E-NAMTILA Publishing
DLS **1** (2020) 44-63

DYSONA - Life Science
DOI: 10.30493/DLS.2020.225404

In silico study of various antiviral drugs, vitamins, and natural substances as potential binding compounds with SARS-CoV-2 main protease

Michael Alabboud[1,2]*; Ali Javadmanesh[3]

1, Department of Horticulture, Al-Baath University, Homs, Syria
2, Department of Horticultural Sciences, UTCAN, University of Tehran, Iran
3, Department of Animal Science, Faculty of Agriculture, Ferdowsi University of Mashhad, Mashhad, Iran

E-mail:
Alabboud@ut.ac.ir

Received: 08/04/2020
Acceptance: 16/04/2020
Available Online: 16/04/2020
Published: 01/07/2020

Keywords: COVID-19, M^{pro}, Antiviral, Molecular docking

Abstract

The novel coronavirus (SARS-CoV-2) has without a doubt escalated to become a global crisis. Taking into consideration our limited knowledge regarding the virus, all the efforts to provide better understanding or explore the solutions are highly welcomed. In this article, 88 conventional drugs, 16 vitamins, and 63 natural (plant) compounds were chosen to perform a binding simulation with the reported COVID-19 main protease (M^{pro}) in search for probable inhibitors. Based on docking results, various vitamins (B9, A, K, and E vitamins) exhibited a significantly strong interaction with the studied receptor which might refer to the importance of these supplements in daily diets. Additionally, the strong ligand-protein interactions of some conventional drugs such as Pleconaril, Adefovir dipivoxil, and Stavudine in addition to plant-based compounds such as Curcumin (*Curcuma longa*), Anolignan A (*Anogeissus acuminata*), and Phyllamyricin B (*Phyllanthus myrtifolius*) render these compounds promising and recommended for further studies.

1. Introduction

The novel coronavirus (SARS-CoV-2) was originally discovered and spread in Wuhan, China in late 2019 and since then, the disease caused by this β-coronavirus was named by the world health organization (WHO) as coronavirus disease 2019 (COVID-19) [1]. The transmission factors for the disease are still debatable; however, the reservoir of the novel virus is thought to be bats [2] as a huge diversity of coronaviruses is found in them and therefore considered natural reservoirs of SARS-like coronaviruses [3]. While on the other hand, the infectious host from which the virus was originally transmitted to humans is still unknown [1] if there is any.

Many foggy points still surround the outbreak; however, the solid facts are that while the major percentage of COVID-19 cases of had developed mild flu-like symptoms, the rest few suffer from a rapidly developed acute respiratory distress syndrome (ARDS) which might lead to respiratory failure, in addition to multiple organ failure, and even death [4]. Additionally, the long incubation period 3–7 days with no clear evidence of the disease and capability of spreading the infection [5][6] have rendered the virus among the most dangerous especially for older patients and those of major underlining health conditions [1]. Thereafter, and based on the rapid increase in COVID-19 confirmed cases outside of China, WHO announced it a pandemic on 11 March 2020 [7].

SARS-CoV-2 genome encodes different structural and nonstructural proteins. The viral spike (S) protein is the main structural protein in cell invasion process as it facilitates the engagement with angiotensin-converting enzyme 2 (ACE2) of the host cell [8][1] and mediates the viral invasion by priming with host cell Transmembrane protease serine 2 (TMPRSS2) [8] which illustrate the importance of these components in drug design for the pandemic. There

DYSONA Life Science ISSN: 2708-6291

are components with the potential of strong binding to the viral spike protein or ACE2 [9][10]. These components could act as molecular blockers for disabling the virus's ability to enter the cell. On the other hand, the nonstructural main protease (M^{pro}) facilitates the proteolytic processing of polyproteins and therefore controls the viral gene expression and replication processes which renders it an interesting target for drug design researches [11][12].

Since the original breakout, the efforts to develop an efficient vaccine and pharmaceutical therapies have been rapidly accelerated. Various drugs are already being tested in clinical trials with many showing promising results such as Chloroquine phosphate [13][14][15], Remdesivir [15], in addition to Hydroxychloroquine and Azithromycin [16]. On the other hand, traditional herbal medicine was used before to treat similar breakouts such as SARS and H1N1 which might render herbal extracts and substances as an alternative approach in COVID-19 treatment [17] especially that many of these extracts and compounds are already being used in the treatment of some chronic diseases such as diabetes, HIV/AIDS, and herpes [18][19][20]. The diversity in medicinal plants and their active products demands a rapid evaluation of the possible viral inhibitory effectiveness which might be assisted initially by ligand binding simulations. Therefore, this study aimed to evaluate the binding potentials of various conventional drugs, vitamins, and plant-derived active compounds with SARS-CoV-2 main protease.

2. Materials and Methods

2.1. Protein preparation

The crystal structure of COVID-19 main protease (M^{pro}) with the ID 6LU7 [12] was retrieved as a PDB file from RCSB protein data bank and imported to Molegro Virtual Docker (MVD) [21]. Taking into consideration the fact that water molecules are not involved in the process of ligand-receptor binding; it is usually preferable to remove them before the molecular docking as this step can significantly enhance the computations and to avoid any probable distortion [22] Water molecules were then deleted and protein molecule was prepared prior to docking simulation via MVD molecule preparation function. Detect cavities function was then used in the search for proper docking constraints on the structure.

2.2. Ligands preparation

In total, 88 conventional antiviral drugs, 16 vitamins, and 63 natural (plant) compounds were chosen from the antivirus lists and literature [18-20][23-26]. All the chosen ligands were downloaded from ZINC15 database in SDF format and then imported into MVD workspace. The ligands were then prepared for docking using MVD molecule preparation function (Fig. 1).

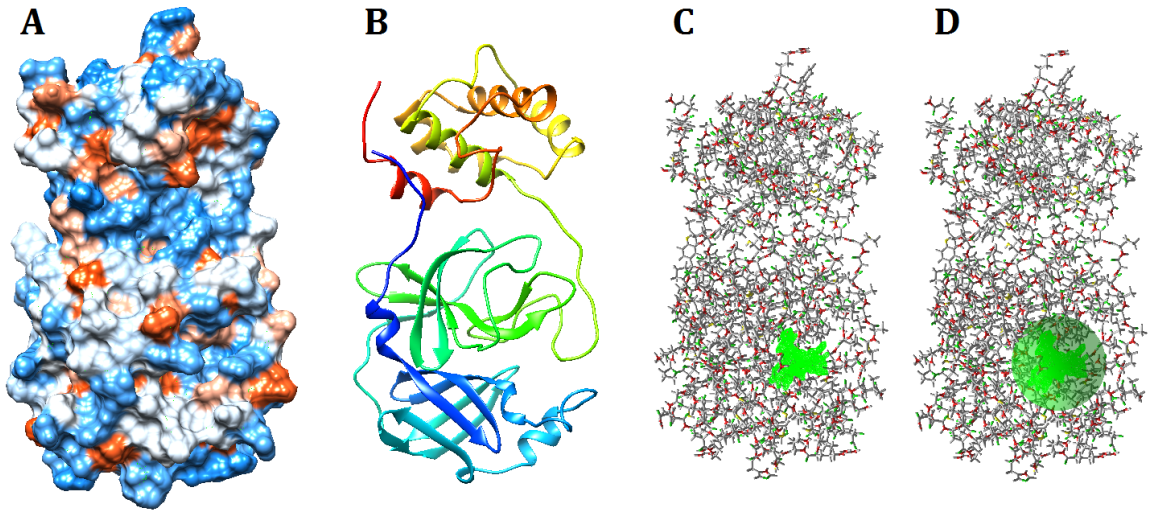

Figure 1. Visualization of SARS-CoV-2 main protease. Visualization using UCSF Chimera hydrophobicity surface **(A)** and ribbons **(B)**. The chosen cavity **(C)** which was used to specify docking constraints dimensions and coordinates **(D)**

2.3. Docking and post-docking analysis

MVD docking wizard was started up and the protein structure along with all the chosen ligands were selected for docking. All docking specifications were left as the original default settings; however, binding site constrain was set to include the largest detected cavity on the protein structure and its dimensions were minimized in order to decrease the simulation processing time and increase accuracy (Fig. 1 D). Furthermore, the number of runs was set to 50 runs/ligand and the maximum population was set to 100 according to MVD recommendations as these settings resulted in better outcomes.

After completion, docking results were imported and the best pose of each ligand, based on their Re-rank score, was loaded into the workspace. The 2D diagrams of receptor-ligand interaction for the best poses were visualized using BIOVIA discovery space visualizer; while docking poses within the protein structure were visualized using UCSF Chimera software after exporting the protein molecule and poses in MOL2 format.

