Structure-based screening of Natural product libraries in search of potential antiviral drug-leads as first-line treatment to Covid-19 infection

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Abstract

The study describes a novel strategy to screen natural products (NPs) based on their structural similarities with chemical drugs and their use as first-line treatment to Covid-19 infection. In the present study, the in-house natural product libraries, consisting of a total of 26,311 structures, were screened against potential targets of 2019-nCoV/SARS-CoV-2 based on their structural similarities with the prescribed chemical drugs. The comparison was based on molecular properties, 2 and 3-dimensional structural similarities, activity cliffs, and core fragments of NPs with chemical drugs. The screened NPs were evaluated for their therapeutic effects based on predicted in-silico pharmacokinetic and pharmacodynamics properties, binding interactions with the appropriate targets, and structural stability of the bound complex. The study yielded NPs with significant structural similarities to synthetic drugs currently used to treat Covid-19 infections. The study proposes the selected NPs as Anti-retroviral protease inhibitors, RNA-dependent RNA polymerase inhibitors, and viral entry inhibitors.

Introduction

Viral infections play an important role in human diseases, and their regular outbreaks repeatedly underlined the need for their prevention in safeguarding public health [1]. The recent outbreak of the novel coronavirus Covid-19 was declared 'public health emergency of international concern' by World Health Organization (WHO) in view of its severity [2]. The Coronavirus disease (COVID-19), previously known as '2019 novel coronavirus' or '2019-nCoV', is an infectious disease caused by a newly discovered coronavirus; severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 [3]. The SARS-CoV-2 is a member of the *Coronavirinae* family belonging to the *Betacorona* genus [4]. Structurally it is spherical or pleomorphic in shape, with a diameter of about 60-140nm. All ages are susceptible to COVID-19 infection, and its clinical manifestations range from asymptomatic to mild to severe and even to death depending on the underlying health conditions of individuals [5, 6]. The most commonly reported symptoms are fever, chills, headache, body aches, dry cough, fatigue, pneumonia, and complicated dyspnea. The virus transmits from person to person via the nasal, oral, eye, and mucosal secretions of the infected patient and direct transmission through the inhalation of droplets released during the patient's cough or sneeze [7, 8].

For the clinical diagnosis of SARS-CoV-2, the reverse transcription-quantitative polymerase chain reaction (RT-qPCR) method is widely being used today [9]. It is a nucleic acid detection test where nasopharyngeal and oropharyngeal samples were used for the detection. However, to provide quick diagnosis techniques like transcription loop-mediated isothermal amplification (RT-LAMP), transcription-mediated amplification (TMA), CRISPR-based assays, rolling circle amplification, and microarray hybridization assays have been developed and are currently in use [10, 11].

To prevent the transmission of SARS-CoV-2, the development of an effective vaccine is highly essential. Therefore, scientists around the world are engaged in developing potential vaccines. However, at this stage, it is unclear which vaccine strategy would be most effective. Figure-1 describes some of the most widely used vaccines currently developed against Covid-19. The other potential treatment strategies include inhibition of RNA-Dependent RNA Polymerase activity, viral protease inhibition, viral entry inhibition, immune modulation, monoclonal antibodies, janus kinase inhibitors, nutritional supplements, and the conventional plasma therapy (Table 1) [11]. The developmental status of different antiviral drugs to treat Covid-19 conditions is shown in figure 3.

Table 1: Mechanism of action of some of the COVID-19 prescribed drugs and their common usage.

COVID-19 prescribed Drugs	Known mechanism of action and their common usage
Inhibiting the RNA-Dependent RNA Polymerase	
Remdesivir	Inhibits viral RNA production and replication of EBOV [12]
Favipiravir	Anti-influenza drug [13]
Galidesivir	Hepatitis C treatment [14]
Ribavirin	Hepatitis C treatment viral hemorrhagic fevers [15]
Sofosbuvir	Hepatitis C treatment [16]
Viral Protease Inhibitors	
Lopinavir/Ritonavir	Anti-retroviral protease inhibitor [17]
Nelfinavir	Inhibits HIV-1 and HIV-2 retroviral proteases [18]
Atazanavir	Anti-retroviral protease inhibitor used to treat HIV infections [19]
Darunavir	anti-retroviral protease inhibitor [20]
Danoprevir	HCV Protease Inhibitor [21]
Viral Entry Inhibitor	
Hydroxychloroquine	Antimalarial drug [22]
Arbidol	Anti- influenza drug [23]
Ivermectin	Antiviral/antiparasitic drug [24]
Immune Modulators	
Interferon-alpha (IFN-2b)	Antiviral and/or anti-neoplastic drug [25]
Tacrolimus	Inhibits T-lymphocyte signal transduction and IL-2 transcription [26]
Monoclonal Antibodies	
Sarilumab	IL-6 receptor blocker [27]
Tocilizumab	Treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Inhibits the IL-6 signaling pathway[28]
Janus Kinase Inhibitors	
Fedratinib	Inhibits JAK2 the treatment of rheumatoid arthritis [29]
Baricitinib	Reversible inhibitor of both JAK1 and JAK2 in the treatment of rheumatoid arthritis [30]
Nutritional Supplements	
Vitamin C	Boosts immunity by stimulating IFN production [31]
Vitamin D	Involved in adaptive immunity, immune cell differentiation, proliferation, and maturation [32]
Folic Acid	Important for rapid cell proliferation [33]
Miscellaneous	
Valsartan	Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers [34]
Entresto	Angiotensin II receptor neprilysin inhibitor [35]
Telbivudine	Antiviral thymidine nucleoside analog against the hepatitis B virus DNA polymerase [36]
Azithromycin	Antibiotic drug [37]
Colchicine	Prevent gout attacks [38]
Methylprednisolone	Anti-inflammatory drug [39]
Naproxen	Anti-inflammatory and antiviral drug used against Influenza A virus [40]
Tilorone	Treatment of influenza, acute respiratory viral infection, viral hepatitis, and viral encephalitis [41]
Cobicistat	Cytochrome P450 (CYP3A) inhibition [42]
Omeprazole	Proton pump inhibitor used to treat gastroesophageal reflux disease, heartburn, and ulcers [43]
Pirfenidone	Antifibrotic and anti-inflammatory drug [44]

Disulfiram	Inhibitor of the peripheral benzodiazepine receptor and acetaldehyde dehydrogenase enzyme [45]
Cyclosporin	Calcineurin inhibitor [46]
Prograf	Inhibits T-lymphocyte signal transduction and IL-2 transcription [26]
Sirolimus	Suppress viral replication [47]
7-Methylguanosine 5'-diphosphate and triphosphate	Translation initiation factor activity [48]
Convalescent Plasma Therapy	Adoptive immunotherapy [49]

Natural products and traditional medicines have been serving as the greatest source for modern drug discovery. Their derivatives are recognized for many years as the source of the therapeutic potential and structural diversity. There are over 200,000 compounds reported in the scientific literature. NPs are more often structurally complex, with well-organized structure and steric properties offering efficacy, efficiency, and selectivity of molecular targets [50]. However, their utilization on many health conditions is well documented; it is in the hands of existing traditional practitioners and herbologists to define their applications for newly emerging diseases. The biological activities reported from different plant extracts often narrow down to pre-reported molecules rather than novel compounds [51], creating a real challenge to medicinal chemists. In this avenue, the search for new therapeutic molecules is the need of the hour to combat against new health challenges.

