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# Natural phenolic compounds from *Satureja* L. as inhibitors of COVID-19 protease (Mpro): Computational investigations

Faika Başoğlu-Ünal[a,*], Selin Tufan[b,*], Nur Tan[b]

[a] *European University of Lefke, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Lefke, Northern Cyprus, TR-10 Mersin, Turkey*
[b] *Istanbul University, Faculty of Pharmacy, Department of Pharmacognosy, Beyazıt, Istanbul, Turkey*

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## ABSTRACT

Coronavirus (SARS-CoV-2) causes a new type of severe acute respiratory syndrome that first appeared in Wuhan in December 2019; it is a very fast-spreading and deadly virus. Therefore, urgent discovery or development of "lead compounds" against this virus is crucial. Natural compounds have always served as a great source, especially the use of traditional medicinal plants, in modern drug discovery. This study aimed to investigate the SARS-CoV-2 protease inhibition potential of the phenolic compounds in the genus *Satureja* L. The affinities of the chosen natural products were understood using molecular docking simulation against the SARS-CoV-2 protease enzyme. The study proved that three different phenolic compounds namely 5,6-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-7,8-dimethoxy-4H-chromen-4-one, 2-(3,4-dimethoxyphenyl)-5,6-dihydroxy-7,8-dimethoxy-4H-chromen-4-one, and 5,6-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-7,8-dimethoxy-4H-chromen-4-one obtained from *Satureja* L. taxa were found as promising against SARS-CoV-2 main protease.

## 1. Introduction

Coronavirus, named after the crown-like spikes on their surface, is defined as a family of enveloped, single-stranded, and positive-stranded RNA viruses containing helical nucleocapsids (Coronaviridiae family, Nidovirales line). It has been known that they cause acute and chronic respiratory, enteric and central nervous system diseases both in animals and humans (Orhan and Deniz, 2020; Weiss and Navas-Martin, 2005). As of December 21, there are 275,839,211 COVID-19 cases, and 5,377,934 deaths from 219 different countries are confirmed, and the numbers, unfortunately, keep rising (WHO, 2020).

It is important to understand the virulence mechanisms of SARS-CoV-2 in order to design an effective drug molecule. Therefore, many studies are being carried out to understand the mechanisms; since the SARS-CoV-2 pandemic begins. As a result of the studies, several points exhibit which receptor/receptors are crucial for antiviral activity. Human ACE-2 can be recognized easier than the former virus by SARS-CoV-2; thus, the transmission capacity of human-to-human is expanding. On the other hand, the main protease determined as the PDB 6LU7 protein structure of SARS-CoV-2 is another significant receptor that plays a role in viral gene replication and expression (Rauf et al., 2021).

Concurrently, another property of the SARS-CoV-2 virus is that it possesses "genomic proofreading" in extremely few viruses. Thus, the virus doesn't become either weak or inactive by repairing the mutated RNA. That is why the old antiviral drugs used for different viruses, such as ribavirin, have no effect (Robson et al., 2020). All in all, novel drugs are required to treat the disease.

Mpro in CoV possesses a key role during viral proteolytic maturation; as a result, it might be useful as a marker or potential target protein needed to reduce infection spread by inhibiting the viral polyprotein cleavage (Wax and Christian, 2020). As a result, Mpro protease in COVID-19 serves as a potential drug target for the treatment of COVID-19 infection. But SARS-CoV-2 has mutated

* Corresponding author:
E-mail address: fabasoglu@eul.edu.tr (F. Başoğlu-Ünal)
Selin.tufan@istanbul.edu.tr (S. Tufan)
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many times; however, the main protease that plays a crucial role in viral gene expression and replication hasn't mutated yet. Therefore, the main protease, Mpro, is chosen to propose a probable natural anti-coronavirus product (Rajagopal et al., 2020; Rauf et al., 2021).

