Polyphenols as alternative treatments of COVID-19

Yifei Wu, Scott D. Pegan, David Crich, Ellison Desrochers, Edward B. Starling, Madelyn C. Hansen, Carson Booth, Lauren Nicole Mullinin, Lei Lou, Kuan Y. Chang, Zhong-Ru Xie

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1. Introduction

In March 2020, the World Health Organization declared a global pandemic of the novel coronavirus disease (COVID-19) [1]. This outbreak continues to wreak havoc around the world, causing over 640,000 deaths in the United States and over 4.5 million deaths worldwide by the end of August 2021 [2]. Thus, rapid discovery of small-molecule antiviral drugs that are therapeutic against COVID-19 continues to be a significant task [3].

SARS-CoV-2, the viral agent responsible for COVID-19, is an enveloped, positive-sense, single-stranded RNA virus [4,5]. Coronaviruses contain the largest-known RNA virus genomes, being roughly 26–32 kb and made up of at least six open reading frames (ORFs) encoding for proteins [5]. RNA viruses such as SARS-CoV-2 are replicated by releasing these RNA genomes into host cells, which in turn translate that RNA into proteins as if the viral RNA were the host cell's own RNA. The major ORF of SARS-CoV-2 encodes two overlapping polyproteins, PP1A and PP1B. These polyproteins are generated in the host cell and then cleaved into 16 non-structural proteins (NSPs) by two proteolytic enzymes: the main protease (Mpro) and papain-like protease (PLpro) [6]. These NSPs then initiate replication and transcription of the viral genome by assembling the viral replicase complex on host cells membranes [7,8]. Thus, Mpro and PLpro play vital roles in the replication of SARS-CoV-2 in the body; without them, the NSPs would not be released from the larger polyproteins, PP1A and PP1B.

The importance of these proteases to the viral life cycle has led researchers to wonder if they could be inactivated, and whether a protease inhibitor would be a useful treatment for COVID-19. Although coronaviruses cannot replicate if the proteolytic activity of PLpro or Mpro is blocked [9], no PLpro and Mpro inhibitors used for COVID-19 treatment have yet been approved. PLpro not only cleaves PP1A and PP1B at three distinct sites between NSP1-4, but also helps coronaviruses to elude the host's immune response through competitive interaction with ubiquitin and ISG15 [10]. Certain inhibitors of the PLpro from SARS-CoV, the virus responsible for the 2003 global outbreak of severe acute respiratory syndrome (SARS), also target the PLpro from SARS-CoV-2 and exhibit antiviral activity in monkey cells in vitro [10]. Furthermore, PLpro inhibition reduces the cytopathogenic effect and replication of SARS-CoV-2 while maintaining the interferon antiviral response in vitro [11]. On the other hand, Mpro exclusively cleaves PP1A and PP1B at 11 distinct sites immediately following a glutamine residue [6]. Because no human host cell proteases have this substrate specificity, Mpro is an ideal drug target [5,12,13]. A drug used to treat feline infectious peritonitis, a lethal coronavirus infection that...
effects cats, has been found to be capable of inhibiting the SARS-CoV-2 M\textsuperscript{pro} and blocking viral replication [14]. Two protease inhibitors approved for treating hepatitis C virus have been demonstrated to inhibit the SARS-CoV-2 M\textsuperscript{pro} and show strong antiviral activity in a mouse model [15]. Thus, further investigation into inhibitors of PL\textsuperscript{pro} and M\textsuperscript{pro} may very likely lead to the discovery of a safe, effective treatment for COVID-19.

