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In silico screening of potent bioactive compounds from honeybee products against COVID-19 target enzymes

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Abstract

After the early advent of the Coronavirus Disease 2019 (COVID-19) pandemic, myriads of FDA-approved drugs have been massively repurposed for COVID-19 treatment based on molecular docking against selected protein targets that play fundamental roles in the replication cycle of the novel coronavirus. Honeybee products are well known of their nutritional values and medicinal effects. Bee products contain bioactive compounds in the form of a collection of phenolic acids, flavonoids, and terpenes of natural origin that display wide spectrum antiviral effects. We revealed by molecular docking the profound binding affinity of 14 selected phenolics and terpenes present in honey and propolis (bees glue) against the main protease (M^{pro}) and RNA-dependent RNA polymerase (RdRp) enzymes of the novel SARS-CoV-2 virus (the causative agent of COVID-19) using AutoDock Vina software. Of these compounds, *p*-coumaric acid, ellagic acid, kaempferol, and quercetin have the strongest interaction with the SARS-CoV-2 target enzymes, and it may be considered an effective COVID-19 inhibitor.

Keywords COVID-19 · Honeybee products · Phenolic compounds · Molecular docking · Drug repurposing · Natural products

Introduction

In December 2019, COVID-19 firstly manifested in Wuhan, province of Hubei in China, where frequent number of patients shared similar symptoms of dry cough, fever, and fatigue; then they developed into dyspnea quickly, ending up with acute respiratory distress syndrome (ARDS) in severe cases (Chen et al. 2020; Chan et al. 2020; Zhu et al. 2020; Huang et al. 2020; Zhou et al. 2020).

As of 1st of May 2021, the cumulative number of cases diagnosed with COVID-19 in the world was more than 153 million, whereas more than 3 million cases died (Coronavirus Update (Live): https://www.worldometers.info/coronavirus - Worldometer 2021). As a direct effect of the outbreak, more than 160 countries are fighting to combat the spread of COVID-19 and taking protective measures to save their citizens from the pandemic; at the same time, research institutes, drug corporations, biotechnology institutes, and research groups all over the world are racing to develop effective drugs or potential vaccines for COVID-19 (Sharpe et al. 2020; Thanh Le et al. 2020; Pooladanda et al. 2020; Hachfi and Ben Lasfar 2020; Mullard 2020; Biopharma products in development for COVID-19 2021).

As a fast track to save the time needed for safety and approval studies, researchers started to massively repurpose already FDA-approved drugs for COVID-19 treatment (Kandeel and Al-Nazawi 2020; Harrison 2020). Computational-based techniques like molecular modeling and virtual screening represent magic tools that help to

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understand the molecular aspects of protein ligand interactions during rational drug design process (Murgueitio et al. 2012). Virtual screening has been encountered in structure-based drug design against emerging and fatal diseases of viral origin (Sirois et al. 2004; Elhefnawi et al. 2012; Raj and Varadwaj 2016; Zhou et al. 2008; Plewczynski et al. 2007).

The key protease (Mpro) and the RNA-dependent RNA polymerase (RdRP), which are responsible for the viral polyprotein proteolytic process as well as viral genome replication and transcription, are two promising drug targets for SARS-CoV-related diseases (Gao et al. 2020) and the main protease (Mpro) responsible for virus maturation in addition to crucial roles in mediating viral replication and transcription (Jin et al. 2020). Based on their crucial role in the life cycle of SARS-CoV-2, these two target sites have been extensively docked to design or distinguish structure-based effective drugs for COVID-19 (Dai et al. 2020).

Bioactive compounds of natural origin are currently screened by molecular docking to in silico test their affinity to molecular targets of COVID-19 taking the advantage that natural products are free from toxic or side effects (Mani et al. 2020; Sayed et al. 2020; Gurung et al. 2020; Khalifa et al. 2020b). Recently, honeybee products have been proposed as a potential compatible antiseptic to help protect against the COVID-19 based on biocidal effect of hydrogen peroxide and other phytochemicals existing in bee products (Al Naggar et al. 2020). These phenolic compounds and terpenes found in honeybee products were documented to possess variable medicinal effects including wound healing, antioxidant, antimicrobial, antiviral, anti-inflammatory, cardioprotective, and neuroprotective activities (Küçük et al. 2007; Mohamed et al. 2009; Al Naggar et al. 2016; Pasupuleti et al. 2017; Jibril et al. 2019; El-Seedi et al. 2020; Al Naggar et al. 2020; Al Naggar et al. 2021).

