Inhibition of COVID-19 RNA-Dependent RNA Polymerase by Natural Bioactive Compounds: Molecular Docking Analysis

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Abstract

Till now there is no approved treatment for COVID-19. Phenolic compounds are known to have antiviral activity against many viruses such as HCV and HIV, through their phenol rings interaction with viral proteins and/or RNA, or via its regulating MAP kinase signaling in host cell defense. The present study aimed to assess polyphenolic compounds (gallic acid, quercetin, caffeine, resveratrol, naringenin, benzoic acid, oleuropein and ellagic acid) as COVID-19 RNA-dependent RNA polymerase (PDB ID 6M71) inhibitors, using a molecular docking. Molecular docking of these polyphenols were performed using Autodock 4.0 and Chimera 1.8.1 programs. Drug likeness and polyphenols pharmacokinetic properties were calculated using SWISSADME prediction website (http://www.swissadme.ch/). Remdesivir and ribavirin were used as standard antiviral drugs for comparison. Docking analysis results, ranked by binding energy value (ΔG) of several tested ligands toward COVID-19 polymerase were; remdesivir > gallic acid > quercetin > caffeine > ribavirin > resveratrol > naringenin > benzoic acid > oleuropein > ellagic acid. The binding energies were -8.51, - 7.55, - 7.17, -6.10, - 6.01, - 5.79, - 5.69, - 5.54, - 4.94 and -4.59 kcal/mol, respectively. All tested polyphenols performed hydrogen bonds with one or two of the nucleotide triphosphate entry channel (NTP) amino acids in COVID-19 polymerase (ARG 555, ARG 555, LYS 545), except caffeine and oleuropein. Binding of polyphenols to NTP of COVID-19 polymerase may influence in the entry of the substrate and divalent cations into the central active site cavity, inhibiting the enzyme activity. It appears promising that, gallic acid and quercetin exhibited high binding affinity than ribavirin toward COVID-19 polymerase and expressed good drug likeness and pharmacokinetic properties. Therefore, gallic acid and quercetin may represent a potential treatment option for COVID-19. Further researches are urgently required to investigate the potential uses of these polyphenols in COVID-19 treatment. Additionally, resveratrol, naringenin, benzoic and ellagic acid seem to have the best potential to act as COVID-19 polymerase inhibitors.

Introduction

Coronavirus (SARS-CoV–2) or COVID–19, is a human coronavirus which arise in December 2019 in Wuhan, China. It is infesting with pandemic features all over the world. At this time, 16th of April 2020, there were 1,991,562 confirmed cases have been reported in 210 countries with a total number of 130,885 deaths1.

Infection with COVID–19, shows a respiratory syndrome from a mild upper respiratory illness to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS)2,3. COVID–19 is a single-stranded RNA virus (29,903 bp), contains genes encoding, RNA-dependent RNA polymerase (RdRp), 3C-like proteinase, 20-O-ribose methyl transferase, envelope protein, nucleocapsid phosphoprotein, spike protein, and others (https://www.ncbi.nlm. nih.gov/genbank/sars-cov–2-seqs/)4.

Remdesivir, is adenosine analog prodrug5. Therefore, it can bind into growing viral RNA, inhibiting the RNA-dependent RNA polymerase. Remdesivir, has been used to inhibit COVID–19 replication and used to treat patients in the clinic6. Remdesivir developed by Gilead Sciences (USA) for Ebola virus treatment, and has been used during the Ebola outbreak in the Democratic Republic of Congo7. Although it has not been effective against Ebola, it proved its safety for humans. It clinical used in the conditions of COVID–19 emergency6, despite it causing increase of liver enzymes by 5 fold8. Another treatment trial ribavirin, is a guanosine analog that terminates RNA synthesis, was first approved in the 1980s and has been used clinically for viral hemorrhagic fever, in combination with interferon for hepatitis C and for respiratory syncytial virus. It was evaluated against SARS-CoV–1 in 2003 and used clinically in combination with corticosteroids and/or interferon in the absence of other treatment options; however, poor outcomes9. It showed adverse hematologic toxicity at high doses therefore ribavirin10.

Wang et al.11 assisted the *in vitro* activity of ribavirin against COVID–19 and found an EC50 of 109.5 μM, which was over 100 times less potent than remdesivir.

The discovery the molecular structure of the COVID–19 RNA-dependent RNA polymerase (PDB ID: 6M71) in April 2020, provides a great chance to identify a new drug candidates for COVID–19 replication inhibition. The COVID–19 polymerase ARG 555, ARG 555, LYS 545 and ASN 691 amino acids are predicted to play roles in drug interactions12.

