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Inhibition of the SARS-CoV-2 RNA-Dependent RNA Polymerase by Natural Bioactive Compounds: Molecular Docking Analysis

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Abstract

Currently, no approved treatment for COVID-19 exists. However, phenolic compounds exhibit antiviral activity. This study aimed to evaluate the activities of polyphenolic compounds (gallic acid, quercetin, caffeine, resveratrol, naringenin, benzoic acid, oleuropein, and ellagic acid) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase (PDB ID 6M71) inhibitors. Molecular docking simulations of these polyphenols were performed using Autodock 4.0 and Chimera 1.8.1. Drug-likeness and pharmacokinetic properties were calculated using the SWISSADME prediction website. Remdesivir and ribavirin were used for comparison. The docking analysis results, ranked by the binding energy value (ΔG) of the tested ligands toward SARS-CoV-2 polymerase, were remdesivir > gallic acid > quercetin > caffeine > ribavirin > resveratrol > naringenin > benzoic acid > oleuropein > ellagic acid, with binding energies of −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 were predicted to form hydrogen bonds with one or two of the nucleotide triphosphate (NTP) entry channels at ARG 553, ARG 555, or LYS 545, except caffeine and oleuropein, which may influence the entry of substrate and divalent cations into the central active site cavity, thereby inhibiting enzyme activity. It appears promising that gallic acid and quercetin exhibited higher binding affinity than ribavirin toward the SARS-CoV-2 polymerase and expressed good drug-likeness and pharmacokinetic properties. Additionally, resveratrol, naringenin, and benzoic and ellagic acids exhibited some efficacy as potential polymerase inhibitors. Further research is required to investigate the potential uses of these polyphenols in the treatment of COVID-19.

Keywords: COVID-19; RNA-Dependent RNA Polymerase; Bioactive Compounds; Docking

1. Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in December 2019 in Wuhan, China. This disease has infected numerous people worldwide. At this time, December 20, 2020, a total of 76,858,506 confirmed cases have been reported in 210 countries, including 1,711,498 deaths [1].

SARS-CoV-2 infection is characterized as a respiratory syndrome with a variable degree of severity, ranging from a mild upper respiratory illness to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) [2, 3]. SARS-CoV-2 belongs to the genus *Betacoronavirus* and contains a positive-sense single-stranded RNA [(+)ssRNA] genome (29,903 bp) encoding an RNA-dependent RNA polymerase (RdRp), 3C-like proteinase, 20-O-ribose methyltransferase, envelope protein, nucleocapsid phosphoprotein, spike protein, and several unknown proteins, according to genome sequencing data (https://www.ncbi.nlm.nih.gov/genbank/sars-cov-2-seqs/) [4].

Remdesivir, one of the trial treatments for COVID-19, is an adenosine analog prodrug [5]. This analog can be incorporated into growing viral RNA and inhibit the RNA-dependent RNA polymerase. It has been reported

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that remdesivir inhibits SARS-CoV-2 replication and has the potential to treat patients in the clinic[6]. It was originally developed by Gilead Sciences (USA) to be used against the Ebola virus and has undergone clinical trials for use during the most recent Ebola outbreak in the Democratic Republic of Congo [6]. Although it was not demonstrated to be effective against Ebola in this trial, it was proven safe for use in humans, which allowed it to immediately enter clinical trials for the emergency treatment of COVID-19 [7]. Treatment with remdesivir exhibited some adverse effects, including elevated liver enzymes by fivefold [8].

Another trial treatment for COVID-19 is ribavirin, a guanosine analog that terminates RNA synthesis, which was first approved in the 1980s and has been used clinically for viral hemorrhagic fever. Moreover, it has been used in combination with interferon for the treatment of hepatitis C and respiratory syncytial virus infection. Its use was evaluated against SARS-CoV-1 in 2003, and it was used clinically in combination with corticosteroids and/or interferon in the absence of other treatment options. However, this treatment yielded poor outcomes [9], including adverse hematologic toxicity at high doses [10]. Wang et al. [11] investigated the *in vitro* activity of ribavirin against SARS-CoV-2 and reported an EC_{50} of 109.5 µM, over 100 times less potent than remdesivir.

