displayed on the x-axis of the RMSF plot, and their RMSF value is displayed on the y-axis. RMSF value observed for the macromolecular backbone was found to be in the range of 1.5–7.5 Å. After evaluation, it was shown that the RMSF value for the complex system was lower for the active amino acid residues with a mean alteration for the ligand Vernonioside A2 was found to be 1.5–3.5 Å, confirming the acceptable fluctuations within the macromolecular active site. RMSF of the viral enzyme complexed with Vernonioside-A2 detected during MD simulation of 100 ns was represented in Figure II.

SSE analysis during whole simulation process revealed that the macromolecular structure had a total of 41.21% of SSE, out of which 26.05% of alpha-helices as well as 15.16% of beta-sheets, which may remain conserved during the simulation. The stability of the protein ligand complexes is due to the formation of hydrogen bonds, hydrophobic contacts, and ionic interactions throughout the MD simulation. To measure the stability of ligand Vernonioside-A2, the intensity of these interactions were observed during the whole timeframe of the simulation. The interaction of the ligand Vernonioside-A2 against the viral reverse transcriptase enzyme were analyzed throughout the simulation process and found that ligand molecules interact with Leu100, Lys102, Val106, Val179, Tyr181, Tyr188, Glu224, Pro225, Phe227, Trp229, Leu234, and Tyr318 amino acid by hydrophobic interaction, and amino acid Lys103, His235, and Pro236, forms a hydrogen bond with the ligand Vernonioside-A2. The ligand interaction observed between the ligand Vernonioside-A2 and macromolecular target reverse transcriptase was demonstrated in Figure III.

RMSD value of the bound ligand Vernonioside-A2 was found to be within the adequate range of 2–3 Å, concluding a few or no oscillation of the vernonioside-A2 withing the macromolecular pocket throughout the simulation. Radius of gyration (rGyr) of ernonioside-A2 was found to be 6.5 Å. Molar surface area (MolSA) of the complex Vernonioside-A2 was observed in the range of 540–550 $Å^2$ having average value of 545 $Å^2$. Ligand's solvent accessible surface area (SASA) was observed within 160–320 $Å^2$ and polar surface area (PSA) for the complexed Vernonioside-A2 was found to be in a range of 270–290 $Å^2$.

Conclusion

In the midst of this enormous worldwide challenge, we are working to develop HIV treatments that can be manufactured fast. Natural products, which have low toxicity and are used in the pharmaceutical sector for their bioactivity, including antiviral activity, could give a solution to this problem. The current research aims to identify plant based potential leads with anti-HIV action from the traditionally used plants to cure viral infection. Molecular docking-based screening of the herbal leads followed by the MD simulation for shortlisted compounds concludes that Vernonioside A2 from plant *Vernonia amygdalina* showing the best Anti-HIV activity by interacting with the retroviral reverse transcriptase enzyme with optimized pharmacokinetic profile without having

presence of any major toxic effect. Vernonioside A2 can be utilized for the development of novel ART post pre-clinical validation followed by its clinical confirmation.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

I, the undersigned, give my consent for the publication of identifiable details, which can include photograph(s), videos, and details within the text (“Material”) to be published in the above Journal and Article.

Availability of data and materials

Yes

Competing interests

Authors declares that there are no financial or non-financial interests that are directly or indirectly related to the work

Funding

No funding or financial aid have been received to support this research.

Authors' contributions

All the authors have contributed equally for the execution of current research. The framework is designed and executed by SM and KS while the validation of the research outcomes and drafting of the manuscript was done by AA, IR, KS, and SM.