3. Results and Discussion

Cavity prediction function results demonstrated the presence of four cavities on the surface of M^{pro} which ranged in volume from 10.24 – 126.98 Å. The largest cavity was chosen for docking as it has originally included the biding ligand 02J-ALA-VAL-LEU-PJE-010 as provided in PDB (Fig. 1 C).

All the chosen compounds were evaluated for binding probability in the same docking session. After docking, the molecules were ranked based on their Re-rank score. The results showed that the best drugs were Tenofovir Alafenamide, Adefovir dipivoxil, Amprenavir, Raltegravir, Intelence, Ganciclovir, Ganciclovir Triphosphate, Pleconaril, Acyclovir Diphosphate, Doravirine, Rilpivirine, Valganciclovir, Victrelis, Stavudine, and Tenofovir Disoproxil with a re-rank scores ranged from -117.493 to -106.829 and MolDock scores between -167.369 and -125.673 (Table 1). Additionally, graphical visualization showed strong hydrogen bonds interaction with protein molecule (Fig. 2-6). All previously mentioned drugs are used in treatment programs of various viral diseases including HIV/AIDS, Cytomegalovirus (CMV), herpes, and Picornavirus (Table 1). Although some of these drugs have entered clinical trials of COVID-19, there are some reports of few with no significant positive results such as Ganciclovir and Acyclovir (no reports of Acyclovir Diphosphate) and therefore, these drugs were not recommended [1][44][45], additionally, Tenofovir Alafenamide trials [46] have also started with no new reports so far. The rest simulated drugs result can be seen in (Table 2).

Among the investigated vitamins, B9, A, K, and E vitamins exhibited promising results with MolDock scores between -131.99 and -148.43 (Table 3). It is always recommended to fortify body immunity through a balanced diet that satisfies the daily body needs of vitamins and minerals. Vitamin B9 was additionally reported to have an Inhibitory effect on RNA-dependent-RNA polymerase activity of SARS-CoV-2 virus's SCV2-nsp12 enzyme. On the other hand, Vitamin K3 was reported to have an inhibitory effect on HIV [47]. Additionally, vitamins E and D were reported to be proper candidates in improving body immunity towards COVID-19 [48], as low levels of these supplements increased viral infections with bovine coronavirus in cattle [49].

As for the studied plant natural compounds, five substances showed promising results. These substances were Curcumin (*Curcuma longa*), Mallotojaponin (*Phyllanthus myrtifolius*), Peltatol A (*Pothomorphe peltata*), Anolignan A (*Anogeissus acuminata*), and Phyllamyricin B (*Phyllanthus myrtifolius*) with rerank scores ranged between -131.59 and -107.42 with MolDock scores between -219.39 and -156.27 (Table 4) and various formed conventional Hydrogen bonds (Fig. 7 and 8). All these substances were reported as HIV inhibitors [24][50-54]. Curcumin was previously reported as a strong SARS main protease inhibitor [55]. The rest of the investigated natural-based molecules can be seen in (Table 5).

2D receptor-ligand interaction diagrams illustrated that among the 15 best drugs; Amprenavir, Intelence, Ganciclovir, Acyclovir Diphosphate, and Rilpivirine had an unfavorable acceptor-acceptor bond as can be seen in (Fig. 2 C), (Fig. 3 B), (Fig. 3 C), (Fig. 4 C), and (Fig. 5 B). On the other hand, among the 5 best natural products, Mallotojaponin had an unfavorable acceptor-acceptor bond (Fig. 7 B) while Peltatol A had an unfavorable bump (Fig. 7 C). Ganciclovir and Acyclovir were previously reported to have no inhibitory effect on the novel virus and were therefore not recommended for treatment which might be partially correlated to the predicted unfavorable bonds illustrated in the

current study. However, in addition to their various conventional hydrogen bonds; the rest shortlisted drugs (except for Ganciclovir Triphosphate and Valganciclovir) and plant compounds were found to have various Alkyl and/or Pi-Alkyl bonds which might positively contribute to the hydrophobic ligand-receptor interaction [56]. Pi-Pi and fluorine bonding which can be seen in the interaction diagram of Pleconaril (Fig. 4 B) play an essential role in protein-ligand binding [57] and might render the binding of this drug as one of the strongest among the tested ligands [56]. Charge transfer which might be involved with Pi-sigma bonds present in Adefovir dipivoxil-protein and Stavudine-protein interaction diagrams (Fig. 2 B) and (Fig. 6 B) respectively can support an intercalating binding between these drugs and the receptor [56].

Table 1. The best predicted poses scores among the chosen antiviral drugs with their reported current uses

Name	ZINC entry	MolDock Score	Rerank Score	HBond	Usages
Tenofovir Alafenamide	ZINC100055899 (Tenofovir Alafenamide)	-167.37	-117.49	-4.93	HIV/AIDS[A] [27]
Adefovir dipivoxil	ZINC3930376 (Pmea)	-145.33	-117.12	-4.37	[28] HBV[B] [29][30], herpes simplex virus [31], and Hepatitis B virus [32]
Amprenavir	ZINC3809192 (Amp)	-160.23	-115.28	-5.46	HIV [33]
Raltegravir	ZINC13831130 (Raltegravir)	-151.86	-115.15	-9.01	HIV/AIDS [34]
Intelence	ZINC602632 (Intelence)	-150.79	-113.89	-8.38	HIV [35]
Ganciclovir	ZINC1505 (Ganciclovir)	-142.14	-113.38	-5.25	CMV[C] [36]
Ganciclovir Triphosphate	ZINC13649787 (Ganciclovir Triphosphate)	-142.03	-113.22	-11.07	CMV [36]
Pleconaril	ZINC1537619 (Pleconaril)	-140.78	-110.08	-7.77	Picornavirus respiratory infections [37]
Acyclovir Diphosphate	ZINC13527401 (Acyclovir Diphosphate)	-130.58	-109.83	-10.22	Herpes simplex and varicella zoster virus [38]
Doravirine	ZINC72317283 (Doravirine)	-137.83	-109.66	-0.81	HIV/AIDS [39]
Rilpivirine	ZINC1554274 (Rilpivirine)	-144.06	-109.63	-6.01	HIV [40]
Valganciclovir	ZINC1543916 (Valganciclovir)	-129.57	-109.55	-7.51	CMV [41]
Victrelis	ZINC14210455 (Victrelis)	-165.62	-109.21	-3.60	HCV [42]
Stavudine	ZINC137884 (Stavudine)	-125.67	-106.98	-6.86	HIV/AIDS [43][D]
Tenofovir Disoproxil	ZINC3929022 (Tenofovir Disoproxil)	-148.71	-106.83	-5.69	HIV/AIDS [27]

A, Human immunodeficiency virus infection / acquired immune deficiency syndrome
B, Hepatitis B virus
C, Cytomegalovirus
D, *In vitro*