Polyphenols are secondary plant metabolites with a plethora of health benefits, including strong antioxidant properties that defend against oxidative damage by free radicals and prevent chronic disease [16]. In light of the ongoing pandemic, researchers have investigated polyphenols’ antiviral efficacy against COVID-19. Ghosh et al. found that the green tea polyphenols epigallocatechin gallate (EGCG), epicatechingallate, and gallocatechin-3-gallate interact strongly with one or both of the catalytic residues of the SARS-CoV-2 M\textsuperscript{pro} [17], and later demonstrated that six polyphenols from Broussonetia papyrifera demonstrated to inhibit the SARS-CoV-2 M\textsuperscript{pro} and show strong inhibition [18]. Khan et al. also found that EGCG interacted strongly with M\textsuperscript{pro} [19]. Ansari et al. found that luteolin had a higher affinity for PL\textsuperscript{pro} than the FDA-approved antiviral drug, remdesivir [20]. However, these studies were extremely limited in scope. There are around 500 unique polyphenol structures available for download on the Phenol-Explorer 3.6 database created by Neveu et al. [21], and current studies investigating polyphenols as M\textsuperscript{pro} and PL\textsuperscript{pro} inhibitors are limited to a very small selection of molecules, mainly coming from green tea. Considering that promising results were found using such a small selection of polyphenols, it is possible that there are even better outcomes to be found within a larger sample.

Thus, to find potential therapeutic agents against COVID-19, this study screens a large number of polyphenols to bind to SARS-CoV-2 M\textsuperscript{pro} or PL\textsuperscript{pro}. The structures of 480 polyphenols were obtained from the aforementioned Phenol-Explorer 3.6 database, and molecular docking was conducted using Maestro. MM-GBSA scores were collected to quantify the affinity of the molecules for the proteins, and then ADME (Absorption, distribution, metabolism, and excretion) and drug-likeness properties were analyzed for further screening. Finally, several polyphenols with high affinities are identified for both proteases: Petunidin 3-O-(6’-p-coumaroyl-glucoside), Malvidin 3,5-O-diglucoside, and Cyanidin 3-O-(6’-p-coumaroyl-glucoside) bind to M\textsuperscript{pro} (−101.21 kcal/mol, −95.07 kcal/mol, and −90.17 kcal/mol, respectively), while Kaempferol 3-O-sophoroside 7-O-glucoside, Cyanidin 3-O-sambubioside 5-O-glucoside, and Malvidin 3-O-(6’-p-coumaroyl-glucoside) are the top polyphenols bound to PL\textsuperscript{pro} (−87.97 kcal/mol, −87.33 kcal/mol, and −85.70 kcal/mol, respectively). This study identifies multiple polyphenols with extremely high binding affinities to the SARS-CoV-2 M\textsuperscript{pro} and PL\textsuperscript{pro} as potential natural products used for COVID-19 treatment.

2.2. Protein preparation

The protein structures of M\textsuperscript{pro} (PDB ID: 7BRP) and PL\textsuperscript{pro} (PDB ID: 6W9C) from RCSB’s Protein Data Bank (https://www.rcsb.org/) [23] were prepared for use by Maestro in three steps: preprocessing, optimization, and minimization. The preprocessing included assigning bond orders, adding hydrogens, creating zero-order bonds to metals, creating disulfide, filling in missing side chains using Prime, deleting water molecules beyond 5.00 Å from hetero groups and generating het states using Epik [24]. PROPKA’s default setting (pH = 7.0) and the OPLS3e force field were applied in optimization and minimization.

2.3. Ligand-protein docking

To estimate the interactions between target proteins and polyphenols, we conducted ligand–protein docking by using the Ligand Docking panel in Maestro. Before running docking jobs, a receptor grid box was generated based on existing ligands in protein structures. For the structure of M\textsuperscript{pro} (PDB ID: 7BRP), the existing ligand boceprevir was used to generate a receptor grid. In the structure of PL\textsuperscript{pro} (PDB ID: 6W9C), the receptor grid was generated according to the same site on SARS-CoV PL\textsuperscript{pro} (PDB ID: 3E9S). The size of the receptor grid box was set as default (20 Å). Ligand-protein docking was performed in extra-precision (XP) mode.

2.4. MM-GBSA calculation

To predict the binding energies of polyphenols bound to M\textsuperscript{pro} or PL\textsuperscript{pro}, we performed Prime MM-GBSA (molecular mechanics generalized Born surface area) in Maestro. In the MM-GBSA panel, the pose viewer files of the docked complex were uploaded into the MM-GBSA panel. The force field used was OPLS3e.