Acknowledgements

Not applicable

References

1. Jha V, Rustagi K, Gharat K, Sonawane N, Rathod M, Patel R, Devkar S, Damapurkar V, Kaur NJJABET (2022) Human immunodeficiency virus type 1: Role of proteins in the context of viral life cycle. 5 (2):307-319
2. Higgs JA, Seely KD, Brooks AEJC, Discovery T (2022) Human gut microbiome in human immunodeficiency virus and acquired immunodeficiency syndrome-related diseases: Clinically relevant observations. 2 (2):e51
3. Coffin JMJTeoH (1999) Molecular biology of HIV.3-40
4. Alimonti JB, Ball TB, Fowke KRJJogV (2003) Mechanisms of CD4+ T lymphocyte cell death in human immunodeficiency virus infection and AIDS. 84 (7):1649-1661
5. Levy JAJMr (1993) Pathogenesis of human immunodeficiency virus infection. 57 (1):183-289
6. Zhu Z-p, Xu Y-y, Li X, Ma T, Wu S-s, Shi H-j, Qiao M-k, Xu W-j, Ding J (2022) Epidemiological analysis of age and spatial differences of HIV prevalence over the last decade in Nanjing, China.
7. Zenu S, Tesema T, Reshad M, Abebe EJPo (2021) Determinants of first-line antiretroviral treatment failure among adult patients on treatment in Mettu Karl Specialized Hospital, South West Ethiopia, a case control study. 16 (10):e0258930
8. Armstrong-Mensah EA, Tetteh AK, Ofori E, Ekhosuehi OJIJoER, Health P (2022) Voluntary Counseling and Testing, Antiretroviral Therapy Access, and HIV-Related Stigma: Global Progress and Challenges. 19 (11):6597
9. Lindegaard B, Hansen A-BE, Pilegaard H, Keller P, Gerstoft J, Pedersen BKJA (2004) Adipose tissue expression of IL-18 and HIV-associated lipodystrophy. 18 (14):1956-1958
10. Chinsembu K, Hijarunguru A, Mbangu AJSAJoB (2015) Ethnomedicinal plants used by traditional healers in the management of HIV/AIDS opportunistic diseases in Rundu, Kavango East Region, Namibia. 100:33-42
11. Chinsembu K, Syakalima M, Semenya SJSAJoB (2019) Ethnomedicinal plants used by traditional healers in the management of HIV/AIDS opportunistic diseases in Lusaka, Zambia. 122:369-384
12. Siegel K, Lekas H-MJA (2002) AIDS as a chronic illness: psychosocial implications. 16:S69-S76
13. Mahy MI, Sabin KM, Feizzadeh A, Wanyeki IJJotIAS (2021) Progress towards 2020 global HIV impact and treatment targets. 24:e25779
14. De Clercq EJIjoaa (2009) Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. 33 (4):307-320
15. Laila U, Akram M, Shariati MA, Hashmi AM, Akhtar N, Tahir IM, Ghauri AO, Munir N, Riaz M, Akhter NJC, Pharmacology E, Physiology (2019) Role of medicinal plants in HIV/AIDS therapy. 46 (12):1063-1073

