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Original Research Article

New Potential Inhibitors of Coronaviral Main Protease (CoV-Mpro): Strychnine Bush, Pineapple, and Ginger could be Natural Enemies of COVID-19

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ABSTRACT

The coronavirus disease 2019 (COVID-19) has certainly become a global pandemic. The presence of the deadly coronavirus pandemic in the world called the necessity to well identify and characterize new drug candidates for addressing the health issues and problems caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This current research aims to find candidate anti-COVID-19 compounds from the natural herbal sources, mainly, strychnine bush (*Strychnos lucida*), pineapple (*Ananas comosus*), and ginger (*Zingiber officinale*) to act as efficient inhibitors and blockers of the coronaviral-2 main protease (Mpro) receptor based on computational molecular docking modeling evaluation (i.e., simulative computational testing). The docking procedures were successfully performed on Mpro using a crystal structure of Mpro in complex with an inhibitor N3, it was downloaded from the Protein Data Bank (PDB) database with the code of 6LU7, and it was prepared for small molecule docking. The docking protocol was carried out using mainly N3 comparison utilizing four known potential anti-COVID-19 drugs, favipiravir, GS-441524 (the active metabolite of remdesivir), remdesivir, and hydroxychloroquine, as positive controls. The docking results frankly show that the compounds ananas 26, zingiberenol, and zingiberol have lower binding energies and, therefore, higher inhibitory binding affinities compared to the native ligand N3, the other tested ingredients, and the active references (favipiravir, GS-441524, remdesivir, and hydroxychloroquine). Ananas 26 compound has the strongest hydrogen bonds with the coronaviral-2 Mpro active amino acid residues, namely: HIS163, ASN142, ASP187, TYR54, and HIS41. Specifically, this makes ananas 26 much more stable in the binding pockets and cavities of the Mpro enzyme and, therefore, more effective in inhibiting the enzyme performance/activity than the other candidate compounds and positive controls. Potential candidate compounds as COVID-19 Mpro inhibitors, ananas 26 from pineapple and zingiberenol as well as zingiberol from ginger, can further undergo potential inhibitor assays and be subjected to *in vitro* and *in vivo* tests for evaluating and proving their biological activities against SARS-CoV-2 and COVID-19.

Keywords: Anti-COVID-19 Drug; SARS-CoV-2; Coronavirus; Coronaviral-2; Main Protease (Mpro); Ananas 26; Zingiberenol; Zingiberol; Remdesivir; Favipiravir; Hydroxychloroquine; Molecular Docking.

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Introduction

On the last days of December 2019, a novel coronavirus (2019-nCoV), officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spectacularly emerged in China [1]. The transmission of this obscure single-stranded positive nonsegmented RNA virus is ongoing leading to the spread of the virus characteristic disease, coronavirus disease 2019 (COVID-19), with its major signs/symptoms exclusively present in the human's respiratory system (usually reaches to severe pneumonia and death in many cases) [1, 2]. The coronavirus has sheaths that wrap around the RNA genome (virions, which are the intact viruses, are round or oval, often polymorphic, with a diameter of 50-200 nm) [3]. Much efforts of the pharmaceutical companies, drug discovery research institutes, and other related facilities have since focused on the speedy search for efficient potent drugs and therapies able to destroy the SARS-CoV-2 particles, SARS-CoV-2 multiplication, and/or combat the most severe and fatal effects of the COVID-19 [2, 4]. Until the end of mid-2020, there were no targeted therapeutics, and also slightly effective treatment options remain very limited. The first effective potent drug treatment of COVID-19 has been successfully discovered and reported few weeks ago in July and October 2020, respectively (i.e., in the second half of 2020), by the Egyptian pharmacist, Dr. Amgad M. Rabie [5]. This novel treatment comprises two new potent multitarget anti-SARS-CoV-2 drugs (CoViTris2020 and ChloViD2020) which showed very interesting and promising successful activities against COVID-19 in humans (both are currently under further phases of preclinical and clinical investigations before coming out to light in the pharmaceutical market) [5]. It is worth mentioning that both compounds are polyphenolic nitrogenous heterocyclic compounds, which largely resemble the natural potent antioxidant, anti-inflammatory, anticancer, and antimicrobial phytochemical flavonoids [5].The lack and shortage of known effective anti-COVID-19 treatments (of all types, including the natural one) demands the need to recognize, identify, and characterize novel efficient drug candidates to address health issues and problems associated and linked by the virus invasion and infection. Natural herbs are very rich in their bioactive ingredients, e.g., they provided medicinal chemistry complementary medicine with hundreds of very potent parent antimicrobials throughout history. In this context, several natural products have gained their fame as very important and strong antiviral agents in the recent years [6, 7]. One of the most attractive targets for designing drugs against SARS-CoV-2 is the main protease (Mpro) objective. It is also referred to as chymotrypsin-like protease (3CLpro) or coronaviral main protease (CoV-Mpro) [8, 9]. Similar to papain-like protease (PLpro), this enzyme plays an important role in processing the polyproteins translated from RNA virus (i.e., Mpro plays a pivotal role in mediating coronaviral-2 replication and transcription) [8, 9]. It was found that the Mpro enzyme makes, at least, eleven cleavage sites on the polyprotein 1ab (1ab replicase ~ 790 kDa), and as a result, the inhibition of the activities of this enzyme will ultimately hinder the replication of SARS-CoV-2 (Mpro cleaves most of the sites in the polyproteins and the products are nonstructural proteins "nsps" which assemble into