The discovery of the molecular structure of the SARS-CoV-2 RNA-dependent RNA polymerase (PDB ID: 6M71) in April 2020 provided an opportunity to identify new drug candidates for replication inhibition of this virus. SARS-CoV-2 polymerase residues ARG 553, ARG 555, LYS 545, and ASN 691 are predicted to play roles in drug interactions [12].

Most natural polyphenols are derived from plant materials, such as fruits, vegetables, herbs, and spices, as low-molecular-weight secondary metabolites [13]. Phenolic compounds and flavonoids are known to exhibit antiviral activity against rhinoviruses [14], HCV [15], HIV [16], yellow fever [17], herpes simplex virus [18], and influenza viruses [19]. The interactions between the phenol rings of flavonoids and viral proteins and/or RNA, or between the mediators of MAP kinase signalling in host cell defense, can explain the antiviral mechanism of polyphenols [20]. The structural features of phenolic acids, such as their type, hydroxylation, methylation, and steric hindrance, can also affect their binding affinity (in terms of free energy, ΔG) with target proteins. The number of hydroxyl groups in phenolic acids is correlated with their binding affinities, whereas steric hindrance reduces their binding ability. Moreover, the impact of methylation is dependent on the phenolic acid type. After binding to phenolic acids, the conformation of targeted proteins can change, disrupting some structures or inhibiting the functions of the target protein [21].

Nowadays, bioinformatics plays a key role in pharmacology, which leads to the manufacture of multiple potential drugs in short periods with low risk [22]. However, there has been no previous docking analysis on the SARS-CoV-2 RNA-dependent RNA polymerase (PDB ID: 6M71). Therefore, the present study focused on the investigation of potential inhibitor candidates of the SARS-CoV-2 polymerase, including quercetin, naringenin, caffeine oleuropein, ellagic acid, benzoic acid, resveratrol, and gallic acid polyphenols, *via* molecular docking simulations. In addition, remdesivir and ribavirin were used as standard antiviral drugs for comparison. The findings in the present study can provide additional knowledge for drug design research to develop an effective drug to combat COVID-19.

2. Experimental Section

Docked SARS-CoV-2 polymerase structure

The structure of the SARS-CoV-2 RNA-dependent RNA polymerase (PDB ID 6M71) used as a target for polyphenol binding was downloaded from the RCSB website [23]. PDB (Protein Data Bank) has enabled breakthroughs in research, such as this study, and education worldwide [24].

Ligand and drug scan

The three-dimensional (3D) structures of all tested compounds were drawn in ACD/ChemSketch and then 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, gallic acid, and standard anti-viral drugs remdesivir and ribavirin. The druglikeness and pharmacokinetic properties of the tested polyphenols were calculated using the SWISSADME prediction website (http://www.swissadme.ch/) [25,26].

Determination of SARS-CoV-2 polymerase hits

The amino acids of the SARS-CoV-2 polymerase NTP entry channel and other sites of docked proteins were

used as target sites for enzyme–polyphenol interaction as described by Afonine et al. [12].

Molecular docking

Ligand optimization was performed using Open Babel, converting ligands from mol into the PDB format. Autodock version 4.0 was used for protein optimization through the removal of water and other atoms and then addition of 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. Docking analyses and determination of hydrogen bonds (H-bonds) were conducted using Chimera 1.8.1 [27].

3. Results and Discussion

SARS-CoV-2 is a new member of the genus *Betacoronavirus* [4]. Compared with SARS-CoV and MERS-CoV, SARS-CoV-2 exhibits faster human-to-human transmission. This caused the WHO to declare a Public Health Emergency of International Concern (PHEIC) [2]. The structure of the SARS-CoV-2 the RNA-dependent RNA polymerase has been deposited in PDB format and has been available to the public since April 2020 (PDB ID: 6M71). The structure 6M71 shares a similarity of 96% with 6NUR, that of the SARS-CoV protein NSP12 [28]. The discovery of the SARS-CoV-2 polymerase structure (PDB ID: 6M71) provides a great opportunity to identify potential drug candidates for the treatment of COVID-19 by inhibiting viral replication [6]. The SARS-CoV-2 polymerase residues ARG 553, ARG 555, LYS 545, and ASN 691 are predicted to play roles in drug interactions [28].