16. Fisher TS (2002) Human immunodeficiency virus type 1 reverse transcriptase: The role of template-primer interactions in polymerase function. Yeshiva University,
17. de Béthune M-PJAr (2010) Non-nucleoside reverse transcriptase inhibitors (NNRTIs), their discovery, development, and use in the treatment of HIV-1 infection: a review of the last 20 years (1989–2009). 85 (1):75-90
18. Mohamed E (2009) Probing the HIV reverse-transcriptase enzyme with novel bifunctional HIV-1 RT inhibitors of the general formula (NRTI)-spacer-(NNRTI).
19. Skasko M (2008) The Mechanistic roles of reverse transcriptase dNTP binding affinity and the central poly purine tract in achieving effective transduction efficiency. University of Rochester School of Nursing,
20. Liu JP, Manheimer E, Yang MJCDoSR (2005) Herbal medicines for treating HIV infection and AIDS. (3)
21. Kloos H, Mariam DH, Kaba M, Tadele GJEJoHD (2013) Traditional medicine and HIV/AIDS in Ethiopia: Herbal medicine and faith healing: A review. 27 (2):141-155
22. Pathak K, Das RJJIJoHM (2013) Herbal medicine-a rational approach in health care system. 1 (3):86-89
23. Ren J, Nichols C, Bird L, Chamberlain P, Weaver K, Short S, Stuart D, Stammers DJJomb (2001) Structural mechanisms of drug resistance for mutations at codons 181 and 188 in HIV-1 reverse transcriptase and the improved resilience of second generation non-nucleoside inhibitors. 312 (4):795-805
24. Bulut H, Hattori S-i, Aoki-Ogata H, Hayashi H, Das D, Aoki M, Davis DA, Rao KV, Nyalapatla PR, Ghosh AKJSr (2020) Single atom changes in newly synthesized HIV protease inhibitors reveal structural basis for extreme affinity, high genetic barrier, and adaptation to the HIV protease plasticity. 10 (1):1-12
25. Karade SS, Hill ML, Kiappes J, Manne R, Aakula B, Zitzmann N, Warfield KL, Treston AM, Mariuzza RAJJoMC (2021) N-substituted valiolamine derivatives as potent inhibitors of endoplasmic reticulum α-glucosidases I and II with antiviral activity. 64 (24):18010-18024
26. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PEJNar (2000) The protein data bank. 28 (1):235-242
27. Kaur A, Mujwar S, Adlakha N (2016) In-silico analysis of riboswitch of Nocardia farcinica for design of its inhibitors and pharmacophores. International Journal of Computational Biology Drug Design 9 (3):261-276
28. Soni N, Pardasani KR, Mujwar S (2015) Insilico analysis of dietary agents as anticancer inhibitors of insulin like growth factor 1 receptor (IGF1R). J Pharm Pharm Sci 7 (9):191-196
29. Pradhan P, Soni NK, Chaudhary L, Mujwar S, Pardasani KR (2015) In-silico prediction of riboswitches and design of their potent inhibitors for H1N1, H2N2 and H3N2 strains of influenza virus. Biosciences Biotechnology Research Asia 12 (3):2173-2186
30. Mujwar S, Harwansh R, K. (2022) In-silico bioprospecting of taraxerol as a main protease inhibitor of SARS-CoV-2 to develop therapy against COVID-19. Structural Chemistry (PREPRINT (Version 1) available at Research Square). doi:10.21203/rs.3.rs-1308726/v1
31. Mujwar S, Sun L, Fidan O (2022) In silico evaluation of food-derived carotenoids against SARS-CoV-2 drug targets: Crocin is a promising dietary supplement candidate for COVID-19. J Food Biochem:e14219. doi:10.1111/jfbc.14219
32. Fidan O, Mujwar S, Kciuk M (2022) Discovery of adapalene and dihydrotachysterol as antiviral agents for the Omicron variant of SARS-CoV-2 through computational drug repurposing. Mol Divers. doi:10.1007/s11030-022-10440-6
33. Mujwar S, Tripathi A (2021) Repurposing Benzbromarone as Antifolate to Develop Novel Antifungal Therapy for Candida Albicans.
34. Mujwar S (2021) Computational bioprospecting of andrographolide derivatives as potent cyclooxygenase-2 inhibitors. Biomedical Biotechnology Research Journal 5 (4):446
35. Mujwar S, Shah K, Gupta JK, Gour A (2021) Docking based screening of curcumin derivatives: a novel approach in the inhibition of tubercular DHFR. International Journal of Computational Biology and Drug Design 14 (4):297-314
36. Mujwar S, Kumar V (2020) Computational Drug Repurposing Approach to Identify Potential Fatty Acid-Binding Protein-4 Inhibitors to Develop Novel Antiobesity Therapy. Assay drug development technologies 18 (7):318-327
37. Shah K, Mujwar S, Krishna G, Gupta JK (2020) Computational Design and Biological Depiction of Novel Naproxen Derivative. ASSAY Drug Development Technologies 18 (7):308-317
38. Pires DE, Blundell TL, Ascher DB (2015) pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. J Med Chem 58 (9):4066-4072. doi:10.1021/acs.jmedchem.5b00104
39. Kciuk M, Gielecińska A, Mujwar S, Mojzych M, Marciniak B, Drozda R, Kontek R (2022) Targeting carbonic anhydrase IX and XII isoforms with small molecule inhibitors and monoclonal antibodies. Journal of Enzyme Inhibition Medicinal Chemistry 37 (1):1278-1298
40. Sharma KK, Singh B, Mujwar S, Bisen PS (2020) Molecular Docking Based Analysis to Elucidate the DNA Topoisomerase IIbeta as the Potential Target for the Ganoderic Acid: A Natural Therapeutic Agent in Cancer Therapy. Curr Comput Aided Drug Des 16 (2):176-189. doi:10.2174/1573409915666190820144759
41. Jain R, Mujwar S (2020) Repurposing metocurine as main protease inhibitor to develop novel antiviral therapy for COVID-19. J Structural Chemistry 31 (6):2487-2499
42. Mishra I MR, Mujwar S, Chandra P,Sachan N, (2020) A retrospect on antimicrobial potential of thiazole scaffold. Journal of Heterocyclic Chemistry 57 (6):2304-2329
43. Shah K, Mujwar S, Gupta JK, Shrivastava SK, Mishra P (2019) Molecular Docking and In Silico Cogitation Validate Mefenamic Acid Prodrugs as Human Cyclooxygenase-2 Inhibitor. Assay Drug Dev Technol 17 (6):285-291. doi:10.1089/adt.2019.943

