In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19

Vipul Kumar
Indian Institute of Technology Delhi, India
Manoj Jena (manoj.20283@lpu.co.in)
Lovely Professional University, Punjab, India

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Abstract

The recent outbreak of the novel coronavirus (SARS-CoV-2) in the Wuhan province of China has taken millions of lives worldwide. In this pandemic situation and absence of known drugs and vaccines against novel coronavirus disease (COVID-19), there is an urgent need for the repurposing of the existing drugs against it. So, here we have examined a safe and cheap alternative against this virus by screening hundreds of nutraceuticals compounds against known therapeutic targets of SARS-COV-2 by molecular docking .The virtual screening results were then analyzed for binding energy and interactive residues in the best binding pose. All these analyses of this study strongly predicted the potential of Folic acid and its derivates like Tetrahydrofolic acid and 5-methyl tetrahydrofolic acid against SARS-COV-2. The strong and stable binding affinity of this water-soluble vitamin and its derivatives against the SARS-COV-2, indicating that they could be valuable drugs against the management of this COVID-19 pandemic. This study could serve as the starting point for further investigation of these molecules through in-vitro and in-vivo assays.

Introduction

The outbreak of novel coronavirus disease (COVID-19) has now been declared as the pandemic worldwide by world health organization (WHO). COVID-19 outbreak happened in December 2019 in Wuhan province of China by a virus called Severe Acute Respiratory Syndrome related to Corona Virus – 2 (SARS-COV-2) [1, 2].This disease has been spread throughout the world, which has infected more than 1 million people, and over 50 thousand people have been died (www.who.int). This virus has given a major challenge to the world medical facilities and economy.

Coronaviruses belong to the family of Coronaviridae, order Nidovirales and realm Riboviria [3]. This virus group contains large positive-sense RNA, around 30 Kb size, which is encapsulated in the membrane envelope [4]. The membrane of the coronavirus is occupied by the glycoprotein projections, which gives the crown-like appearance to the virus; hence the name is Coronavirus [5]. Coronaviruses are divided into four classes, namely alpha, beta, gamma and delta. The SARS-CoV2, Middle East Respiratory Syndrome Virus (MERS) and SARS-CoV are included in the beta class of the coronavirus [4, 6]. All the beta class viruses are known to attack the respiratory system of the human and cause pneumonia [7, 8]. In several cases, it is reported that SARS-CoV-2 can be responsible for multiple organ failure too [9, 10]. Dry cough, difficulty in breathing, fever, and tiredness are the major symptoms found in COVID-19 patients [11]. The current pandemic and number of reported cases are showing that SARS-COV-2 is more contagious and transmissive in comparison to MERS, SARS-CoV, and other previous coronaviruses [12-14].

SARS-CoV-2 encodes for various structural as well as non-structural proteins, which helps in the viral entry as well as replication inside the host cell. One of the major inducers of the host immune response is a structural protein that is embedded in the virus membrane known as Spike (S) glycoprotein [15, 16]. The glycosylated S protein facilitates the entry of the virus into the host cell [17, 18]. The S protein binds to the host cell membrane receptor, Angiotensin-Converting Enzyme-2 (ACE-2), and further its invasion and

fusion inside the host cell membrane is mediated by host Transmembrane Serine Protease (TMPRSS2) [19, 20]. Recently it also reported that the affinity of SARS-CoV-2 towards the ACE-2 is 10-20 times higher than SARS-CoV, which can be the reason for its higher severity in terms of transmission in comparison to previously known coronaviruses [21, 22]. Other than S glycoprotein, SARS-CoV-2 encodes various non-structural proteins, which include the main protease (M^{pro}/$3CL^{pro}$) , papain-like protease (PL^{pro}), RNA dependent RNA polymerase (RdRp) and Nsp15 an endoribonuclease. These non-structural proteins help in the replication and life cycle of the virus inside the host cell. Once the Virus enters inside the cell, its SS RNA is translated into various polyproteins using host translation machinery, and these viral polyproteins are then cleaved into functional viral proteins by M^{pro} and PL^{pro} [23, 24]. These cleavage yields various Nsps, which exhibits multiple enzymatic activities. All the functions and roles of these cleaved Nsps are not clearly known, but some are specifically linked to the replication of the viral RNA. One such Nsps is Nsp15, which is RNA uridylate specific endoribonuclease associated with the viral RNA processing [25, 26]. RdRp is an enzyme that makes a negative-strand RNA template for the synthesis of more viral RNAs [27].