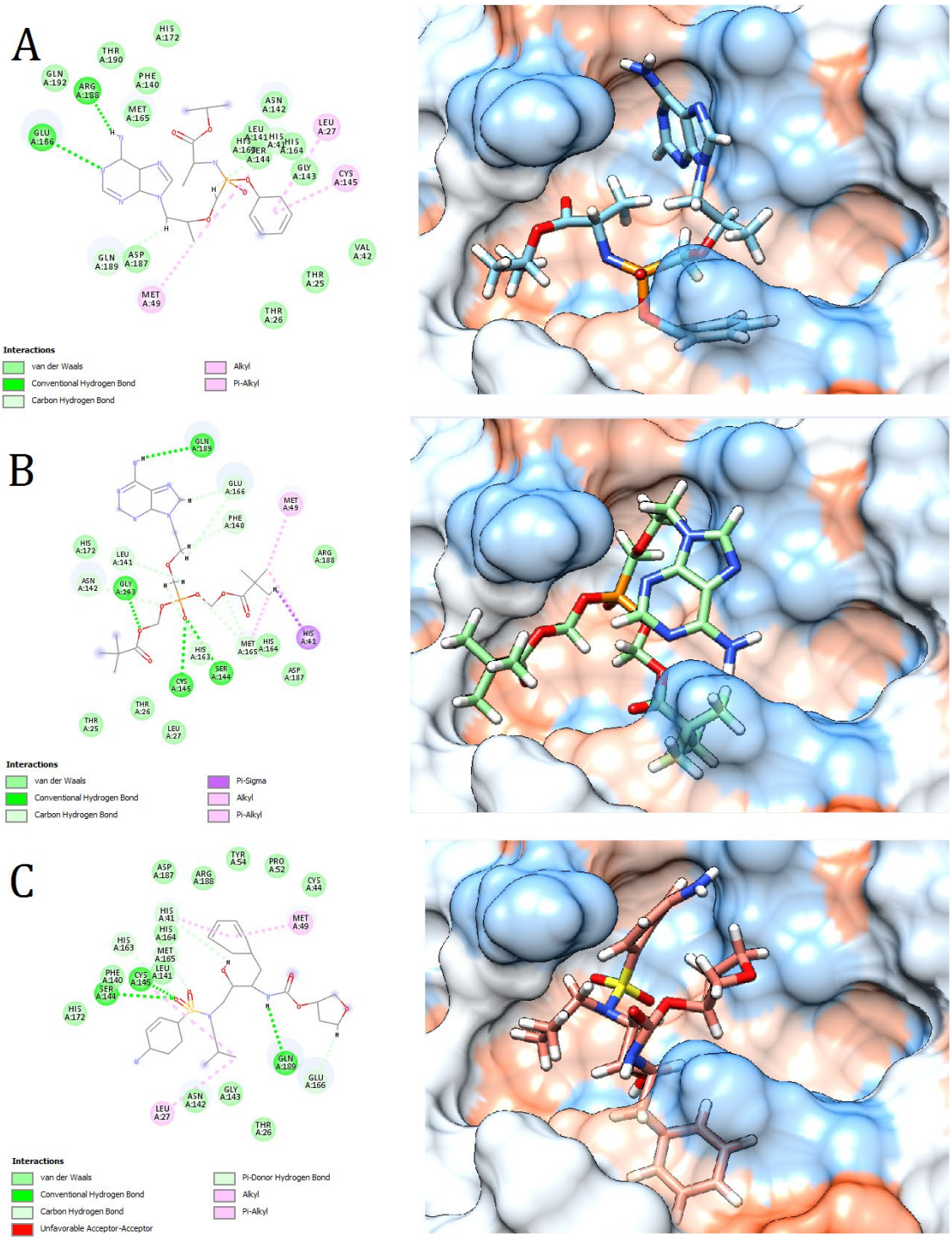

Figure 2. Docking pose visualization for the drugs with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Tenofovir Alafenamide, (B) Adefovir dipivoxil, (C) Amprenavir

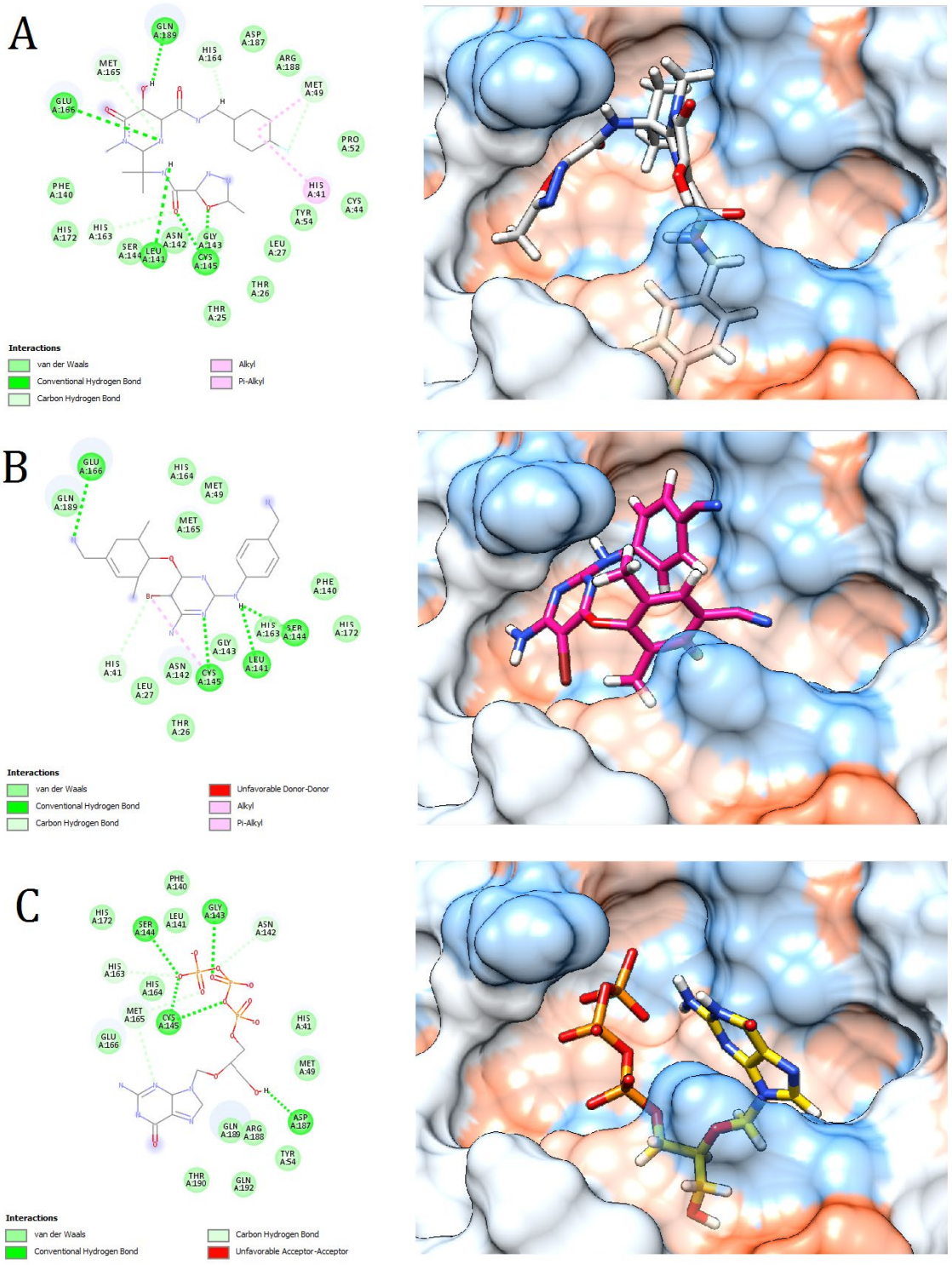

Figure 3. Docking pose visualization for the drugs with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Raltegravir, (B) Intelence, (C) Ganciclovir

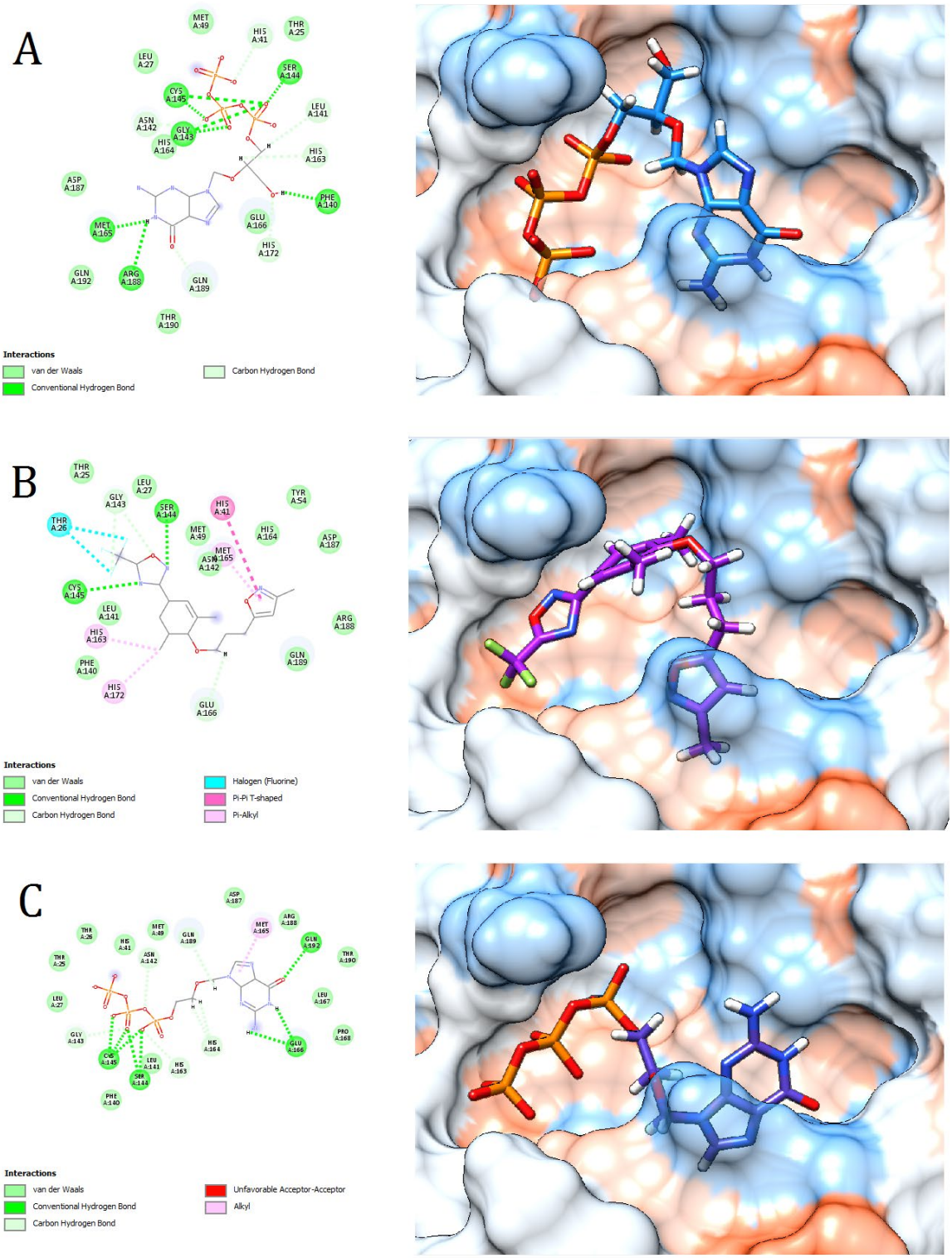

Figure 4. Docking pose visualization for the drugs with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Ganciclovir Triphosphate, (B) Pleconaril, (C) Acyclovir Diphosphate

