In silico screening of potent bioactive compounds from honey bee products against *COVID-19* target enzymes

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Abstract

From the early days of the COVID-19 pandemic, side by side to immense investigates to design specific drugs or to develop a potential vaccine for the novel coronavirus. Myriads of FDA approved drugs are massively repurposed for COVID-19 treatment based on molecular docking of selected protein targets that play vital for the replication cycle of the virus. Honey bee products are well known of their nutritional values and medicinal effects. Antimicrobial activity of bee products and natural honey have been documented in several clinical studies and was considered a good alternative for antiviral medications to treat some viral infections. Bee products contain bioactive compounds in the form of a collection of phenolic acids, flavonoids and terpenes of natural origin. 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 2019-nCoV coronavirus. Of these compounds, *p*-coumaric acid, ellagic acid, kaemferol and quercetin has the strongest interaction with the 2019-nCoV target enzymes, and they may be considered as an effective 2019-nCoV inhibitors.

Key words: COVID-19, Honey Bee products, Phenolic compounds, Molecular docking, Drug repurposing, Natural products.

Introduction

Owing to increased global travel and rapid urbanization, viruses are responsible for a variety of human pathologies. In December 2019, several cases of pneumonia of unknown cause were detected in Wuhan, province of Hubei in China. Most patients shared similar symptoms of dry cough, fever, and fatigue, then they developed into dyspnea quickly, ending up with acute respiratory distress syndrome (ARDS) (Chen et al. 2020, Chan et al. 2020, Zhu et al. 2020, Huang et al. 2020, Zhou et al. 2020). By whole-genome sequencing of samples obtained from lower respiratory tract of the patients, a new coronavirus was detected, further investigations revealed that the novel corona virus is different from severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) coronavirus (Zhu et al. 2020). On February 11, 2020, World Health Organization (WHO) named it coronavirus disease-19 (COVID-19) officially, then declared it a pandemic on March 12, 2020 (World Health Organization 2020).

As of June 06, 2020, the cumulative number of cases diagnosed with COVID-19 in the world was more than 7 million, while the cumulative number of cured cases was more than 3,4 million whereas more than 400,000 cases died (2020b). As a direct effect of the outbreak of COVID-19 , 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, research groups in different universities all over the world are racing to develop effective drugs or potential vaccines for COVI-19. Internationally by June 2020, there are over 159 vaccine candidates (Sharpe et al. 2020, Thanh Le et al. 2020) and more than 300 potential therapies for COVID-19 disease in various stages of preclinical or clinical research (Pooladanda et al. 2020, Hachfi and Ben Lasfar 2020, 2020a, Mullard 2020).

As a fast track to save time needed for safety and approval studies, researchers started to massively repurpose already FDA approved drugs for Covid19 treatment (Kandeel and Al-Nazawi 2020, Harrison 2020). Computational based techniques like molecular modeling and virtual screening represent magic tools to 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).

Based on their crucial role in the life cycle of SARS CoV2 , COVID -19 RNA-dependent RNA polymerase (RdRp) (Gao et al. 2020) and the main protease (Mpro) (Jin et al. 2020) have been extensively docked to design or distinguish effective drugs for COVID-19. Bioactive compounds from 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 product are free from toxic or side effects (Mani et al. 2020, Sayed et al. 2020, Gurung et al. 2020). Of the natural products that recently acquired increasing prophylactic importance to combat viral infections in general and COVID-19 in particular are honey bee products.

Honey bees are the "Golden insects" that produce honey and other vital honeybee products. Their products have a long history in medicine. All cultures have traditions of folk medicine which include the use of honey bee products, i.e. honey, bee pollen, propolis, royal jelly, beeswax, and bee venom. It was found that these products display anti-inflammatory, anti-bacterial , anti-fungal, anti-viral, antioxidant activities and neuroprotection (Pasupuleti et al. 2017, El-Seedi et al. 2020). Recently, honey has been proposed as a potential compatible antiseptic prophylaxis to help protect against the COVID-19 based on biocidal effect of

97   hydrogen peroxide that produced in most traditional honeys (Al Naggar et al. 2020, in press).

98   However, the potential bioactive compounds derived from honey and other bee products are not

99   identified yet and deserve more attention.

100   Therefore, the aim of the present study is to perform deep virtual screening via molecular

101   docking to test binding affinity of various selected bioactive compounds such as terpenes and

102   flavonoids of honey and propolis as inhibitors against COVID-19 essential enzymes: RNA-

103   dependent RNA polymerase and the main protease.