To date, there are no such specific antiviral agents for the treatment of COVID-19 [28]. The fast and best option for its treatment is to repurpose already known drugs, natural molecules and nutraceuticals. Various nutraceutical compounds have reported to be beneficial against viruses [29-31]. Ascorbic acid or Vitamin C has been reported as beneficial against the influenza virus [32, 33]. Similarly, resveratrol against herpes simplex virus (HSV) is well documented [34]. The effect of folic acid malnutrition on rotaviral infected mice has been shown through dose dependent manner [35]. Recently the role of folic acid in the management of COVID-19 by the prevention of SARS-CoV 2 entry inside the human cells has been reported [36]. Nutraceuticals are safe to consume and have many antimicrobial activities reported to date [37], so taking these properties into consideration, we performed the molecular docking based virtual screening of the nutraceutical compounds against S protein-ACE2 complex, M^{pro} , PL^{pro} and Nsp15 .Analysis of the virtual screening results shows that folic acid (Vitamin B9) and its derivative were in the top three compounds against all the proteins studied. Other than folic acid and its derivatives, Gingkoglide -A, a terpene lactone mainly found in tree Ginkgo biloba was found best against PL^{pro} and Magnesium ascorbate against M^{pro}. Although screening of 106 nutraceuticals compounds against all these target proteins and getting folic acid and its derivatives in the top 3 lead compounds against every protein target indicates that these compounds could play a potential role in the prevention and management of the COVID-19.

Methods

Retrieval and preparation of protein structures

The structure of all the SARS-CoV-2 targets was retrieved from the RCSB protein data bank. Four targets, namely S protein (Receptor Binding Domain)-ACE2 complex, M^{pro}, PL^{pro}, Nsp15 having PDB IDs 6LZG (*To be published*), 6LU7 [38], 6W9C (*To be published*), and 6W01(*To be published*) respectively. The water

molecules are removed, polar hydrogens were added, and non-essential heteroatoms were deleted as part of protein preparation before docking with the help of Discovery studio software 2020 [39].

Virtual screening of the nutraceuticals against SARS-CoV-2 proteins

A total of 106 compounds library of the latest release (2020-1) of nutraceutical was retrieved from the drug bank database (www.drugbank.ca) in SDF format . All these compounds were minimized using UFF forcefield with conjugate gradient protocol having 500 steps, with the help of PyRx software [40]. Then both proteins and ligands were converted to pdbqt file format for virtual screening using Autodock vina [41], inbuilt in PyRx software. The top 3 compounds have been reported against all the targets through this virtual screening study.

Interactions of the ligand with critical residues

Top 3 lead compounds based on the binding energy of the docked complex were analyzed for the visualization of the best binding pose. As the importance of hydrogen bonding is well documented in drug discovery and design, further hydrogen bond and other non-polar interactions of best binding poses were analyzed using Discovery studio software [39] .

Results

Folic Acid and its derivatives can prevent the interaction of S protein with ACE-2 receptor

Prepared structure of the S protein (Receptor Binding Domain)- ACE2 complex (PDB ID: 6LZG) was first analyzed in the native conformation to investigate the major interactions between spike protein and ACE-2 receptor. In the analysis, it was found that the TYR41, ASP38, GLU35, ASP30 of ACE-2 receptor was making the hydrogen bond with THR500, GLY496, GLN493 and LYS417 of S protein respectively (Fig.1) .Further, the complex was taken for the screening of nutraceuticals against it. For the docking of the ligands, the grid was generated, taking interacting residues in the center of the box. The coordinates of the grid X = -35.07, Y = 25.72, Z = 0.66 and the dimension of the grid was 25 Angstrom^3. The ligands having the best binding affinity towards the complex were taken further for the analysis of their interacting residues. It was found that, out of 106 nutraceuticals screened; Folic Acid had the strongest binding energy of -9.0 Kcal/mol, followed by tetrahydrofolic acid (-8.9 Kcal/mol) and 5-methyltetraydrofolic acid (-8.6 Kcal/mol). The interaction analysis further showed that these nutraceuticals have the potential to break or prevent the interactions between the protein complex. Folic acid could break the hydrogen bond interaction Of ASP30 of ACE-2 with S protein; similarly, GLY496 of S protein, which previously interacting with ACE-2, was interacting with folic acid after docking. Likewise, GLY493, LYS417 of spike protein, was interacting with Folic acid (Fig 2 A). These significant reductions of the major interacting residues between the spike protein and ACE2 showing the potential of folic in the prevention of viral entry. Similarly, when we analyzed the Tertrahydrofolic acid interactions, we found that it was also able to break the crucial interactions and was making interactions with GLN493, GLN496 of spike protein and ASP38 of ACE-2 receptor (Fig. 2B). Furthermore, 5-methyl-tetrahydrofolic acid was

making the hydrogen bond with ASP30 of ACE-2 and LYS417 of S protein and was making various non-polar interactions with the crucial amino acids, which were previously helping the interaction of spike protein with ACE-2 receptor (Fig 2 C) . All these analyses of the binding energy and interactions with crucial residues of the complex indicating the possibility of folic acid and its derivatives to be lead molecules against SARS-CoV-2 entry inside the human cells (Supplementary Table 1).