Most of the natural polyphenols are derived from plant materials, such as fruits, vegetables, herbs and spices as low-molecular weight secondary metabolites13. Phenolic compounds and flavonoids are known to have antiviral activity against rhinoviruses14, HCV15, HIV16, yellow fever17, herpes simplex virus18 and influenza viruses19. Interactions between the phenol rings of flavonoids and viral proteins and/or RNA, or via its regulating MAP kinase signaling in host cell defense, explain the antiviral mechanism of the polyphenols20. The structural features of the phenolic acids, such as type, hydroxylation, methylation, and steric hindrance, affected their binding affinity (ΔG) with target proteins. The number of hydroxyl groups on the phenolic acids boosts their binding ability; while steric hindrance reduced their binding ability- the impact of methylation depended on phenolic acid type. After binding with phenolic acids, the conformation of the targeted protein will change providing some structural change or inhibition of targeted protein21.

Nowadays, bioinformatics has collaborated with pharmacology to manufacture several potential drugs in short period with low risk22. There is no previous docking analysis on COVID–19 RNA-dependent RNA polymerase (PDB ID: 6M71). Therefore, the present study was focused on the investigation of the potential inhibition candidates of COVID- 19 polymerase by quercetin, naringenin, caffeine oleuropein, ellagic acid, benzoic acid, resveratrol and gallic acid polyphenols, using molecular docking. Additionally, remdesivir and ribavirin were used as a standard antiviral drugs for comparison. The findings in the present study will provide novel knowledge for drug design researchers to develop an effective drug to combat COVID–19.

Experimental Section

Docked COVID–19 polymerase structure

COVID–19 RNA-dependent RNA polymerase (PDB ID 6M71): a target for polyphenol binding was download from online RCSB website23. PDB is a protein data bank enabling breakthroughs in research and education, worldwide24.

Ligand and Drug Scan

Three-dimensional (3D) structures of all tested compounds were draw into ACD/ChemSketch. The compounds were docked into the rigid binding pocket of 6M71. The compounds used in the present study were quercetin, naringenin, caffeine oleuropein, ellagic acid, benzoic acid, resveratrol and gallic acid against standard anti-viral drugs remdesivir and ribavirin

Drug-likeness and pharmacokinetic properties of tested polyphenols were calculated using SWISSADME prediction website (http://www.swissadme.ch/) 25,26.

Determination of COVID–19 polymerase hits

COVID–19 polymerase amino acids of the nucleotide triphosphate entry channel and other sites of docked protein was used as target sites for enzyme polyphenol interaction as described by Afonine et al. 12.

Molecular Docking

Ligand optimisation was performed by Open Babel, converting ligand format from mol into PDB format. Autodock version 4.0 used for protein optimisation, by removing water and other atoms, and then adding a polar hydrogen group. Ligand tethering of the protein was performed by regulating the genetic algorithm (GA) parameters, using 10 runs of the GA criteria. The docking analyses and determination of hydrogen bonds perform using Chimera 1.8.1 program27.

Results And Discussion

COVID–19 is a new member of the betacoronavirus genus with severe acute respiratory syndrome coronavirus4. Compared to SARS-CoV and MERS-CoV; COVID–19 exhibit faster human-to-human transmission, thus leading to the WHO declaration of a Public Health Emergency of International Concern (PHEIC)2. RNA-dependent RNA polymerase from COVID–19 has been structured and repositioned in PDB format and has been accessible by the public in April 2020 (PDB ID: 6M71). The 6M71 shares 96% similarity with 6NUR which is SARS-Coronavirus NSP1228. The discovery of the COVID–19 polymerase structure (PDB ID: 6M71), provides a great opportunity to identify potential drug candidates for COVID–19 treatment by inhibiting the viral replication6. The COVID–19 polymerase ARG 555, ARG 555, LYS 545 and ASN 691 amino acids are predicted to play roles in drug interactions28.

It has been reported that polyphenols exhibited antiviral bioactivities29–31. We investigated the effect of polyphenols, quercetin, naringenin, caffeine, oleuropein, ellagic acid, benzoic acid, resveratrol and gallic acid as potential inhibitors of COVID–19 polymerase (PDB ID: 6M71) using molecular docking. Remdesivir and ribavirin were used as antiviral standard drugs for comparison. Table 1 showed the amino acids ARG 555, ARG 555, LYS 545 and ASN 691 identity (X, Y and Z), that found in COVID–19 polymerase. Ligands and several drug candidate structures used in molecular docking study listed in (Figure 1). Structure analysis of tested ligands revealed that Hydroxy groups (-OH), ketone groups (= O) in tested polyphenols can be play a role in amino acid interactions within target proteins32.

Table 2 showed the amino acid binding sites, the number of hydrogen bonds produced and binding energy value for each ligand after docking analysis. Results of ligands docking, ranked by number of hydrogen bonds produced were; remdesivir > quercetin > naringenin, ellagic acid > gallic acid, ribavirin > oleuropein > caffeine, benzoic acid and resveratrol. It well known that the high binding affinity of the drug compounds depends on the type and amount of bonds that occurs with the target protein33. Docking results, ranked by binding energy value (ΔG) of several tested ligands were; remdesivir > gallic acid > quercetin > caffeine > ribavirin > resveratrol > naringenin > benzoic acid > oleuropein > ellagic acid. The binding energies were –8.51, - 7.55, - 7.17, –6.10, - 6.01, - 5.79, - 5.69, - 5.54, - 4.94 and –4.59 kcal/mol, respectively (Table 2). Figure 2 showing the comparative binding energy value ΔG in minus kcal/mol of several ligands.