Polyphenols have been reported to exhibit antiviral bioactivities against HCV, HIV, and other viruses [29-31]. Khaerunnisa [33] described the potential activity of many polyphenols toward the SARS-CoV-2 main protease (M^{pro}), which is a potential drug target [33]. We investigated the effect of polyphenols quercetin, naringenin, caffeine, oleuropein, ellagic acid, benzoic acid, resveratrol, and gallic acid as potential inhibitors of the SARS-CoV-2 polymerase (PDB ID: 6M71), postulating that these compounds are capable of interfering with viral replication. Remdesivir and ribavirin are nucleotide analogues currently used as antiviral standard drugs for comparison. Table 1 presents the locations of amino acids ARG 553, ARG 555, LYS 545, and ASN 691 (X, Y, and Z coordinates) in the SARS-CoV-2 polymerase structure. The polyphenol compounds and several drug candidate structures were used as ligands in molecular docking simulations (Figure 1). Structural analysis of modeled ligands revealed that hydroxy groups (−OH) and ketone groups (=O) in polyphenols may play a role in amino acid interactions within the target protein [32].

Table 2 presents the amino acid binding sites, number of H-bonds hypothesized, and predicted binding energy values for each ligand after the docking simulation. The results of ligand docking, ranked by number of produced H-bonds, were as follows: remdesivir > quercetin > naringenin, ellagic acid > gallic acid, ribavirin > oleuropein > caffeine, benzoic acid, and resveratrol. It is known that the high binding affinity of the drug compounds depends on the type and amount of bonds occurring with the target protein [33]. Docking strength, ranked by binding energy (ΔG) of the tested ligands, was in the following order: 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 presents the comparative binding energy ΔG in kcal/mol of these ligands.

Figure 3 presents the predictions that remdesivir forms H-bonds with the SARS-CoV-2 polymerase at ASN 691, CYS 622, LYS 621, TYR 619, THR 680, and THR 687 residues (Figure 3A); that ribavirin forms H-bonds