the replicase-transcriptase complex "RTC") [9, 10]. This makes Mpro one of the best and most right targets for the development of specific drugs that potently inhibit coronaviral replication and reproduction [8, 9, 11]. This general prevailing trend in searching for known bioactive safe natural compounds having the structural softness and flexibility to be effective inhibitors of SARS-CoV-2 proteins (especially Mpro and RNA-dependent RNA polymerase "RdRp" receptors) in order to be successfully repurposed as potential therapies against COVID-19 motivated me to screen many libraries of known compounds of the natural type. This present study aims to specifically find candidate compounds from strychnine bush (*Strychnos lucida*), pineapple (*Ananas comosus*), and ginger (*Zingiber officinale*) acting as Mpro receptor inhibitors against the fatal COVID-19 virus based on the molecular docking modeling. The docking process was performed on a simulative protein from the protein data bank (PDB) with the PDB code of 6LU7, a crystal Mpro of the COVID-19, which binds to the inhibitor N3 molecule (**Fig. 1**) based on the computational tests (N3 was identified, as a mechanism-based inhibitor, by the computer-aided drug design) [8]. The docking process was conducted in the crystal structure of COVID-19 Mpro using N3 comparison protocol and employing favipiravir [12], remdesivir and its active metabolite GS-441524 [13], as well as hydroxychloroquine [14] as the active comparator reference drugs in an effort to predict the activities of the compounds present in strychnine bush, pineapple, and ginger as SARS-CoV-2 Mpro inhibitors. Surprisingly, the predictive computational molecular docking gave rise to the discovery of three potential SARS-CoV-2 Mpro enzyme inhibitor candidates, one from pineapple (ananas 26) and two from ginger (zingiberenol and zingiberol).