44. Mujwar S, Deshmukh R, Harwansh RK, Gupta JK, Gour A (2019) Drug Repurposing Approach for Developing Novel Therapy Against Mupirocin-Resistant Staphylococcus aureus. Assay Drug Dev Technol 17 (7):298-309. doi:10.1089/adt.2019.944
45. Minaz N, Razdan R, Hammock BD, Mujwar S, Goswami SK (2019) Impact of diabetes on male sexual function in streptozotocin-induced diabetic rats: Protective role of soluble epoxide hydrolase inhibitor. Biomedecine & pharmacotherapie 115:108897. doi:10.1016/j.biopha.2019.108897
46. Mujwar S, Pardasani KR (2015) Prediction of riboswitch as a potential drug target and design of its optimal inhibitors for Mycobacterium tuberculosis. International Journal of Computational Biology and Drug Design 8 (4):326-347
47. Kciuk M, Mujwar S, Szymanowska A, Marciniak B, Bukowski K, Mojzych M, Kontek R (2022) Preparation of Novel Pyrazolo [4, 3-e] tetrazolo [1, 5-b][1, 2, 4] triazine Sulfonamides and Their Experimental and Computational Biological Studies. International Journal of Molecular Sciences 23 (11):5892
48. Mujwar S (2021) Computational repurposing of tamibarotene against triple mutant variant of SARS-CoV-2. Comput Biol Med 136:104748. doi:10.1016/j.compbiomed.2021.104748
49. Cousins KR (2005) ChemDraw Ultra 9.0. CambridgeSoft, 100 CambridgePark Drive, Cambridge, MA 02140. www. cambridgesoft. com. See Web site for pricing options. ACS Publications,
50. Agrawal N, Upadhyay P, Mujwar S, Mishra P (2020) Analgesic, anti-inflammatory activity and docking study of 2-(substituted phenyl)-3-(naphthalen1-yl)thiazolidin-4-ones. Journal of Indian Chemical Society 97:39-46
51. Mujwar S, Pardasani KR (2015) Prediction of Riboswitch as a potential drug target for infectious diseases: An Insilico case study of anthrax. Journal of Medical Imaging and Health Informatics 5 (1):7-16