TABLE 1. Protein target amino acids for molecular docking

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

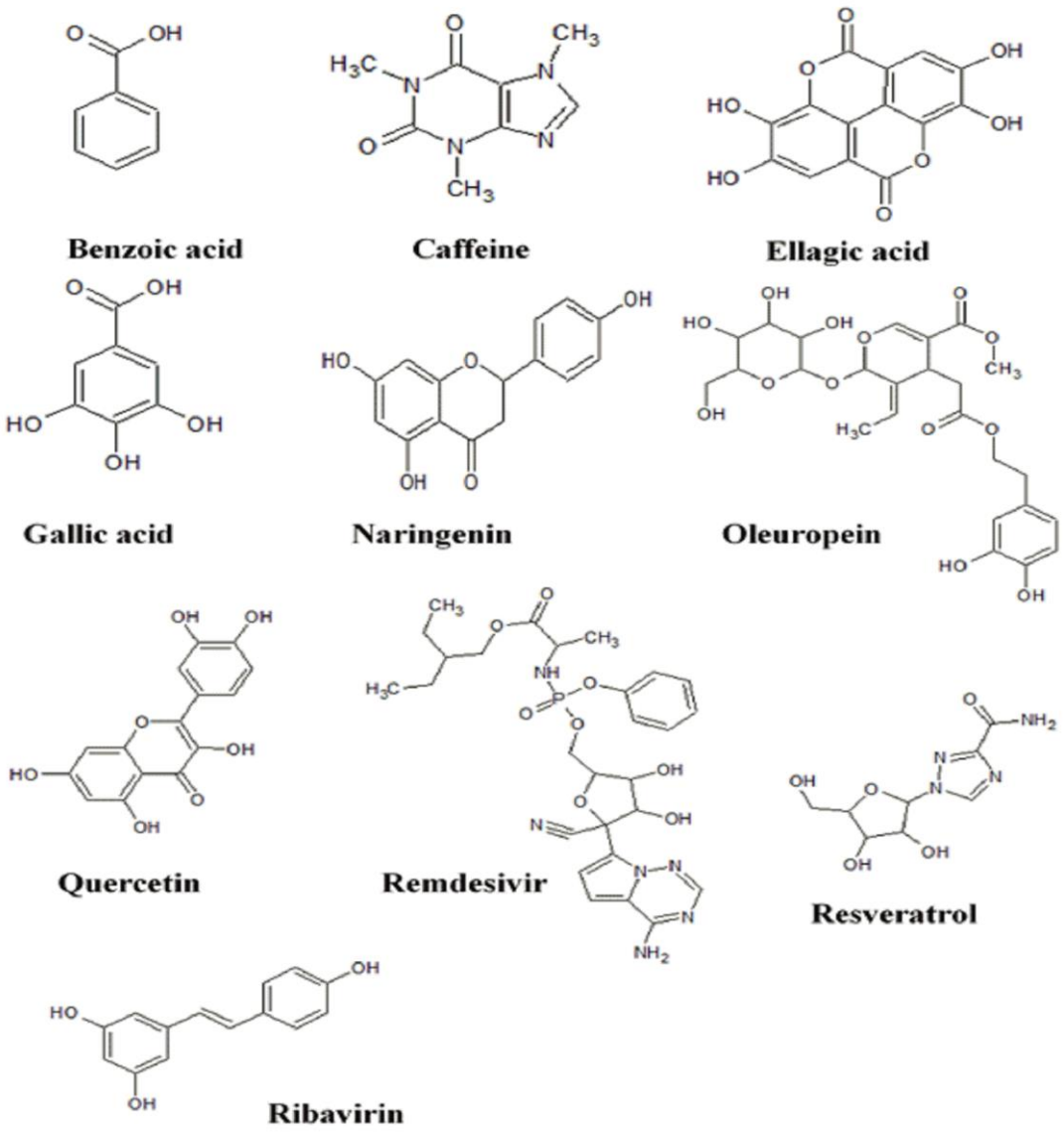

Fig. 1. Alphabetical list of structures of docking ligands

with ARG 553, ARG 555, ARG 624, and SER 681 residues (Figure 3B); that gallic acid forms H-bonds with ARG 553, PHE 442, and ALA 547 residues (Figure 3C); that naringenin forms H-bonds with ARG 553, ARG 555, SER 682, and THR 556 residues (Figure 3D); that quercetin forms H-bonds with ARG 553, ARG 624, LYS 545, ASP 452, ALA 554, and SER 682 residues (Figure 3E); that benzoic acid forms H-bonds with ARG 555 and GLN 444 residues (Figure 3F); that ellagic acid forms H-bonds with ARG 553, ARG 555, SER 682, and THR 556 residues (Figure 3G); that resveratrol forms H-bonds with ARG 555 and SER 682 residues (Figure 3H); that oleuropein forms H-bonds with ASP 445, ASP 452, ASN 552, and TYR 455 residues (Figure 3I); and that caffeine forms H-bonds with PHE 442 and GLN 444 residues (Figure 3J). Based on the above results, all the tested polyphenols were predicted to form H-bonds with at least one or two of the amino acids of the NTP entry channel of the SARS-CoV-2 polymerase, except for remdesivir, caffeine, and oleuropein. It has been postulated that the binding of polyphenols to ARG 553, ARG 555, and LYS 545 of this polymerase may prevent the entry of the substrate and divalent cations into the central active site cavity, thus inhibiting enzyme activity and preventing RNA

replication [34]. Figure 4 presents the proposed mechanism of COVID-19 inhibition by polyphenols.