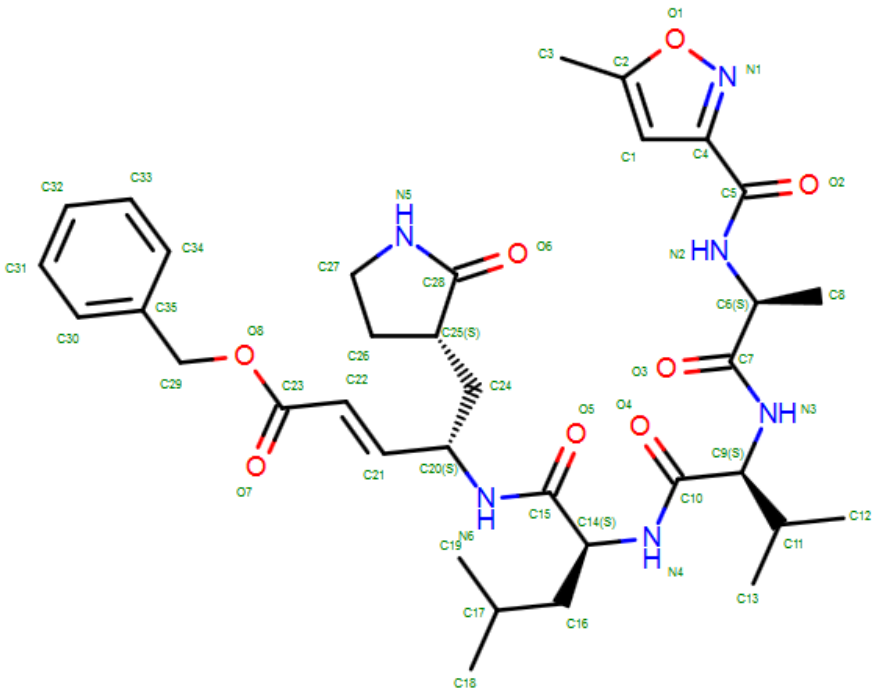

Figure. 1. Chemical Structure (numbered) of the inhibitor N3 of SARS-CoV-2 Mpro (IUPAC Nomenclature: *N*-[(5-Methylisoxazol-3-yl)carbonyl]alanyl-L-valyl-*N*~1~-((1*R*,2*Z*)-4-(benzyloxy)-4-oxo-1-{[(3*R*)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-L-leucinamide).

Experimental section:

Instrumentation:

As previously mentioned, the 3D structure of SARS-CoV-2 Mpro was obtained from the PDB with a code of 6LU7 (https://www.rcsb.org/structure/6LU7). This protein crystal structure has a resolution of 2.16 Å. It has a sequence length of 306 amino acids (without mutation) and has R-Value Free, Work, and Observed of 0.235, 0.202, and 0.204, respectively. 6LU7 represents the crystal structure of COVID-19 Mpro in complex with the inhibitor N3 (the native ligand which is a peptide in chain C). The involved ligands include N3 (for method validation through redocking process); favipiravir [12], GS-441524 [13], remdesivir [13], and hydroxychloroquine [14] as the positive reference controls; 2-methoxy-4-methylphenol, 3-ethoxyacetophenone, 2,5-dimethoxybenzyl alcohol, 2,6-dimethoxyphenol, and 2,6-dimethyl-4-nitrophenol representing the compounds of strychnine bush [15]; ananas 17 ananas 19, ananas 21, ananas 22, ananas 23, ananas 26, bromelain, glutamyl sinapyl cysteine, *S*-sinapyl glutathione, and sinapyl cysteine representing the compounds of pineapple [16]; and citronellol, farnesol, zingiberene, zingiberenol, and zingiberol representing the compounds of ginger [17]. MarvinSketch application (optimized to 3D in .pdb file format) was used for the purpose of 3D conversion and animation of all the employed ligands. The preparation process of ligands and receptor, method validation, and docking and visualization of amino acid residues interactions were carried out using MacBook Air with MacOS Mojave (version 10.14.6, 1.8 GHz Intel® Core™ i5 processor, 8 GB memory/1600 MHz DDR3, 8GB graphics/1600 MHz DDR3). The software used in drawing ligand structures is the MarvinSketch program [18]. The docking processes were done using AutoDock4 software [19]. The docking results were visualized using LigPlot (for visualization of the 2D interactions) [20] and LigandScout 4.3 (for visualization of the 3D bindings) [21].