The biological activity of any molecule is attributed to its structural arrangements. If two molecules have a similar structure, they will most probably have a similar biological effect [52–54] (Fig.3). The computational chemists are successful in exploiting this principle for the construction of diverse compound libraries and select compounds for high-throughput screening experiments [52]. Computational advancements with the introduction of parallel processing clusters, cloud-based computing, and highly effective graphical processing units (GPUs), tremendous success has been achieved in the field of modern drug discovery [55]. The knowledge of natural products and ligands, earlier used as starting points for drug discovery, has greatly influenced computational biology techniques [56]. These advancements have been speeded up by the creation of new algorithms for more accurate predictions, simulations, and interpretations [57–62]. The extensive molecular dynamics (MD) simulations can provide insights into the host-virus interactions, disease spread, and possible regulative/preventive mechanisms [63]. The present study proceeds to identify natural products as first-line treatment options for Covid-19 infections in this avenue. By considering the structural properties of prescribed chemical drugs currently used to treat different Covid-19 conditions, natural product libraries were screened to identify potential antiviral drug molecules. The study extends to describe the possible mechanism of their therapeutic actions creating new opportunities for nature-based therapeutics.

Materials And Methods

Dataset collection and library construction:

An in-house natural product library consisting of 26,311 natural product structures was constructed using natural products information from different databases like Dr. Duke's database (https://phytochem.nal.usda.gov/phytochem/search) [64], Phytochemical Interactions Database (http://www.genome.jp/db/pcidb), and Natural product activity and species source database (NPASS) (http://bidd.group/NPASS/index.php) [65]. The natural product library was further categorized as flavans (339), flavones (193), and isoflavonoids (457), and the rest of the molecules as a general group. The broad-spectrum antiviral drugs currently under investigation to treat Covid-19 conditions were collected from the drugvirus.info server (https://drugvirus.info). For comparison, the small molecule synthetic drugs were categorized into molecules present in Pubchem Covid19 portal (306) [66] (https://pubchem.ncbi.nlm.nih.gov/#query=covid-19), and molecules present at different stages of clinical trials (138) (As of 31st August 2020) based on the available information from ClinicalTrials.gov database [67] (https://www.clinicaltrials.gov/ct2/home). Further, the study was extended to compare the most promising investigational drugs like Remdesivir, Arbidol, Lopinavir, and Ritonavir. The top 10 structures most similar to investigational drugs were selected for *in-silico* PK/PD analysis and HTVS studies.

Structure-based screening of Natural products:

The non-redundant natural product libraries were compared against chemical drugs currently under prescription/study to treat COVID 19 infection. The comparison is based on 2 and 3-dimensional structural similarities, activity cliffs (ACs), and core fragments (CFs). The structural similarities were assessed based on the number of fragments that both molecules have to the number of fragments found in any two structures [68]. The structural scaffolds (SSs) were analyzed based on plane ring system to determine the sub-structures. ACs, CFs, and SSs were determined employing Osiris DataWarrior V.4.4.3 software [68].

Molecular properties based PK/PD analysis:

Natural products are the major source of oral drugs 'beyond Lipinski's rule of five' [69–71]. The druglikeness assessment, pharmacokinetic (PK), and pharmacodynamics (PD) of NPs were determined based on their molecular properties like molecular weight, cLogP, hydrogen atom donors, hydrogen atom acceptors, and rotatable hydrogen bonds. These properties are used as filtering parameters to estimate the oral bioavailability, solubility, and permeability of new drug candidates [69, 71, 72]. The natural products obtained from structural comparison were considered as hits for *in-silico* PK/PD assessment. Molecular properties were predicted using Osiris Data warrior V.4.4.3 software [68]. The admetSAR server [73] was used to predict different parameters constituting the PK/PD properties of the selected molecules.

Molecular interactions studies using automate docking:

Automated docking was performed to deduce the binding interactions of selected natural products with appropriate target proteins. Broyden-Fletcher-Goldfarb-Shanno algorithm implemented in the AutoDockVina was employed to study proper binding modes of the selected natural products in different conformations [74]. The antiviral drugs currently being prescribed for Covid-19 first-line treatment were retrieved from the drugvirus.info server, and their action mechanisms were studied using the Inxight: Drugs database (https://drugs.ncats.io/) (Table 1).

Based on the action mechanism of the standard drugs, HIV-1 protease I50V isolate, influenza virus hemagglutinin, SARS-CoV NSP12 polymerase and HIV-1 protease A02 isolate were selected for the docking studies. The protein structures were retrieved from protein databank (https://www.rcsb.org/) and were prepared for docking studies. For each target, residues forming the binding site were identified using the PDBsum server. The antiviral drug; Lopinavir and its related natural products were docked against anti-retroviral protease inhibitor (I50V isolate) (PDB ID 3OXV), Ritonavir and its related natural products were docked against anti-retroviral protease inhibitor (A02 isolate) (PDB ID 4NJV), Remdesivir, and its related natural products were docked against anti-retroviral protease inhibitor (PDB ID 7BV2), and Arbidol and its related natural products were docked against anti-retroviral protease inhibitor (PDB ID 5T6S). For the ligand molecules, all the torsions were allowed to rotate during docking. The *in-silico* studies were performed on a local machine equipped with AMD Ryzen 5 six-core 3.4 GHz processor, 8GB graphics, and 16 GB RAM with Microsoft Windows 10 and Ubuntu 16.04 LTS dual boot operating systems.

Molecular dynamic simulations to predict the protein structural stability:

the structural stability of the free and bound targets was assessed using MD simulations run for a time scale of 20 ns [75, 76] by employing the GROMOS96 54a7 [77] force field implemented in the GROMACS-2018 package [78]. A periodic cubic solvated box was created around the target proteins with at least 10 Å distance from the edge of the box and solvated using the simple point charge (SPC) model [79] and neutralized using sodium and chloride ions. Temperature coupling at 300K was done using V-rescale thermostat [80], and pressure coupling at 10^5 Pa was done using Parrinello-Rahman barostat [81]. Bond parameters were adjusted using the LINCS algorithm [82], and the particle mesh Ewald method (PME) [83] was used to evaluate electrostatic interactions. The final MD trajectories were prepared for a time scale of 20ns at a time step of 2fs with trajectory coordinates updated at 10ps intervals. The final trajectories were analyzed using *gmx energy*, *gmx rms, gmx rmsf, gmx gyrate, gmx do_dssp,* and *gmx sasa* modules of GROMACS along with interaction energies in terms of electrostatic and van der Waals energy between the ligand and the macromolecule.

Biding free energy calculations using g_mmpbsa:

For Molecular mechanics/Poisson-Boltzmann surface area (MMPBSA) calculations, trajectory files were created from the final 10 ns with coordinates updated every 200ps. The g_mmpbsa package was used for binding energy calculations[84]. The g_mmpbsa package uses the following equation to calculate the binding energy of the protein-ligand complex;

$$\Delta G_{Binding} = G_{Complex} - (G_{Protein} + G_{Ligand}) \quad (I)$$

The 'G' term can be further decomposed into the following components-

$$\Delta G = \Delta E_{MM} + \Delta G_{Solvation} - T\Delta S = \Delta E_{(Bonded + Non\text{-}bonded)} + \Delta G_{(Polar + Non\text{-}polar)} - T\Delta S \quad (II)$$

Where,

$G_{Complex}$ = total free energy of the binding complex,

$G_{Protein}$ and G_{Ligand} = total free energies of protein and ligand, respectively.