It has also been reported that the NTP entry channel of the RNA-dependent RNA polymerase is formed by hydrophilic residues, including LYS 545, ARG 553, and ARG 555 in motif F. The RNA template is expected to enter the active site, which is composed of motifs A and C, through a groove clamped by motifs F and G. Motif E and the thumb subdomain support the primer strand, and the product-template hybrid exits the active site through the RNA exit tunnel on the front side of the polymerase [35]. Due to the structural conservation of the polymerase catalytic chamber between the SARS-CoV-2 polymerase (PDB ID: 6M71) and HCV ns5b polymerase (PDB ID: 4WTG) [36], a model of SARS-CoV-2 polymerase with remdesivir diphosphate was proposed with a similar binding mechanism of action. In this proposed model, remdesivir forms H-bonds 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 F [35]. Applying this model to our results, we predicted that remdesivir forms H-bonds with THR 680 and ASN691, similar to the proposed binding model but not to ASP 623 or VAL 557. This difference between the results may be due to the small structural difference between the SARS-CoV-2 polymerase and HCV ns5b polymerase. Polyphenols gallic acid and quercetin demonstrated higher predicted binding affinities toward the SARS-CoV-2 polymerase than ribavirin (Table 2).

Table 3 presents the drug-likeness and pharmacokinetic properties of the tested SARS-CoV-2 polymerase ligands. All the tested compounds are in the molecular weight range of 122.12 to 302.197 kDa (<500 kDa), except for oleuropein. All the tested compounds also have fewer than 15 rotatable bonds, and all have less than 5 hydrogen bond donors (NH and OH), except for quercetin and oleuropein. In addition, the numbers of hydrogen bond acceptors (O and N atoms) predicted in all compounds are less than 10, except for oleuropein (Table 3). At the same time, the number of rotatable bonds in all the tested compounds ranged from 0 to 2, except for oleuropein had 11. The permeability (logP) of these ligands has also been investigated, and it was found that these polyphenols exhibited logP values of less than 5. Moreover, the topological polar surface area (TPSA) values of all ligands are less than 140 Å, except for oleuropein and ellagic acid. Lipinski's rule of five is generally used as an indicator of the drug-likeness of certain compounds and whether those compounds have certain pharmacological activities that would make them orally active drugs in humans [37]. The rule also describes the molecular characteristics that influence a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME) [38]. It has been previously reported that drug molecules typically have low molecular weight (<500 kDa) and are transported, diffused, and absorbed easily compared with large molecules [39]. The number of rotatable bonds is a measure of molecular flexibility and is important in the determination of oral bioavailability of a drug [40].

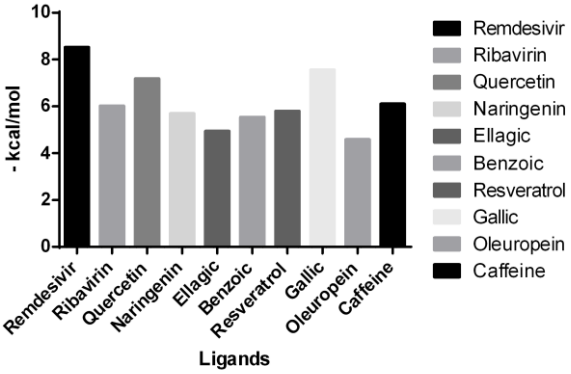

Fig. 2. Histogram showing molecular docking results between 6M71 and several drug candidate compounds (the binding energy value ΔG is shown in minus kcal/mol).

TABLE 2. Molecular docking analysis of several compounds against 6M71

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 3. Predicted drug likeness and pharmacokinetics of 6M71 potential inhibitors