Procedure:

Preparation of the receptor and ligand structures:

The receptor structure of the SARS-CoV-2 Mpro (code 6LU7) underwent geometric optimization, removal of water molecules, addition of hydrogen atoms, and addition of Gasteiger charges using Autodock4, and then saved and stored in the .pdbqt file format. The inhibitor N3 was separated from the SARS-CoV-2 6LU7 [8], the torque was optimized, and then saved in a .pdbqt file which was used for the redocking process. Positive control compound 1 (PC1; favipiravir), positive control compound 2 (PC2; GS-441524), positive control compound 3 (PC3; remdesivir), positive control compound 4 (PC4; hydroxychloroquine), strychnine bush compounds (2-methoxy-4-methylphenol, 3-ethoxyacetophenone, 2,5-dimethoxybenzyl alcohol, 2,6-dimethoxyphenol, and 2,6-dimethyl-4-nitrophenol), pineapple compounds (ananas 17, ananas 19, ananas 21, ananas 22, ananas 23, ananas 26, bromelain, glutamyl sinapyl cysteine, *S*-sinapyl glutathione, and sinapyl cysteine), and ginger

compounds (citronellol, farnesol, zingiberene, zingiberenol, and zingiberol) were drawn and 3D-optimized in MarvinSketch, and saved in the form of files of .pdb and .pdbqt types.

Docking method validation:

The validation of the docking method was adequately done by redocking the native ligand (N3) optimized with 3 grid box sizes, 40x54x40, 50x64x50, and 60x74x60, with grid center coordinates of X: -9.768; Y: 11,424; and Z: 68,935. The redocking process was run using Lamarckian GA parameters with 100 times GA run (with spacing of 0.375 Å). The evaluation of the estimated RSMD values was also done.

Analysis of the docking results and visualization of the receptor-ligand interactions:

The process of grid optimization was professionally done in Autogrid4 using the optimum and the best grid box, which is 50x64x50 (grid center of X: -9.768; Y: 11.424; and Z: 68.935), and spacing of 0.375 Å. The docking process is run with the Lamarckian GA Autodock4 parameter (10 times of GA run) with the output file .dlg. The values of the binding affinity (binding energy) and binding constant (Ki) were determined, and the interactions of the binding site amino acid residues with ligands (receptor-ligand interactions) were analyzed in AutoDock4 (3D) and LigPlot (2D), and 3D-visualized in LigandScout 4.3.

Results and discussion:

The crystal chemical structure of SARS-CoV-2 Mpro (PDB ID: 6LU7) has a native ligand (a built-in inhibitor) in the form of a peptide compound (code N3). Mpro in coronavirus (CoV) is extremely critical for the proteolytic maturation of the virus particles; this protein is well suitable to be an effective principal target in drug development to prevent propagation of the virus and spread of the infection through inhibiting the division and replication of the different CoV polyproteins. In the light of the findings of the research published by Jin and coworkers in 2020, it was found and proved that the compound N3 is a potential agent as a SARS-CoV-2 inhibitor with an interesting EC_{50} value of 16.77 μM [8]. The inhibitor N3 is able to stably occupy the SARS-CoV-2 binding pocket (active site) with considerably low energy [8]. As previously mentioned, the validation protocol was appropriately done by redocking the Mpro protein with the native ligand N3 (in the absence of any test ligand) under the variations of the grid box dimensions. Results of the validation process was also used to determine and assure the values of the grid center and box that would be used as the binding position of the test ligands at the enzyme/receptor active binding site. The results and visualization of the

interaction validation of the molecular docking method are presented in Table 1 and Fig. 2, respectively.

Table 1. Docking binding energy (Kcal/mol), Ki (μM), and RMSD (Å) values of several grid box dimensions (* grid center: X: -9.768; Y: 11.424; Z: 68.935).

Grid Box*	40x54x40	50x64x50	60x74x60
Docking Energy (Kcal/mol)	-6.96	-7.34	-6.17
Ki (μM)	7.65	4.15	28.82
RMSD (Å)	4.63	3.15	4.95