E_{MM} = vacuum potential energy; $G_{Solvation}$ = free energy of solvation

Results

Structure-based screening of Natural products:

The natural product library consisting of 26,311 structures was screened against local Pubchem Covid19 library of Covid 19 prescribed drugs and Covid 19 clinical trials drug library. Among the total number of molecules screened, 17,798 natural product structures were found to have more than 60% structural similarities against Pubchem Covid19 library, of which 41 molecules were flavans, 41 were flavones, and 272 were isoflavonoids. The comparison against clinical trials drug library yielded 14,689 natural products with more than 60% structure similarity consisting of 30 flavans, 18 flavones, and 78 isoflavonoids. The study was extended to compare the complete natural product library against the most promising investigational drugs, viz. Remdesivir, Arbidol, Lopinavir, and Ritonavir molecules yielded 35 natural product structures with considerable structural similarity (Table 2).

Table 2: Natural products structurally similar to prescribed Covid-19 drugs and their similarity score.

Synthetic drug and the identified NPs	Similarity score
Remdesivir	
12_28_Oxa_8_Hydroxy_Manzamin_A	0.7676
Marineosin_A	0.7558
Bis(Gorgiacerol)Amine	0.8107
Methylstemofoline	0.7645
Chetracin_B	0.7877
Oxyprotostemonine	0.7644
Stemocurtisine	0.7569
Munroniamide	0.7705
Alstolobine_A	0.7598
Discorhabdin_H	0.7665
Arbidol	
Phellibaumin_A	0.6838
Difloxacin	0.7363
Lamellarin_D	0.7175
Lamellarin_Gamma_Acetate	0.6682
Hydroxy-6-Methylpyran-2-One_Derivative	0.6822
Cyathuscavin_C	0.7363
Cyathusal_B	0.7135
Clausarin	0.6770
Cyathuscavin_B	0.7135
Pulvinatal	0.7010
Lopinavir	
Hexahydrodipyrrol derivative	0.7458
Beauvericin	0.7478
Chaetocin	0.7615
Mollenine_A	0.7462
Chetracin_B	0.7877
Beauvericin_H1	0.7549
Dragonamide_A	0.7703
Chetracin_D	0.7892
Dimethyl-3-Oxodecanamide derivative	0.7569
Symplocamide_A	0.7481
Ritonavir	
Bionectin_B	0.7146
Luteoalbusin_A	0.6906
Bionectin_A	0.7122
Oidioperazine_A	0.7153
Holstiine	0.6876
Chetracin_B	0.7142
Mollenine_A	0.6796
Methaniminium derivative	0.7274
Verticillin_E	0.7181

Chaetocin	0.6888

Molecular properties based PK/PD analysis:

Molecular properties and Pharmacokinetics prediction of natural products were predicted using Osiris data warrior software and the admetSAR server. The druglikeness estimated based on the molecular properties of the selected structures indicated that out of 35 molecules, 23 molecules with positive scores indicated their potential drug-like effects. Gastrointestinal (GI) absorption is an important parameter to screen orally administered drugs. A positive value shown in Table 3A for gastrointestinal (GI) absorption suggests a high probability of success for absorption into the intestinal tract [85]. While the blood-brain barrier (BBB) penetration indicates the potentials of a drug to cross into the brain, it can bind to specific receptors and activate specific signaling pathways. Therefore, the prediction of BBB penetration is crucial in the drug development pipeline [86]. In the present study, 33 molecules were found to penetrate the human intestine barrier, 17 molecules penetrating the blood-brain barrier, and none of them being the substrate for Cytochromes P450 group of isozymes which regulates drug metabolism, indicating a high possibility of their bioavailability (Table 3A). Further, out of 35 molecules, 34 were predicted to be non-mutagenic and non-tumorigenic and non-irritant, with 10 molecules predicted to have reproductive effects (Table 3B). Among the 35 structures, 29 compounds were non-AMES toxic, 34 non-carcinogens, and 34 were not readily biodegradable.

Table 3: A) Molecular properties and Pharmacokinetics prediction of natural products filtered in for screening against COVID-19 condition.

Identified NPs	Bioavailability and Druglikeness								*In silico* Pharmac	
	cLogP	Mol. wt	H-Acceptors	H-Donors	Rotatable Bonds	Total Surface Area	Polar Surface Area	Druglikeness	Human intestinal absorption	Ca per
12_28_Oxa_8_Hydroxy_Manzamin_A	5.2547	562.755	6	2	1	414.34	60.33	-2.227	0.696+	0.5
Alstolobine_A	2.4707	398.457	7	1	6	297.41	80.86	-8.1671	0.988+	0.5
Beauvericin	5.2239	783.96	12	0	9	610.8	139.83	4.3764	0.991+	0.6
Beauvericin_H1	5.3247	801.95	12	0	9	617.15	139.83	3.0364	0.990+	0.5
Bionectin_A	2.9631	450.542	7	3	1	282.66	139.27	5.5488	0.889+	0.5
Bionectin_B	2.6488	494.595	8	4	2	311.68	159.5	5.0182	0.900-	0.5
Bis(Gorgiacerol)Amine	5.4399	757.83	13	3	10	560.06	183.97	-19.005	0.965-	0.6
Chaetocin	2.7962	696.852	12	4	3	409.82	246.96	5.8356	0.900+	0.6
Chetracin_B	1.092	760.916	14	6	3	437.49	312.72	5.4873	0.885+	0.5
Chetracin_D	0.3976	788.99	14	6	7	496.04	287.42	5.6124	0.922+	0.5
Clausarin	5.9768	380.482	4	1	4	295.44	55.76	-5.9217	0.975+	0.8
Cyathusal_B	0.5256	346.29	8	3	3	243.75	122.52	-4.326	0.915+	0.5
Cyathuscavin_B	0.5053	376.316	9	3	4	264.22	131.75	-4.7328	0.878+	0.6
Cyathuscavin_C	0.0774	362.289	9	4	3	248.31	142.75	-2.2479	0.868+	0.5
Difloxacin	1.251	399.396	6	1	3	283.48	64.09	5.1997	0.985+	0.8
Discorhabdin_H	-10.123	762.664	10	3	5	337.61	198.19	2.7192	0.734+	0.6
Dragonamide_A	3.7111	653.905	10	2	18	539.59	125.32	-3.0172	0.969+	0.5
Hexahydrodipyrrol derivative	0.2123	427.456	9	3	2	288.36	119.41	6.7335	0.946+	0.6
Holstiine	1.5964	382.458	6	1	0	270.15	70.08	5.6428	0.972+	0.6
Hydroxy-6-Methylpyran-2-One_Derivative	5.228	500.586	8	4	11	387.58	141.36	-13.889	0.984+	0.5
Lamellarin_D	4.3105	499.474	9	3	4	352.71	119.09	1.8379	0.983+	0.6
Lamellarin_Gamma_Acetate	5.3	573.596	10	1	8	423.68	106.84	2.3739	0.987+	0.6
Luteoalbusin_A	3.1416	464.569	7	3	2	295.59	139.27	5.9847	0.890+	0.5
Marineosin_A	4.6896	409.572	5	2	2	323.4	62.4	-2.232	0.986+	0.6
Methaniminium derivative	-0.4649	910.463	21	10	14	679.31	329.1	6.1103	0.795+	0.6
Methylstemofoline	0.9975	345.394	6	0	1	220.03	57.23	4.0559	0.922+	0.6
Mollenine_A	3.3511	368.475	5	1	4	275.46	58.64	3.6919	0.980+	0.5
Munroniamide	-0.4894	597.663	12	2	7	419.88	166.86	-8.9989	0.940+	0.6
Oidioperazine_A	1.9865	538.647	9	3	4	357.08	167.78	6.2082	0.843+	0.5
Oxyprotostemonine	1.004	431.483	8	0	2	289.89	83.53	2.3627	0.890+	0.6
Phellibaumin_A	2.8483	352.297	7	4	2	248.17	120.36	0.0022	0.952+	0.8
Pulvinatal	0.9535	360.317	8	2	4	259.66	111.52	-6.9354	0.919+	0.6
Stemocurtisine	1.4247	347.41	6	0	1	239.64	57.23	2.9196	0.922+	0.6
Symplocamide_A	0.6976	1052.03	23	11	18	763.41	359.52	1.3524	0.915+	0.6
Verticillin_E	1.7482	752.872	14	4	3	439.8	281.1	4.5639	0.895+	0.5