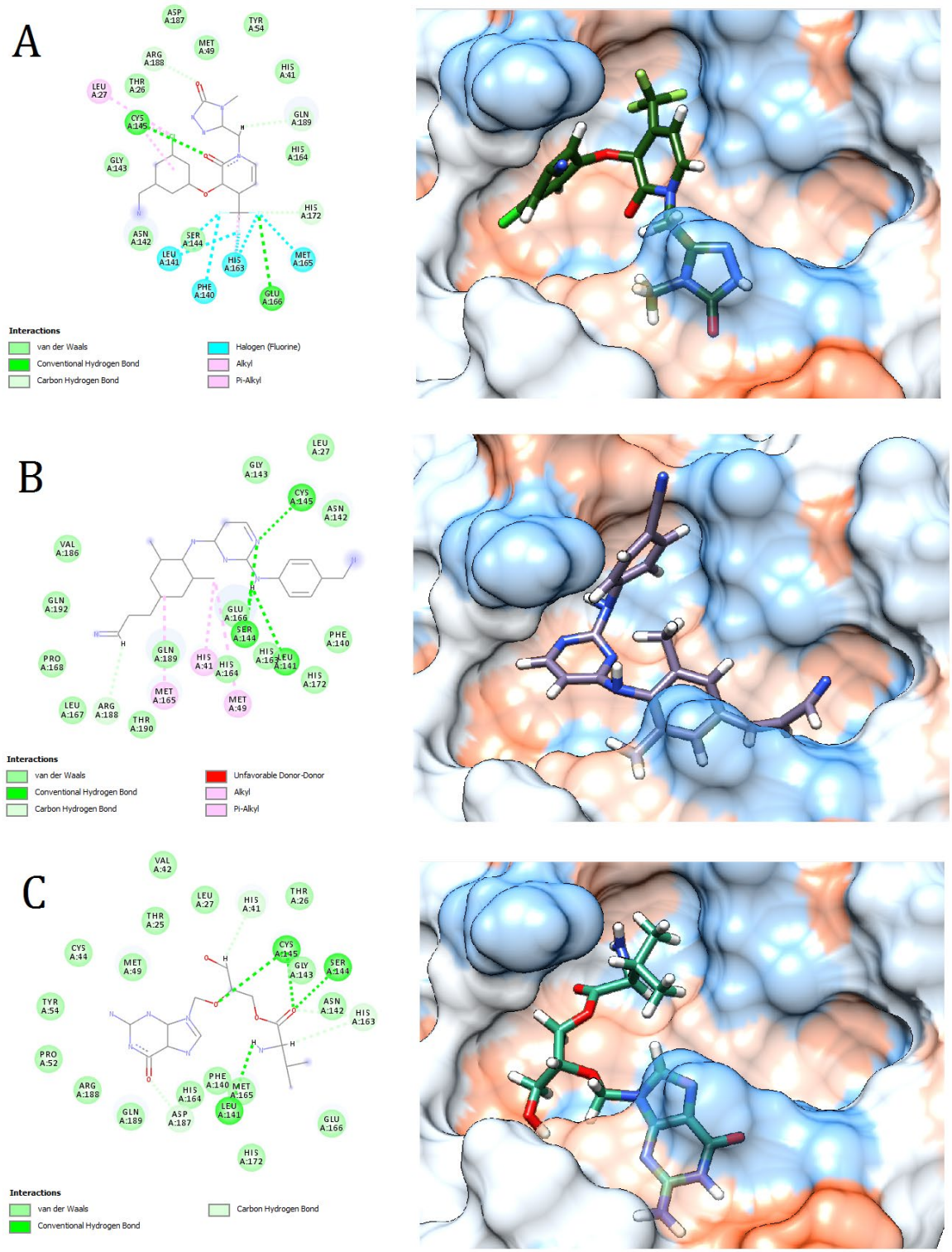

Figure 5. Docking pose visualization for the drugs with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Doravirine, (B) Rilpivirine, (C) Valganciclovir

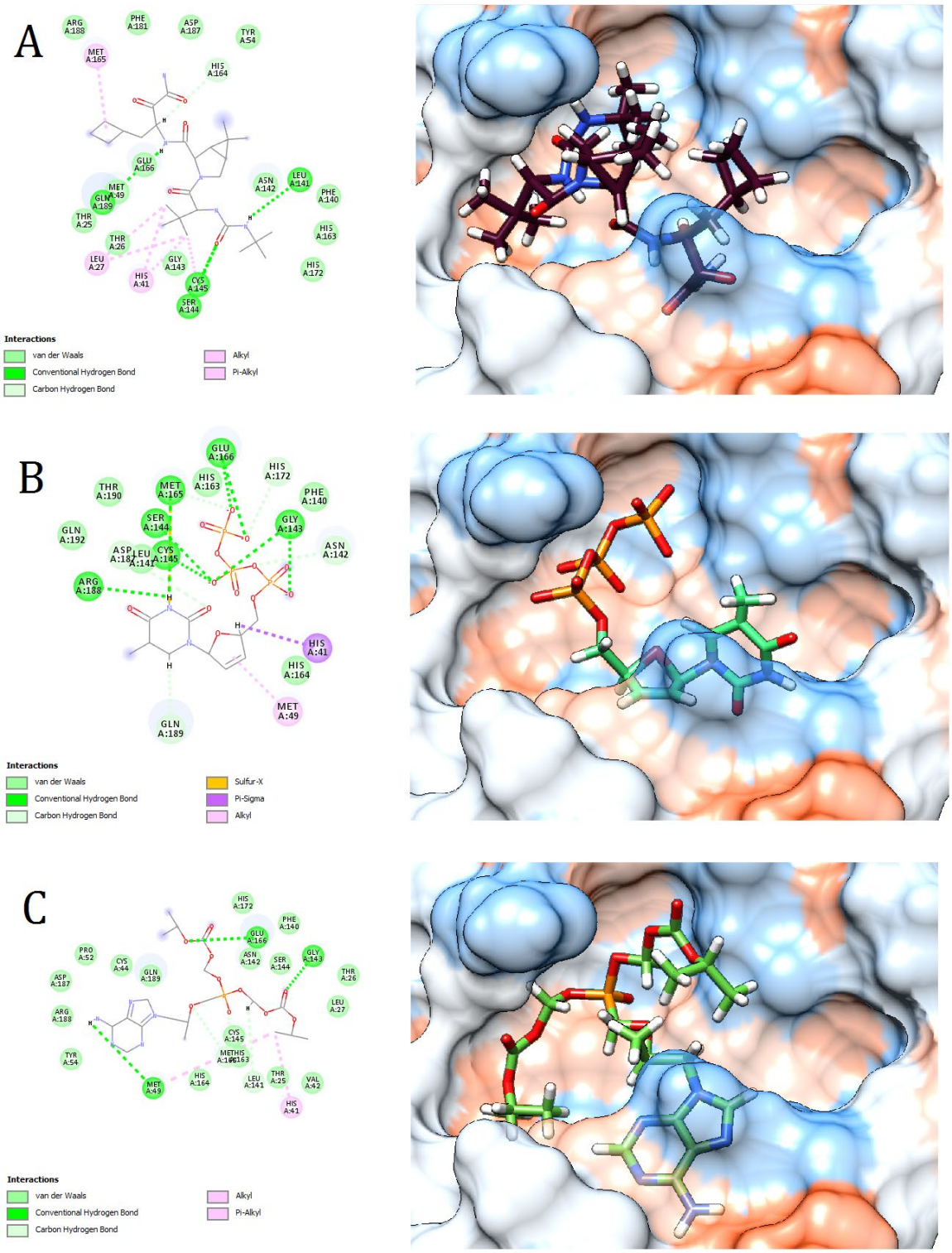

Figure 6. Docking pose visualization for the drugs with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Victrelis, (B) Stavudine, (C) Tenofovir Disoproxil