104   **Docking methodology**

105   The crystal structure of COVID -19 RNA-dependent RNA polymerase (RdRp) (PDB

106   code: 6M71) (Gao et al. 2020) and the main protease (M^{pro}) (PDB code: 6LU7) (Jin et al. 2020)

107   were retrieved from Protein Data Bank. This study was carried out on 14 compounds (Fig. 1)

108   from honey and propolis into the receptor active site using AutoDock Vina (Trott and Olson

109   2010). Ligand structures were drawn into Marvin Sketch V19.12 (2020c) and the most

110   energetically favored conformer was exported as (*.pdb) file format. AutoDockTools package

111   (Morris et al. 2009) was used to assign Gasteiger atomic partial charges and all the rotatable

112   bonds in ligands were set to be flexible. For receptor preparation, all water molecules were

113   removed, the co-crystalized ligand was removed, Gasteiger atomic partial charges were assigned

114   and all receptors and ligands were converted to the PDBQT format using AutoDockTools

115   package for docking process. In the AutoDock Vina configuration files, the parameter num

116   modes was set to 10 and exhaustiveness to 14. The grid boxes of center (x= 118.23, y= 103.32

117   and z= 118.37) with size (x=17, y=25, z=17) for the RNA-dependent RNA polymerase and

118   center (x= -10.71, y= 12.41 and z= 68.83) with size (x=16, y=18, z=16) for the main protease

119   were used to define the active site. AutoDock Vina was executed. Pymol (2020d) was used for

120 3D visualization and the 2D schematic presentation was generated using LigPlot+ V1.4.5

121 (Laskowski and Swindells 2011).

Results and discussion

123   Honey bee products contain minor amounts of flavonoids, phenols, phenolic acids,

124 carotenoids and terpenes **(Fig. 1).** These phenolic compounds and terpenes found to possess

125 variable medicinal effects including wound healing, antioxidant, antimicrobial, antiviral, anti-

126 inflammatory, cardioprotective, and neuroprotective activities (Biesalski et al. 2009; Küçük et al.

127 2007; El-Seedi et al. 2020). Recently many drugs that are designed and clinically implicated for

128 other medicinal aspects have been repurposed for COVID-19 treatment (Kandeel and Al-Nazawi

129 2020, Oliveira et al. 2020). Therefore, honey bee products represent a natural pharmacy that

130 harbor collection of remedies of broad medicinal effects and might be repurposed against

131 COVID-19.

132   Bioinformatics is one of the most important and innovative approaches to design new

133 drugs (Li *et al.,* 2020). Due to the high cost of clinical and laboratory trials, the time consuming

134 and the possibility of error, different bioinformatics techniques are nowadays used in the design

135 of new drugs (Shaghaghi, 2020). In the current study, computational docking was implemented

136 to predict the binding mode of 14 compounds from honey and propolis with two different targets

137 from COVID-19; RNA-dependent RNA polymerase (RdRp) (PDB code: 6M71) and the main

138 protease (M^{pro}) (PDB code: 6LU7). We revealed that the bioactive compounds; ellagic acid,

139 hesperetin, and kaempferol are the most promising compounds on COVID-19 RdRp while

140 artepillin C, ellagic acid, hesperetin, kaempferol and quercetin were the most active on the main

141 protease (Mpro). The binding scores for each compound into the two targets are shown in **Table**

142 **1.** The binding mode for ellagic acid to COVID-19 RdRb site was attributed to H-bond

143 interaction with Gly808, pro809, His816, Thr817 and Tyr 831, while amino acid residues

144 Trp617, Asp760 and Asp761 are positioned at distance of H-bond with hesperetin, and also

145 kaempferol interacts with Glu811 and Asp761 by H-bond. Furthermore, the aromatic ring system

146 of ellagic acid, hesperetin and kaempferol make π-ion hydrophobic interaction with Lys798 **(Fig.**

147 **2).** We spot the light on the high affinity bioactive compounds like phenolic and flavonoids of

148 honey as potent inhibitors of viral replication.