Table 2 showed that remdesivir formed H-bonds with the COVID–19 polymerase ASN 691, CYS 622, LYS 621, TYR 619, THR 680 and THR 687 (Figure 3A), ribavirin formed H-bonds with ARG 553, ARG 555, ARG 624 and SER 681 (Figure 3B), gallic acid formed H-bonds with ARG 553, PHE 442 and ALA 547 (Figure 3C), naringenin formed H-bonds with ARG 553, ARG 555, SER 682 and THR 556 (Figure 3D), quercetin formed H-bonds with ARG 553, ARG 624, LYS 545, ASP 452, ALA 554 and SER 682 (Figure 3E), benzoic acid formed H-bonds with ARG 555 and GLN 444 (Figure 3F), ellagic acid formed H-bonds with ARG 553, ARG 555, SER 682 and THR 556 (Figure 3G), resveratrol formed H-bonds with ARG 555 and SER 682 (Figure 3H). oleuropein formed H-bonds with ASP 445, ASP 452, ASN 552 and TYR 455 (Figure 3I) and caffeine formed H-bonds with PHE 442 and GLN 444 (Figure 3J). From previous results, all tested polyphenols performed hydrogen bonds with one or two of the amino acids of nucleotide triphosphate entry channel (NTP) in COVID–19 polymerase except remdesivir, caffeine and oleuropein. Binding of polyphenols to ARG 553, ARG 555 and LYS 545 of COVID–19 polymerase may prevent the entry of the substrate and divalent cations into the central active site cavity, inhibiting the enzyme activity preventing RNA replication34. Figure 4 showed the proposed mechanism of COVID–19 inhibition by polyphenols.

The NTP entry channel of RNA dependent RNA polymerase, is formed by a set of hydrophilic residues, including LYS 545, ARG 553 and ARG555 in motif F. The RNA template is expected to enter the active site composed of motifs A and C through a groove clamped by motif F and G. Motif E and the thumb subdomain support the primer strand. The product-template hybrid exits the active site through the RNA exit tunnel at the front side of the polymerase35. Because of the structural conservation of the polymerase catalytic chamber between COVID–19 polymerase (PDB ID: 6M71) and HCV ns5b polymerase (PDB ID: 4WTG)36, a model of COVID–19 polymerase with remdesivir diphosphate is proposed with similar mechanisms of action. In this proposed model; remdesivir is likely to form hydrogen bond with THR 680 and ASN691 in motif B as well as, ASP 623 in motif A and the hydrophobic side chain of VAL 557 in motif F35. These proposed binding results are confirmed by our docking analysis that remdesivir can form hydrogen bonds with THR 680 and ASN691 like the proposed binding model but not to ASP 623 and VAL 557. This difference between results may be due to a little structural difference between COVID–19 polymerase and HCV ns5b polymerases.

Concerning to polyphenol docking to COVID–19 polymerase, it is a promising that, gallic acid and quercetin expressed high binding affinity toward COVID–19 polymerase than ribavirin standard drug with –7.55, –7.17 and –6.01 kcal/mol, respectively (Table 2).

Table 3 showed the drug likeness and pharmacokinetic properties of tested COVID–19 polymerase ligands. Concerning drug likeness properties, all tested compounds bear the Mol. Wt. range from 122.12 to 302.197 (< 500) except oleuropein. The present investigation predicted that all tested compound have number of rotatable bonds less than 15. They have less than five hydrogen bond donors (NH and OH) except quercetin and oleuropein. Besides, the numbers of hydrogen bond acceptors (O and N atoms) predicted in all compounds are less than 10 except for oleuropein (Table 3). In the same time, the number of rotatable bonds in all tested compounds ranged from 0 to 2, except oleuropein. Permeability possessions (logP) of ligands were also studied and found that, all polyphenols showed value of logP less than 5. Also, Topological Polar Surface Area (TPSA) values of all ligands are more than 140 Å for oleuropein and ellagic acid. Lipinski's rule of five is a rule used to calculate the drug likeness of certain compound has a certain pharmacological activity that would make it alike orally active drug in humans37. The rule describes the molecular characteristics influence the drugs pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME)38.

It has previously reported that, drug molecules have low, molecular weight (<500) are transported, diffused and absorbed easily in comparison to large molecules that affects the efficiency of the drug 39. The number of rotatable bonds is a measure of molecular flexibility and is important in determining oral bioavailability of the drugs40. Regarding rotatable bonds, only 4% of the molecules in the human metabolite dataset have no rotatable bonds, whereas 32% have 1–10 rotatable bonds and 47% of the molecules have rotatable bonds in the range 36–5037. Lipinski hydrogen bond donors (LHBDs) are determined by counting the numbers of OH and NH bonds in each molecule.