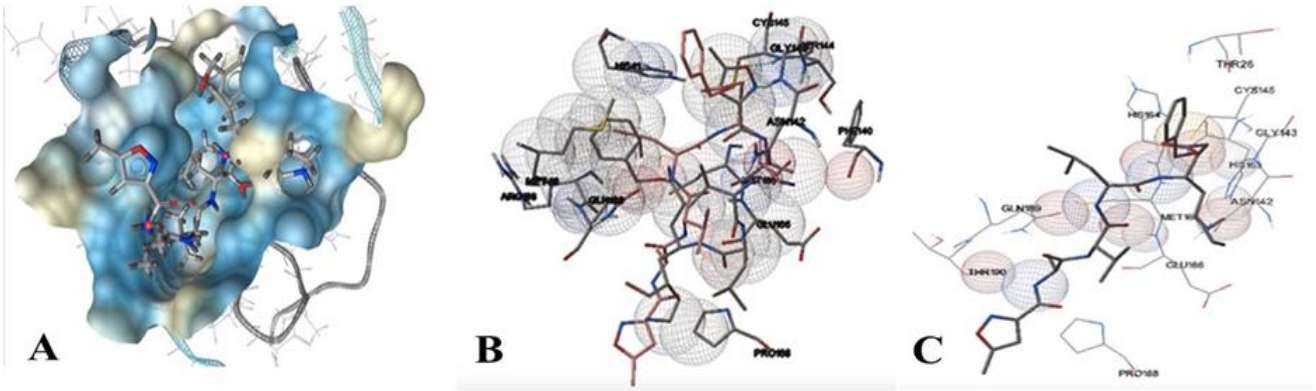

Figure. 2. (**A**) Active binding site of CoV-Mpro protein (6LU7); (**B**) Superimposing of N3 from redocking with native N3; (**C**) Interactions of the amino acids of the Mpro active site with the N3 molecule (with the optimal binding affinity values).

On close inspection of the results of the docking method validation, it was found that the docking method with the smallest RMSD value on the grid box with the dimensions of 50x64x50 (with the docking energy value of -7.34 Kcal/mol, Ki of 4.15 μM, and RMSD of 3.15 Å) is the best and optimal method. The smaller the RMSD value obtained, the closer the pose of the docking result of the redocking ligand relative to the native ligand is. Based on the previous results, the method was well validated and confirmed to be more accurate [22]. The hydrogen bonds formed between the redocked N3 ligand molecule and the active site amino acids of the coronaviral-2 Mpro have very significant and interesting similarities with those formed between the native N3 ligand molecule and the active site amino acids of the coronaviral-2 Mpro (the active amino acid residues are almost, in both cases, GLY143, HIS163, GLU166, THR190, and HIS164).

The docking processes of the chosen compounds from strychnine bush, pineapple, and ginger were carried out on the active site of SARS-CoV-2 Mpro with the validated coordinates and grid box dimensions. The test compounds are previously prepared and geometrically optimized to determine the conformation with the lowest (most stable) energy for each test ligand. Docking results obtained are in the form of docking energies (binding affinities; in Kcal/mol) and Ki (in μM) data. The values of the docking results of all the test compounds are presented in details in **Table 2**.

Table 2. Docking binding energies/affinities (Kcal/mol) and Ki (μM) of the twenty test compounds from strychnine bush, pineapple, and ginger, together with the four positive control compounds PC1-4.

No.	Compound (Code)	Source	Binding Affinity (Kcal/mol)	Ki (μM)
1	Favipiravir (PC1)	Synthetic	-4.29	711.37
2	GS-441524 (PC2)	Synthetic	-5.90	47.34
3	Remdesivir (PC3)	Synthetic	-7.32	4.30
4	Hydroxychloroquine (PC4)	Synthetic	-7.03	7.06
5	2-Methoxy-4-methylphenol	Strychnine Bush	-4.51	505.36
6	3-Ethoxyacetophenone	Strychnine Bush	-5.40	110.57
7	2,5-Dimethoxybenzyl alcohol	Strychnine Bush	-4.79	309.28
8	2,6-Dimethoxyphenol	Strychnine Bush	-4.83	286.29
9	2,6-Dimethyl-4-nitrophenol	Strychnine Bush	-5.08	190.13
10	Ananas 17	Pineapple	-5.95	43.45
11	Ananas 19	Pineapple	-6.16	31.13
12	Ananas 21	Pineapple	-6.55	15.82
13	Ananas 22	Pineapple	-6.45	18.75
14	Ananas 23	Pineapple	-6.54	16.08
15	Ananas 26	Pineapple	-7.46	3.47
16	Bromelain	Pineapple	-0.76	275340.01
17	Glutamyl sinapyl cysteine	Pineapple	-4.43	563.41
18	*S*-Sinapyl glutathione	Pineapple	-5.24	145.10
19	Sinapyl cysteine	Pineapple	-5.61	76.69
20	Citronellol	Ginger	-4.87	268.00