In our study, we performed deep virtual screening via molecular docking to test binding affinity of various selected bioactive compounds such as terpenes and flavonoids of honey and propolis as inhibitors against the COVID-19 essential enzymes: RNA-dependent RNA polymerase and the main protease.

Docking methodology

The crystal structures of COVID-19 RNA-dependent RNA polymerase (RdRp) (PDB code: 6M71) (Gao et al. 2020) and the main protease (M^{pro}) (PDB code: 6LU7) (Jin et al. 2020) were retrieved from Protein Data Bank. This docking study was carried out on 14 compounds (Fig. 1) from honey and propolis into the receptor active site using AutoDock Vina (Trott and Olson 2010). These compounds were selected based on previously reported antiviral activities against related viruses to COVID-19 (Al Naggar et al. 2020; Shahidi and Yeo 2018); in the same context, several studies employing virtual screening of closely related members or categories of the selected phytochemicals were performed against SARS-CoV-2 proteins since these phytochemicals are naturally existing in plants and spices (Sayed et al. 2020; Ibrahim et al. 2020; Umesh et al. 2020).

Ligand structures were drawn into Marvin Sketch V19.12 (Marvin | ChemAxon 2020), and the most energetically favored conformer was exported as (*.pdb) file format. AutoDockTools package (Morris et al. 2009) was used to assign Gasteiger atomic partial charges, and all the rotatable bonds in ligands were set to be flexible. For receptor preparation, all water molecules were removed, the co-crystalized ligand was removed, Gasteiger atomic partial charges were assigned, and all receptors and ligands were converted to the PDBQT format using AutoDockTools package for docking process. In the AutoDock Vina configuration files, the parameter num modes was set to 10 and exhaustiveness to 14. The grid boxes of center (x= 118.23, y= 103.32, and z= 118.37) with size (x=17, y=25, z=17) for the RNA-dependent RNA polymerase and center (x= −10.71, y= 12.41, and z= 68.83) with size (x=16, y=18, z=16) for the main protease were used to define the active site. AutoDock Vina was executed. Pymol (PyMOL Molecular Visualization System 2020) was used for 3D visualization, and the 2D schematic presentation was generated using LigPlot+ V1.4.5 (Laskowski and Swindells 2011).

Results and discussion

Computational docking was implemented to predict the binding mode of 14 compounds representing flavonoids, phenolic acids, and terpenes from honey and propolis (Fig. 1) with two different targets from COVID-19.

The bioactive compounds, ellagic acid, hesperetin, and kaempferol, are the most promising compounds on COVID-19 RdRp, while artepillin C, ellagic acid, hesperetin, kaempferol, and quercetin were the most active on the main protease (Mpro). The binding scores for each compound into the two targets are shown in Table 1. The binding mode for ellagic acid to COVID-19 RdRb was attributed to H-bond interaction with Gly808, pro809, His816, Thr817, and Tyr 831, while amino acid residues Trp617, Asp760, and Asp761 are positioned at distance of H-bond with hesperetin, and also kaempferol interacts with Glu811 and Asp761 by H-bond. Furthermore, the aromatic ring system of ellagic acid, hesperetin, and kaempferol makes π-ion hydrophobic interaction with Lys798 (Fig. 2). We repurpose the compounds of interesting binding scores as potent inhibitors of viral replication.