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

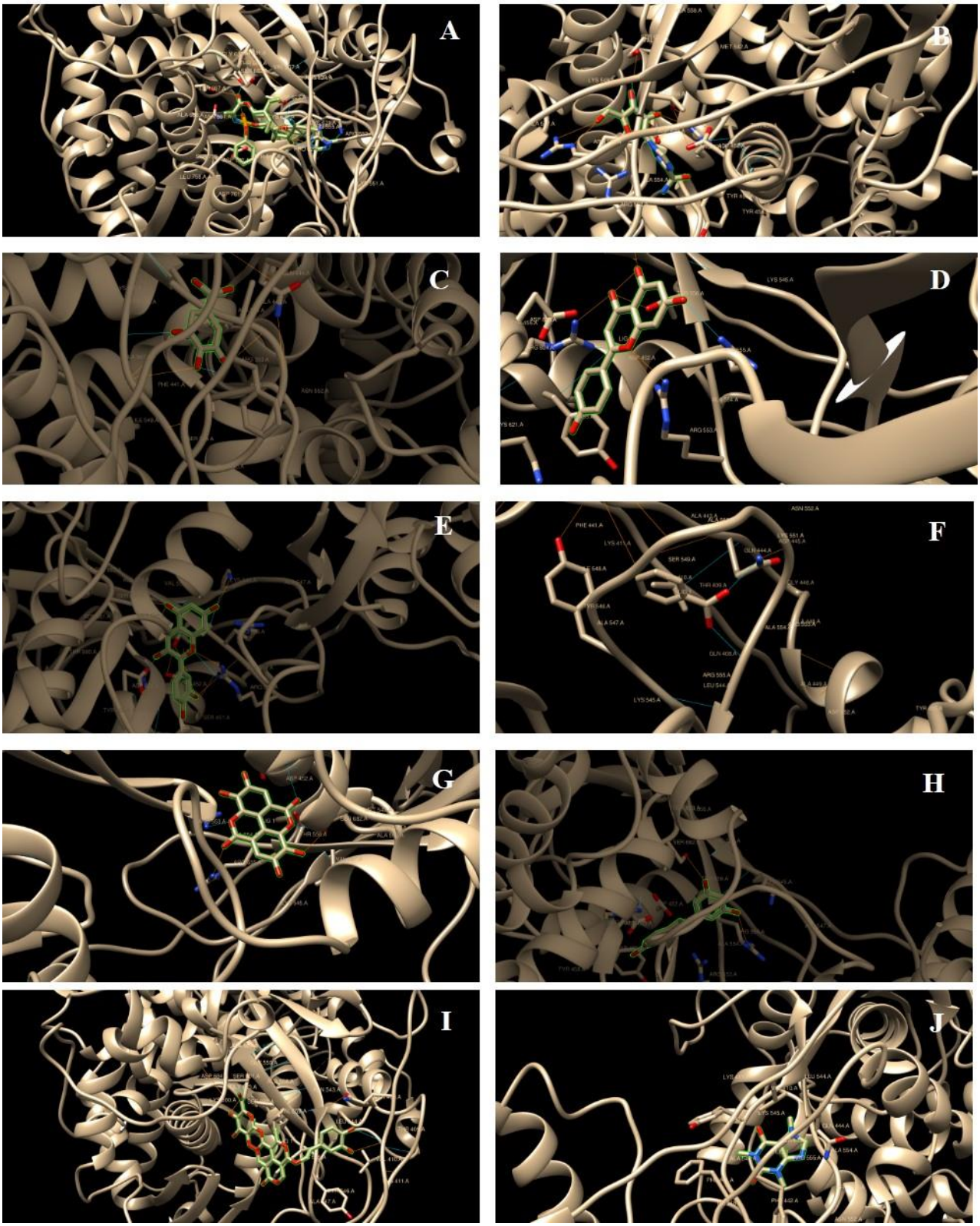

Fig. 3. Chimera visualization of 6M71 docking with Remdesivir (A), Ribavirin (B), Gallic (C), Naringenin (D), Quercetin (E), Benzoic (F), Ellagic (G), Resveratrol (H), Oleuropein (I) and Caffeine (J). The yellow dots show H-bonds.