149 From the docking of all identified compounds into the active site of SARS-CoV-2 main

150 protease (M^{pro}) in the current study, artepillin C showed H-bond interaction with Cys145,

151 Arg188, Thr190 and Gln192, while amino acid residues His41, Gly143 and Arg188 are

152 positioned at distance of   H-bond with ellagic acid **(Fig. 3).** In addition, hesperetin interacts

153 with Gly143 by H-bond while amino acid residues Tyr54, Leu141, Ser144, Asp 187 and Gln189

154 are positioned at distance of H-bond with kaempferol, and also quercetin makes H-bond with

155 Tyr54, Leu141, Ser144, His163, and Gln189. Furthermore, the aromatic ring system of artepillin

156 C, ellagic acid, hesperetin, kaempferol and quercetin make π-ion hydrophobic interaction with

157 either Met165 or Glu166 **(Fig. 4).** Taken together we propose phenolic acids and flavonoids from

158 honey bee products as potential inhibitor of the main protease of SARS-CoV-2 (COVID-19).

159 In the same context, our promising candidates like *p*-coumaric acid, ellagic acid,

160 kaemferol and quercetin were previously found to have potential antiviral activity against the

161 common cold human rhinovirus which is RNA virus like SARS-CoV2. Surprisingly the

162 mentioned bioactive compounds were suggested in the same study to block or reduce the viral

163 entry into the cells to protect the cells from the virus cytopathic effects and subside virus

164 replication (Kwon et al. 2019), supporting our virtual screening. Moreover, quercetin and its

165 derivatives were previously confirmed to inhibit the SARS-CoV proteases (Nguyen et al. 2012).

166 and other coronaviruses including SARS-CoV proteases (3CLpro and PLpro) as well as the

167 Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) 3CLpro protease. Quercetin

168 was also able to inhibit both enzymes *in vitro* in micromolar doses (Park et al. 2017).

169 **Conclusions**

170   Theoretical studies through molecular docking of collection of bioactive compounds of

171 honey bee products against selected targets of COVID-19 including Mpro and RdRb enzymes of

172 the 2019-nCoV virus have distinguished promising bioactive compounds of natural origin that

173 exhibited profound binding to the respective COVID- 19 targets. Among the investigated

174 bioactive compounds derived from honey and propolis, *p*-coumaric acid, ellagic acid, kaemferol

175 and quercetin are the most promising compounds on 2019-nCoV active sites (RdRb and Mpro)

176 These potent bioactive compounds were also found to have potential antiviral activity against the

177 common cold human rhinovirus which is RNA virus like SARS-CoV2. Taken all together and

178 based on our theoretical studies supported by previous *in vitro* confirmatory studies, we

179 recommend further *in vivo* investigations to assess the predicted affinity of the selected

180 compounds against the novel coronavirus (COVID-19) target enzymes.

181 **Acknowledgments**

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308　**Figure legends**

309　**Figure 1**. Chemical structure of important bioactive compounds in honey, propolis, and royal
310　jelly.

311　**Figure 2.** The docking complex of (a) **Ellagic acid**, (b) **Hesperetin** and (c) **Kaempferol** (green)
312　with the X-ray structure of **6M71;** SARS-CoV-2 RNA-dependent RNA polymerase (left, Tint)
313　that showed hydrogen bond (blue) interaction and 2D schematic diagram of the interaction
314　(right).

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

318　**Figure 4.** The docking complex of (a) **Hesperetin** (b) **Kaempferol** and (c) **Quercetin** (green)
319　with the X-ray structure of **6LU7;** SARS-CoV-2 main protease (M^{pro}) (left, Tint) that showed
320　hydrogen bond (blue) interaction and 2D schematic diagram of the interaction (right).