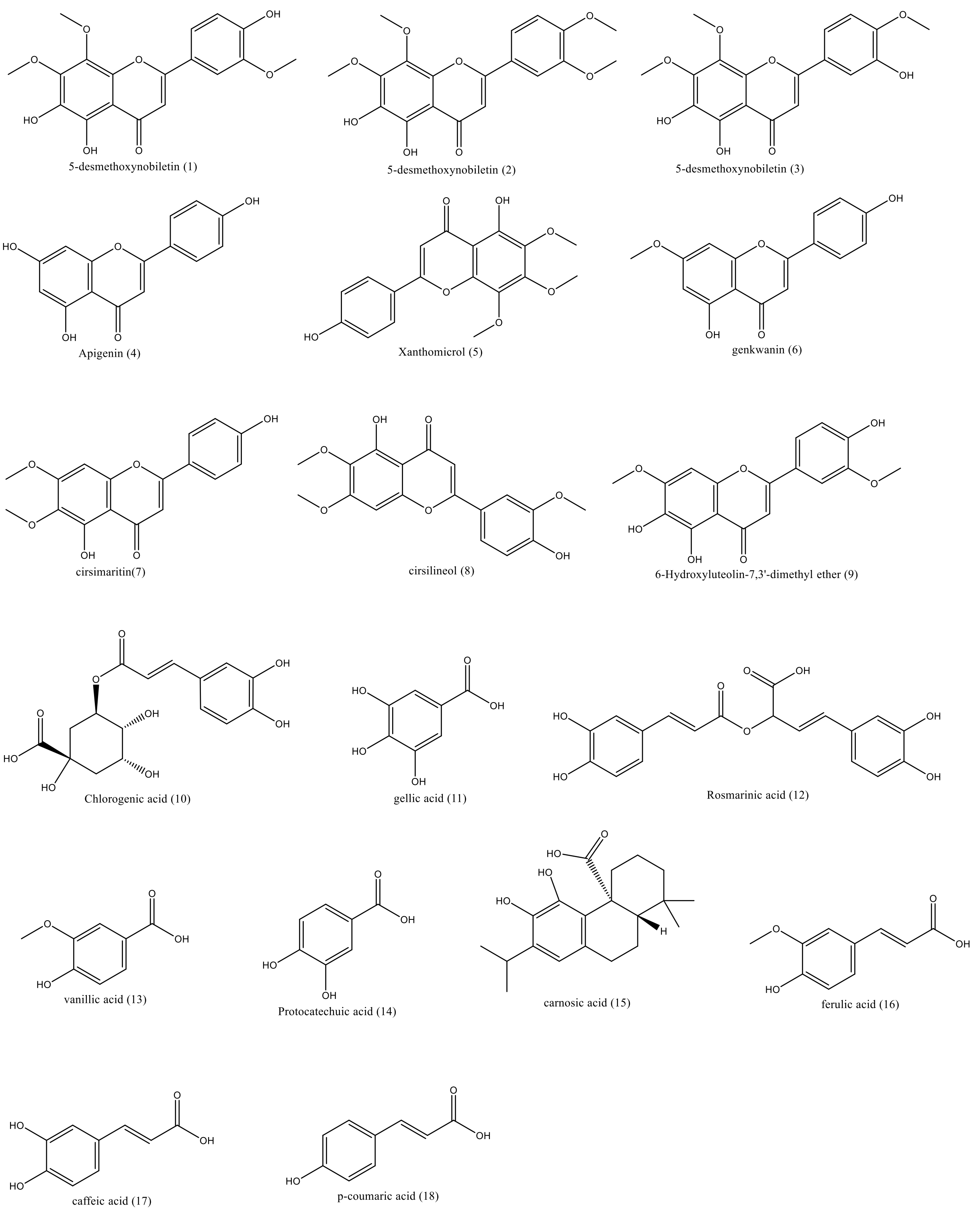


**Figure 1.** Natural phenolic compounds from *Satureja* L.

Under the given circumstances and urgent need to treat COVID-19 natural products, especially medicinal plants, have gone under investigation by different research groups (Bekut et al., 2018; Orhan and Deniz, 2020). The selection of medicinal plants is a deliberate process. Plant material itself or extracts obtained from medicinal plants have been safely used by various cultures worldwide for years (Barnes et al., 2007; Heinrich, 2000; Momtaz and Abdollahi, 2010; Mukhtar et al., 2008). The efficacy, availability, and affordability of medicinal plants have always been the key point in folk medicine. Also, the use of these medicinal plants for years eliminates most of the question marks against their safety as well as their use as food (Barnes et al., 2007). Along with direct use of plant material or extracts, approximately 25% of the synthetic active compounds in current treatment are derived from natural compounds (Momtaz and Abdollahi, 2010).