Approximately 21% of the metabolites, 12% of the drugs and 34% of the toxin molecules don't possess any LHBDs37. Hydrogen bond acceptors (LHBAs), computed by summing the numbers of nitrogen and oxygen atoms in each. Only a fraction of molecules in all the datasets (0.35% of metabolites, 0.40% of drugs and 3.6% of toxins) do not possess LHBAs, molecule37. TPSA and the value of logP are

the two essential properties in analyzing bioavailability of drug molecule and permeability through bio-membranes41. Topological Polar Surface Area (TPSA) was calculated from surface areas occupied by oxygen, nitrogen and the hydrogen atoms that are attached to them. Thus, the TPSA is closely related to the H- bonding ability of a compound42. It can illustrate the drug absorption, including intestinal absorption, Caco–2 permeability, BBB penetration, and bioavailability. For the compounds with ten rotatable bonds and TPSA of ≤ 140 Å can be said to have good bioavailability40.

Pharmacokinetic properties prediction of tested polyphenols showed in (Table 3) results revealed that all polyphenols showed a high absorption rat through GI tract except oleuropein. Also, all tested ligands have no ability to pass through the blood brain barrier except benzoic acid and resveratrol. Also, naringenin only can be act as substrates for P- gp that reduced its efficacy in further clinical use43. The present results expressed that only caffeine, oleuropein and benzoic acid have no inhibitory effect for any of cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2D6 and CYP3A4). Caffeine, oleuropein, benzoic acid and gallic acid have no inhibitory activity toward CYP1A2. Also, CYP2C19 and CYP2D6 activity does not affected by any tested compounds. Furthermore, CYP2C9 activity does not affected by any of tested compounds except resveratrol. Besides, caffeine, oleuropein, ellagic acid and benzoic have no predicted inhibitory effect toward CYP3A4.

Pharmacokinetic analysis provides a mathematical basis to assess the time course of drugs and their effects in the body. It enables the following processes to be quantified: Absorption, Distribution, Metabolism, and Excretion (ADME)44. Understanding of these parameters is required to design an appropriate drug regimen for a patient45. It is known that, the gastrointestinal tract absorption affected by several factors such as physicochemical parameters of the drug, gastrointestinal motility, drug concentration at the site of absorption46. The distribution of a drug is influenced by many factors such as lipid-solubility, concentration in plasma and binding ability to plasma proteins, transport proteins 47. Also, metabolism of any drug is the process of irreversible transformation of parent compounds into daughter metabolites. The major site of metabolism in the body is the liver48. Metabolism in the liver occurs in two stages: Phase I pathways in liver microsomes, are catalyzed by a group of enzymes known as the cytochrome P450 system including aromatic hydroxylation, aliphatic hydroxylation, oxidative N dealkylation, oxidative O-dealkylation, S-oxidation, reduction and hydrolysis so the drug become more soluble, facilitating its elimination through the kidneys. Phase II pathways in liver cells where the parent or the metabolite from Phase I gets conjugated occurs by glucuronidation, sulfation, amino acid conjugation, acetylation, methylation or glutathione conjugation to facilitate elimination49. There are several factors that influence drug metabolism including route of administration, dose, genetics, disease state, and metabolic activity50. From docking analysis and prediction of drug likeness and pharmacokinetic properties of 8 tested polyphenols, gallic acid and quercetin exhibited high binding affinity than ribavirin toward COVID–19 polymerase and expressed good drug likeness and pharmacokinetic properties. Therefore, gallic acid and quercetin may represent a potential treatment option for COVID–19.

Quercetin, naringenin, ellagic acid, benzoic acid, resveratrol and gallic acid are group of polyphenols, and many of them have been found in plant-based foods. Dietary polyphenols have received tremendous attention among nutritionists, food scientists and consumers due to their roles in human health 51. Table 4 showed the natural sources of some bioactive compounds. Concerning fruit and vegetable processing, industries produced huge amount of by-products in the form of peels, cores, seeds, leaves and others that are discarded. These by-products regarded as rich sources in phenolic compounds, and they could be used as a food additives and nutraceuticals52. Quercetin, naringenin, ellagic acid and resveratrol are already present in the form of dietary supplement for public use, which reported as anti-inflammatory, antioxidant, supporting cardiovascular health and promoting heath immune function and brain function 53,54,55. From our results we recommend use of dietary supplement quercetin and producing gallic acid dietary supplement then starting evaluate its activity against COVID–19.

Conclusions

Currently, COVID–19 is a potential threat to global health. Till date, there is no specific vaccine or antiviral drug for. However, there are many ongoing clinical trials evaluating potential treatments. The aim of this study was to examine eight polyphenols that may be used to inhibit the COVID–19 polymerase and stop the COVID–19 replication. The obtained data in the present study revealed that, gallic acid and quercetin have high binding affinity to COVID–19 polymerase with expected good drug likeness and pharmacokinetic properties, and resveratrol, naringenin, benzoic and ellagic acid come next. Further researches are urgently required to investigate the potential uses of these compounds for designing and developing an effective medicine against COVID–19.