Table 3: B) *In-silico* Pharmacodynamics prediction of natural products selected for screening against COVID-19 condition.

Identified NPs	Mutagenic	Tumorigenic	Reproductive effective	Ocular irritancy	Aerobic biodegradibility	Ames tooxicity score	Carcinogen
12_28_Oxa_8_Hydroxy_Manzamin_A	NONE	NONE	NONE	0.946-	1.00-	0.707-	0.607-
Alstolobine_A	NONE	HIGH	NONE	0.979-	1.00-	0.714-	0.573-
Beauvericin	NONE	NONE	NONE	0.925-	0.912-	0.772-	0.622-
Beauvericin_H1	NONE	NONE	NONE	0.922-	0.996-	0.776-	0.536-
Bionectin_A	NONE	NONE	NONE	0.972-	0.986-	0.733-	0.609-
Bionectin_B	NONE	NONE	NONE	0.965-	0.988-	0.870-	0.611-
Bis(Gorgiacerol)Amine	NONE	NONE	HIGH	0.901-	0.623-	0.573-	0.487-
Chaetocin	NONE	NONE	NONE	0.918-	0.994-	0.645-	0.623-
Chetracin_B	NONE	NONE	NONE	0.911-	0.973-	0.679-	0.644-
Chetracin_D	NONE	NONE	NONE	0.904-	0.996-	0.678-	0.627-
Clausarin	NONE	NONE	HIGH	0.607+	0.993-	0.506-	0.472-
Cyathusal_B	NONE	NONE	HIGH	0.561-	0.937-	0.707+	0.465-
Cyathuscavin_B	NONE	NONE	HIGH	0.590-	0.966-	0.712+	0.515+
Cyathuscavin_C	NONE	NONE	HIGH	0.574-	0.937-	0.707+	0.465-
Difloxacin	NONE	NONE	NONE	0.949-	1.00-	0.885+	0.610-
Discorhabdin_H	NONE	NONE	NONE	0.960-	1.00-	0.593-	0.532-
Dragonamide_A	NONE	NONE	NONE	0.922-	1.00-	0.812-	0.678-
Hexahydrodipyrrol derivative	NONE	NONE	NONE	0.927-	1.00-	0.658-	0.597-
Holstiine	NONE	NONE	NONE	0.986-	0.951-	0.572-	0.501-
Hydroxy-6-Methylpyran-2-One_Derivative	NONE	NONE	NONE	0.732-	0.500+	0.815-	0.723-
Lamellarin_D	NONE	NONE	HIGH	0.833-	0.993-	0.586-	0.389-
Lamellarin_Gamma_Acetate	NONE	NONE	HIGH	0.989-	0.995-	0.880-	0.599-
Luteoalbusin_A	NONE	NONE	NONE	0.986-	0.987-	0.670-	0.630-
Marineosin_A	NONE	NONE	NONE	0.972-	1.00-	0.655-	0.651-
Methaniminium derivative	NONE	NONE	NONE	0.905-	0.962-	0.615-	0.570-
Methylstemofoline	NONE	NONE	NONE	0.891-	1.00-	0.755-	0.470-
Mollenine_A	NONE	NONE	NONE	0.986-	0.997-	0.572-	0.528-
Munroniamide	LOW	HIGH	LOW	0.978-	1.00-	0.512-	0.562-
Oidioperazine_A	NONE	NONE	NONE	0.987-	0.997-	0.670-	0.606-
Oxyprotostemonine	NONE	NONE	NONE	0.943-	0.994-	0.681-	0.440-
Phellibaumin_A	HIGH	NONE	HIGH	0.528-	0.911-	0.550+	0.419-
Pulvinatal	NONE	NONE	HIGH	0.547-	0.966-	0.712+	0.515+
Stemocurtisine	NONE	NONE	NONE	0.914-	0.995-	0.781-	0.420-
Symplocamide_A	NONE	NONE	NONE	0.901-	0.945-	0.644-	0.594-
Verticillin_E	NONE	NONE	HIGH	0.900-	0.986-	0.763-	0.610-

Molecular interactions studies using automate docking:

The *in-silico* molecular interaction studies were used to predict the most effective natural product drug to bind to the appropriate target involved in the regulation of virus entry, replication, assembly and release, as well as host-specific interactions. In the present study, the docking studies were carried for synthetic antiviral agents as well as their structurally similar natural products against different targets proteins of SARS-CoV-2 to deduce the structural insight of molecular interactions. The study yielded natural products being effectively bound to their respective targets (Table 4). The results were expressed in terms of docking energy (kcal/mol). Many of the selected natural products have displayed docking energies higher than their structurally similar standard drug counterparts. The natural products structurally similar to Remdesivir interact with SARS-CoV NSP12 polymerase with docking energies comparably higher than the standard drug. The natural products tested as influenza virus hemagglutinin inhibitors are also bound to the target with docking energies higher than

the standard drug arbodol. The binding interactions of natural products tested as viral protease inhibitors were compared with standard drugs lopinavir and ritonavir. Further, their molecular interactions were found stabilized by the formation of many hydrogen bonds. The effectiveness of these binding of natural product with highest interaction energy in each group was selected for protein stability assessment using molecular dynamics simulations (Fig. 4).

Table 4: Molecular interactions between the selected natural products with targets of their structurally similar chemical drugs expressed as docking energies along with their structure similarity score.