Lamiaceae is one of the most important and large plant families, which is widespread. Due to their chemical constituent profile is widely used in both pharmaceutical and food industries (Bekut et al., 2018; Raja, 2012). Moreover, taxa in the Lamiaceae family have drawn attention due to their antiretroviral properties (Abad et al., 1999; Bekut et al., 2018). Newly published studies exhibited that the extracts from Lamiaceae such as *Mentha piperita*, *Mosla* sp., *Ocimum kilim,* and *scharicum* possessed antiviral effects against coronavirus. Additionally, the extracts were reported to have high inhibitory activities on ACE2 receptors and COVID Mpro (Jalali et al., 2021).

The genus *Satureja* L. belongs to the Lamiaceae and contains terpenoids and phenolic compounds as major compounds (Davis, 1982; Tepe and Cilkiz, 2016). Especially infusions and decoctions, which are rich in phenolic compounds, prepared from the *Satureja* L. taxa, have traditionally been used against cold, flu, wound antiseptic, cough in Turkey (Chorianopoulos et al., 2006; Emre et al., 2020; Giweli et al., 2012; Güllüce et al., 2003; Ilhan et al., 2020; Ozcelik et al., 2011), a muscle pain reliever, tonic, and carminative in the treatment of stomach and intestinal ailments such as cramps, nausea, indigestion, and diarrhea (Zargari, 1990). Along with ethnobotanical uses, researches revealed that *Satureja* L. taxa have antimicrobial, antioxidant, antiviral, anti-diabetes, anti-hyperlipidemic, reproductive stimulating, expectorant, and vasodilator activities (Abdollahi et al., 2003; Amanlou et al., 2005; Momtaz and Abdollahi, 2010; Sahin et al., 2003; Tepe and Cilkiz, 2016; Vosough-Ghanbari et al., 2010).

**Table 1.** Natural phenolic compounds docking results based on binding energy calculations and their ADMET properties

| Compound name | Docking score[a] | MW[b] | QlogPo/w[c] | Human oral absorption %[d] | PSA[e] | HBD[f] | HBA[g] | Lipinski rule of five |
|---|---|---|---|---|---|---|---|---|
| NativeLigand (RZS) | -5.421 | 147.18 | 1.872 | 93 | 48.57 | 1 | 3 | 0 |
| 1 | -7.190 | 360.32 | 2.004 | 79 | 117.30 | 2 | 6 | 0 |
| 2 | -7.182 | 374.35 | 2.715 | 92 | 103.50 | 1 | 6 | 0 |
| 3 | -6.903 | 360.32 | 1.994 | 79 | 117.30 | 2 | 6 | 0 |
| 4 | -6.803 | 272.26 | 1.603 | 74 | 99.25 | 2 | 4 | 0 |
| 5 | -7.018 | 346.34 | 2.594 | 91 | 95.27 | 1 | 5.5 | 0 |
| 6 | -6.889 | 284.27 | 2.384 | 87 | 84.81 | 1 | 3.75 | 0 |
| 7 | -6.573 | 314.29 | 2.593 | 90 | 91.05 | 1 | 4.5 | 0 |
| 8 | -6.533 | 344.32 | 2.655 | 91 | 98.81 | 1 | 5.25 | 0 |
| 9 | -6.690 | 330.29 | 1.815 | 76 | 113.16 | 2 | 5.25 | 0 |
| 10 | -7.804 | 354.31 | -0.298 | 18 | 180.43 | 6 | 9.65 | 0 |
| 11 | -6.870 | 170.12 | -0.586 | 41 | 115.35 | 4 | 4.25 | 0 |
| 12 | -6.570 | 372.33 | 1.392 | 40 | 165.92 | 5 | 7 | 0 |
| 13 | -5.599 | 168.15 | 1.005 | 66 | 80.25 | 2 | 3.5 | 0 |
| 14 | -4.915 | 154.12 | 0.014 | 53 | 93.92 | 3 | 3.5 | 0 |
| 15 | -5.208 | 332.44 | 3.543 | 89 | 67.22 | 3 | 3.5 | 0 |
| 16 | -4.872 | 194.19 | 1.268 | 66 | 82.41 | 2 | 3.5 | 0 |
| 17 | -4.968 | 180.13 | 0.519 | 54 | 96.08 | 3 | 3.5 | 0 |
| 18 | -8.841 | 164.16 | 1.403 | 67 | 74.65 | 2 | 2.75 | 0 |