Table 2. The predicted poses scores of the rest inspected antiviral drugs

Name	ZINC entry	MolDock Score	Rerank Score	HBond
Ribavirin Triphosphate	ZINC12402860 (Ribavirin Triphosphate)	-134.87	-106.17	-8.66
Adefovir	ZINC21297308 (Adefovir)	-128.44	-105.49	-7.68
Tenofovir Diphosphate	ZINC13516399 (Tenofovir Diphosphate)	-141.99	-103.40	-5.93
Alinia	ZINC3956788 (Alinia)	-124.56	-100.84	-5.10
Arbidol	ZINC19907652 (Arbidol)	-141.21	-100.36	-0.11
Dihydroclusin	ZINC1575136 (Dihydroclusin)	-126.11	-100.33	-7.64
Abacavir	ZINC2015928 (Abacavir)	-122.62	-100.21	-5.36
Famciclovir	ZINC1530635 (Fcv)	-122.00	-100.13	-4.71
Acyclovir	ZINC1530555 (Acyclovir)	-115.40	-98.02	-6.13
Elvitegravir	ZINC13682481 (Elvitegravir)	-120.11	-94.79	-2.93
Abreva	ZINC6920384 (Abreva)	-126.90	-92.55	-1.86
Valacyclovir	ZINC1530713 (Valacyclovir)	-108.63	-92.34	-3.51
Letermovir	ZINC100369359 (Letermovir)	-129.77	-92.21	-4.57
Ganciclovir Triphosphate	ZINC13649789 (Ganciclovir Triphosphate)	-106.20	-91.83	-9.24
Vidarabine Phosphoric Acid	ZINC13543718 (Vidarabine Phosphoric Acid)	-117.88	-90.17	-13.36
Tipranavir	ZINC100016058 (Tipranavir)	-146.96	-88.25	-1.99
Adefovir Diphosphate	ZINC13518757 (Adefovir Diphosphate)	-102.95	-87.39	-2.67
Tenofovir	ZINC1543475 (Tdf)	-111.53	-87.19	-3.20
Ribavirin Monophosphate	ZINC12402859 (Ribavirin Monophosphate)	-99.13	-86.93	-6.74
Lamivudine-Triphosphate	ZINC13556853 (Lamivudine-Triphosphate)	-117.80	-86.27	-5.65
Lopinavir	ZINC3951740 (Lpv)	-154.29	-85.48	-7.34
Darunavir	ZINC3955219 (Darunavir)	-156.52	-84.92	-5.52
Penciclovir	ZINC1899 (Penciclovir)	-101.26	-83.84	-8.77
Oseltamivir Carboxylic Acid	ZINC3929509 (Oseltamivir Carboxylic Acid)	-105.64	-83.16	-7.23
Acyclovir Triphosphate	ZINC13649795 (Acyclovir Triphosphate)	-98.99	-83.07	-8.75
Indinavir	ZINC22448696 (Indinavir)	-124.14	-82.86	-3.65
Delavirdine	ZINC18516586 (Delavirdine)	-122.21	-82.26	-5.25
Loviride	ZINC598073 (Loviride)	-90.30	-80.28	-0.18
Lamivudine-Monophosphate	ZINC95618598 (Lamivudine-Monophosphate)	-96.43	-79.58	-5.76
Tromantadine	ZINC4214578 (Tromantadine)	-87.23	-78.96	0.00
Idoxuridine	ZINC3834173 (Id2)	-87.55	-77.83	-8.50
Viroptic	ZINC3842753 (Viroptic)	-89.81	-77.79	-9.05
Efavirenz	ZINC2020233 (Efv)	-91.20	-77.71	0.96
Vidarabine Phosphate	ZINC2126310 (Vidarabine Phosphate)	-92.51	-76.39	-12.04
Metisazone	ZINC13516175 (Metisazone)	-95.07	-76.16	-10.41
Nevirapine	ZINC4778 (Nev)	-86.24	-75.60	-2.02
Vidarabine	ZINC970363 (Ara-A)	-83.73	-74.52	-8.66
Dolutegravir	ZINC58581064 (Dolutegravir)	-109.63	-74.46	-3.51
Fosamprenavir	ZINC3941829 (Fosamprenavir)	-150.62	-73.66	-8.13

Continued in the following page

Table 2. The predicted poses scores of the rest inspected antiviral drugs (Continued)

Name	ZINC entry	MolDock Score	Rerank Score	HBond
Cidofovir	ZINC1530600 (Cidofovir)	-92.05	-73.39	-3.09
Imiquimod	ZINC19632912 (Imiquimod)	-93.27	-73.11	-2.35
Zanamivir Heptyl Ester	ZINC72112216 (Zanamivir Heptyl Ester)	-96.93	-73.07	-9.29
Oseltamivir	ZINC3929508 (Oseltamivir)	-91.98	-72.73	-0.77
Entecavir Triphosphate	ZINC40915440 (Entecavir Triphosphate)	-121.24	-71.86	-11.85
Simeprevir	ZINC85540268 (Simeprevir)	-139.18	-71.10	-5.63
Inosine	ZINC8855117 (Hxr)	-77.11	-68.48	-9.44
Baraclude	ZINC3802690 (Baraclude)	-83.79	-67.97	-8.41
Norvir	ZINC3944422 (Norvir)	-162.98	-67.87	-3.60
Moroxydine	ZINC9302211 (Moroxydine)	-78.09	-66.54	-3.27
Ribasphere	ZINC1035331 (Ribasphere)	-81.43	-64.53	-3.85
Videx	ZINC13597823 (Videx)	-78.17	-63.76	-2.90
Epivir	ZINC12346 (Epivir)	-74.04	-63.04	-3.38
Mp-424	ZINC3992480 (Mp-424)	-129.25	-62.85	-1.25
Stavudine Triphosphate	ZINC12502783 (Stavudine Triphosphate)	-78.30	-62.58	-4.68
Lamivudine Sulfoxide	ZINC6524885 (Lamivudine Sulfoxide)	-81.45	-62.36	-3.73
Nelfinavir	ZINC3833846 (Nelfinavir)	-151.57	-61.79	-6.10
Emtriva	ZINC3629271 (Emtriva)	-75.30	-60.48	-9.75
Saquinavir	ZINC3914596 (Saquinavir)	-138.52	-60.28	-3.39
Rapivab	ZINC3981610 (Rapivab)	-85.20	-60.07	-11.09
Ibacitabine	ZINC17174212 (Ibacitabine)	-74.79	-59.31	-8.27
Zalcitabine	ZINC39906 (Ddc)	-71.27	-58.91	-5.48
Maraviroc	ZINC100003902 (Maraviroc)	-131.77	-57.65	-1.55
Edoxudine	ZINC3956771 (Edoxudine)	-78.20	-54.78	-4.65
Phosphonoacetate	ZINC3869741 (Phosphonoacetate)	-65.64	-52.84	-0.49
Amantadine	ZINC968256 (Amantadine)	-53.16	-52.78	-0.07
Foscarnet	ZINC8101109 (Foscarnet)	-55.17	-45.71	-0.74
Rimantadine	ZINC3831429 (Rimantadine)	-45.52	-43.41	-1.36
Podofilox	ZINC3861806 (Podofilox)	3911.54	-35.15	-3.70
Vicriviroc	ZINC22010579 (Vicriviroc)	-65.54	-31.24	-1.12
Zanamivir	ZINC3918138 (Zanamivir)	4944.28	-17.29	-6.45
Cobicistat	ZINC85537014 (Cobicistat)	-118.43	-15.53	0.00
Atazanavir	ZINC3941496 (Atazanavir)	-30.23	55.70	-3.57
Daclatasvir	ZINC68204830 (Daclatasvir)	-45.44	106.02	0.00

Table 3. The predicted poses scores of the inspected vitamins

Vitamin	Name	ZINC entry	MolDock Score	Rerank Score	HBond
B9	Folic acid	ZINC8577218 (Pga)	-147.26	-112.78	-3.78
A	Retinol	ZINC3831417 (Retinol)	-139.19	-112.66	-5.50
E	Tocopherol	ZINC2539618 (Tocopherol)	-131.99	-102.88	-0.15
K	K-Ject	ZINC3831332 (K-Ject)	-148.43	-99.22	0.00
B2	Riboflavin	ZINC2036848 (Riboflavin)	-110.81	-95.42	-14.73
B1	Thiamine	ZINC49153 (Thiamine)	-99.47	-83.08	-6.12
B5	Vitamin B5	ZINC5356858 (Vitamin B5)	-67.81	-65.48	-5.69
D	Alfacalcidol	ZINC12484965 (Alfacalcidol)	-122.59	-59.32	-3.51
C	Ascorbic acid	ZINC100006770 (Vasc)	-64.69	-58.33	-6.39
B6	Pyridoxine	ZINC49154 (Pyridoxine)	-62.42	-57.27	-9.62
B7	Biotin	ZINC35024346	-93.21	-53.76	-8.56
B3	Niaspan	ZINC1795 (Niaspan)	-56.67	-50.07	-2.11
D	Dihydrotachysterol	ZINC4212953 (Dihydrotachysterol)	-90.02	-14.35	-0.63