Declarations

Conflict of interest

The authors declare no conflict of interest.

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Author Contributions

Nourhan M. Abd El-Aziz and Mohamed G. Shehata conceived and designed the experiments. Nourhan M. Abd El-Aziz and Mohamed G. Shehata carried out the experiments. Nourhan M. Abd El-Aziz, Mohamed G. Shehata, Olfat M. Eldin Awad and Sobhy A. El-Sohaimy analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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Tables

Binding hits	X	Y	Z
ARG 555	120.535	116.572	140.185
ASP 623	120.142	120.563	127.503
LYS 545	116.821	118.681	142.960
ARG 55	124.628	111.958	139.619

Table 1. Protein target amino acids for molecular docking

Ligands name	Remdesivir	Ribavirin	Quercetin	Naringenin	Caffeine	Oleuropein	Ellagic acid	Benzoic acid	Resveratrol	Gallic acid
Molecular formula	$C_{27}H_{35}N_6O_8P$	$C_8H_{12}N_4O_5$	$C_{15}H_{10}O_7$	$C_{15}H_{12}O_5$	$C_8H_{10}N_4O_2$	$C_{25}H_{32}O_{13}$	$C_{14}H_6O_8$	$C_7H_6O_2$	$C_{14}H_{12}O_3$	$C_7H_6O_5$
Binding energy ΔG	-8.51	-6.01	-7.17	-5.69	-6.10	-4.59	-4.94	-5.54	-5.79	-7.55
No. of H bonding	11	5	10	6	2	4	6	2	2	5
Binding sites	ASN 691, CYS 622, LYS 621, TYR 619, THR 680, THR 687	ARG 553, ARG 555, ARG 624, SER 681	ARG 553, ARG 624, LYS 545, ASP 452, ALA 554, SER 682	ARG 553, ARG 555, SER 682, THR 556,	PHE 442, GLN 444	ASP 445, ASP 452, ASN 552, TYR 455	ARG 553, ARG 555, SER 682, THR 556	ARG 555, GLN 444	ARG 555, SER 682	ARG 553, PHE 442, ALA 547

Table 2. Molecular docking analysis of several compounds against COVID-19 6M71

Ligands name	Quercetin	Naringenin	Caffeine	Oleuropein	Ellagic	Benzoic	Resveratrol	Gallic
Lipinski's rule of five								
Molecular weight (<500 Da)	302.236	272.257	194.19	540.51	302.197	122.12	228.25	170.12
LogP (<5)	1.23	1.84	0.08	0.02	1.06	1.44	2.48	0.21
No. rotatable bonds (<15)	1	1	0	11	0	1	2	1
No. H-Bond donors (5)	5	3	0	6	4	1	3	4
No. H-bond acceptors (<10)	7	5	3	13	8	2	3	5
TPSA Å	131.36	86.99	61.82	201.67	141.34	37.30	60.69	97.99
Violations	0	0	0	3	0	0	0	0
Pharmacokinetics								
GI absorption	High	High	High	Low	High	High	High	High
BBB	No	No	No	No	No	Yes	Yes	No
P-gp substrate	No	Yes	No	No	No	No	No	No
CYP1A2 inhibitor	Yes	Yes	No	No	Yes	No	Yes	No
CYP2C19 inhibitor	No	No	No	No	No	No	No	No
CYP2C9 inhibitor	No	No	No	No	No	No	Yes	No
CYP2D6 inhibitor	Yes	No	No	No	No	No	No	No
CYP3A4 inhibitor	Yes	Yes	No	No	No	No	Yes	Yes

Table 3. Predicted drug likeness and pharmacokinetics of COVID-19 potential inhibitors

Name of polyphenol	Plant source	Refrence
Quercetin	Grapes, berries, apples, citrus fruits, onions, broccoli, tomatoes and black tea	(Panche *et al.*[56])
Naringenin	Citrus fruits such as oranges, mandarins, grapefruit, and acid citrus fruits, namely lemons, bergamots, and limes	(Alam *et al.*[57])
Oleuropein	Extra-Virgin Olive Oil	(Nocella *et al.* [58])
Caffeine	Cocoa beans, kola nuts, tea leaves and coffee beans	(Heckman *et al.*[59])
Ellagic acid	Pomegranate, strawberries, nuts and seeds	(Adams *et al.* [60])
Benzoic acid	Strawberries, cayenne pepper and mustard seeds, cloves and cinnamon	(Olmo, *et al.*[61])
Resveratrol	Grapes, wine, peanuts, and soy	(Burns *et al.*[62])
Gallic acid	Blueberry, blackberry, strawberry, grapes, mango and tea	(Daglia *et al.*[63])