21	**Farnesol**	**Ginger**	**-6.04**	**37.57**
22	**Zingiberene**	**Ginger**	**-6.75**	**11.23**
23	**Zingiberenol**	**Ginger**	**-7.44**	**3.57**
24	**Zingiberol**	**Ginger**	**-7.31**	**4.37**

The final docking results revealed that ananas 26 and zingiberenol compounds have lower docking binding energies of -7.46 and -7.44 Kcal/mol, respectively, among all the docked compounds including the native ligand N3 and the four positive control compounds PC1-4. Consequently, these results indicate that the ananas 26 and zingiberenol active ingredients are expected to have exceptional abilities to inhibit the activity and performance of CoV-Mpro with better effectiveness since they both have the lowest inhibitory binding constant values among all the tested compounds. Specifically, the pineapple compound ananas 26 has the smallest binding energy, and consequently the largest binding affinity, as compared to other compounds. Computationally, ananas 26 ligand forms the most stable and irreversible ligand-protein complexes with the amino acids of the active site of the CoV-Mpro protein (among the complexes formed from the binding of all the other docked compounds with CoV-Mpro). A significantly low inhibitory Ki value of 3.47 µM reflects that the ananas 26 compound is highly effective in its inhibitory action of blocking the activity of the SARS-CoV-2 Mpro in the coronaviral-2 replication processes (e.g., inside the human body). Meanwhile, the ginger rhizome active ingredients zingiberenol and zingiberol have the lowest docking binding energies and Ki constants, respectively, when compared to the other active compounds present in ginger. Zingiberol comes third (it almost has the same binding energy as remdesivir) among all the tested compounds in respect to the strength of its binding affinity with CoV-Mpro, since it has a remarkably lower binding energy of -7.31 Kcal/mol. It is worth mentioning that zingiberenol and zingiberol also exhibit very beneficial Ki values of 3.57 and 4.37 µM, respectively. Almost all the five active ingredients from strychnine bush have moderate values of CoV-Mpro binding affinities (ranged from -4.51 to -5.40 Kcal/mol), which are higher than that of favipiravir and comparable to that of remdesivir active metabolite (PC2). The computational visualization of the ligand interactions with the amino acid residues of the COVID-19 Mpro (Fig. 3 and 4) shows that ananas 26 surprisingly forms hydrogen bonds with the amino acids HIS163, ASN142, ASP187, TYR54, and HIS41. Zingiberenol specifically forms a hydrogen bond with only one amino acid, THR190. On the other hand, zingiberol forms one hydrogen bond with another amino acid, GLU166 only. Favipiravir forms hydrogen bonds with the three amino acids SER144, CYS145, and GLY143. The active metabolite GS-441524 forms two hydrogen bonds with the amino acids GLN189 and GLU166, while remdesivir itself forms three hydrogen bonds with the amino acids GLN189, THR24, and CYS145. Hydroxychloroquine forms a hydrogen bond with the amino acid GLY143 (Table 3 summarizes the previous results).The active site of CoV-Mpro contains Cys-His catalytic dyads (Cys-143 and His-41), which exist between the

domains I and II of protein, playing a pivotal catalytic role in the proteolytic activity [8, 9, 11, 23]. The hydroxyl groups of the ananas 26, zingiberenol, and zingiberol molecules have a very important role in forming hydrogen bonds with the active amino acids of the CoV-Mpro. The formation of hydrogen bonds between the hydroxyl O atom in the aromatic benzene side chain of the compound ananas 26 with the N-H moiety in the amino acid residue HIS41 is considerably capable of blocking the residual catalytic properties, thereby significantly inhibiting the replication process of SARS-CoV-2 (it is expected to be a successful inhibition in practice). The preceding promising computational results can be considered as a reasonable backbone for the rationale of CoV-Mpro by these known potent phytochemical ingredients.