| Compound | Estimated binding energy (kcal/mol) | QPlogS\textsuperscript{a} | RO5\textsuperscript{b} | RO3\textsuperscript{c} | Predicted IC\textsubscript{50} (nM) |
|----------|-----------------------------------|--------------------------|------------------|------------------|---------------------|
| Petunidin 3-O-(6’-p-coumaroyl-glucoside) | −101.21 | −4.479 | 3 | 2 | 44.47 |
| Malvidin 3,5-O-diglucoside | −95.07 | −2.335 | 3 | 2 | 45.73 |
| Cyanidin 3-O-(6’-p-coumaroyl-glucoside) | −90.17 | −2.303 | 3 | 2 | 43.00 |
| *Saquinavir | −93.58 | −2.164 | 3 | 2 | 52.48 |
| **Epigallocatechin gallate (EGCG) | −65.04 | −3.554 | 2 | 2 | 60.73 |
| ***Pyriflavinol A | −58.38 | −6.287 | 0 | 2 | 76.96 |
| ****Boceprevir | −72.56 | −4.372 | 1 | 0 | 46.72 |

\textsuperscript{a}The best-scored potential drug identified by our previous study [36]

\textsuperscript{b}The best-scored potential drug identified by a previous study [17]

\textsuperscript{c}The best-scored potential drug identified by a previous study [18]

\textsuperscript{d}The original ligand of 7BRP [37]

\textsuperscript{e}The best-scored potential drug identified by our previous study [36]

\textsuperscript{f}The best-scored potential drug identified by a previous study [17]

\textsuperscript{g}The original ligand of 7BRP [37]
Fig. 1. The docking poses and 2-D ligand–protein interaction diagrams of 7BRP and the top three ligands: A, Petunidin 3-O-(6'-p-coumaroyl-glucoside); B, Malvidin 3,5-O-diglucoside; C, Cyanidin 3-O-(6'-p-coumaroyl-glucoside). For the docking poses, S1/S2 subsites are being shown. The purple arrow indicates the hydrogen bond; the green line represents π–π stacking; the red line represents π -cation interaction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
The results of the top 3 polyphenols bound to PLpro.

| Compound                        | Estimated binding energy (kcal/mol) | QPlogS | RO5 | RO3 | Predicted IC50 (nM) |
|---------------------------------|-------------------------------------|--------|-----|-----|---------------------|
| Kaempferol 3-O-sophoroside 7-O-glucoside | -87.97                              | -1.440 | 3   | 2   | 253.25              |
| Cyanidin 3-O-sambubioside 5-O-glucoside | -87.33                              | -1.618 | 3   | 2   | 253.25              |
| Malvidin 3-O-(6'-p-coumaroyl-glucoside) | -85.70                              | -4.664 | 3   | 2   | 243.37              |
| *GRL-0617                        | -60.75                              | -4.952 | 0   | 0   | 483.16              |
| **Uttelin                         | -43.53                              | -3.067 | 0   | 0   | 253.25              |
| ***VIR251                        | -64.40                              | -0.066 | 2   | 2   | 261.62              |

*a* known prodrug of PLpro identified in our previous study [10].
*b* the best-scored potential drug identified by the previous study [20].
***a* peptide inhibitor in the structure of 6WX4 [75].

To seek effective inhibitors from polyphenols against SARS-CoV-2 Mpro, 480 polyphenols (ligand) were docked onto SARS-CoV-2 Mpro (protein: PDB ID: 7BRP). Based on the docking poses, binding energies between the protein and ligand were calculated by MM-GBSA. Compared to three top drug candidates proposed by previous studies [17,18], in Table 1, the best three protein–ligand complexes, 7BRP- Petunidin 3-O-(6'-p-coumaroyl-glucoside) (−101.21 kcal/mol), 7BRP-Malvidin 3,5-O-diglucoside (−95.07 kcal/mol), and 7BRP- Cyanidin 3-O-(6'-p-coumaroyl-glucoside) (−90.17 kcal/mol) all have better estimated binding affinities. These top three polyphenols are members of anthocyanins, which can be found in black raspberry [32]. Meanwhile, we selected four ligands: saquinavir (−93.58 kcal/mol), EGCG (−65.04 kcal/mol), papyriflavonol A (−58.38 kcal/mol), and boceprevir (−72.56 kcal/mol) as a control group. From Table 1, we find that the binding energy of Saquinavir is slightly better than that of Cyanidin 3-O-(6'-p-coumaroyl-glucoside) (−90.17 kcal/mol), however, the binding energies of Petunidin 3-O-(6'-p-coumaroyl-glucoside) and Malvidin 3,5-O-diglucoside are better than those of the control group, which suggests the potential inhibitory effects of these polyphenols against SARS-CoV-2 Mpro.