Table 4. The best predicted poses scores among the chosen plant-based compounds with their reported current uses

Name	Zinc	MolDock Score	Rerank Score	HBond	Usages
Curcumin	ZINC100067274 (Curcumin)	-188.30	-131.59	-9.66	[19] Inhibits HIV-1 integrase [50] and protease [51] (at high concentrations) and inhibits the activation of TNF induced NF-κB [52]
Mallotojaponin	ZINC14585770 (Mallotojaponin)	-175.67	-127.43	-11.63	Inhibits HIV-1 RTase activity [24]
Peltatol A	ZINC5839876 (Peltatol A)	-219.39	-118.96	-8.46	Inhibits HIV-RTase activity [53]
Anolignan A	ZINC1641881 (Anolignan A)	-156.27	-110.57	-5.96	Inhibits HIV-1 RTase activity [54]
Phyllamyricin B	ZINC6483137 (Phyllamyricin B)	-161.92	-107.42	-0.97	Inhibits HIV-RTase activity [53]

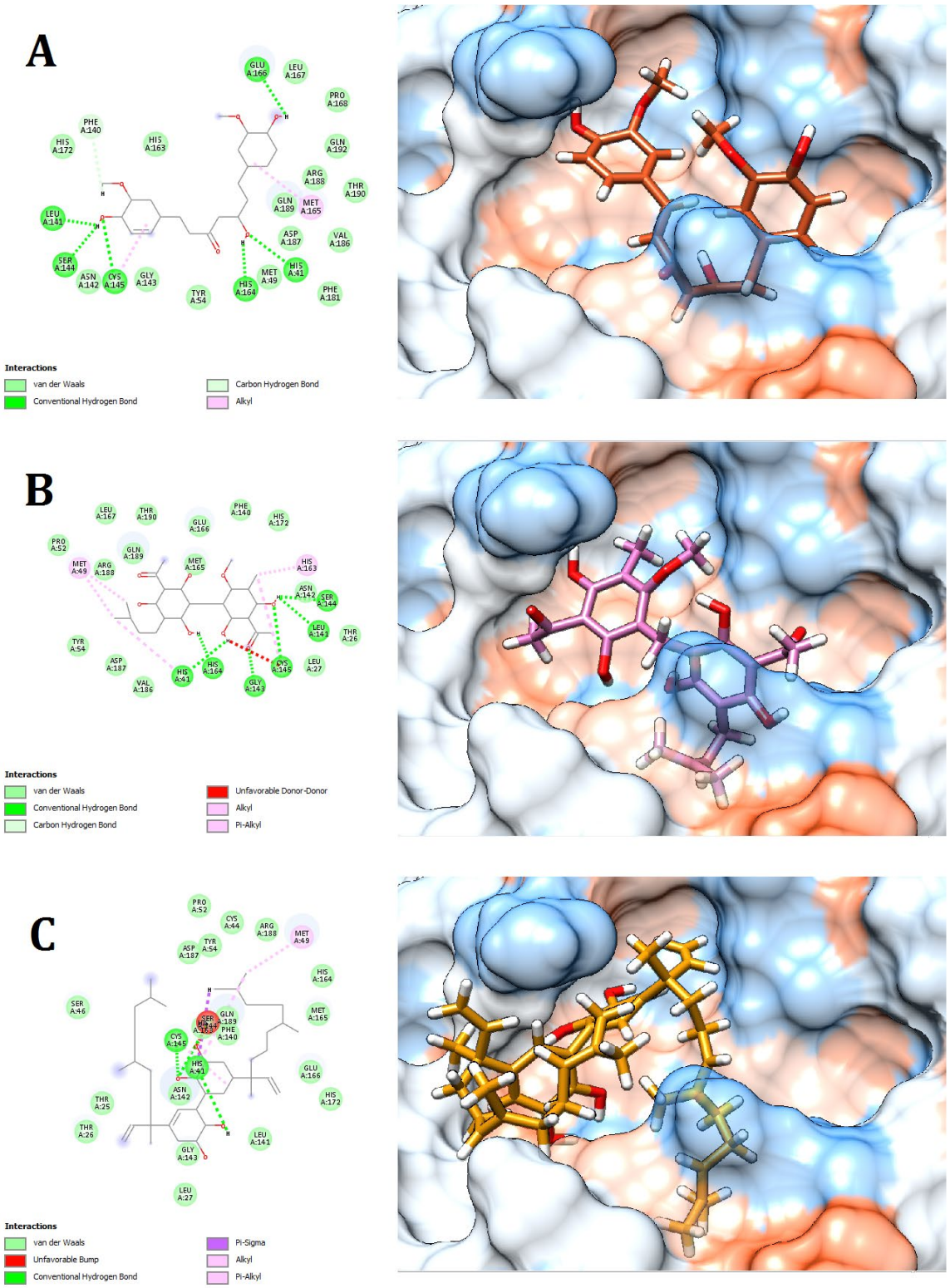

Figure 7. Docking pose visualization for the plant compounds with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Curcumin (*Curcuma longa*), (B) Mallotojaponin (*Phyllanthus myrtifolius*), (C) Peltatol A (*Pothomorphe peltata*)

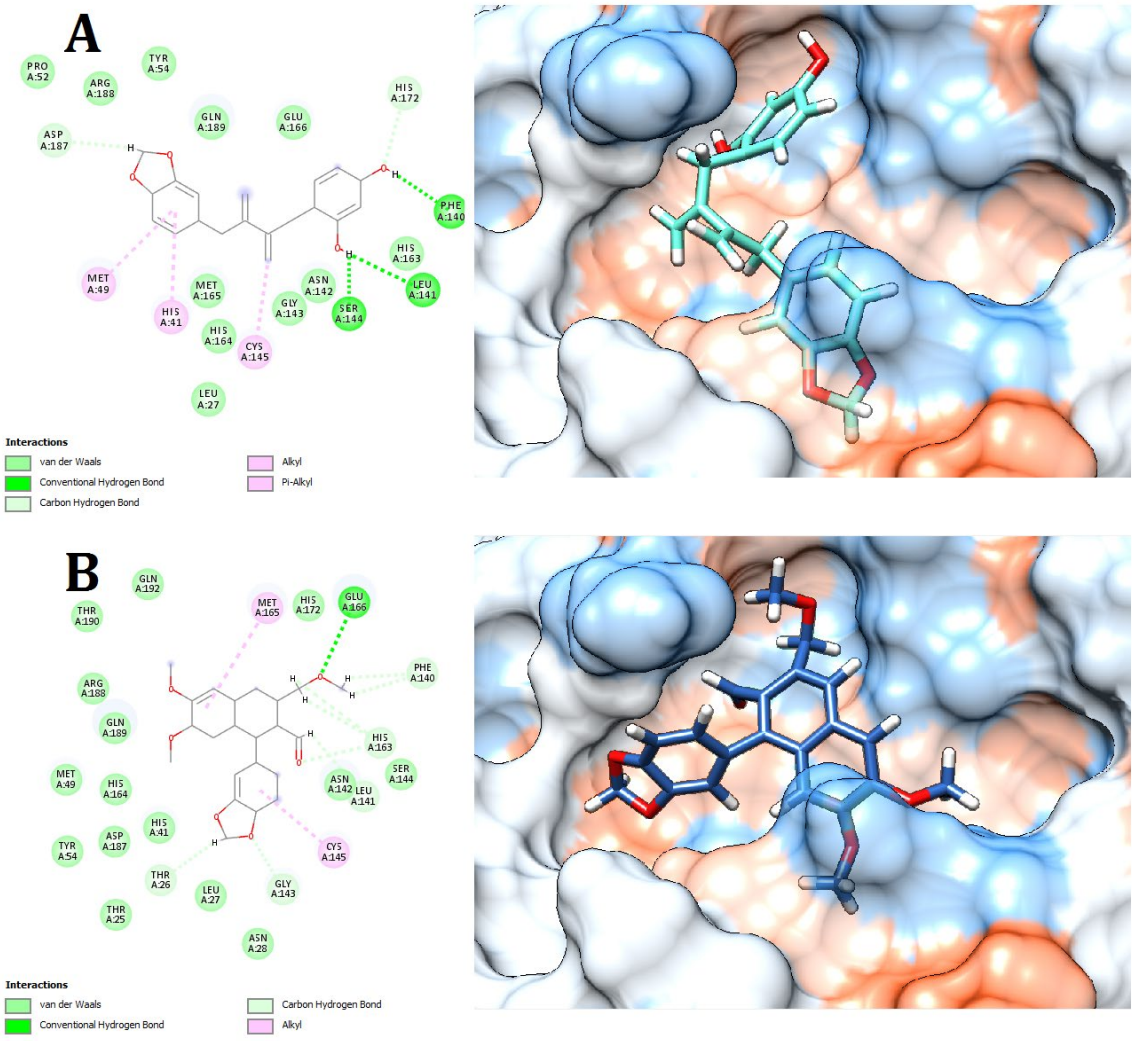

Figure 8. Docking pose visualization for the plant compounds with the best predicted results (Right) and their 2D receptor-ligand interaction diagram (Left). (A) Anolignan A (*Anogeissus acuminata*), (B) Phyllamyricin B (*Phyllanthus myrtifolius*)