[a]Docking score (kcal/mol).
[b]Molecular weight (g/mol) (recommended value ≤ 500)
[c]Logarithm of the octanol/water ratio coefficient of compound (recommended value < 5).
[d]Percentage oral absorption (< 25% weak and > 85% strong).
[e]Polar surface area (Å) (recommended value ≤ 140 Å).
[f]Hydrogen bond donar (recommended value ≤ 5)
[g]Hydrogen bond acceptor (recommended value ≤ 10)

Initially, it is necessary to evaluate the probable inhibitory effects of natural compounds by screening. For this reason, keeping in view the pharmacological activities based on previous literature, 18 natural compounds from *Satureja* L. were selected. ADMET property calculations were also estimated for all selected compounds, and the interactions with the active site (PDB ID: 5R82) were visualized.

In light of the information provided above, phenolic compounds of *Satureja* L. are a great "starting point" in discovering and developing lead compounds against COVID-19. In this research, molecular docking studies were performed on 18 phenolic compounds (Figure 1).

## 2. Materials and methods

### *2.1. Data set*

Chlorogenic acid (1) (Silva et al., 2009; Tepe and Cilkiz, 2016), 5,6-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-7,8-dimethoxy-4H-chromen-4-one (2) (Moghaddam et al., 2007), 2-(3,4-dimethoxyphenyl)-5,6-dihydroxy-7,8-dimethoxy-4H-chromen-4-one (3) (Gohari et al., 2009), 5,6-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-7,8-dimethoxy-4H-chromen-4-one (4) (Gohari et al., 2009), gallic acid (5) (Cetojevic-Simin et al., 2004), apigenin (6) (Cetojevic-Simin et al., 2004), xanthomicrol (7) (Malmir et al., 2012), genkwanin (8) (Skoula et al., 2005), cirsimaritin (9) (Skoula et al., 2005), rosmarinic acid (10) (Cetojevic-Simin et al., 2008), cirsilineol (11) (Skoula et al., 2005), 6-hydroxyluteolin-7,3i-dimethyl ether (12) (Skoula et al., 2005), vanillic acid (13) (Palavra et al., 2011), protocatechuic acid (14) (Palavra et al., 2011), carnosic acid (15) (Kosar, 2003), ferulic acid (16) (Askun et al., 2013; Cetojevic-Simin et al., 2012), caffeic acid (17) (Cetojevic-Simin et al., 2012), and *p*-coumaric acid (18) (Askun et al., 2013; Cetojevic-Simin et al., 2012) were identified previously in *Satureja* L. taxa.

### *2.2. Molecular docking*

The molecular docking studies of 18 phenolic compounds on COVID-19 Mpro (Hall Jr and Ji, 2020) were examined using the Schrödinger program. COVID-19 protease crystal structure was retrieved from protein data bank (PDB ID: 5R82: Resolution 1.31 Å) (Rajagopal et al., 2020; Wax and Christian, 2020). The docking calculations were carried out using the Glide SP (standard precision) module of the Schrödinger Suite (Friesner et al., 2004, 2006; Halgren et al., 2004). The RMSD value between the docked pose and the crystal conformation of the native ligand (6-(ethylamino)pyridine-3-carbonitrile) was found as 1.595 Å.

The ADMET properties of the selected compounds such as molecular weight, HBA, HBD, logPo/w were determined by the QikProp module (Ligprep and Macromodel, 2011) of the Schrodinger suite (Table 1).

## 3. Results and discussion

A docking study was performed on 18 phenolic compounds from *Satureja* L. against SARS-CoV-2 protease (Mpro). Tables 1 and 2 show the docking score and amino acid residues, which form various interactions with the chosen compounds, while Figure 2 shows 2-dimensional ligand-receptor interactions of probable more active compounds. Additionally, their 3-dimensional ligand-receptor interactions are displayed in Figure 3.