Table 4. The natural sources of some bioactive compounds

Figures

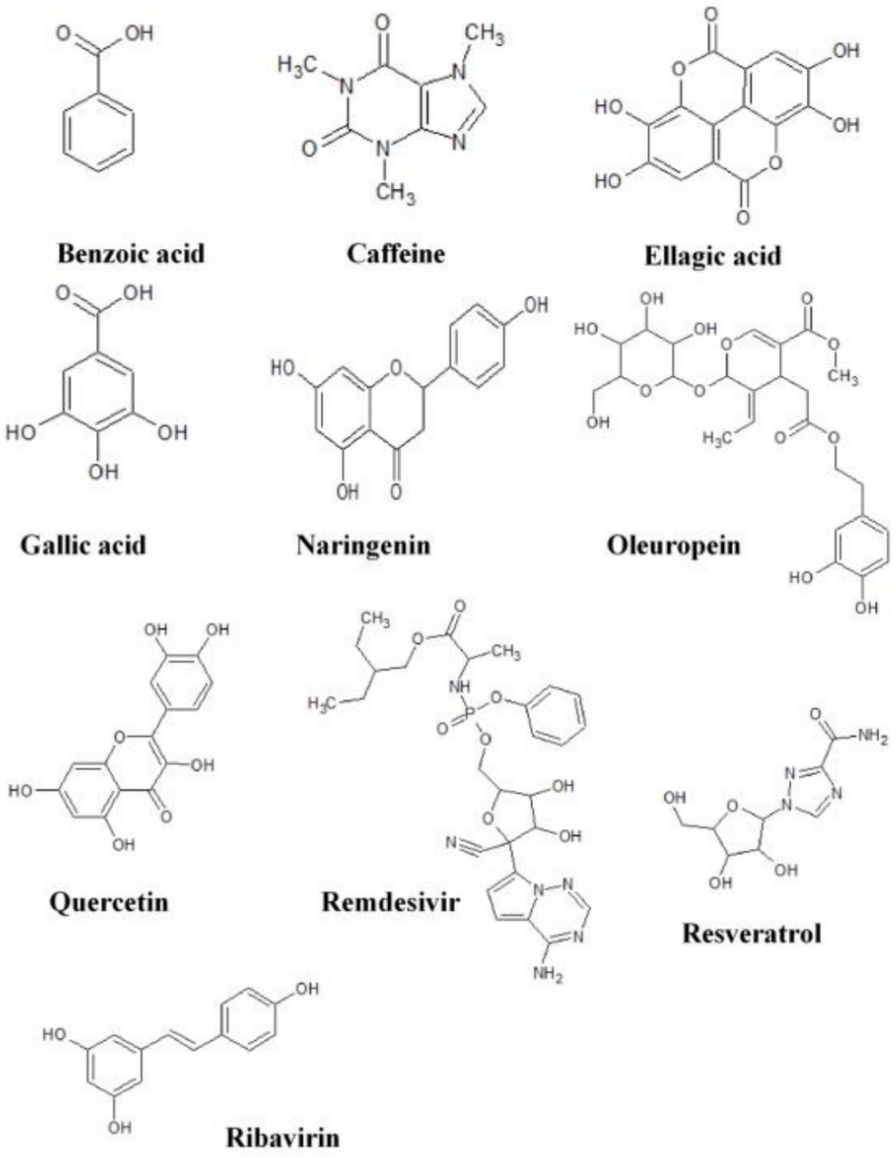

Figure 1

Alphabetical list of structures of docking ligands

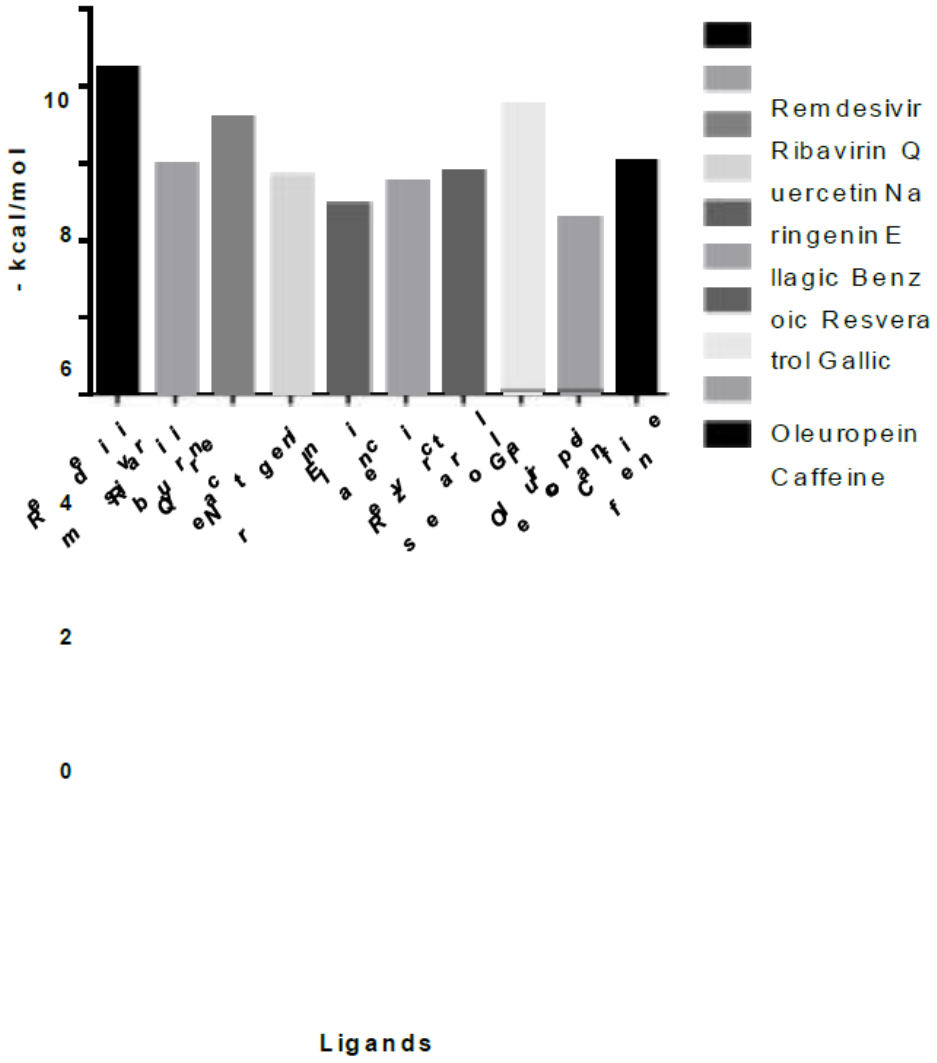

Figure 2

Histogram showing molecular docking results between COVID-19 6M71 and several drug candidate compounds (the binding energy value ΔG is shown in minus kcal/mol).