Figures

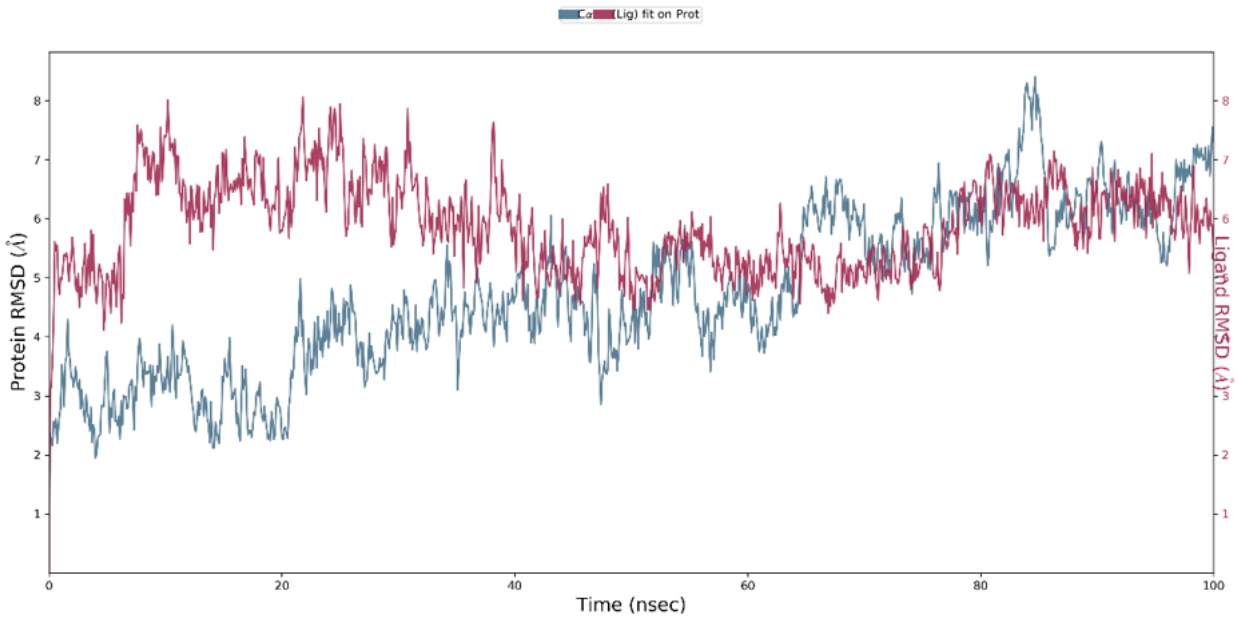


Figure 1

RMSD trajectory for the complex ligand Vernonioside-A2 and macromolecular backbone of viral reverse transcriptase showing stable behavior with a very little fluctuation as determined by MD simulation of 100 ns.