In this study, 18 phenolic compounds show hydrogen bond and π- π interaction with many amino acid residues in the active region but active/inactive ranking of the compounds cannot be done precisely based on the energy values obtained as a result of primitive scoring algorithms (Başoğlu et al., 2021). Despite that, pharmacologically active conformations of the ligands and the determination of their binding modes to the receptor can be done successfully. Therefore, the binding affinities of the chosen natural phenolic compounds were determined by analyzing binding conformations and interactions of each compound with the active site of the receptor.

**Table 2.** Receptor interaction with chosen phenolic compounds and RZS into the binding site in the COVID-19 main protease

| Compound name | Receptor amino acids |
|---|---|
| NativeLigand (RZS) | Gln189, His41 |
| 1 | Thr26, Gln189, Gly143 |
| 2 | Thr26, Gly143, His41 |
| 3 | Thr26, Gly143, His164, His41 |
| 4 | Phe140, Glu166, Arg188 |
| 5 | Glu166, Gly143, Cys44 |
| 6 | Thr190 |
| 7 | Arg188 |
| 8 | Thr26, Gly143, Glu189 |
| 9 | Thr26, Gly143, Glu189 |
| 10 | Gly143, Thr190 |
| 11 | Gly143, His41 |
| 12 | Phe140, Glu166 |
| 13 | Gly143, Glu166 |
| 14 | His41, Gly143 |
| 15 | Glu166 |
| 16 | Gly143, Gln189, His41 |
| 17 | Gly143, Gln189, His41 |
| 18 | His41 |

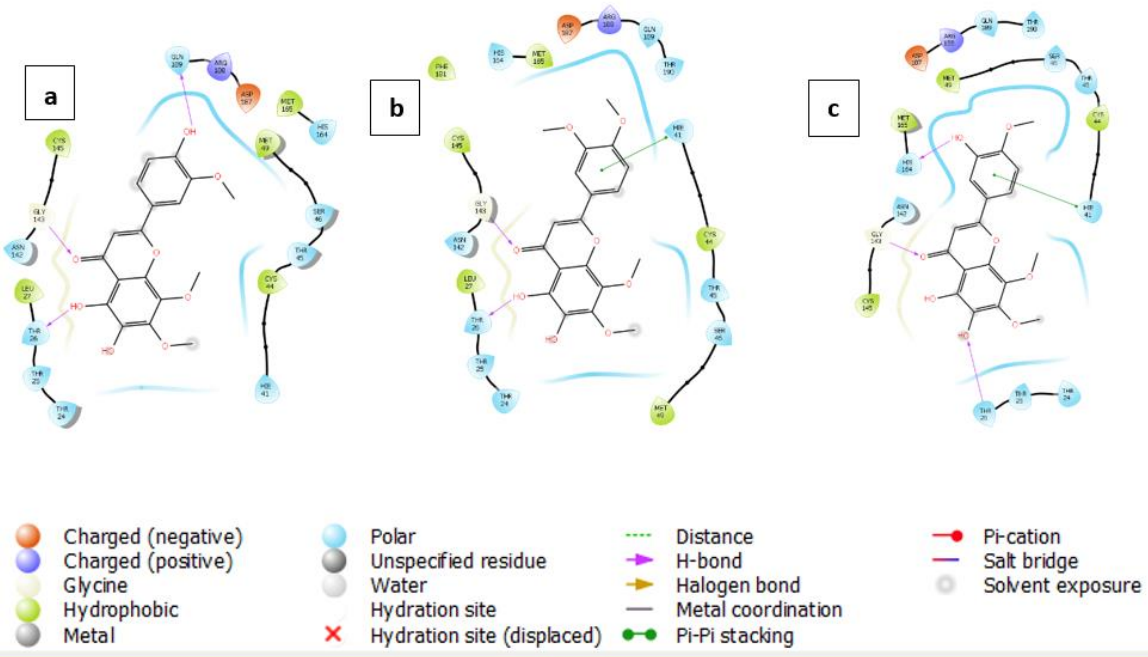


**Figure 2.** 2D representation of docking of compounds: compound 1 (a), compound 2 (b), compound 3 (c) into the binding site of the COVID-19 main protease

Considering the previous *in silico* studies reported in the literature, it is obvious that some amino acid residues such as Gln19, Thr24, Thr25, Thr26, Leu27, His41, Ser46, Met49, Asn119, Asn142, Gly143, His164, Met165, Glu166, Asp187, Arg188, and Gln189, might play a strong role in the inhibitory activity (Rajagopal et al., 2021; Thirumalaisamy et al., 2021).