From the docking of all identified compounds into the active site of SARS-CoV-2 main protease (M^{pro}) in the current

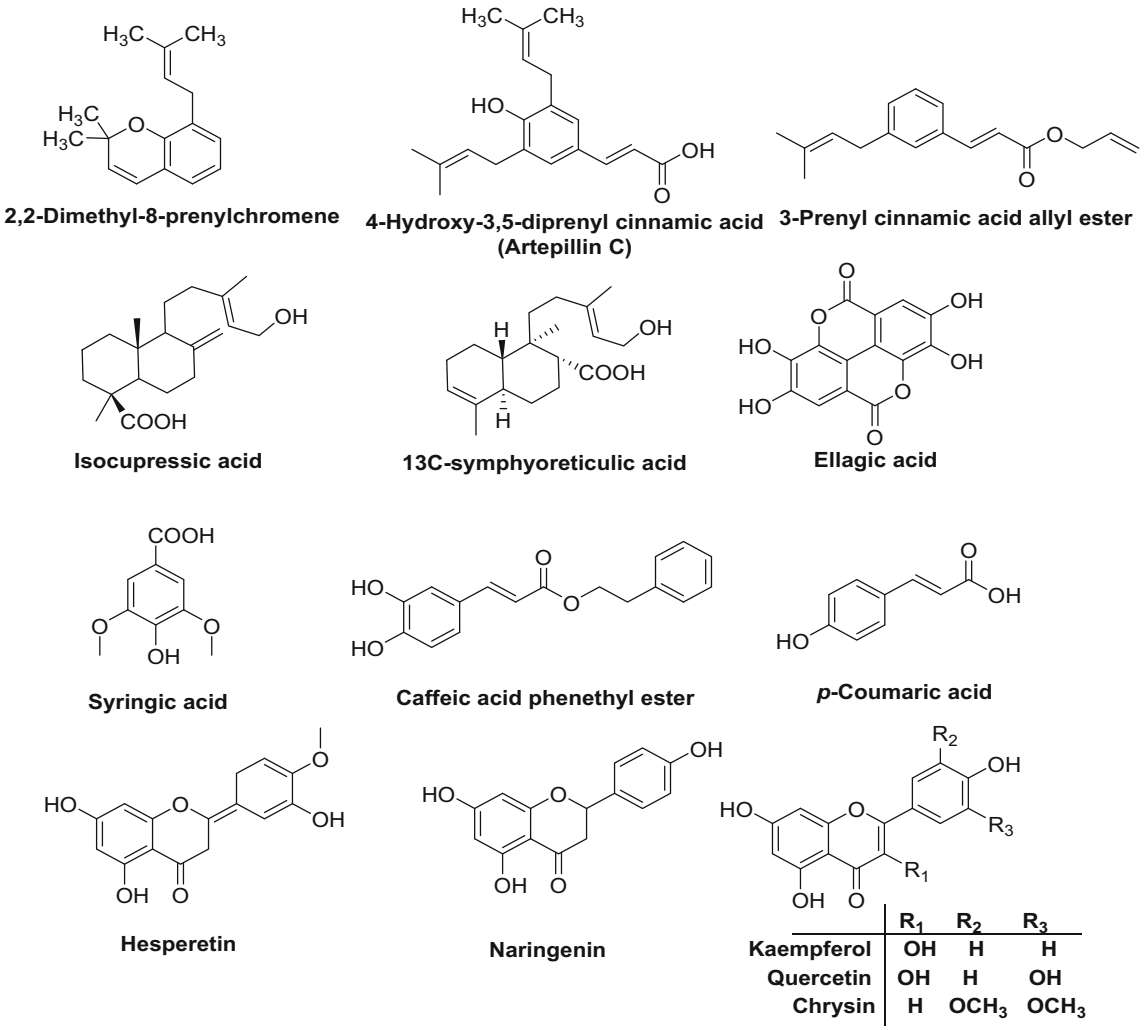

Fig. 1 Chemical structure of important bioactive compounds in honeybee products

Table 1 The binding scores for each compound into the two target enzymes of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) and the main protease (M^{pro})