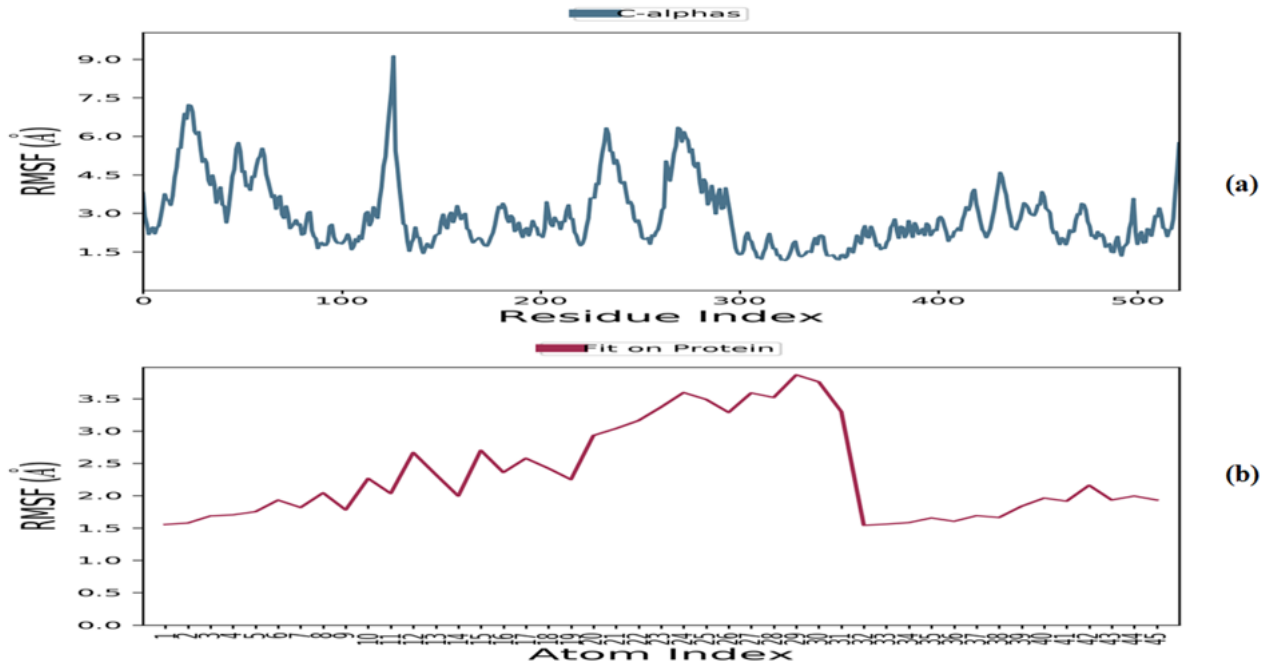


Figure 2

RMSF of the monomeric subunit of the viral reverse transcriptase (a) and complexed Vernonioside-A2 (b) recorded during the MD simulation for 100 ns.

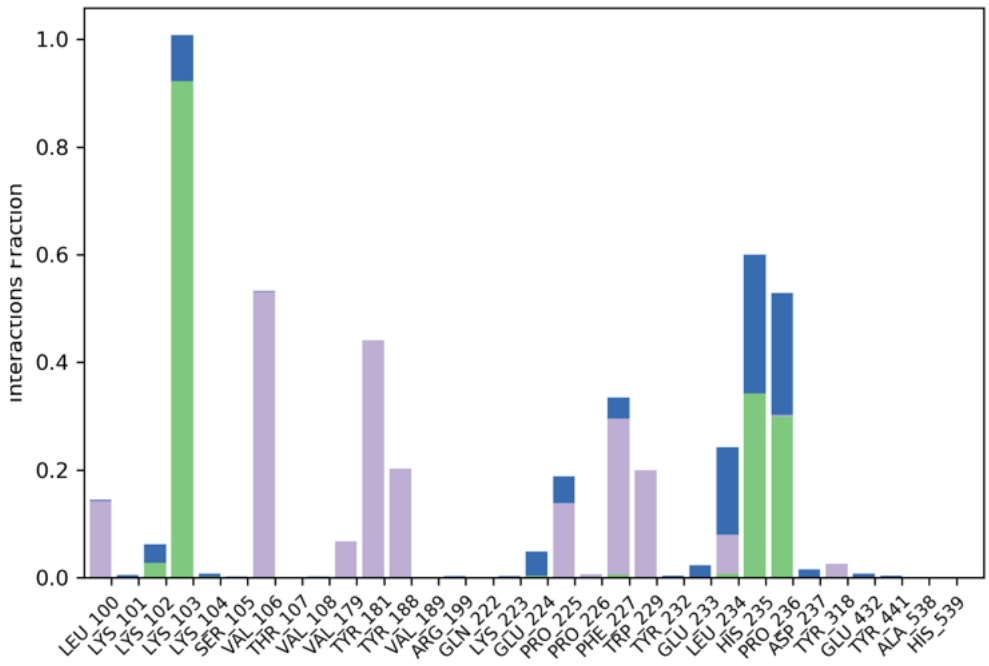


Figure 3

The specific interactions between macromolecular complexes that were seen during the 100 ns MD simulation. Hydrogen bonds are represented by green bars, water bridges by blue bars, hydrophobic interactions by purple bars, and ionic interactions by pink bars.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AyanVideo.mpeg
- desmondmdjob4outpl1.pdf