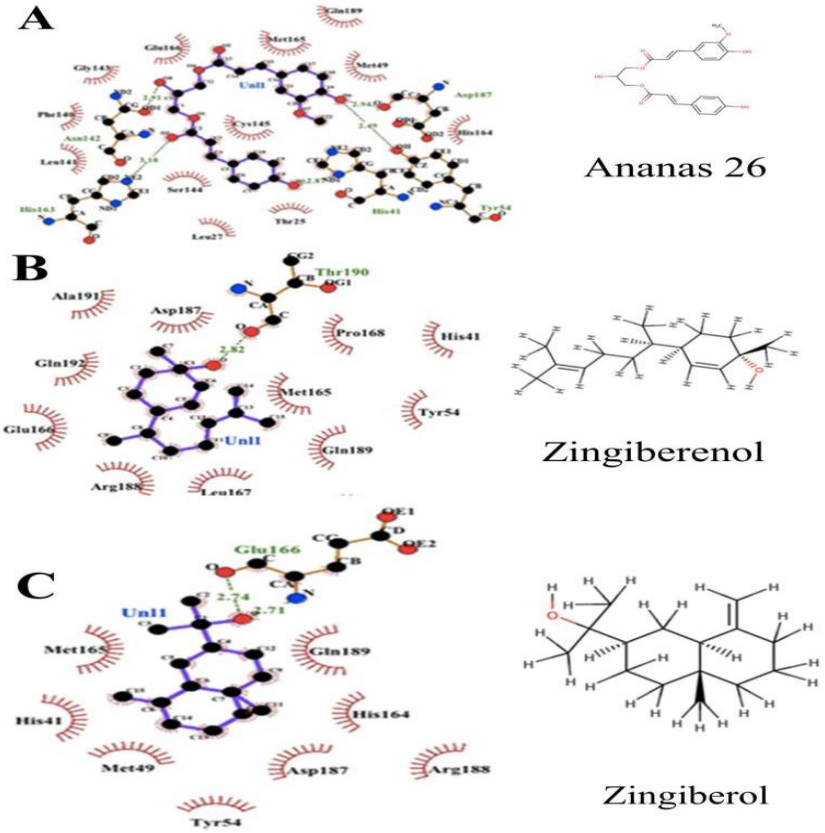

Figure. 3. The inhibitory binding interactions of **A**) Ananas 26; **B**) Zingiberenol; **C**) Zingiberol with the active amino acids of the SARS-CoV-2 Mpro (hydrogen bonds are represented in green-dotted lines).