Only 4% of human metabolites have no rotatable bonds, whereas 32% have 1–10 rotatable bonds, and 47% of these molecules have 36 –50 rotatable bonds [37]. Lipinski hydrogen bond donors (LHBDs) are determined by counting the number of OH and NH bonds in each molecule. Approximately 21% of metabolites, 12% of drugs, and 34% of toxins do not possess any LHBDs [37]. Lipinski hydrogen bond acceptors (LHBAs) are computed by summing up the numbers of nitrogen and oxygen atoms in a molecule. Only a fraction of molecules in these datasets (0.35% of metabolites, 0.40% of drugs, and 3.6% of toxins) do not possess LHBAs [37]. The TPSA and the logP values are the two essential characteristics in the analysis of the bioavailability of drug molecules and permeability toward bio-membranes [41]. TPSA is calculated from the surface areas occupied by oxygen, nitrogen, and hydrogen atoms. Thus, TPSA is closely related to the H-bonding ability of a compound [42]. It can demonstrate drug absorption, including intestinal absorption, intestinal cell permeability, blood–brain-barrier penetration, or bioavailability. Compounds with 10 rotatable bonds and TPSA of ≤140 Å can be predicted to have good bioavailability [40].

The pharmacokinetic properties of the tested polyphenols presented in Table 3 predicted that all polyphenols demonstrate a high absorption rate in the GI tract, except for oleuropein. Moreover, none of the tested ligands were predicted to be able to pass through the blood–brain-barrier, except for benzoic acid and resveratrol. Also, naringenin is the only compound predicted to act as a substrate for P-gp, which may reduce its efficacy and further clinical use [43]. These predicted results indicate that only caffeine, oleuropein, and benzoic acid would have no inhibitory effect on any cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2D6, and CYP3A4). Caffeine, oleuropein, benzoic acid, and gallic acid have no known inhibitory activity toward CYP1A2; also, CYP2C19 and CYP2D6 activities have not been reported to be influenced by any of the tested compounds. Furthermore, CYP2C9 activity is only known to be affected by resveratrol, whereas caffeine, oleuropein, ellagic acid, and benzoic have no predicted inhibitory activity toward CYP3A4. The inhibition of cytochrome P450 enzymes may influence drug metabolism, leading to increased toxicity.

Pharmacokinetic analysis provides a mathematical basis to evaluate the time course of drugs and their effects on the body. Pharmacokinetics encompasses ADME [44]. A sufficient understanding of these parameters is required to design an appropriate drug regimen for any patient [45]. Absorption in the gastrointestinal tract is affected by several factors, including the physicochemical parameters of the drug, gastrointestinal motility, and drug concentration at the site of absorption [46]. Drug distribution is influenced by several factors, such as lipid solubility, plasma concentration, and binding ability to plasma proteins and transport proteins [47]. The 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 liver [48], and metabolism occurs in two stages: Phase I pathways in liver microsomes are catalyzed by cytochrome P450 enzymes and include aromatic hydroxylation, aliphatic hydroxylation, oxidative N-dealkylation, oxidative O-dealkylation, S-oxidation, reduction, and hydrolysis, making the drug more soluble and facilitating its elimination through the kidneys. Phase II pathways in liver cells involve conjugation of the parent or metabolite *via* glucuronidation, sulfation, amino acid conjugation, acetylation, methylation, or glutathione conjugation to facilitate elimination [49]. There are several factors that influence drug metabolism, such as the route of administration, dose, genetics, disease state, and metabolic activity [50]. Based on the docking simulations and prediction of drug-likeness and pharmacokinetic properties of the eight tested polyphenols, gallic acid and quercetin exhibited the highest binding affinity toward the SARS-CoV-2 polymerase and expressed good drug-likeness and pharmacokinetic properties. Therefore, gallic acid and quercetin may represent potential treatment options for COVID-19.

Quercetin, naringenin, ellagic acid, benzoic acid, resveratrol, and gallic acid are polyphenols, many of which are present in plant-based foods. Dietary polyphenols have received considerable attention among nutritionists, food scientists, and consumers owing to their roles in human health [51]. Table 4 presents natural sources of some bioactive compounds. Industries produce huge amounts of fruit and vegetable by-products in the form of peels, cores, seeds, leaves, and other parts that are discarded. These by-products can be rich sources of phenolic compounds and could

TABLE 4. The natural sources of some bioactive compounds

Name of polyphenol	Plant source	Reference
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]