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340 **Fig.1**
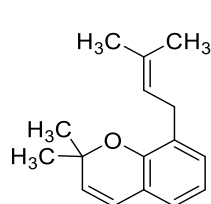
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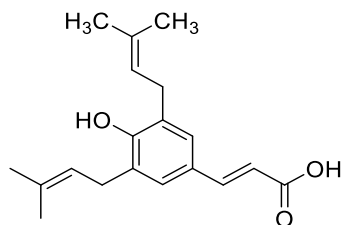
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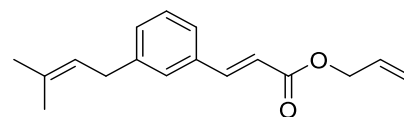
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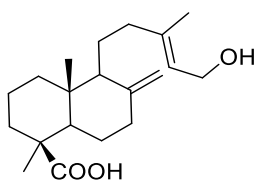
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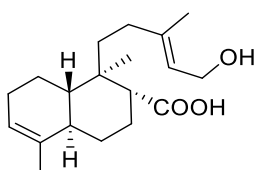
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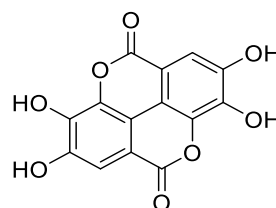
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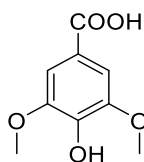
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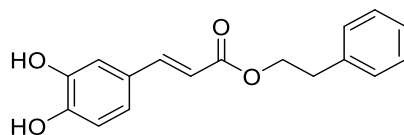
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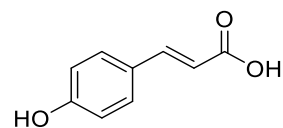
***p*-Coumaric acid**
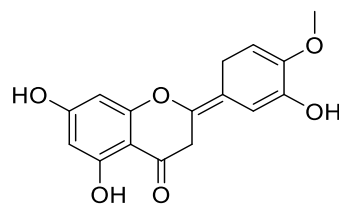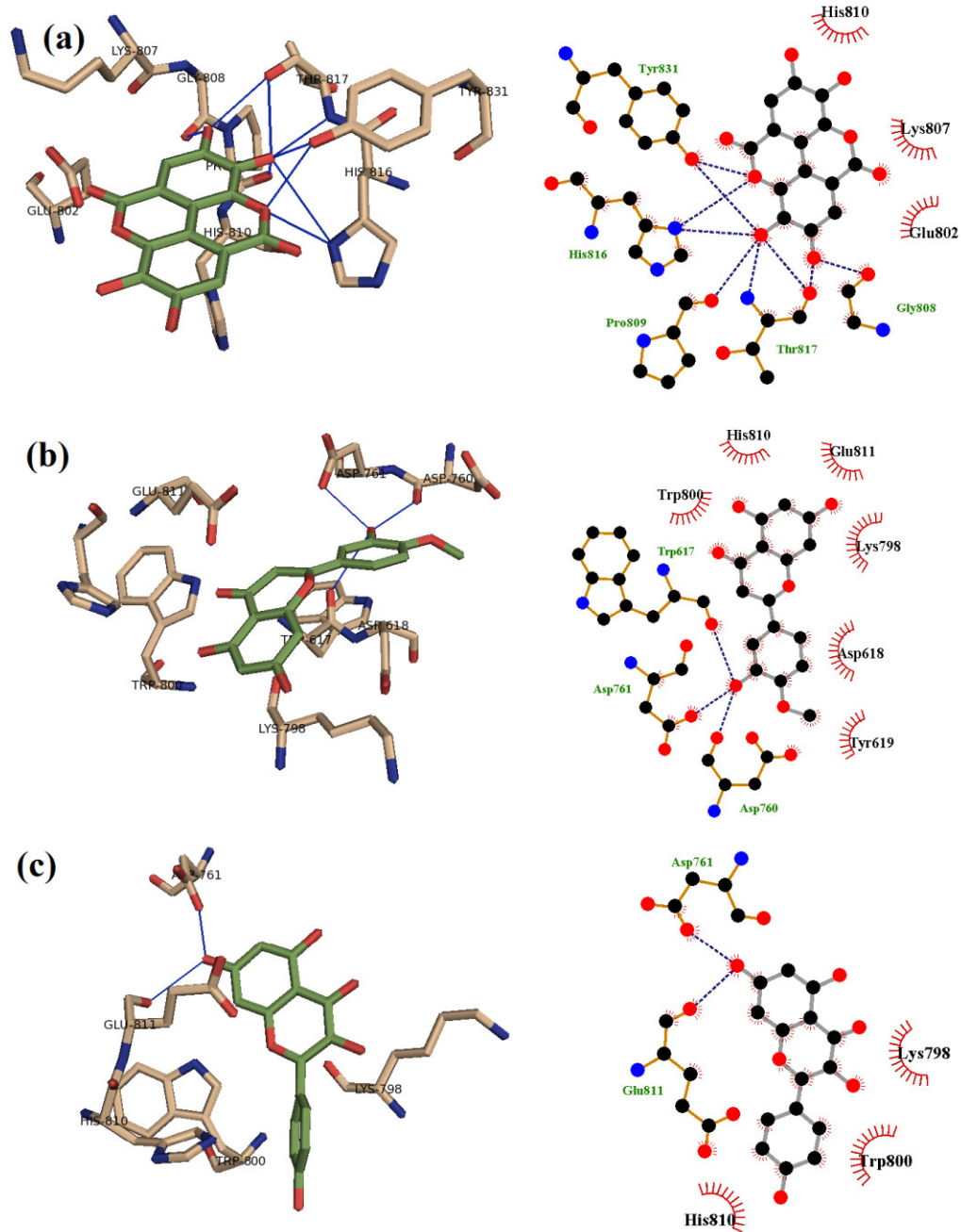
Hesperetin
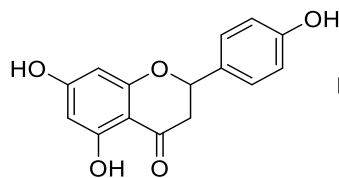
Naringenin
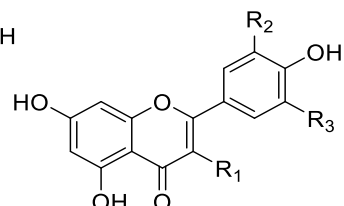
	R$_1$	R$_2$	R$_3$
Kaempferol	OH	H	H
Quercetin	OH	H	OH
Chrysin	H	OCH$_3$	OCH$_3$