Target protein	Synthetic drug and the identified NPs	Docking Energy*	H-bonds	Interacting Residues
SARS-CoV NSP12 POLYMERASE	**Remdesivir**	-7.2	03	ILE23, LEU126, GLY48
	12_28_Oxa_8_Hydroxy_Manzamin_A	-10.4	02	GLY130, ALA38
	Marineosin_A	-7.9	00	-
	Bis(Gorgiacerol)Amine	-7.8	02	ILE23, GLY130
	Methylstemofoline	-7.7	02	SER128, ALA129
	Chetracin_B	-7.5	01	PHE156
	Oxyprotostemonine	-7.5	02	SER128, ALA129
	Stemocurtisine	-7.5	01	GLY48
	Munroniamide	-6.9	05	VAL49, ILE131, GLY48, GLY130, LEU126
	Alstolobine_A	-6.8	03	PHE156, ASP157, ALA154
	Discorhabdin_H	-6.7	02	GLY48, ASP22
INFLUENZA VIRUS HEMAGGLUTININ	**Arbidol**	-7.1	01	GLU64
	Phellibaumin_A	-9.4	04	ASP280, SER290, LYS58, ILE288
	Difloxacin	-8.4	03	LYS58, LEU292, PRO293
	Lamellarin_D	-8.4	02	LYS58, CYS305
	Lamellarin_Gamma_Acetate	-7.8	01	GLU57
	Hydroxy-6-Methylpyran-2-One_Derivative	-7.6	03	THR59, GLU57, THR59
	Cyathuscavin_C	-7.5	02	GLU57, PRO306
	Cyathusal_B	-7.4	02	GLU57, PRO306
	Clausarin	-7.3	02	GLU64, ARG85
	Cyathuscavin_B	-7.3	00	-
	Pulvinatal	-7.3	01	THR59
HIV-1 PROTEASE I50V ISOLATE	**Lopinavir**	-6.5	03	GLY49, GLY51, GLY52
	Hexahydrodipyrrol derivative	-8.4	03	PRO81, ASP25, GLY48
	Beauvericin	-7.2	01	GLY49
	Chaetocin	-7.1	06	THR74, ASN88, GLN92, ASP30, ILE72, GLY73
	Mollenine_A	-7.1	00	-
	Chetracin_B	-6.9	00	-
	Beauvericin_H1	-6.6		VAL50, GLY51, THR80
	Dragonamide_A	-6.3	02	ASP30, VAL50
	Chetracin_D	-6.2	04	THR74, ARG87, ASP29, GLY73
	Dimethyl-3-Oxodecanamide derivative	-5.6	03	VAL50, GLY51, PHE53
	Symplocamide_A	-4.6	00	-
HIV-1 PROTEASE A02 ISOLATE	**Ritonavir**	-7.7	04	ASP29, ASP30, GLY48, GLY49
	Bionectin_B	-8.1	03	ILE50, THR82, GLY51
	Luteoalbusin_A	-8.0	04	GLY51, GLY52, PRO81, PRO79
	Bionectin_A	-7.7	02	THR96, ASN98
	Oidioperazine_A	-7.7	02	ILE50, ASP25
	Holstiine	-7.1	00	-
	Chetracin_B	-7.0	02	ARG87, LUE97
	Mollenine_A	-6.9	00	-

	Methaniminium derivative	-6.6	01	PRO81
	Verticillin_E	-6.6	02	THR74, ASN88
	Chaetocin	-6.4	02	ARG08, THR26

*kcal/mol

Molecular dynamic simulations to predict the protein structural stability:

In the present study, united-atom MD simulations were performed to confirm the accuracy of binding resulted from docking studies. The result of the MD simulation displayed the conformational changes acquired by different target proteins of SARS-CoV-2 upon binding and inferred the structural insight on molecular stability (fig 4).

The RMSD analysis was done to understand the deviation of Cα atoms of the protein from its backbone, and RMSF analysis was done to study the fluctuations associated with the amino acid residues of the protein during the simulation. The average RMS deviations and RMS fluctuations were calculated from the MD trajectories of natural product, and synthetic drug bound HIV-1 protease (I50V isolate), Influenza virus haemagglutinin, SARS-CoV NSP 12 polymerase, and HIV-1 protease (A02 isolate) and were compared with their respective unbound structures. Lesser RMS deviations were observed in the bound structure of HIV-1 protease (I50V isolate) after the binding of Hexahydropyrrolo Derivative compared to Lopinavir standard drug. The protein SARS-CoV NSP 12 polymerase displayed lesser RMS deviations after the binding of HydroxyManzamin_A. In comparison, HIV-1 protease (A02 isolate) exhibited lesser RMS deviations after the binding of Bionectin_B compared to their respective chemical drug counterparts. RMS deviations were lower in Arbidol bound Influenza virus haemagglutinin than natural product Phellibaurin_A bound structure (Fig. 4a-d). Lesser RMS fluctuations were observed in the natural product bound structures of HIV-1 protease, Influenza virus haemagglutinin, and HIV-1 protease than their respective chemical drug bound structures (fig.4e-h). From the RMDF plots, it can be inferred that, though the residues displayed higher fluctuations at certain positions, the protein was able to retain its secondary structure's packability. This was inferred based on the Rg plots (Fig.4i-l), where the structures were found to be very tightly packed, as the secondary structure elements like α-helix, β-sheet, and turn, were remodelled at each time step of the MD simulation. The SASA plots (Fig. 4m-p) also supported these findings.

The binding free energy calculations performed using the g_mmpba module displayed better binding of natural products with their respective target proteins compared to their chemical drug counterparts. The binding free energies of 12_28_Oxa_8_Hydroxy_Manzamin_A (-56.19kJ/mol), Phellibaurin_A (-125.49kJ/mol), and Hexahydropyrrolo Derivative (-91.66kJ/mol) were found to be higher than their respective structurally similar standard drug counterparts; remdesivir (-48.74kJ/mol), arbidol (-102.17), and lopinavir (-81.19kJ/mol) indicating their firm binding with their respective targets. However, the standard drug ritonavir displayed a higher binding energy of -180.82kJ/mol compared to its structurally similar natural product bionectin B (-162.08kJ/mol. The associated terms for binding free energy calculations along with the calculated MD parameters for unbound and ligand-bound targets detailing RMSD, RMSF, Rg, SASA, Secondary structure, Coul-SR energy, and LJ-SR energy are detailed in table 5.

Table 5: Calculated MD parameters for native and ligand-bound SARS CoV2 drug targets obtained from the MD simulation along with binding energies and the contributing energy terms of the prescribed drugs and their most similar natural product calculated using g_mmpbsa module.