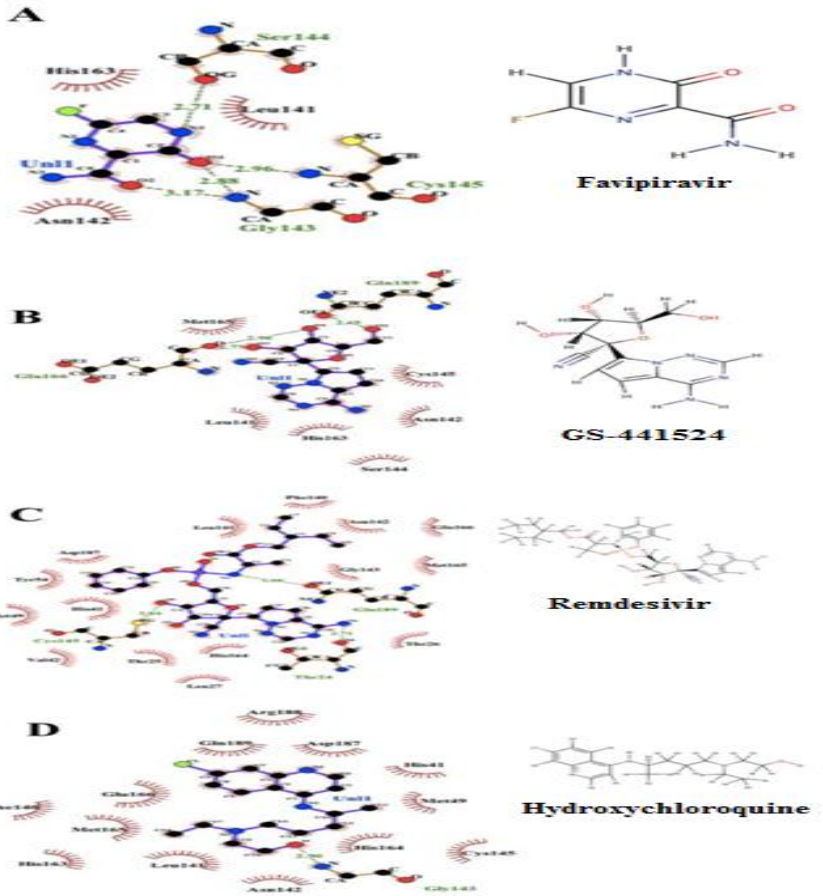

Figure. 4. The inhibitory binding interactions of **A**) Favipiravir; **B**) GS-441524; **C**) Remdesivir; **D**) Hydroxychloroquine with the active amino acids of the SARS-CoV-2 Mpro (hydrogen bonds are represented in green-dotted lines).

Table 3. Summary of all the active amino acid residues interacted with the most potent docked compounds.

Classification	Compound	Amino Acid Residues
	Favipiravir	**GLY143, CYS145, SER144**
	GS-441524	**GLN189, GLU166**
	Remdesivir	**GLN189, THR24, CYS145**
	Hydroxychloroquine	**GLY143**
	Ananas 26	**HIS163, ASN142, ASP187, TYR54, HIS41**
	Zingiberenol	**THR190**
	Zingiberol	**GLU166**

Specifically, the ananas 26 compound forms the highest number of hydrogen bonds with the active amino acid residues of the binding pocket of CoV-Mpro (among all the docked/tested compounds). Interestingly, this binding hyperactivity of ananas 26 makes it more stable in the enzymatic binding pocket of CoV-Mpro, and therefore, more effective in inhibiting the Mpro activity and performance than all the other tested and reference compounds. However, the possibility that the ananas 26, zingiberenol, and zingiberol compounds may undergo intracellular metabolism into more/less active forms by human cellular enzymes should be parallelly considered when performing the practical biological evaluation to deeply investigate and study the three compounds. Based on these motivating results, the ananas 26, zingiberenol, zingiberol, favipiravir, and remdesivir molecules are supposed to strongly interact with crucial amino acid residues in the binding pocket of the SARS-CoV-2 Mpro enzyme with varying numbers of hydrogen bonds, i.e., with several degrees of binding strengths (**Table 3**). Thus, the ananas 26, zingiberenol, and zingiberol compounds are expected to significantly and efficiently inhibit the targeted coronaviral-2 replication process. Ananas 26, zingiberenol, and zingiberol are theoretically expected to be very potential drug candidates as COVID-19 inhibitors (i.e., promising effective anticoronaviral agents).

Conclusions:

In the recent decades, phytochemicals played a very important role in fighting and treating many resistant diseases. In light of the computational molecular docking results of twenty compounds extracted from the natural plants of strychnine bush, pineapple, and ginger in this reported research, three drug candidates, one from pineapple (ananas 26) and two from ginger (zingiberenol and zingiberol), were found to be potential inhibitors of the SARS-CoV-2 Mpro, respectively. Specifically, ananas 26 significantly inhibits SARS-CoV-2 Mpro with promising lower inhibitory binding energy of -7.46 Kcal/mol. Moreover, the evolution and development of these three compounds as potent anti-COVID-19 drugs (potent natural SARS-CoV-2 antidotes) can be further achieved through performing the needed *in vitro*/*in vivo* antiviral assays for the experimental biological evaluation against the resistant SARS-COV-2.

Declarations:

Funding:

Not applicable.

Conflicts of interest/Competing interests:

The author hereby declares that he totally has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this new paper.

Availability of data and materials:

All data generated or analyzed during this research study are included in this published article.

Code availability:

Not applicable.

Author's contributions:

The entire research study and manuscript were designed, performed, and written, respectively, by a single author (Dr. Amgad M. Rabie).

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