341

342

343

344   **Fig.2**

345

374   **Fig.3**

375

376

Fig.4

(a)

(b)

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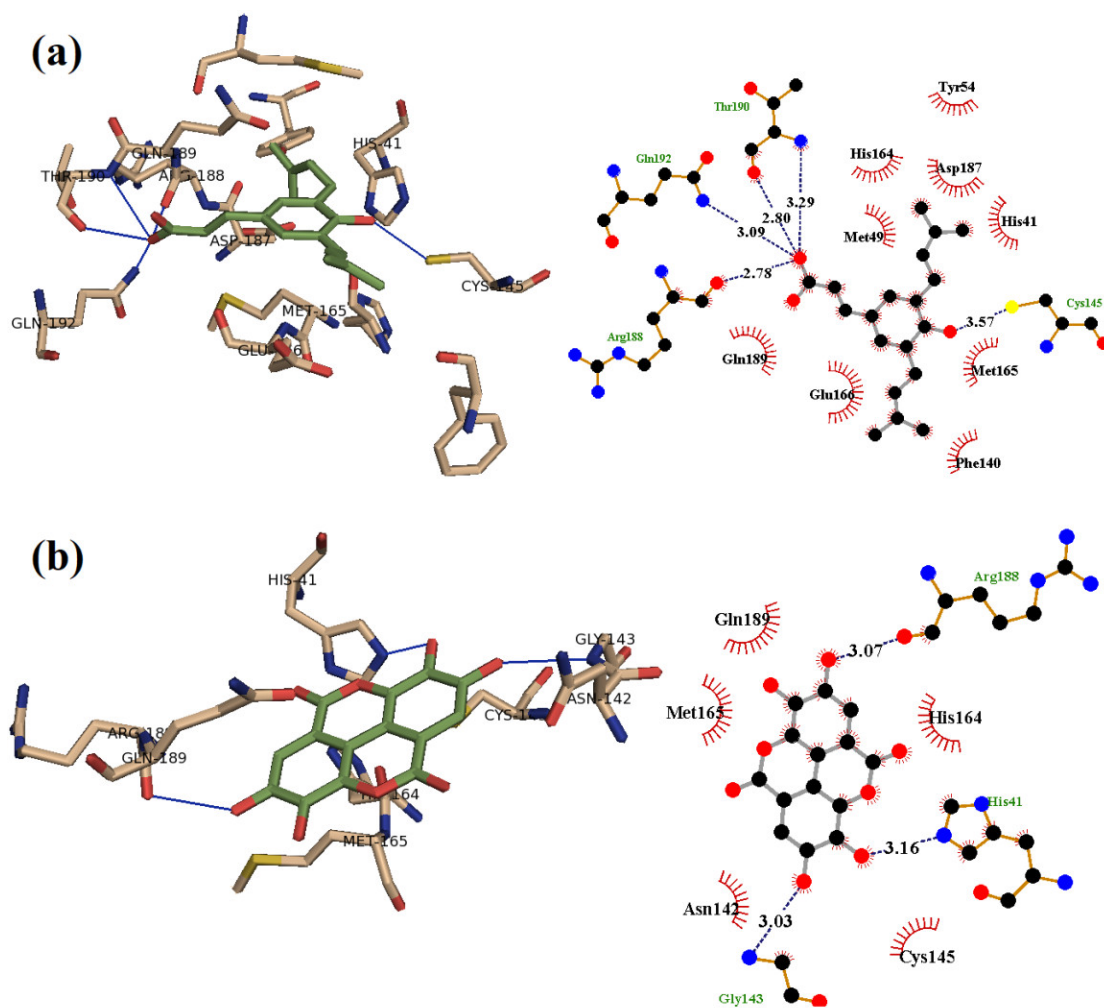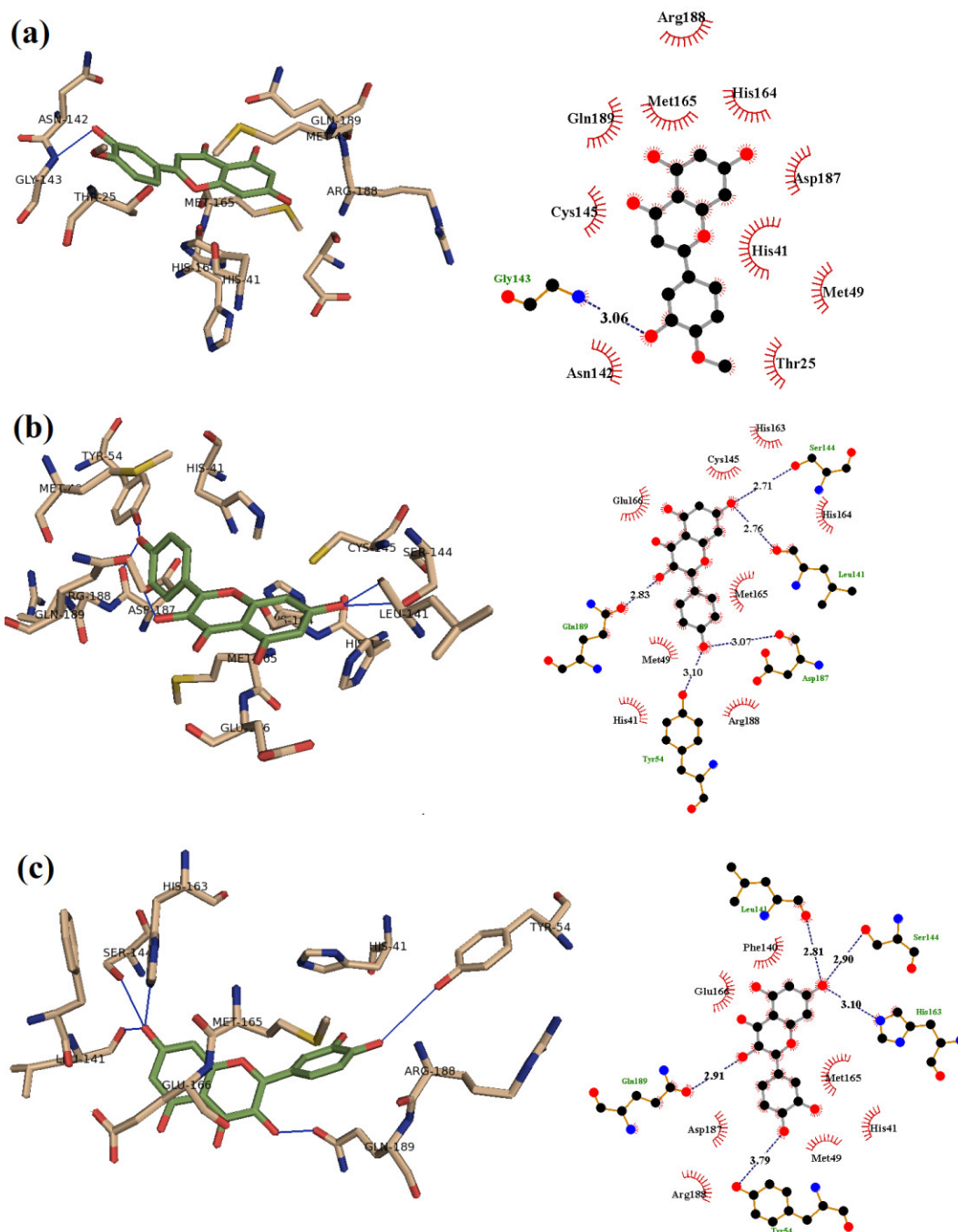
Table 1. The binding scores for each compound into the two target enzymes of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) and the main protease (M^{pro})

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