Folic acid and it's derivative and Ginkgolide A against PL^{pro}

PL^{pro}, a crucial papain-like protease of the SARS-CoV2, helps in the cleavage of viral polyproteins and making them functional. The inhibition of the functional activity of this protease could inhibit the viral replication inside the host cell. So, the virtual screening was done with all the 106 nutraceuticals compounds, and the grid was generated at the substrate-binding site. Grid was generated around main catalytic residues ASP164, VAL165, CYS270, LYS274, VAL303 at catalytic site [42] for docking of compounds. The center of the Grid was X= -30.19, Y = 31.61, Z= 31.04 with dimension of 25 $Angstrom^3$. After screening, it was found that 5-methyl-hydrofolic acid had the best binding energy (-7.1Kcal/mol) followed by Ginkgolide -A(-7.0 Kcal/mol), a terpene lactone compound mainly found in Ginkgo biloba and Folic acid (-6.9 Kcal/mol). The 5methylhyrofolic acid had the highest number of hydrogen bond interactions with residues (ASP164, ARG166, ALA246, THR301) at the catalytic site of PL^{pro} (Fig 3 A). While, Gingkoglide was making the hydrogen bond with GLY163, in the best binding pose. And, Folic acid was making the hydrogen bond with GLY163 and ASP164 (Fig 3B).The ASP164 has been reported to be a main catalytic residue of $PL^{pro,}$ which helps in proteolysis of the substrate (Fig 3C).Here we could see that all tree best compounds had multiple polar as well as non-polar interactions at the catalytic site , but 5-methyl-hydrofolic acid and Folic acid were making contact with ASP164. All these analyses were again indicating the value of the folic acid and its derivative and Ginkgolide -A potential against the inhibition of COVID-19 (Supplementary Table 2).

Water-soluble Vitamins against $M^{pro}$of SARS-CoV-2

Another crucial protease enzyme for SARS-CoV-2 is Main protease or Cysteine like protease, which helps in the cleavage of polyproteins and make them functional. The structure of the main protease (6LU7) docked with an N3 inhibitor at the substrate-binding site. The main interacting residues of N3 was taken for creating a grid for the molecular docking of 106 Nutraceutical compounds. So, Grid was generated around PHE140, ASN142, GLY143, HIS164 and Centre of grid was, X= -19.50, Y = 19.24, Z= 64.35; the dimension was 25 *25*25 Angstrom. Magnesium Ascorbate, a buffered (non-acidic) form of Vitamin C (Ascorbic acid), was found to be the top lead compound among 106 nutraceuticals. It had binding energy of -8.1 Kcal/mol and was making the hydrogen bond with LEU141, SER144 and HSI164 (Fig 4A). Followed by Folic acid and Riboflavin had a similar binding affinity towards Mpro with the binding energy of -7.7 Kcal/mol. Folic was making polar contact with TYR54, ASP187, ARG188 and THR190 (Fig 4B), while Riboflavin with LEU141, GLY143, CYS145 in their best binding pose at the catalytic site of M^{pro} (Fig 4C).Virtual screening of the nutraceutical against Mpro shown that water-soluble vitamins could be

helpful in preventing the functional activity of the enzyme and hence COVID19 infection (Supplementary Table 3)

Folic Acid and its derivative and NADH can prevent the endoribonuclease activity

Once the virus enters inside the host cell, it uses the host translational machinery to produce various Nsps, which helps virus replication. One such Nsp is Nsp15, which is RNA uridylate specific endoribonuclease associated with the viral RNA processing. Inhibition of the functional activity of Nsp15 could help in the inhibition of viral replication inside the body. So the grid was generated at the substrate-binding site, Grid was generated around LEU246, GLY248, LEU249, TYR343 [43]. The center of grid was X= -62.80, Y = 67.89, Z= 34.93 and the dimension was 25 *25*25 Angstrom. The result of the screening shown that NADH, Folic acid, and 5-methyl-hydrofolic acid with the binding energy of -7.2, 7.1 and 7.1 Kcal/mol, respectively, were the top lead compounds against Nsp15. At the best binding pose, NADH was making one hydrogen bond with TYR343 (Fig 5A). Folic acid had 3 three hydrogen bond interactions with ASP240, HIS243, and TYR343(Fig 5B). 5-methyl-hydrofolic acid was also making 3 hydrogen bonds with ASP240, GLU340 and TYR343 (Fig 5C). These binding energy and number of interacting residues together were indicating that folic acid and its derivatives had a good binding affinity towards Nsp15, which could be lead compounds in the prevention of COVID-19. (Supplementary Table 4).