Bioactive compounds	SARS-CoV-2 RNA-dependent RNA polymerase	SARS-CoV-2 main protease (M^{pro})
2,2-Dimethyl-8-prenylchromene	−5.6	−6.8
Artepillin C	−5.9	−7.5
3-Prenyl cinnamic acid allyl ester	−5.3	−6.2
Isocupressic acid	−5.8	−6.4
13C-symphyoreticulic acid	−5.7	−6.9
Ellagic acid	−6.4	−7.5
Syringic acid	−5.5	−5.6
Caffeic acid phenethyl ester	−5.4	−7.0
p-Coumaric acid	−5.3	−5.6
Hesperetin	−6.3	−7.4
Naringenin	−6.0	−6.5
Kaempferol	−6.2	−7.8
Quercetin	−6.1	−7.4
Chrysin	−6.1	−7.2

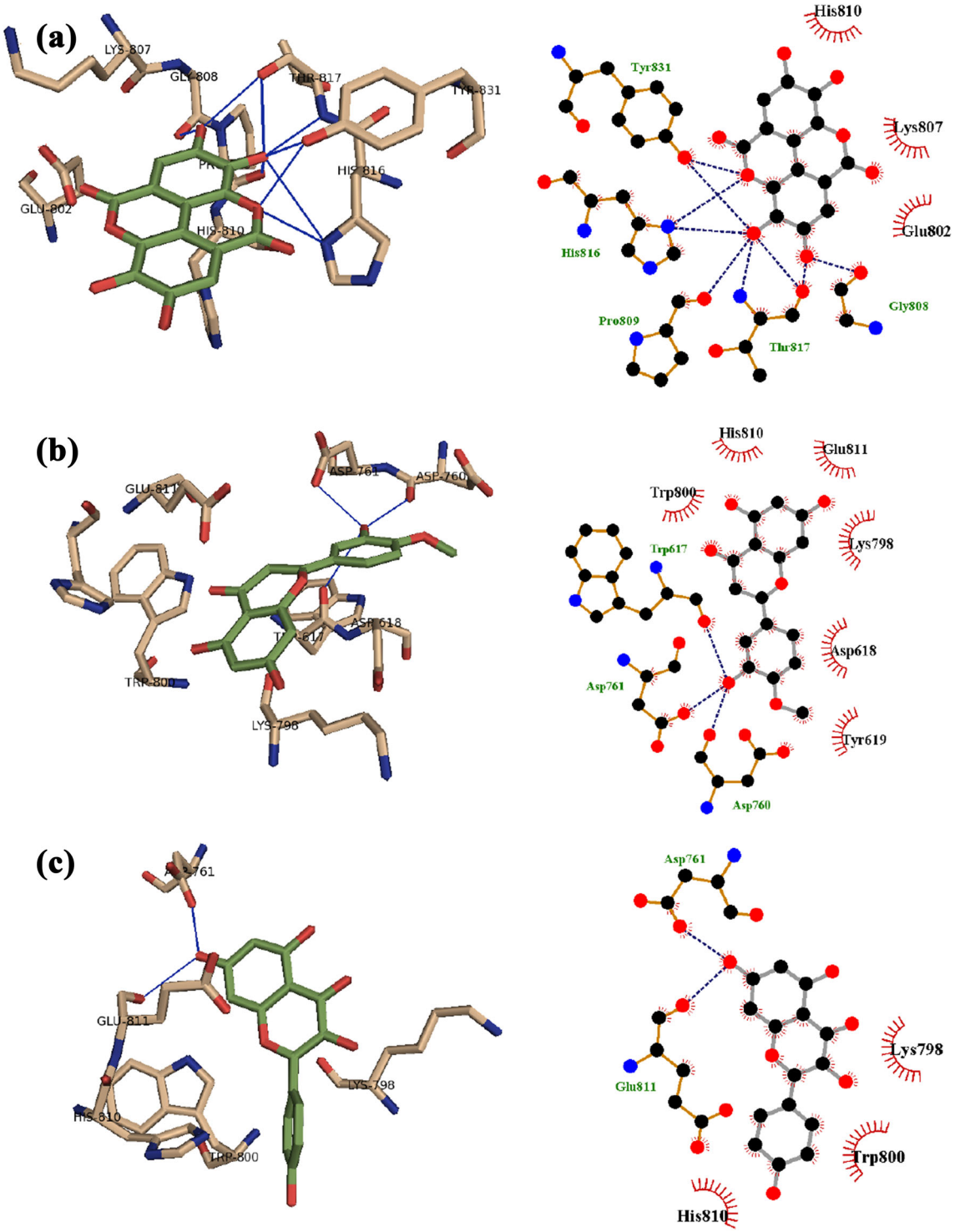

Fig. 2 The docking complex of **a** ellagic acid, **b** hesperetin, and **c** kaempferol (green) with the X-ray structure of 6M71; SARS-CoV-2 RNA-dependent RNA polymerase (left, tint) that showed hydrogen bond (blue) interaction and 2D schematic diagram of the interaction (right)

study, artepillin C showed H-bond interaction with Cys145, Arg188, Thr190, and Gln192, while amino acid residues His41, Gly143, and Arg188 are positioned at distance of H-bond with ellagic acid (Fig. 3). In addition, hesperetin interacts with Gly143 by H-bond, while amino acid residues Tyr54, Leu141, Ser144, Asp 187, and Gln189 are positioned at distance of H-bond with kaempferol, and also quercetin makes H-bond with Tyr54, Leu141, Ser144, His163, and Gln189. Furthermore, the aromatic ring system of artepillin C, ellagic acid, hesperetin, kaempferol, and quercetin makes