		SARS-CoV NSP12 POLYMERASE			INFLUENZA VIRUS HEMAGGLUTININ			HIV-1 PROTEASE I50V ISOLATE			HI
Gromacs Modules		**Native Protein**	**Remdesivir**	**Hydroxy Manzamin_A**	**Native Protein**	**Arbidol**	**Phellibaurin_A**	**Native Protein**	**Lopinavir**	**Hexahydropyrrolo Derivative**	**Na Pr**
	Potential Energy ($x\ 10^{-6}$)	-0.638	-0.638	-0.637	-4.605	-4.604	-4.604	-0.436	-0.434	-0.436	-0.
	RMSD (nm)	0.213	0.195	0.186	0.481	0.429	0.549	0.247	0.270	0.254	0.
	RMSF (nm)	0.105	0.055	0.099	0.176	0.216	0.231	0.130	0.141	0.130	0.
	Rg (nm)	1.558	1.523	1.524	2.802	2.835	2.763	1.316	1.307	1.342	1.
	SASA (nm^2)	92.95	85.00	87.13	175.24	176.47	177.43	59.57	60.05	60.92	64
	Secondary Structure	210.49	221.97	219.29	283.92	295.63	285.29	119.47	112.07	118.78	11
	Coul-SR*	-	-47.22	-3.84	-	-9.45	-65.80	-	-40.29	-30.24	-
	LJ-SR*	-	-92.72	-64.15	-	-109.61	-114.98	-	-113.62	-109.54	-
MMPBSA Module	Binding Energy*	-	-48.74	-56.19	-	-102.17	-125.49	-	-81.19	-91.66	-
	SASA Energy*	-	-18.86	-8.23	-	-13.52	-52.63	-	-14.04	-14.10	-
	Polar Solvation Energy*	-	177.89	32.97	-	43.77	129.78	-	98.18	70.62	-
	Electrostatic Energy*	-	-68.45	-4.00	-	-7.75	-13.76	-	-29.35	-15.37	-
	van der Waals Energy*	-	-139.31	-76.93	-	-124.66	-62.11	-	-135.98	-132.81	-

* kJ/mol

Discussion

Viral infections have always been creating challenges in human healthcare research. The recent outbreak of navel Coronavirus disease, Covid-19, due to the advent of globalization and ease of travel has underscored the need for prevention and safeguarding public health [1]. Despite the advancements in modern drug research, many viruses lack preventive vaccines or effective therapies. In addition, the constant mutations undergone by the virus made it highly [87] challenging for scientists. Further, the potential development of drug-resistant mutants, especially for viral enzyme-specific inhibitors, have significantly hampered the drug efficacy [1, 88, 89]. Therefore, identifying efficacious and cost-effective antiviral drugs in the absence of potential vaccines or standard therapies is of utmost importance. Herbal medicines and purified natural products have been serving as an excellent source for modern drug research programs. The mechanistic elucidation of antiviral drug actions has shed light on the viral life cycle, including their entry, replication, assembly and release, and host-specific interactions.

Due to the advancements in virology, molecular biology, and computational biology, we were quickly able to decipher the patho-physiology of Covid-19 infection [87]. This was followed by pharmacological investigations, drug repurposing and vaccine development. Enormous Covid-19 related publications and treatment strategies shows that scientists are trying every possible possibilities to find cure for this infection [11].

The computational models have been designed to predict the interactions of potential human target proteins with specific viral strains. By relying on the available interaction information, these models predict the novel host-virus interactions. These predictions have been reliable in the past in understanding the infection mechanism of SARS-CoV [90], MERS-CoV [90], Ebola virus [91], and Zika virus [92]. However, these computational methods play a significant role in modern drug research; the experimental verifications of virus-host interactions are needed to substantiate the potential interactions. Along with this, the availability of verified interactions and relevant information is a prerequisite for computational drug discovery methods.

Natural products can be an important complementary medicine to combat against viral infections. Their origin, availability, safety, and cost-effectiveness make them a better choice than synthetic drugs [93]. The present study suggests natural products can exert their therapeutic effects similar to their synthetic drug counterparts. Molecular interaction studies suggests that natural products 12_28_Oxa_8_Hydroxy_Manzamin_A, Marineosin_A, Bis(Gorgiacerol)Amine, Methylstemofoline, Chetracin_B, Oxyprotostemonine, and Stemocurtisine can inhibit RNA-Dependent RNA Polymerase activity similar to remdesivir by binding with SARS-CoV NSP12 polymerase enzyme. Further, all the ten molecules identified to be structurally similar to arbidol displayed binding energies higher than arbidol, suggesting viral entry inhibitory effects. The interactions of natural products structurally similar to Lopinavir and Ritonavir can act as viral protease inhibitors.

The structural stability imposed by the selected natural products after binding to their respective targets supports their effective binding. Several studies have shown that some natural products can interact with key viral proteins associated with virulence [11, 94–97]. Nevertheless, the screening and selection methods that rely on the structural representations involving physiochemical properties, topological indices, molecular graphs, pharmacophore features, molecular shapes, molecular fields, or quantitative measures are expected to reduce false-positive results and yield more effective structures. In this avenue, the current research compares natural products with synthetic drugs and proposes the probable mechanism of action, suggesting a reliable option for first-line treatment against Covid-19 infection.

Abbreviations

ADME- Absorption, Distribution, Metabolism, and Excretion; APBS- Adaptive Poisson- Boltzmann Solver; HTVS- High Throughput Virtual Screening; MD- Molecular Dynamics; MM- Molecular mechanical; MMPBSA- Molecular mechanics/Poisson-Boltzmann surface area; NCATS- National Center for Advancing Translational Sciences; NPASS- Natural product activity and species source database; NPs - Natural products; PD- Pharmacodynamics; PDB- Protein Data Bank; PK
Pharmacokinetics; PME- Particle Mesh Ewald method; Rg- Radius of Gyration; RMSD- Root Mean Square Deviation; RMSF- Root Mean Square Fluctuation; RO5- Rule-of-Five; SASA- Solvent Accessible Surface Area; SMILES- Simplified Molecular Input Line Entry System; SPC- Simple Point Charge; TPSA- Topological polar surface area.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All the data used during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no conflicts of interest.

Availability of data and materials: All the data used during the current study are available from the corresponding author on reasonable request.

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Author contribution: ARSJ: designed and conceived the study, performed the research and wrote the manuscript. NPS: participated in the results discussion and technical support. Both the authors read and approved the final manuscript.