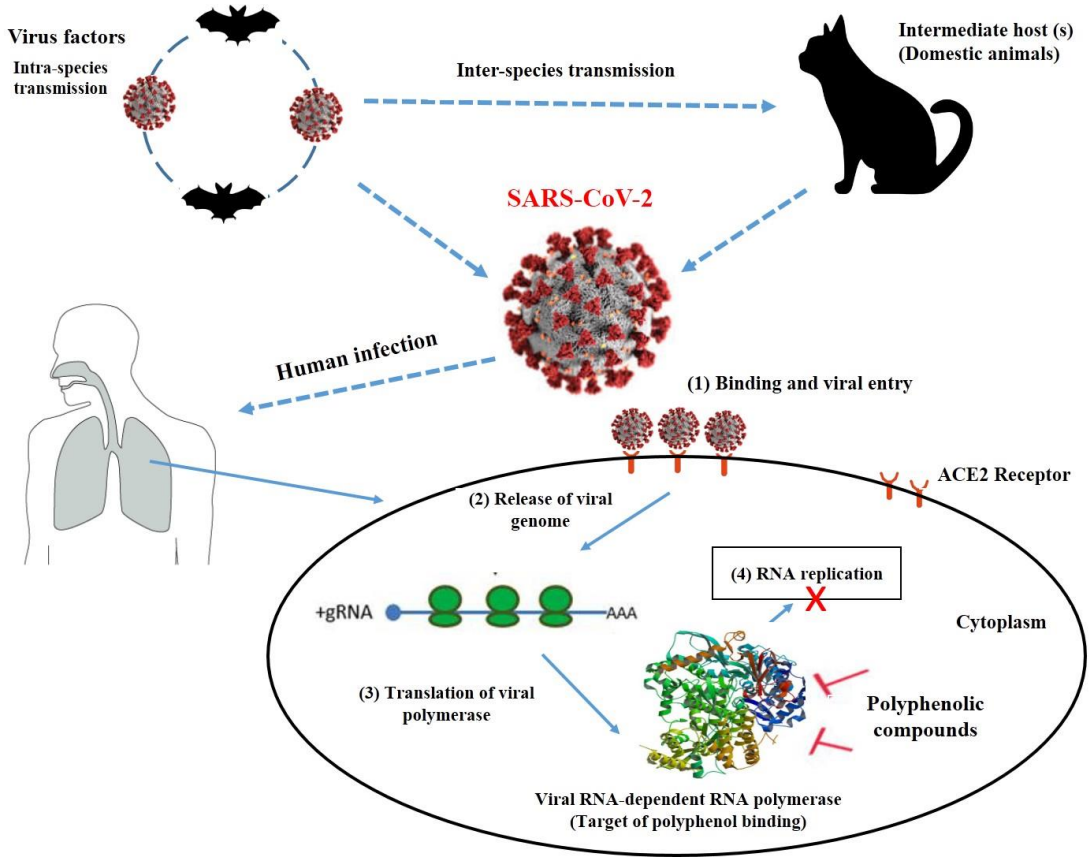

Fig. 4. The proposed mechanism of SARS-CoV-2 inhibition by polyphenols.

be used as food additives and nutraceuticals [52]. Quercetin, naringenin, ellagic acid, and resveratrol are already available for public consumption in the form of dietary supplements, which are reported as anti-inflammatory agents and antioxidants. They have also been reported to support cardiovascular health and promote healthy immune function and brain function [53-55]. Based on our results, we recommend the evaluation of dietary supplements quercetin and gallic acid and their activity against SARS-CoV-2 and COVID-19.

Conclusions

COVID-19 is a potential threat to global health. To date, there is no specific vaccine or antiviral drug to prevent or treat COVID-19. However, there are many ongoing

clinical trials evaluating potential treatments. This study examined eight polyphenols that may be used for the inhibition of the SARS-CoV-2 polymerase and for stopping viral replication. Our data revealed that gallic acid and quercetin exhibit high binding affinities for the SARS-CoV-2 polymerase, with good expected druglikeness and pharmacokinetic properties, followed by resveratrol, naringenin, and benzoic and ellagic acids. Further research is urgently required to investigate the potential uses of these compounds in designing and developing an effective treatment for COVID-19.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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