By comparing the 2D ligand–protein interactions of the top three polyphenols with Mpro (Fig. 1), we find that they all interact with Glu166 by forming hydrogen bonds: two hydrogen bonds for Petunidin 3-O-(6'-p-coumaroyl-glucoside), three for Malvidin 3,5-O-diglucoside, and one for cyanidin 3-O-(6'-p-coumaroyl-glucoside) (Table 2). This result suggests that Glu166 is an essential residue in the binding pocket. According to the previous studies, Glu166 plays an important role in connecting the substrate binding site with the dimer interface [33], and it also forms critical interactions with the residues of N-terminal finger on the heterologous site with the dimer interface [33], and it also forms critical interactions with the residues of N-terminal finger on the heterologous monomer [33,34]. In addition, the equivalent Glu169 on the Mpro of MERS-CoV is also a key residue, which is crucial in both dimerization and catalysis [35].

Furthermore, these top three polyphenols all interact with Thr26, Leu141, and Glu192 by forming hydrogen bonds. Petunidin 3-O-(6'-p-coumaroyl-glucoside) and Cyanidin 3-O-(6'-p-coumaroyl-glucoside) interact with Phe140 and Gly143 by forming hydro-}

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Furthermore, these top three polyphenols all interact with Thr26, Leu141, and Glu192 by forming hydrogen bonds. Petunidin 3-O-(6'-p-coumaroyl-glucoside) and Cyanidin 3-O-(6'-p-coumaroyl-glucoside) interact with Phe140 and Gly143 by forming hydrogen bonds. Petunidin 3-O-(6'-p-coumaroyl-glucoside) and Malvidin 3,5-O-diglucoside both interact with Asp187 by forming hydrogen bonds. Petunidin 3-O-(6'-p-coumaroyl-glucoside) and Malvidin 3,5-O-diglucoside both interact with Asp187 by forming hydrogen bonds.
one hydrogen bond each. Additionally, His41 is also a critical residue which can interact with the top three polyphenols. Petunidin 3-O-(6′-p-coumaroyl-glucoside) interacts with His41 by forming two \( \pi \)-\( \pi \) stackings and one \( \pi \)-cation interaction, and Cyanidin 3-O-(6′-p-coumaroyl-glucoside) interacts with His41 via one \( \pi \)-cation interaction. The number of hydrogen bonds between the

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**Fig. 2.** The docking poses and 2-D ligand–protein interaction diagrams of 6W9C and the top three ligands: A, Kaempferol 3-O-sophoroside 7-O-glucoside; B, Cyanidin 3-O-sambubioside 5-O-glucoside; C, Malvidin 3-O-(6′-p-coumaroyl-glucoside). The pink arrow indicates the hydrogen bond; the green line represents \( \pi \)-\( \pi \) stacking; the red line represents \( \pi \)-cation interaction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Accordingly, we propose that Petunidin 3-O-(6'-p-coumaroyl-glucoside), Malvidin 3,5-O-diglucoside, and Cyanidin 3-O-(6'-p-coumaroyl-glucoside) are the three best drug candidates among all 480 polyphenols tested against SARS-CoV-2 Mpro.

To further screen the drug candidates for Mpro, we calculated drug-likeness properties and predicted IC\textsubscript{50} on the top three polyphenols by using Qikprop and AutoQSAR, respectively. The results are shown in Table 1. The polyphenols whose Qikprop descriptors (QPlogS, RuleOfFive, and RuleOfThree) fell out of the recommended range were excluded. For the results of AutoQSAR, it is interesting to note that the predicted IC\textsubscript{50} values of the top three polyphenols are all lower than 50 nM and Cyanidin 3-O-(6'-p-coumaroyl-glucoside) shows the best predicted IC\textsubscript{50}, which is generally consistent with the docking results.