Discussion

The computational methods are considered as the quick and reliable way to predict the action of the drugs against various targets. The recent pandemic situation around the globe has given a specific requirement for innovating new drugs and repurposing the existing drugs against COVID-19. The recent availability of the crystal structures of various structural and non-structural proteins of SARS-CoV-2 has given the opportunity for structure-based screening of existing compounds against them. Various studies on molecular docking-based screening of existing antiviral, antibacterial and other FDA approved drugs and phytochemicals has already been done and further experimental analysis is still going on. Although the less attention has been given to nutraceutical compounds, which could serve better in the pandemic situation mainly in the poor and developing countries. Taking these points into the considerations we tried the investigating the binding affinities of the nutraceutical molecules against various SARS-CoV-2 and found good binding affinity vitamins and their derivatives. However, in this study, major limitation was validation with molecular dynamics simulations experimental assays due to inaccessibility of the resources in this lockdown period. But we have explored the multitarget ability of these nutraceutical compounds against four main therapeutic targets of SARS-CoV2 through structure based molecular docking which could serve as starting point for further validations. The screening results have shown that folic acid alone or with combination with its derivates tetrahydrofolic acid and 5-methyl-tetrahydrofolic acid could be potential molecules against the COVID-19 infection.

Conclusions

This computational study strongly suggests a need to investigate folic acid and its derivatives through in-vitro and in-vivo assays against SARS-CoV-2. In this current pandemic situation and unavailability of the drugs, this cheap and safe alternative can provide a significant value against the combat of COVID-19.

Declarations

Conflicts of interest

No conflicts of interest is there among the authors.