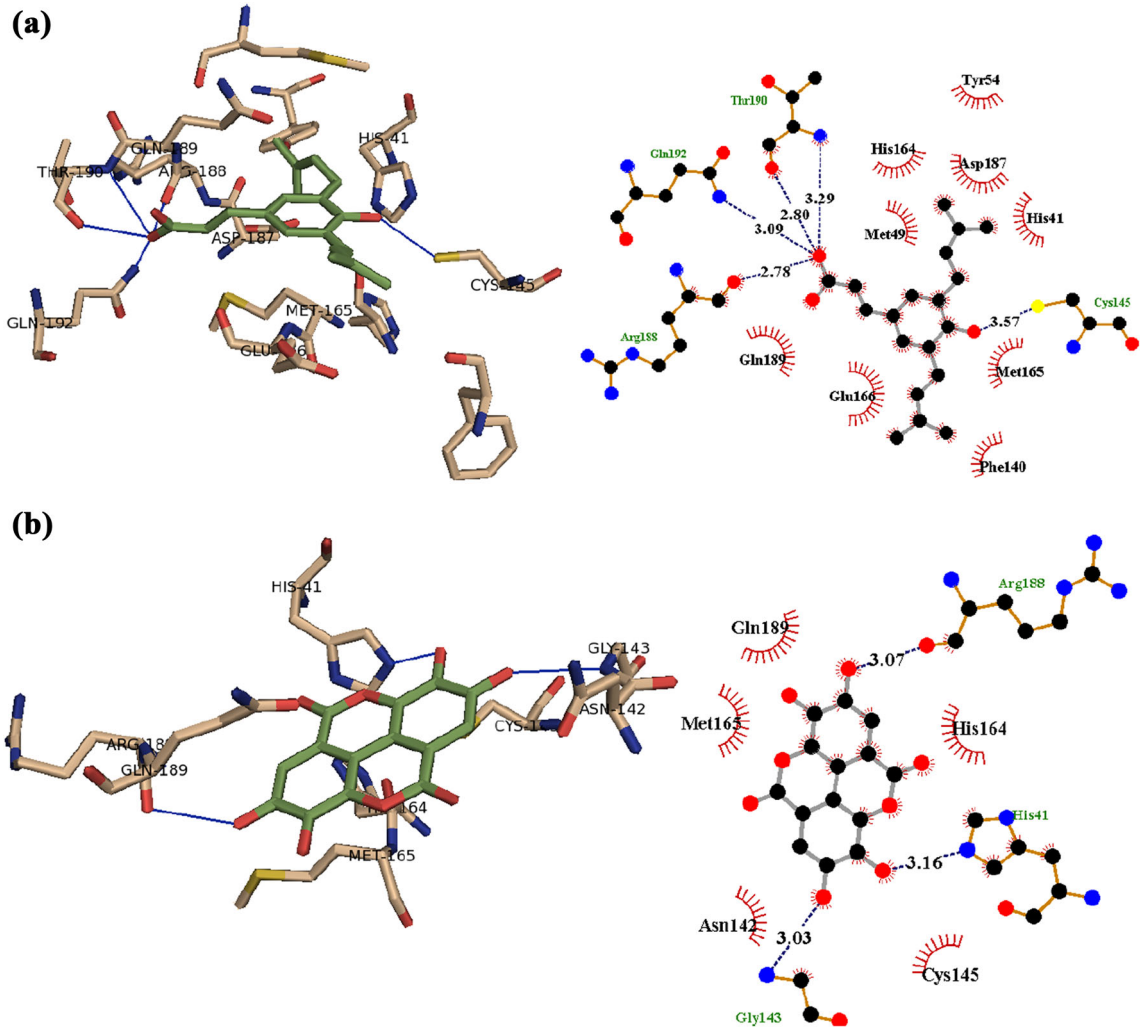

Fig. 3 The docking complex of **a** artepillin C and **b** ellagic acid (green) with the X-ray structure of 6LU7; SARS-CoV-2 main protease (M^{pro}) (left, tint) that showed hydrogen bond (blue) interaction and 2D schematic diagram of the interaction (right)

π-ion hydrophobic interaction with either Met165 or Glu166 (Fig. 4). Taken together we propose the indicated flavonoids as potential inhibitors of the main protease of COVID-19, thus limiting viral maturation.

In line with our finding, promising candidates identified in our study like *p*-coumaric acid, ellagic acid, kaempferol, and quercetin were previously found to have potential antiviral activity against the common cold human rhinovirus which is RNA virus like SARS-CoV-2; surprisingly the mentioned bioactive compounds were suggested in the same study to block or reduce the viral entry into the cells to protect the cells from the virus cytopathic effects and subside virus replication (Kwon et al. 2019), supporting our virtual screening. Moreover, quercetin and its derivatives were previously confirmed to inhibit the SARS-CoV proteases of other coronaviruses including SARS-CoV proteases (3CLpro and PLpro) which share 97% homology to COVID-19 main protease (Bafna et al. 2020) as well as the Middle Eastern respiratory syndrome coronavirus (MERS-CoV) 3CLpro protease (Nguyen et al. 2012). Quercetin was also able to inhibit both enzymes in vitro in micromolar doses (Park et al. 2017); in general SARS-CoV and MERS-CoV share 82.45 and 69.58 percentage identity of their genome to SARS-CoV-2 (Kaur et al. 2020). The existence of this mixture of phytomedicines in bee products create a broad spectrum anti-COVID-19 cocktail that targets more than one crucial enzyme of the virus. Aside from the two enzymes we docked in our sample, other studies investigated the binding affinity of bee phytochemicals, especially propolis from various geographical origins, against other COVID-19 targets through virtual screening (Khalifa et al. 2020a; Ibrahim et al. 2020; Khalifa et al. 2020b; Khayrani et al. 2021; Güler et al. 2020). Taken all together, from our study and other studies, we spot the light on the protective and preventive role of honeybee products against COVID-19.