### 3.2. Docking analysis of polyphenols against SARS-CoV-2 PLpro

To identify the best inhibitors of SARS-CoV-2 PLpro, we also docked 480 polyphenols on SARS-CoV-2 PLpro (PDB ID: 6W9C) by performing ligand–protein docking and MM-GBSA calculations (see Table 3). Consequently, the three best compounds with the top MM-GBSA binding energies were Kaempferol 3-O-sophoroside 7-O-glucoside (–87.97 kcal/mol), Cyanidin 3-O-sambubioside 5-O-glucoside (–87.33 kcal/mol), and Malvidin 3-O-(6'-p-coumaroyl-glucoside) (–85.70 kcal/mol). Kaempferol 3-O-sophoroside 7-O-glucoside belongs to the group of flavonols. Cyanidin 3-O-sambubioside 5-O-glucoside and Malvidin 3-O-(6'-p-coumaroyl-glucoside) belong to the group of anthocyanins. Meanwhile, a known PLpro inhibitor GRL-0617 [10], the best-scored potential drug luteolin [20], and a peptide inhibitor in the structure 6WX4 were selected as control. From Table 3, we find that the top three polyphenols show better binding energies than the control compounds, which indicates that these polyphenols might have stronger inhibitory effects.

From the 2D ligand–protein interactions in Fig. 2, we find that the top three compounds all can interact with Asp164 and Arg166 by forming hydrogen bonds. Kaempferol 3-O-sophoroside 7-O-glucoside and Malvidin 3-O-(6'-p-coumaroyl-glucoside) interact with Asp164 by forming one hydrogen bond, respectively. Cyanidin 3-O-sambubioside 5-O-glucoside interacts with Asp164 by forming two hydrogen bonds. These three compounds form one hydrogen bond with Arg166, respectively. Moreover, Kaempferol 3-O-sophoroside 7-O-glucoside can interact with Gly266 and Asn267 by forming one hydrogen bond, respectively. Cyanidin 3-O-sambubioside 5-O-glucoside interacts with Asp164 by forming two hydrogen bonds. These three compounds form one hydrogen bond with Arg166, respectively. Notably, Gly266, Asn267, and Tyr268 are residues on blocking loop 2 (BL2), and BL2 plays an important role in inhibitor binding [40]. Hence, the interactions between the top two polyphenols and BL2 suggest strong inhibitory effects. Accordingly, we conclude that these two polyphenols can tightly bind onto the binding pocket. The number of hydrogen bonds between these three compounds and the essential residues are listed in Table 4.

### 3.3. Molecular dynamics (MD) simulation

To further analyze the stability of complexes, we conducted MD simulation to calculate RMSD and energy for the top two candi-

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**Table 4**

The number of hydrogen bonds formed between the top three polyphenols and essential residues of SARS-CoV-2 PLpro.

| Kaempferol 3-O-sophoroside 7-O-glucoside | Cyanidin 3-O-sambubioside 5-O-glucoside | Malvidin 3-O-(6’-p-coumaroyl-glucoside) |
|------------------------------------------|------------------------------------------|------------------------------------------|
| Gly163                                   | 1                                        | 1                                        |
| Asp164                                   | 2                                        | 1                                        |
| Arg166                                   | 1                                        | 1                                        |
| Glu167                                   | 1                                        | 1                                        |
| Ser170                                   | 1                                        | 1                                        |
| Pro248                                   | 1                                        | 1                                        |
| Tyr264                                   | 1                                        | 1                                        |
| Gly266                                   | 1                                        | 1                                        |
| Asn267                                   | 1                                        | 1                                        |
| Tyr268                                   | 1                                        | 1                                        |
| Tyr273                                   | 1                                        | 1                                        |
| Thr301                                   | 1                                        | 1                                        |
| Asp302                                   | 1                                        | 1                                        |