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Figures

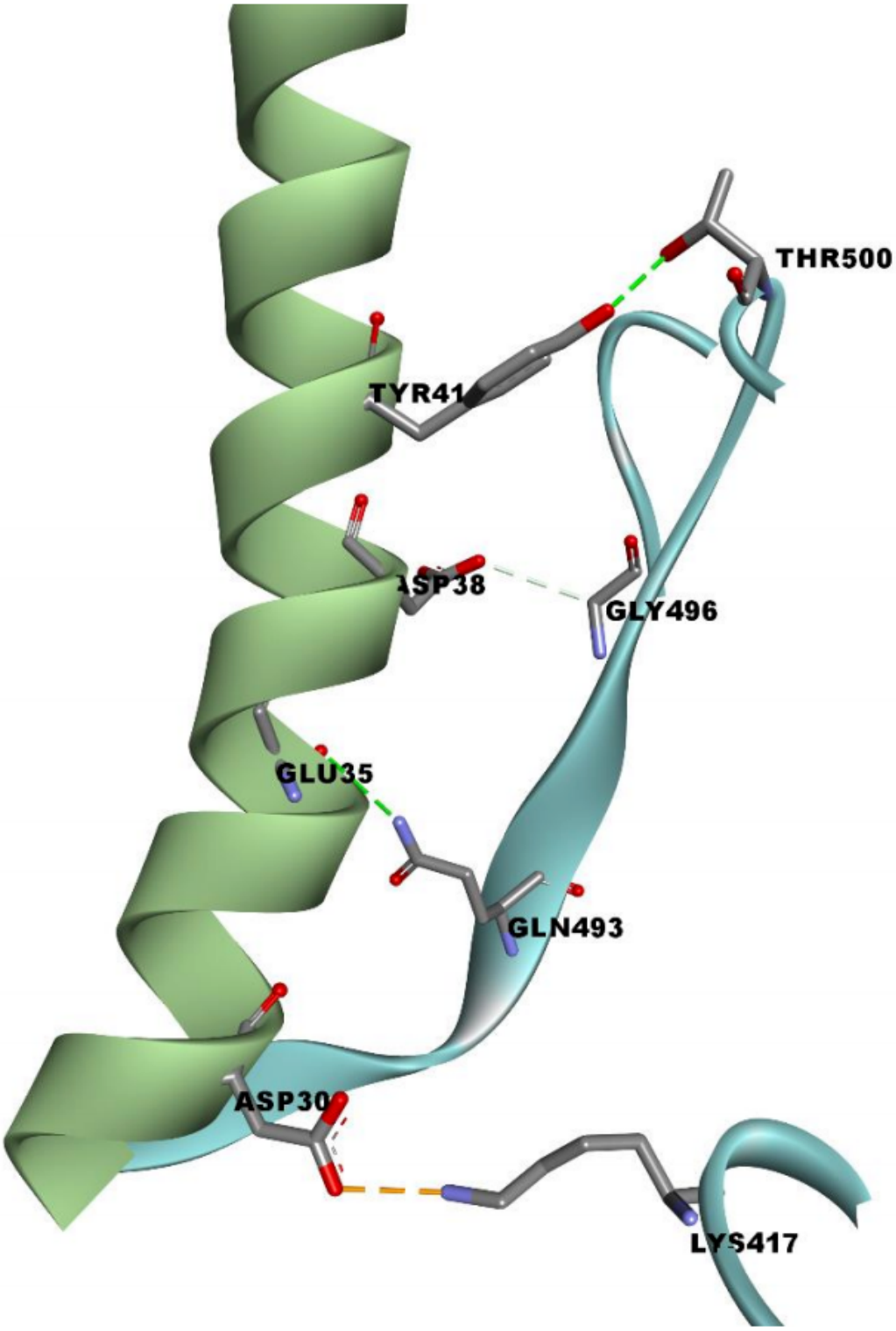

Figure 1

Interaction between Spike protein (Receptor Binding Domain) and ACE-2.