Compounds 1, 2, 3, 8, and 9 looks similar with minor differences. Considering these differences and their binding poses, -OH at 4$^{th}$ position on phenyl is required for H-bond with Gln189, a critical amino acid residue. The significant H-bond with Gln189 is formed with -OH at the 4$^{th}$ position of the phenyl of compounds 16 and 17.

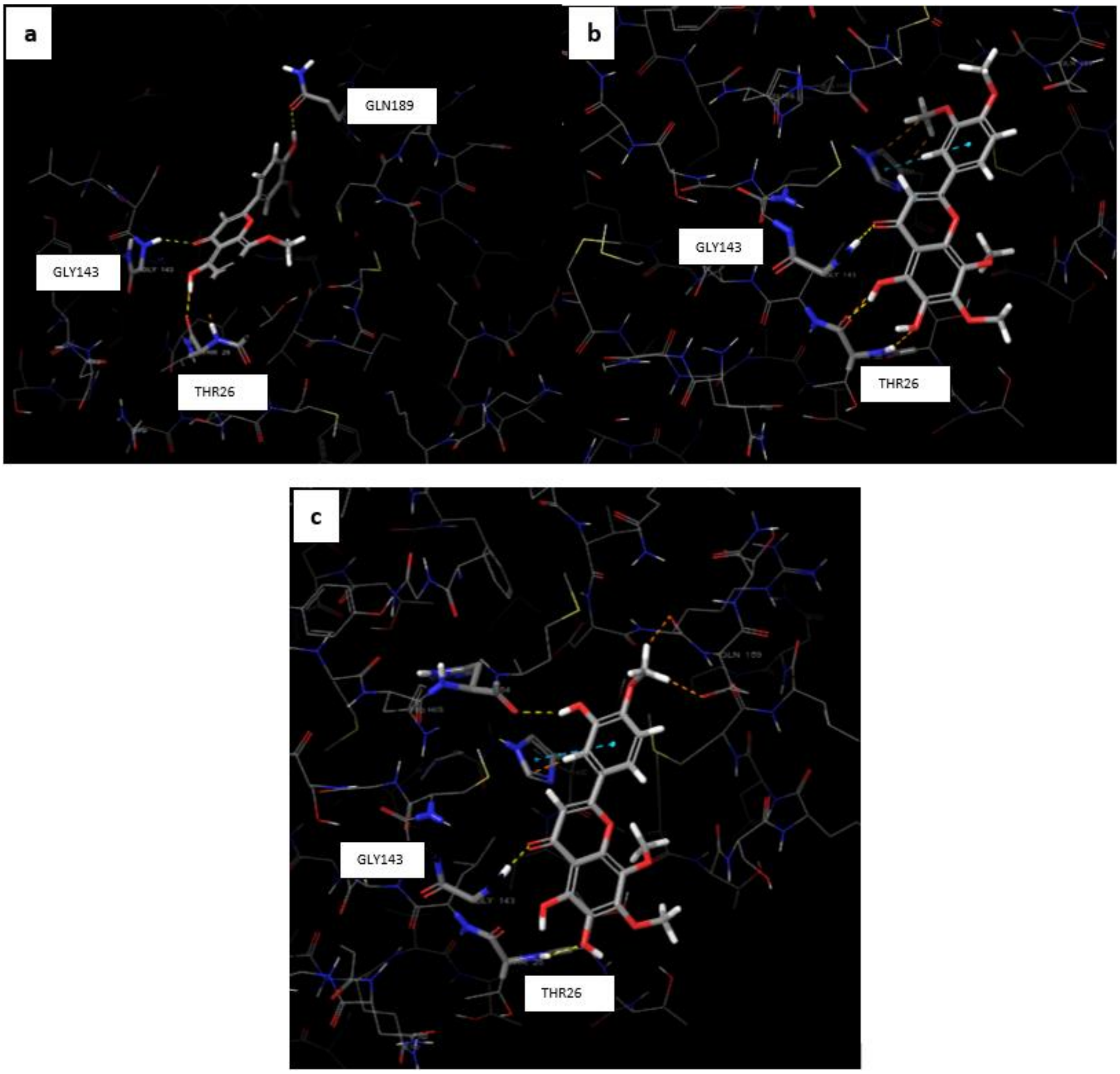


**Figure 3.** 3D representation of docking of compounds: compound 1 (a), compound 2 (b), compound 3 (c) into the binding site of the COVID-19 main protease
(The yellow dash bond indicates H-bond, the blue dash bond illustrates pi-pi interaction.)