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Figures

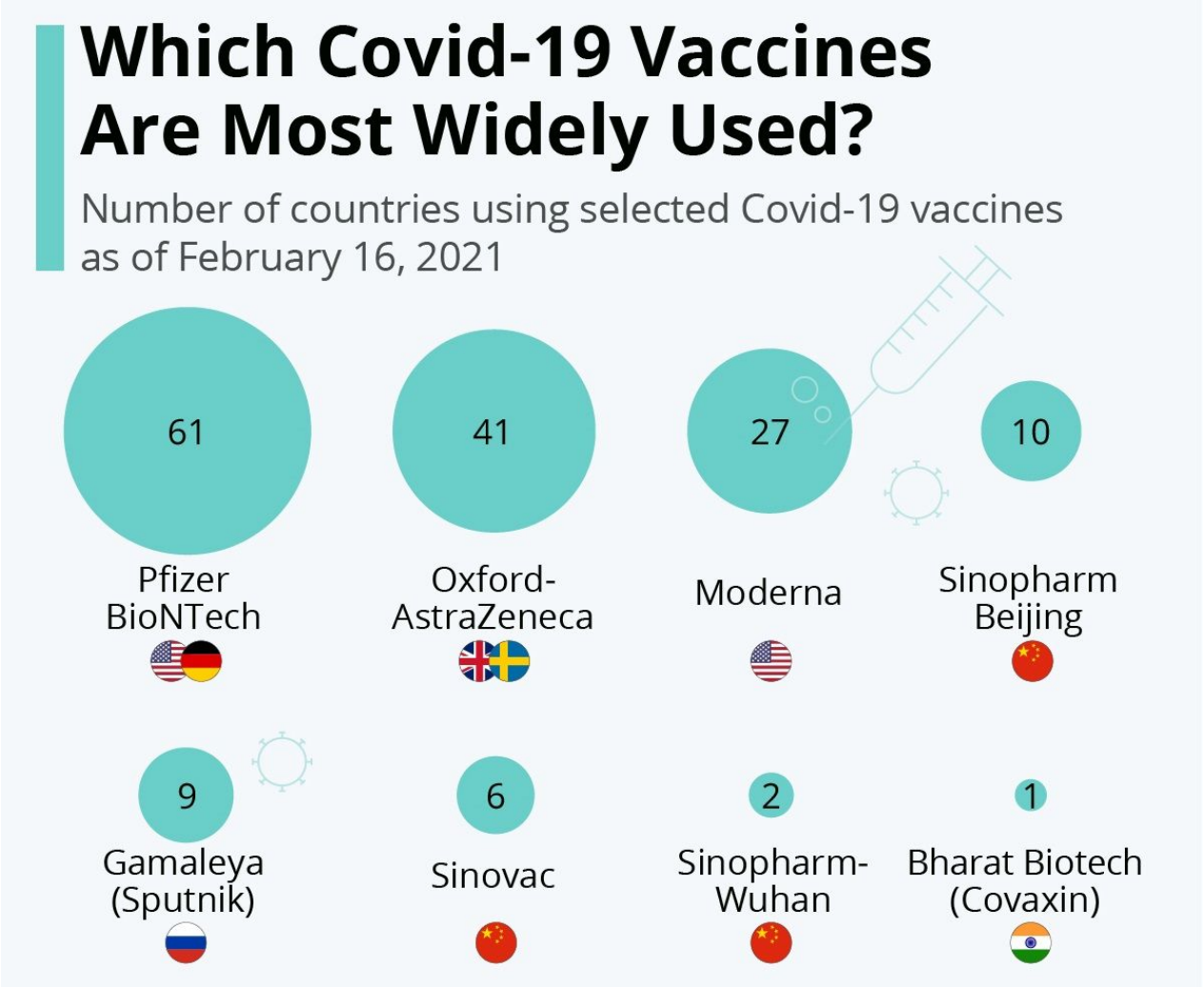

Figure 1

Most widely used vaccines currently developed against Covid-19.

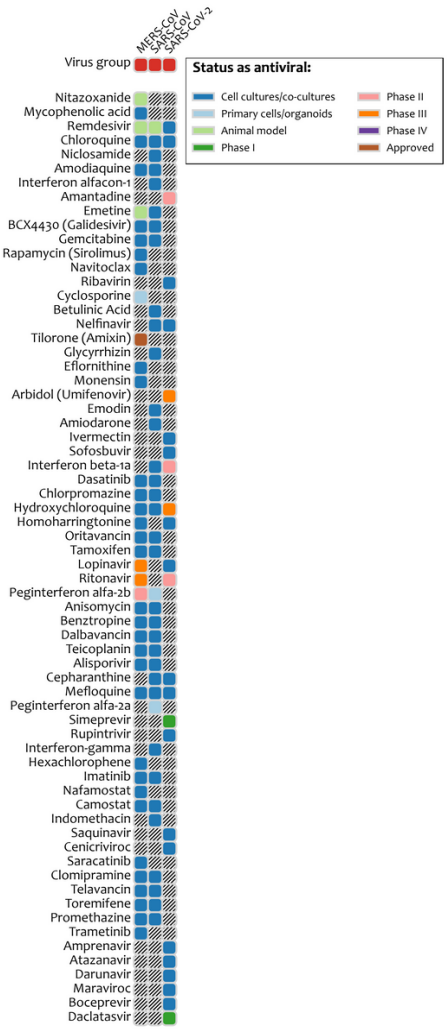

Figure 2

The broad-spectrum antiviral drugs currently being investigated to treat the Covid-19 condition.

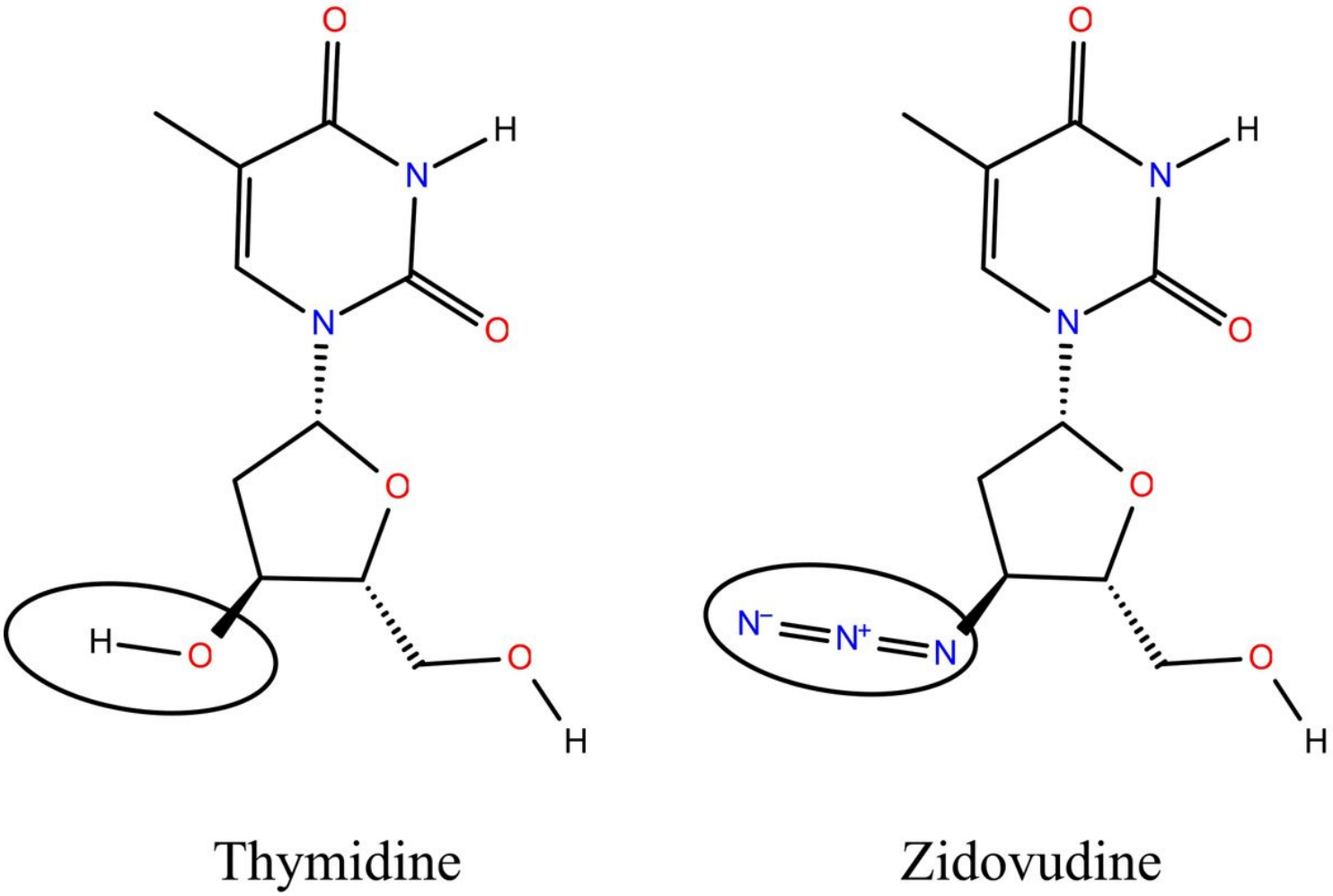

Figure 3

A comparison describing the structural similarities with variations highlighted inside the ellipse between thymidine, a naturally occurring nucleotide base, and zidovudine, a synthetic drug used to treat HIV patients. Structurally both the molecules share >93% identity.