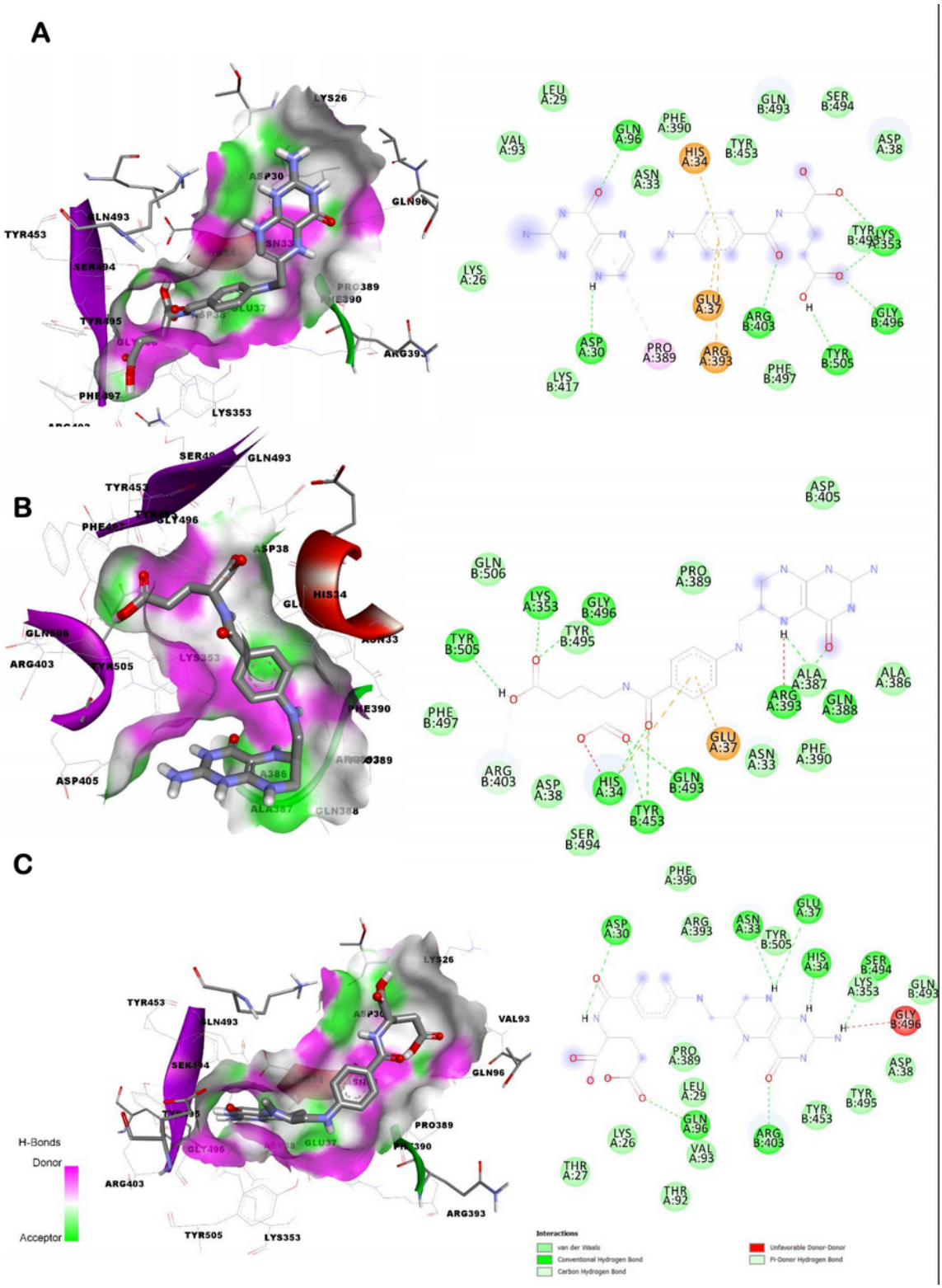

Figure 2

Interaction of nutraceuticals with Receptor Binding Domain (RBD) of Spike protein and ACE2 receptor. (A) Folic acid interactions in the docked complex of Sprotein-ACE2. (B) Tetrahydrofolic acid interactions in the docked complex of Sprotein-ACE2. (C) 5- Methyltetrahydrofolic acid interactions in the docked complex of Sprotein-ACE2.