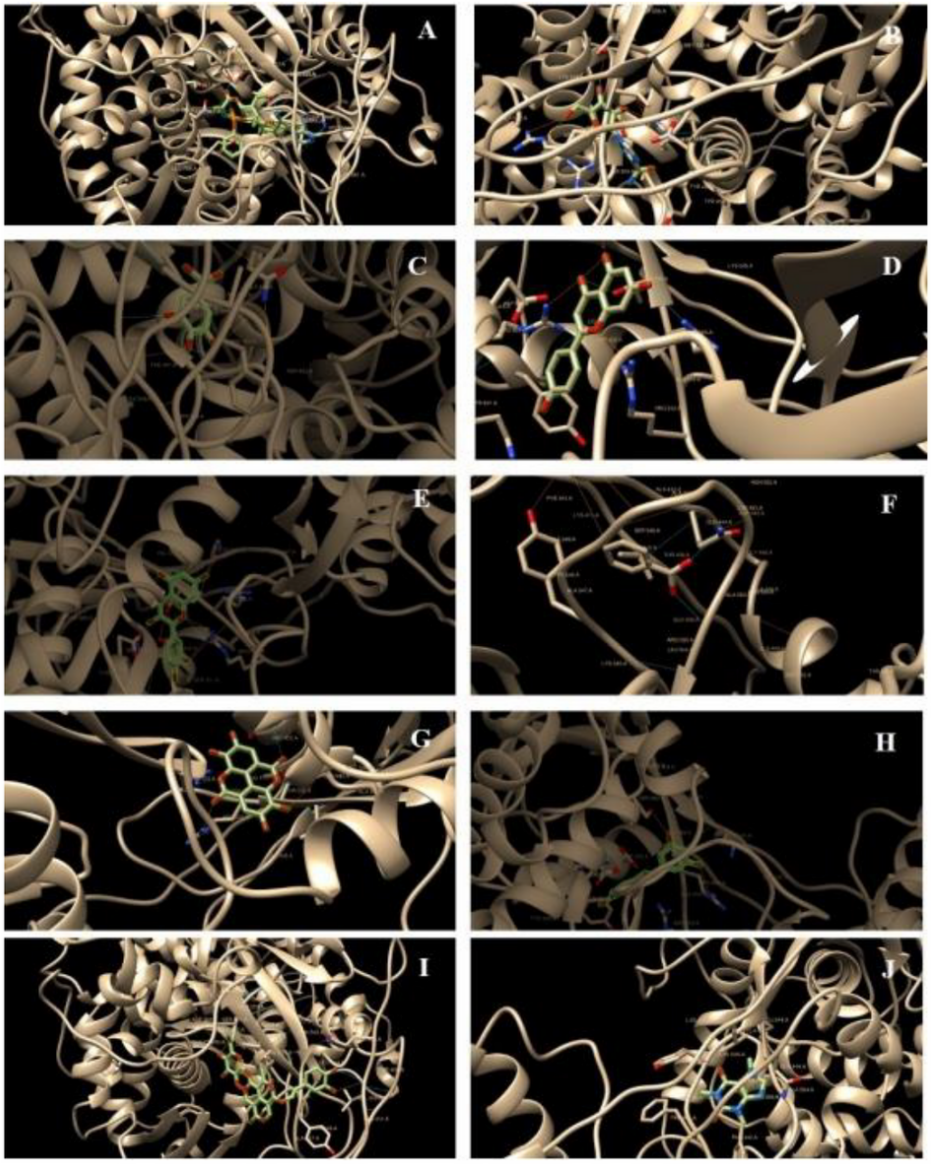

Figure 3

Chimera visualization of COVID-19 6M71 docking with Remdesivir (A), Ribavirin (B), Gallic (C), Naringenin (D), Quercetin (E), Benzoic (F), Ellagic (G), Resveratrol (H), Oleuropein (I) and Caffeine (J). The yellow dots show H-bonds.

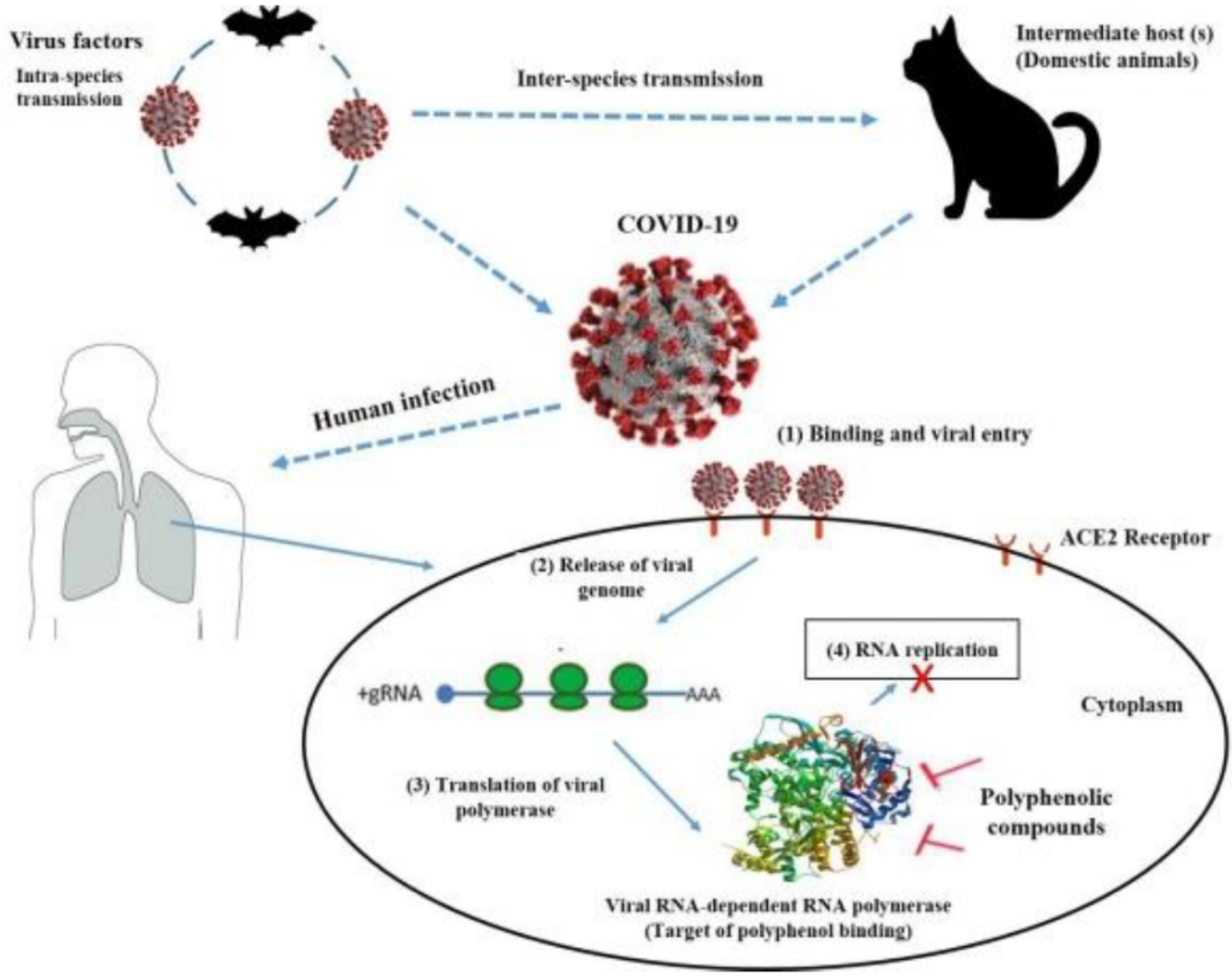

Figure 4

The proposed mechanism of COVID-19 inhibition by polyphenols.

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