Table 5. The predicted poses scores of the rest inspected antiviral plant based compounds

Name	Zinc	MolDock Score	Rerank Score	HBond
Epigallocatechin gallate	ZINC3870412 (Egcg)	-147.44	-97.82	-12.76
Swertifrancheside	ZINC49898469 (Swertifrancheside)	-153.20	-97.07	-14.54
Macluraxanthone B	ZINC5849303 (Macluraxanthone B)	-137.93	-94.90	-6.20
Caffeic Acid Phenethyl Ester	ZINC1083 (Caffeic Acid Phenethyl Ester)	-128.70	-91.60	-8.61
Lithospermic Acid	ZINC4097774 (Lithospermic Acid)	-174.83	-89.81	-12.93
3-O-Feruloylquinic acid	ZINC14919008 (3-Ferulylquinic Acid)	-131.87	-89.45	-5.63
Anolignan B	ZINC1641882 (Anolignan B)	-126.43	-89.18	-7.78
B-Farnesene	ZINC59586886 (B-Farnesene)	-121.28	-86.63	0.00
1-O-Caffeoylquinic acid	ZINC13382386 (1-Caffeoylquinic Acid)	-102.38	-84.38	-12.38
Cryptochlorogenic acid	ZINC100038257 (4-Caffeoylquinic Acid)	-124.82	-80.32	-9.59
Epigallocatechin	ZINC3870336 (Egc)	-97.03	-77.92	-10.02
Suksdorfin	ZINC3809580 (Suksdorfin)	-116.69	-76.91	-0.06
Zingiberene	ZINC8234296 (Zingiberene)	-104.96	-74.08	0.00
Neochlorogenic acid	ZINC4096248 (5z-Caffeoylquinic Acid)	-102.29	-73.44	-10.46
7,8-Dihydrocalanolide B	ZINC3809864 (7,8-Dihydrocalanolide B)	-117.32	-73.03	0.15
A-Santalol	ZINC3875791 (A-Santalol)	-121.28	-73.01	-3.90
Gomisin	ZINC1574836 (Gomisin K3)	-134.02	-72.68	-2.46
Chlorogenic acid	ZINC2138728 (Heriguard)	-103.68	-72.53	-4.71
Staurosporine	ZINC3814434 (Staurosporine)	-138.46	-71.24	-1.00
Tashironin	ZINC101623293 (Tashironin)	6857.51	-70.09	-4.28
Picrocrocin	ZINC5766380 (Picrocrocin)	918.52	-65.34	-5.26
Conocurvone	ZINC150343087 (Conocurvone)	-207.80	-64.10	-1.15
Santalen	ZINC64634147 (Santalen)	-103.15	-62.54	0.00
Carvacrol	ZINC967563 (Carvacrol)	-80.47	-59.31	-5.96
Anislactone B	ZINC95909493 (Anislactone B)	-86.94	-58.86	-8.74
Catechin	ZINC119978 (Catechin)	-91.39	-58.78	-8.27
Calanolide A	ZINC600322 (Calanolide A)	-111.00	-58.67	-2.78
Bisabolol	ZINC968461 (Bisabolol)	-85.64	-57.92	-2.68
Thymol	ZINC967597 (Thymol)	-78.46	-56.35	-1.87
Picrocrocin	ZINC12496608 (Picrocrocin)	-92.39	-55.99	-11.30
Menthol Acetate	ZINC1850068 (Menthol Acetate)	-74.13	-55.97	-4.57
Menthol	ZINC967511 (Menthol)	-84.63	-55.96	-1.12
Origanol	ZINC3861537 (Origanol)	-71.01	-55.46	-5.20
P-Cymene	ZINC968246 (P-Cymene)	-76.31	-54.69	0.00
Gomisin	ZINC1574834 (Gomisin K3)	-105.72	-53.23	-1.79
Neomajucin	ZINC101826214 (Neomajucin)	4896.23	-51.36	-4.43
Schisanhenol	ZINC1574833 (Schisanhenol)	-115.50	-48.78	-6.09
Gomisin	ZINC1574835 (Gomisin K3)	-110.65	-48.25	-5.78
Isomenthone	ZINC967523 (Isomenthone)	-64.33	-47.65	-0.23

Continued in the following page

Table 5. The predicted poses scores of the rest inspected antiviral plant based compounds (Continued)

Name	Zinc	MolDock Score	Rerank Score	HBond
Limonene	ZINC967513 (Limonene)	-71.11	-47.47	0.00
Antiseptic	ZINC967566 (Antiseptic)	-66.57	-46.87	0.00
Bisabolol Oxide B	ZINC5767132 (Bisabolol Oxide B)	-84.39	-44.80	0.00
Menthone	ZINC967796 (Menthone)	-66.06	-44.33	-1.56
Picrocrocin	ZINC12496604 (Picrocrocin)	935.22	-44.14	-4.54
Camphene	ZINC968230 (Camphene)	-68.13	-43.27	0.00
Tashironin	ZINC169371251 (Tashironin)	9892.92	-38.83	-2.35
Shikimate	ZINC3860720 (Shikimate)	-66.47	-36.71	-7.40
Picrocrocin	ZINC12496602 (Picrocrocin)	932.75	-32.08	-6.52
Spathulenol	ZINC5765855 (Spathulenol)	-73.51	-27.17	-2.50
Lancilactone C	ZINC31997044 (Lancilactone C)	-105.40	-21.49	-2.31
Anisatin	ZINC40933353 (Anisatin)	-11.23	-20.99	-7.10
Prostratin	ZINC3915682 (Prostratin)	6904.75	-20.18	-8.34
Bisaboloxide A	ZINC14859987 (Bisaboloxide A)	-60.14	-19.54	-2.48
Oleanolic acid	ZINC3785416 (Caryophyllin)	-23.06	43.70	-4.29
Betulinic acid	ZINC118937400 (Mairin)	-20.32	80.99	-4.05
Chebulagic Acid	ZINC169293868 (Chebulagic Acid)	2967.48	92.65	-8.41
Punicalin	ZINC95615728 (Punicalin)	-39.29	112.25	-15.77
Crocin	ZINC245224178	-2.32	355.30	-13.20

4. Conclusions

COVID-19 is without a doubt a crisis that grew to a global scale affecting the lives of billions worldwide. Therefore, all the efforts that may lead to a better understanding or provide significant relief of the major symptoms are highly welcomed. The results of the current study emphasize on the importance of vitamins in daily diets for their probable inhibitory effect on the virus especially B9, A, K, and E vitamins. Additionally, various conventional drugs and plant-based compounds have shown interesting ligand-protein interactions and therefore worth further investigation especially Pleconaril, Adefovir dipivoxil, and Stavudine in addition to Curcumin (*Curcuma longa*), Anolignan A (*Anogeissus acuminata*), and Phyllamyricin B (*Phyllanthus myrtifolius*). Molecular blockers for the virus or cell surface receptors were not investigated in the current study; however, these approaches might find other alternative potential drugs for this global epidemic.

Conflict of interest statement

The authors declared no conflict of interest.

Funding statement

The authors declared that no funding was received in relation to this manuscript.

Data availability statement

The authors declared that all related data are included in the article.