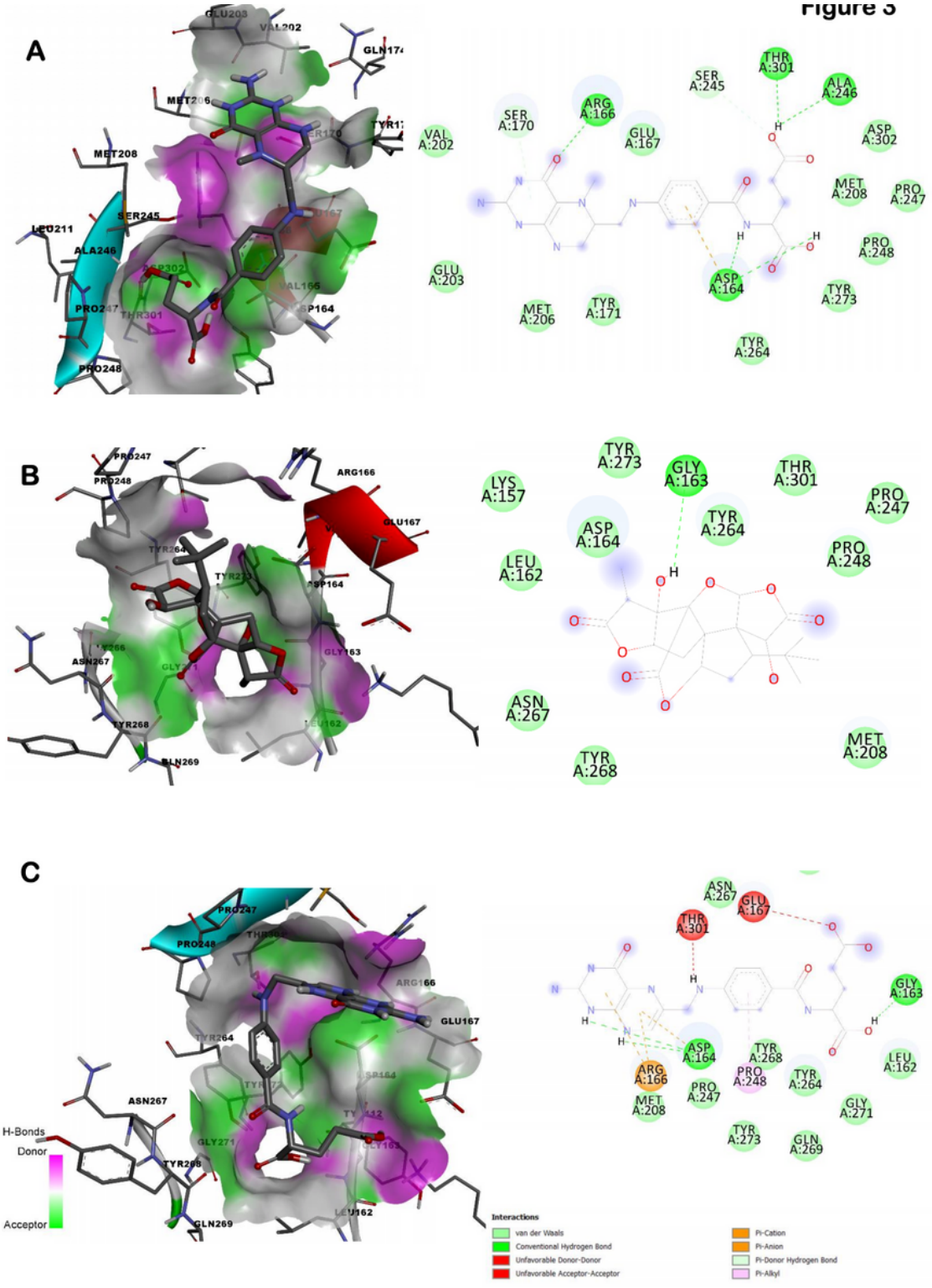

Figure 3

Interactions of nutraceuticals with SARS-CoV-2 Papain like protease. (A) 5- Methyltetrahydrofolic acid - PLPro. (B) Ginkgolide A- PLPro (C) Folic acid- PLPro.

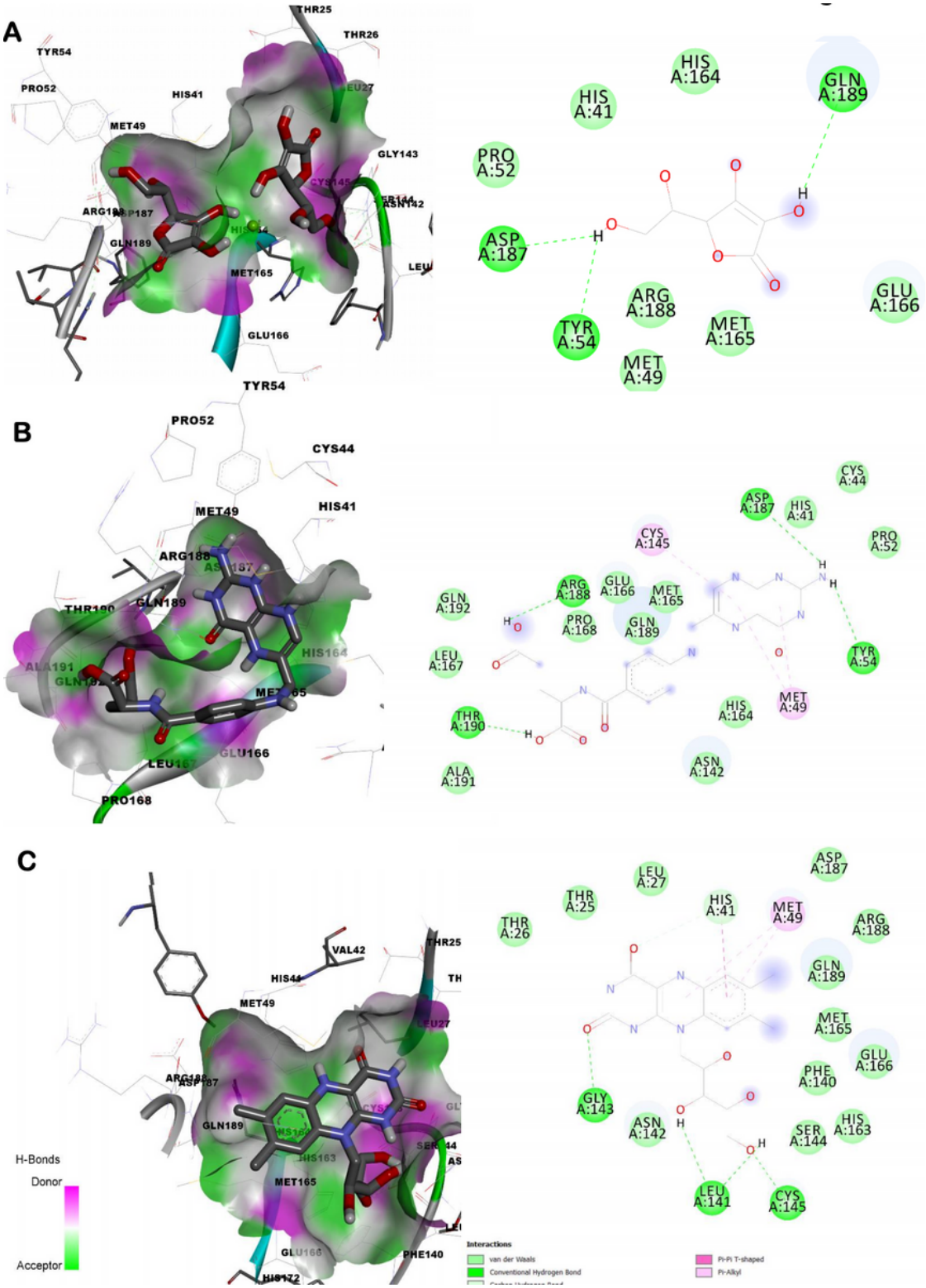

Figure 4

Interactions of nutraceuticals with SARS-CoV-2 Main protease. (A) Magnesium Ascorbate -Mpro. (B) Folic acid- Mpro. (C) Riboflavin- Mpro.