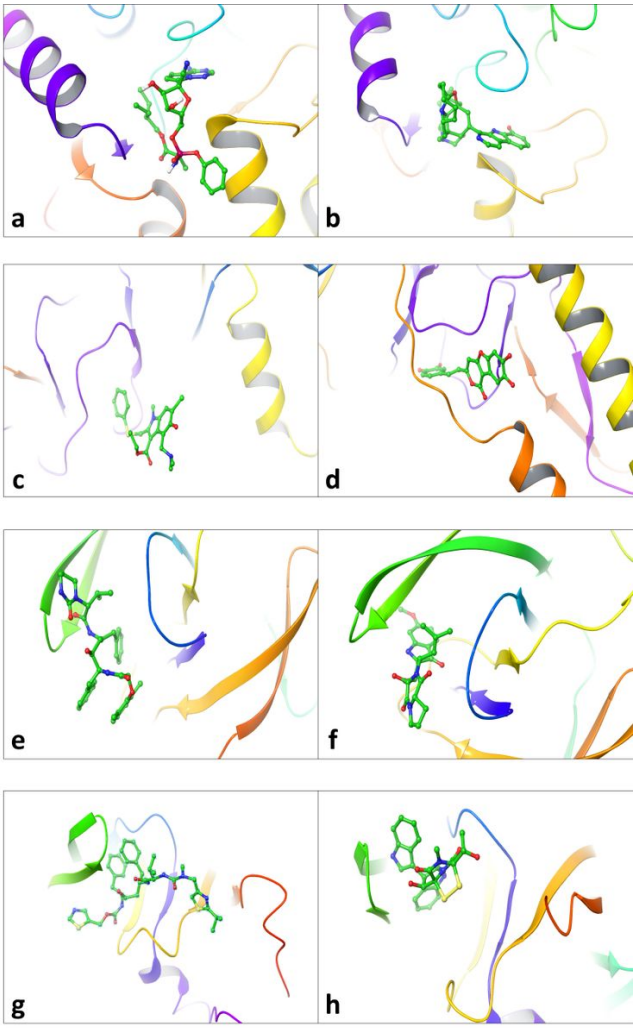

Figure 4

Docking interaction between Remdesivir (a), and 12_28_Oxa_8_Hydroxy_Manzamin_A (b) with SARS-CoV NSP12 polymerase, Arbidol (c), and Phellibaumin_A (d) with influenza virus hemagglutinin, Lopinavir (e), and Hexahydrodipyrrol derivative (f) with HIV-1 protease I50V isolate and Ritonavir (g), and Bionectin_B (h) with HIV-1 protease A02 isolate.

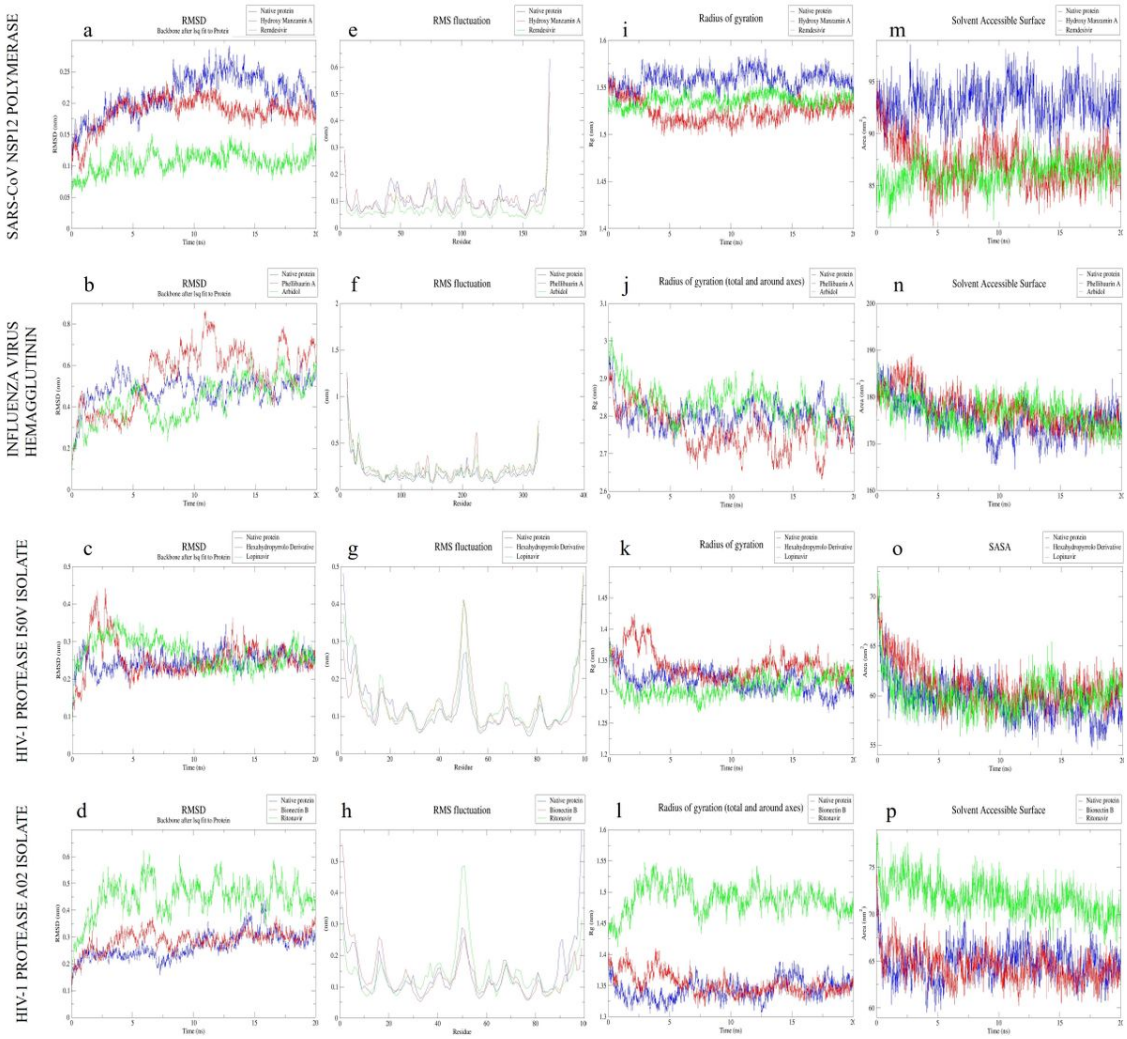

Figure 5

RMSD (a-d), RMSF (e-h), Rg (i-l) and SASA (m-p) plots obtained from MD trajectories analysis of native, Natural product bound, and chemical drug bound structure of SARS-CoV NSP12 polymerase, influenza virus hemagglutinin, , and HIV-1 protease of I50V isolate and A02 isolates.