**Fig. 3.** The RMSD of protein–ligand complexes. A, 7BRP- Petunidin 3-O-(6’-p-coumaroyl-glucoside); B, 7BRP- Malvidin 3,5-O-diglucoside; C, 6W9C- Kaempferol 3-O-sophoroside 7-O-glucoside; D, 6W9C- Cyanidin 3-O-sambubioside 5-O-glucoside.
dates. First, RMSD can be used to assess the stability of a protein–ligand complex. As shown in Fig. 3A, the RMSD for the complex of 7BRP- Petunidin 3-O-(6'-p-coumaroyl-glucoside) stabilized around 0.25 nm between 5 ns and 100 ns. In Fig. 3B, the RMSD of 7BRP-Malvidin 3,5-O-diglucoside stabilized at 0.25 nm from 10 ns to 40 ns, and then stabilized around 0.3 nm after 40 ns. The RMSD of 6W9C with Kaempferol 3-O-sophoroside 7-O-glucoside stabilized at 0.25 nm from 4 to 100 ns (Fig. 3C). From Fig. 3D, we find that the RMSD of 6W9C with Cyanidin 3-O-sambubioside 5-O-glucoside stabilized at 0.25 nm before 30 ns, and then stabilized around 0.35 nm from 30 to 90 ns. Moreover, the total energies of these four complexes are shown in Fig. 4. The energies of 7BRP complexes stabilized at around $-1.13 \times 10^6$ KJ/mol (Fig. 4A and B). Interestingly, the energy of 6W9C complexes stabilized at around $-1.365 \times 10^6$ KJ/mol (Fig. 4C and D). The RMSD and energy analysis show that the complexes of Mpro or PLpro with their respective top two polyphenols stay stable during the simulation process.

4. Discussion

Many studies have shown natural products possessing antiviral properties against the Epstein-Barr virus [41,42], herpes simplex virus [43,44], influenza virus [45], and other viruses targeting the respiratory tract [45,46–50,74]. Since the 2003 outbreak of SARS, a number of natural products have been reported to inhibit the coronavirus which causes SARS (SARS-CoV) or its target proteins [49–64]. In addition, previous studies demonstrate that many polyphenols, including quercetin and its glycosylated derivatives, inhibit cell proliferation of tumor cells or microorganisms [65–68]. Glycosylation of polyphenols could enhance water solubility, bioavailability, and their binding affinities to significant enzymes and improve the drug efficacy [69–71]. This result not only suggests that polyphenols are potential drug candidates, but also indicates that this study discovered more polyphenols for COVID-19 treatment.

Based on the docking pose of each target protein, we find that the key residue(s) can interact with the best inhibitor candidate via multiple interactions. First, in the structure of Mpro, Glu166 is a key residue for Mpro dimerization and substrate binding pocket creation [72]. The best inhibitor candidate Petunidin 3-O-(6'-p-coumaroyl-glucoside) interacts with Glu166 side chain by forming two hydrogen bonds (Fig. 5A), which makes an impact on increasing the binding energy. This result is consistent with the finding in our previous research which showed that saquinavir interacts with Glu166 [36]. Accordingly, Glu166 is a key residue for Mpro inhibitor discovery. In the structure of PLpro, the residues (Gly266-Gly271) in the BL2 loop are critical for inhibitor binding [7,73]. From Fig. 5B, we find that the best candidate of PLpro Kaempferol 3-O-sophoroside 7-O-glucoside forms hydrogen bonds with Gly266 and Asn267 which are the residues in the BL2 loop. Additionally, the second-best candidate Cyanidin 3-O-sambubioside 5-O-glucoside form one hydrogen bond with Tyr268 which is also an important residue in the BL2 loop. Therefore, more interactions between the inhibitor and the BL2 loop may increase the binding affinity.

In summary, this study demonstrates the potential of polyphenols being an alternative treatment of COVID-19. The docking results agree with previous studies identifying the key residues interacting with the binding inhibitors or produgs, but the proposed inhibitors in this study possess even better estimated binding affinities. However, most of the top-ranked polyphenols cannot be ordered for validation experiments currently. We are attempting to obtain some of them from other labs or produce them ourselves. The much better estimated binding affinities than previously identified compounds and rational binding mechanisms support their potential efficacy and provide the clues for the future drug development.
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2021.09.022.

Fig. 5. 3D interaction diagrams showing the interactions between the best ligand and the key residue(s). A, Petunidin 3-O-(6’-p-coumaroyl-glucoside) interacts with the side chain of Glu166 via hydrogen bonds (yellow dash lines) on Mpro (PDB ID: 7BRP); B, Kaempferol 3-O-sophoroside 7-O-glucoside interacts with Gly266 and Asn267 via hydrogen bonds (yellow dash lines) on PLpro (PDB ID: 6W9C). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