References

1. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Mil. Med. Res. 2020;7(1):1-10. DOI

2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. DOI

3. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, Wang H, Crameri G, Hu Z, Zhang H, Zhang J. Bats are natural reservoirs of SARS-like coronaviruses. Science. 2005;310(5748):676-9. DOI

4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. DOI

5. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, Fang C, Huang D, Huang LQ, Huang Q, Han Y. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil. Med. Res. 2020 Dec 1;7(1):4. DOI

6. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann. Intern. Med. 2020 Mar 10. DOI

7. who.int [Internet]. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [cited 2020 Mar 25]. Available from: Link

8. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020. DOI

9. Adedeji AO, Severson W, Jonsson C, Singh K, Weiss SR, Sarafianos SG. Novel inhibitors of severe acute respiratory syndrome coronavirus entry that act by three distinct mechanisms. J. Virol. 2013;87(14):8017-28. DOI

10. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov. 2020;6(1):1-8. DOI

11. Xue X, Yu H, Yang H, Xue F, Wu Z, Shen W, Li J, Zhou Z, Ding Y, Zhao Q, Zhang XC. Structures of two coronavirus main proteases: implications for substrate binding and antiviral drug design. J. Virol. 2008;82(5):2515-27. DOI

12. Jin, Z., Du, X., Xu, Y. et al. Structure of M^{pro} from COVID-19 virus and discovery of its inhibitors. Nature (2020). DOI

13. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci. Trends. 2020. DOI

14. Touret F, de Lamballerie X. Of chloroquine and COVID-19. Antivir. Res. 2020:104762. DOI

15. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71. DOI

16. Gautret P, Lagier JC, Parola P, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honoré S. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents. 2020:105949. DOI

17. Chan KW, Wong VT, Tang SC. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease. Am. J. Chin. Med. 2020:1-26. DOI

18. Heck CI, De Mejia EG. Yerba Mate Tea (*Ilex paraguariensis*): a comprehensive review on chemistry, health implications, and technological considerations. J. Food Sci. 2007;72(9):R138-51. DOI

19. Cos P, Maes L, Vanden Berghe D, Hermans N, Pieters L, Vlietinck A. Plant substances as anti-HIV agents selected according to their putative mechanism of action. J. Nat. Prod. 2004;67(2):284-93. DOI

20. Allahverdiyev AM, Bagirova M, Yaman S, Koc RC, Abamor ES, Ates SC, Baydar SY, Elcicek S, Oztel ON. Development of new antiherpetic drugs based on plant compounds. InFighting Multidrug Resistance with Herbal Extracts, Essential Oils and Their Components 2013:245-59. Academic Press. DOI

21. Thomsen R, Christensen MH. MolDock: a new technique for high-accuracy molecular docking. J. Med. Chem. 2006;49(11):3315-21. DOI

22. Wong SE, Lightstone FC. Accounting for water molecules in drug design. Expert opinion on drug discovery. 2011;6(1):65-74.

23. Wikipedia contributors. List of antiviral drugs [Internet]. Wikipedia, The Free Encyclopedia; 2020 Mar 20, 06:47 UTC [cited 2020 Mar 25]. Available from: Link

24. Patra JK, Das G, Bose S, Banerjee S, Vishnuprasad CN, del Pilar Rodriguez-Torres M, Shin HS. Star anise (*Illicium verum*): Chemical compounds, antiviral properties, and clinical relevance. Phytother. Res. 2020. DOI

25. Kurapati KR, Atluri VS, Samikkannu T, Garcia G, Nair MP. Natural products as anti-HIV agents and role in HIV-associated neurocognitive disorders (HAND): a brief overview. Front. Microbiol. 2016;6:1444. DOI

26. Soleymani S, Zabihollahi R, Shahbazi S, Bolhassani A. Antiviral effects of saffron and its major ingredients. Curr. Drug Deliv. 2018;15(5):698-704. DOI

27. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, Pozniak A, Thompson M, Podzamczer D, Molina JM, Oka S. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15. DOI

28. Wikipedia contributors. Tenofovir alafenamide [Internet]. Wikipedia, The Free Encyclopedia; 2020 Mar 26, 05:58 UTC [cited 2020 Apr 2]. Available from: Link

29. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J. Adefovir dipivoxil for the treatment of hepatitis B e antigen–positive chronic hepatitis B. N. Engl. J. Med. 2003;348(9):808-16. DOI

30. Manolakopoulos S, Bethanis S, Koutsounas S, Goulis J, Vlachogiannakos J, Christias E, Saveriadis A, Pavlidis C, Triantos C, Christidou A, Papatheodoridis G. Long-term therapy with adefovir dipivoxil in hepatitis B e antigen-negative patients developing resistance to lamivudine. Alimentary pharmacology & therapeutics. 2008;27(3):266-73. DOI

31. ADHOC International Steering Committee. A randomized placebo-controlled trial of adefovir dipivoxil in advanced HIV infection: the ADHOC trial. HIV Med. 2002;3(4):229-38. DOI

32. Qaqish RB, Mattes KA, Ritchie DJ. Adefovir dipivoxil: a new antiviral agent for the treatment of hepatitis B virus infection. Clin. Ther. 2003;25(12):3084-99. DOI

33. Noble S, Goa KL. Amprenavir. Drugs. 2000;60(6):1383-410. DOI

34. Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, Loutfy MR, Lennox JL, Gatell JM, Rockstroh JK, Katlama C. Raltegravir with optimized background therapy for resistant HIV-1 infection. N. Engl. J. Med. 2008;359(4):339-54.

35. Eraikhuemen N, Thornton AM, Branch III E, Huynh ST, Farley C. Combating non-nucleoside reverse transcriptase inhibitor resistance with a focus on etravirine (Intelence) for HIV-1 infection. Pharm. Ther. 2008;33(8):445.

36. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA, Roche Ganciclovir Study Group. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. N. Engl. J. Med. 1999;340(14):1063-70. DOI

37. Hayden FG, Coats T, Kim K, Hassman HA, Blatter MM, Zhang B, Liu S. Oral pleconaril treatment of picornavirus-associated viral respiratory illness in adults: efficacy and tolerability in phase II clinical trials. Antivir. Ther. 2002;7(1):53-66.

38. Kawamura K, Hayakawa J, Akahoshi Y, Harada N, Nakano H, Kameda K, Ugai T, Wada H, Yamasaki R, Ishihara Y, Sakamoto K. Low-dose acyclovir prophylaxis for the prevention of herpes simplex virus and varicella zoster virus diseases after autologous hematopoietic stem cell transplantation. Int. J. Hematol. 2015;102(2):230-7. DOI

39. Colombier MA, Molina JM. Doravirine: a review. Curr Opin HIV AIDS. 2018;13(4):308-14. DOI

40. Jackson A, McGowan I. Long-acting rilpivirine for HIV prevention. Curr Opin HIV AIDS. 2015;10(4):253-7. DOI

41. Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, Ashouri N, Englund JA, Estrada B, Jacobs RF, Romero JR. Valganciclovir for symptomatic congenital cytomegalovirus disease. N. Engl. J. Med. 2015;372(10):933-43. DOI

42. Vermehren J, Park JS, Jacobson IM, Zeuzem S. Challenges and perspectives of direct antivirals for the treatment of hepatitis C virus infection. Int. J. Hepatol. 2018;69(5):1178-87. DOI

43. Nayak D, Boxi A, Ashe S, Thathapudi NC, Nayak B. Stavudine loaded gelatin liposomes for HIV therapy: Preparation, characterization and *in vitro* cytotoxic evaluation. Mater. Sci. Eng. C. 2017;73:406-16. DOI

44. Li H, Wang YM, Xu JY, Cao B. Potential antiviral therapeutics for 2019 Novel Coronavirus. Chinese journal of tuberculosis and respiratory diseases. 2020;43:E002-. DOI

45. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020. DOI

46. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. Int. J. Antimicrob. Agents. 2020:105955. DOI

47. Min BS, Miyashiro H, Hattori M. Inhibitory effects of quinones on RNase H activity associated with HIV-1 reverse transcriptase. Phytother. Res. 2002;16(S1):57-62. DOI

48. Wang LS, Wang YR, Ye DW, Liu QQ. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int. J. Antimicrob. Agents. 2020:105948. DOI

49. Nonnecke BJ, McGill JL, Ridpath JF, Sacco RE, Lippolis JD, Reinhardt TA. Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. Journal of dairy science. 2014;97(9):5566-79. DOI

50. Sui Z, Salto R, Li J, Craik C, de Montellano PR. Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. Bioorg. Med. Chem. 1993;1(6):415-22. DOI

51. Singh S, Aggarwal BB. Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane). J. Biol. Chem. 1995;270(42):24995-5000. DOI

52. Natarajan K, Singh S, Burke TR, Grunberger D, Aggarwal BB. Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. Proc. Natl. Acad. Sci. U.S.A. 1996;93(17):9090-5. DOI

53. Liu JS, Li L. Schisantherins P and Q, two lignans from Kadsura coccinea. Phytochemistry. 1995;38(4):1009-11. DOI

54. Rimando AM, Pezzuto JM, Farnsworth NR, Santisuk T, Reutrakul V, Kawanishi K. New lignans from Anogeissus acuminata with HIV-1 reverse transcriptase inhibitory activity. J. Nat. Prod. 1994;57(7):896-904. DOI

55. Wen CC, Kuo YH, Jan JT, Liang PH, Wang SY, Liu HG, Lee CK, Chang ST, Kuo CJ, Lee SS, Hou CC. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. J. Med. Chem. 2007;50(17):4087-95. DOI

56. Arthur DE, Uzairu A. Molecular docking studies on the interaction of NCI anticancer analogues with human Phosphatidylinositol 4, 5-bisphosphate 3-kinase catalytic subunit. J. King Saud Univ. Sci. 2019;31(4):1151-66. DOI

57. Zhou P, Zou J, Tian F, Shang Z. Fluorine Bonding — How Does It Work In Protein− Ligand Interactions?. J Chem Inf Model. 2009;49(10):2344-55. DOI