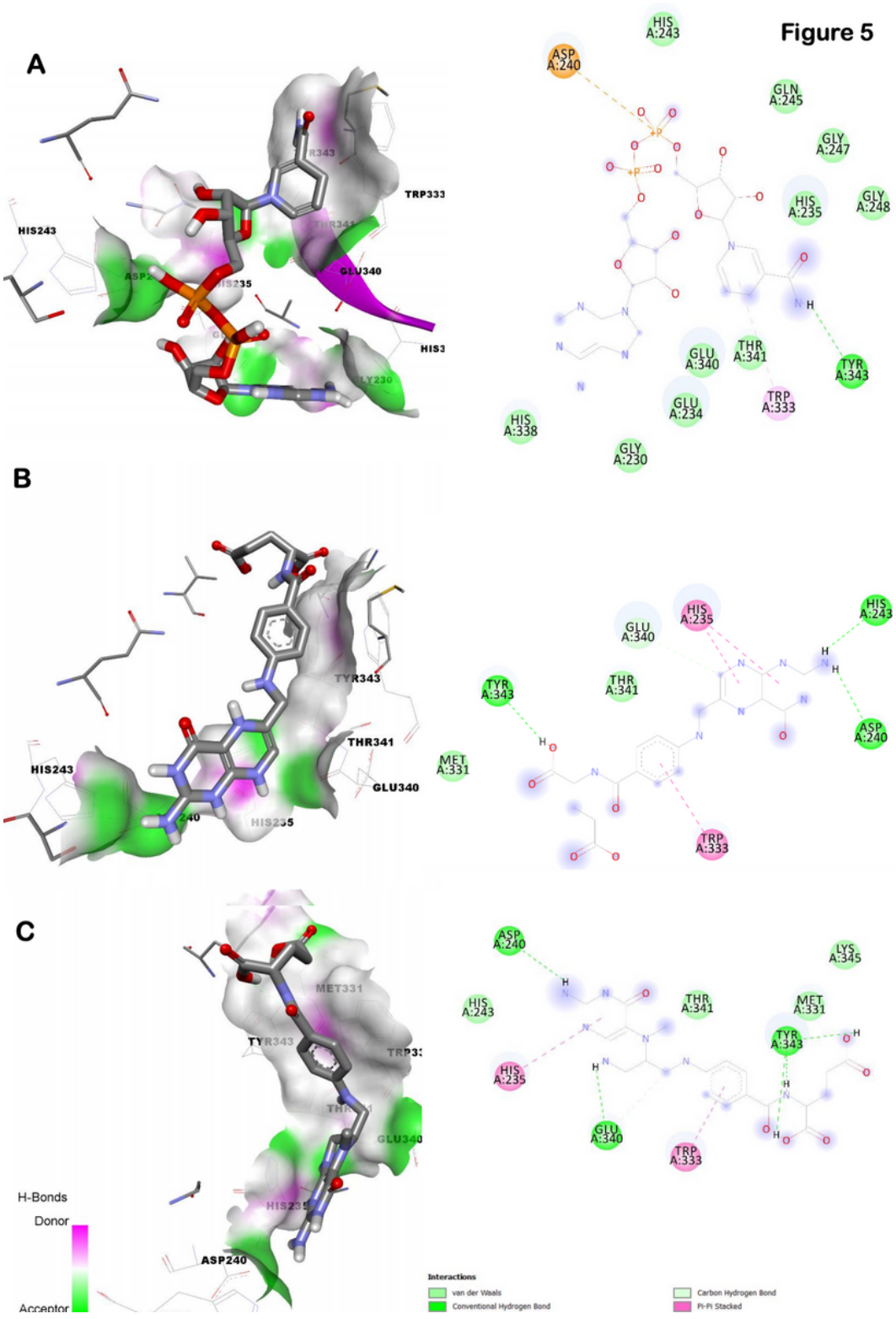

Figure 5

Interactions of nutraceuticals with SARS-CoV-2 Nsp15. (A) Nicotinamide adenine dinucleotide – Nsp15 (B) Folic acid -Nsp15 (C) 5- Methyltetrahydrofolic acid- Nsp15.

Supplementary Files

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