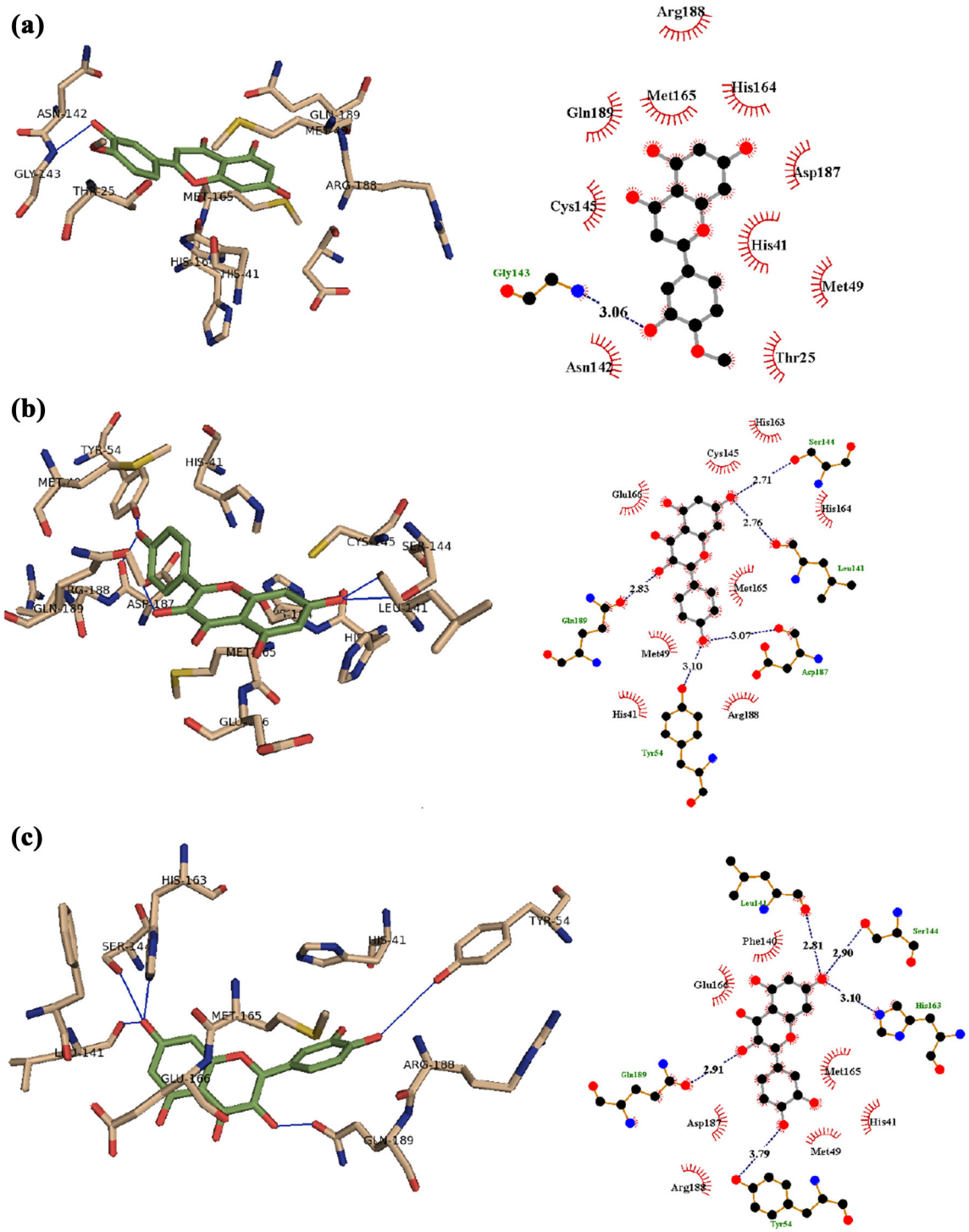

Fig. 4 The docking complex of **a** hesperetin, **b** kaempferol, and **c** quercetin (green) with the X-ray structure of 6LU7; SARS-CoV-2 main protease (M^{pro}) (left, tint) that showed hydrogen bond (blue) interaction and 2D schematic diagram of the interaction (right)

Conclusions

Molecular docking of honeybee products' set of bioactive compounds against unique COVID-19 targets, including Mpro and RdRb enzymes, has distinguished promising compounds of natural origin with deep binding to the respective COVID-19 targets. *P*-coumaric acid, ellagic acid, kaempferol, and quercetin are the most promising compounds on COVID-19 active sites (RdRb and Mpro). These bioactive compounds were also found to have potential antiviral activity against the common cold human rhinovirus which is RNA virus like SARS-CoV-2. In summary and based on our theoretical

studies supported by previous in vitro confirmatory studies, we recommend further in vivo investigations to assess the predicted affinity of the selected compounds against the novel coronavirus target enzymes.

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Availability of data and materials All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate No human or animal specimens were used in this work.

Consent for publication Not applicable

Competing interest The authors declare no competing interests.

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