Compounds 1, 2, 3, 8, and 9 generate H-bond with Thr26, which is also among one of the crucial amino acid residues against SARS-CoV-2. Flavonoids could be a significant moiety for H-bond generation since these carry hydroxy moiety at either 5$^{th}$ or 6$^{th}$ position. However, compounds 6 and 7 have an H-bond with different amino acid residues, Thr190 and Arg188, respectively. Interestingly, their structures are similar to compounds 1, 2, 3, 8, and 9. Carbonyl group and 5$^{th}$ position -OH of flavonoid are located at 5Å distance from the Gln189, Thr26 amino acid residue due to their positions within the receptor active site. Therefore, no H-bond is formed with these amino acids, which are predicted to be important for activity. The same state is true for compound 18. The only amino acid residue that can form H-bond with -OH at the 4$^{th}$ position of phenyl is His41; therefore, it's important for its activity.

Additionally, an extra pi-pi interaction is observed between compounds 2, 4, 11, 16, 17, and 18's aromatic ring and His41 amino acid residue.

Compounds 1, 2, and 3 generated more hydrophobic interactions with amino acid residues, significant for the inhibition effectiveness. As seen clearly in Figure 3, compound 1 showed hydrophobic interaction with Thr26, compound 2 exhibited hydrophobic interaction with Thr26 and His41, and compound 3 generated 3 hydrophobic interactions with different amino acids residues Arg188, Gle189, and His49. That might be why the docking scores of compounds 1, 2, and 3 are higher than the other chosen phenolic compounds.

Furthermore, chemo-informatic properties were calculated using the QikProp module in Maestro Schrödinger. The compounds' permeability and solubility must be estimated using these evaluations, especially for novel drug discovery, which will be administrated orally. Lipinski's rule of 5 foretells whether compounds have good absorption and permeation. Regarding the rule of 5, for good absorption and permeation properties, the number of hydrogen bond donors, acceptors, molecular weight, and octanol/water coefficients should be within certain limits (Lipinski et al., 1997). The selected 18 phenolic compounds from *Satureja* L. showed acceptable values and obeyed the rule of 5 (Table 1). By considering their logPo/w values, it might be possible that the affinity for the target of protease increased when logPo/w approached two.

Moreover, PSA is another parameter used for the drug's optimization ability to permeate cells. Preferably, from the previous research point, the PSA value should be less than 90 (Başoğlu et al., 2021). But almost all the chosen 18 compounds except compounds 6, 13, 15, and 16 possess higher values than the standard.

## 4. Conclusions

Medicinal plants have always had an important role in modern drug discovery and may also be a pioneer for COVID-19 treatment. As a result of this study, we recommended 3 different natural phenolic compounds found in *Satureja* L. taxa as promising against SARS-CoV-2 main protease inhibitors by evaluating their affinities against SARS-CoV-2 main protease and also ADMET properties. It is anticipated that compounds 1, 2, and 3 might be promising inhibitors of the main protease, and further *in vitro* studies can be conducted based on the preliminary *in silico* study carried out in this work.

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## Conflict of interest

The authors confirm that there are no known conflicts of interest.

## CRediT authorship contribution statement

**Faika Başoğlu-Ünal:** Resources, Conceptualization, Visualization, Formal analysis, Writing-original draft, Investigation, Methodology
**Selin Tufan:** Resources, Conceptualization, Data curation, Writing-original draft, Methodology
**Nur Tan:** Supervision

## ORCID Numbers of the Authors

**F. Başoğlu-Ünal:** 0000-0002-4890-3124
**S. Tufan:** 0000-0002-9173-3423
**N. Tan:** 0000-0001-7958-1917

## Supplementary File

None.

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**Reviewed by:**

Emine ERDAG: Near East University, Nicosia, NORTHERN CYPRUS
Mustafa EMIRIK: Recep Tayyip Erdoğan University, Rize, TURKEY

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