

Evaluation of Peppermint Leaf Flavonoids as SARS-CoV-2 Spike Receptor-Binding Domain Attachment Inhibitors to the Human ACE2 Receptor: A Molecular Docking Study

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Abstract Virtual screening is a computational technique widely used for identifying small molecules which are most likely to bind to a protein target. Here, we performed a molecular docking study to propose potential candidates to prevent the RBD/ACE2 attachment. These candidates are sixteen different flavonoids present in the peppermint leaf. Results showed that Lutetolin 7-O-neohesperidoside is the peppermint flavonoid with a higher binding affinity regarding the RBD/ACE2 complex (about -9.18 Kcal/mol). On the other hand, Sakuranetin presented the lowest affinity (about -6.38 Kcal/mol). Binding affinities of the other peppermint flavonoids ranged from -6.44 Kcal/mol up to -9.05 Kcal/mol. The binding site surface analysis showed pocket-like regions on the RBD/ACE2 complex that yield several interactions (mostly hydrogen bonds) between the flavonoid and the amino acid residues of the proteins. This study can open channels for the understanding of the roles of flavonoids against COVID-19 infection.

Keywords

Coronavirus, Sars-CoV-2, Peppermint Flavonoids, RBD/ACE2 Inhibitors.

1 Introduction

The COVID-19 is an infectious disease caused by the coronavirus SARS-CoV-2 [1–5]. It has reached the status of a pandemic in March of 2020. Up to January of

2021, it has already infected more than 100 million people, leading to the death of more than 2 million ones [6]. Since the earlier stages of this pandemic, a worldwide effort has been devoted to producing vaccines and antiviral drugs to combat this virus. Some successful investigations yielded vaccines that have started to be applied very recently [7–15]. Despite the beginning of vaccination, no consensus about an efficient treatment for already infected patients has been reached so far.

Sars-CoV-2 has a crown-like (spherical) form, and its surface protein (Spike) is directly involved in the infectious process [16–18]. The receptor of this virus in human cells is the angiotensin-converting enzyme 2 (ACE2) [19–21]. Sars-CoV-2 surface protein has two subdivisions named S1 and S2, being S1 the receptor-binding domain (RBD) [22–25]. The RBD plays a major role in the attachment mechanism of Spike protein to ACE2 [26]. After the attachment between them, the virus enters the cell and starts the replication process [22]. In this sense, the strategy of virtual screening for possible inhibitors for the RBD/ACE2 attachment [27] may pave the way for novel therapeutic approaches for the treatment of COVID-19.

Drug repurposing is a feasible way to combat diseases with some similarities [28–30]. In this scenario, the use of phytochemicals is always an important option to be considered [31]. Among their sub-classes, the flavonoids — a class of small molecules found in fruits, vegetables, flowers, honey, teas, and wines — stand out [32–34]. Their pharmacological properties include antimicrobial, antioxidant, anti-inflammatory, and antiviral functions [35–37].

Flavonoids have been employed as inhibitors for the infection mechanism of several diseases [38]. Among them, one can mention malaria, leishmaniasis, Chagas, and dengue [39–44]. They have also been considered

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in studies aimed at developing therapeutic approaches for cancer treatment [45–47]. Very recently, it was reported that Luteolin (a flavonoid found in leaves and shells) is efficient as an anti-inflammatory that can interact with the Sars-CoV-2 surface [48] and its main protease [49]. More specifically, it is adsorbed in the Spike protein, inhibiting the Sars-CoV-2 attachment to the ACE2, thus preventing infection. Ngwa and colleagues used computer simulations to address the feasibility of Caflanone, Hesperetin, and Myricetin flavonoids in acting as inhibitors for the ACE2 active site attachment [50]. Their results pointed to the ability of Caflanone in inhibiting the transmission of the Sars-CoV-2 virus from mother to fetus in pregnancy. Pandey *et. al.* conducted molecular docking and dynamics simulations considering ten flavonoid and non-flavonoid compounds (by using phytochemicals and hydroxychloroquine, respectively) to verify their performance in inhibiting the RBD/ACE2 interaction [51]. Their findings indicate that Fisetin, Quercetin, and Kamferol molecules couple to RBD/ACE2 complex with good binding affinities. In this sense, they can be explored as possible anti-Sars-CoV-2 agents. Despite the success of these molecules inhibiting the RBD/ACE2, other flavonoids should be tested to broaden the list of possible inhibitors and to confirm their potential in developing new therapeutic approaches for the treatment of COVID-19.

Herein, *in silico* molecular docking analysis was carried out to propose potential flavonoid candidates in preventing the RBD/ACE2 attachment. These candidates are sixteen different flavonoids present in the Peppermint (*Mentha piperita*) leaf [52–58]. Peppermint is a perennial herb and medicinal plant native to Europe widely used for treating stomach pains, headaches, and inflammation of muscles [53, 57, 58]. Well-known for their flavoring and fragrance traits, peppermint leaves and the essential oil extracted from them are used in food, cosmetic and pharmaceutical products [52–55]. Our results revealed that Luteolin 7-O-neohesperidoside is the peppermint flavonoid with a higher binding affinity regarding the RBD/ACE2 complex (about -9.18 Kcal/mol). On the other hand, Sakuranetin was the one with the lowest affinity (about -6.38 Kcal/mol). Binding affinities of the other peppermint flavonoids ranged from -6.44 Kcal/mol up to -9.05 Kcal/mol. These binding affinities are equivalent to other ones reported in the literature for the interaction between flavonoids and the RBD/ACE2 complex [48, 49, 59–66]. Moreover, the binding site surface analysis showed pocket-like regions on the RBD/ACE2 complex that yield several interactions (mostly hydrogen bonds) between the flavonoid and the amino acid residues of the proteins. Defin-

tively, experimental studies and clinical trials should be further performed to evaluate the efficacy of these compounds in the inhibition of the RBD/ACE2 attachment.

2 Materials and Methods

Since Sars-CoV-2 infects human cells through the RBD/ACE2 coupling, the idea of checking for small molecules that may inhibit this interaction is recurring and can be useful to propose a combatant drug [68]. Here, we used molecular docking to study the interaction between the peppermint flavonoids with the RBD/ACE2 complex. Below, we present the proteins, inhibitors (flavonoids), and the computational protocol involved in our study.

2.1 Protein Preparation

Figure 1 presents the main proteins involved RBD/ACE2 interaction that were obtained from Protein Data Bank, ID 6M0J [67]. In the left panel of this figure, the ACE2 protein is in blue, while the RBD Sars-CoV-2 one is in red. Three essential regions of inhibition between these proteins were highlighted with the black squares R1, R2, and R3. In the right side of Figure 1 we show the binding site surface colored as gray, red, blue, and white for carbon, oxygen, nitrogen, and hydrogen atoms, respectively. The yellow rectangle highlights the total surface for inhibition with a clear cavity within region R2. The protein resolution is 2.45 Å, and no pKa prediction was carried out. The modeled structure has 41 residues less than the deposited one, but all the important residues in the RBD/ACE2 interface were considered in our study. Just metal ions were considered in the docking study, water molecules were not included.

2.2 Ligand Preparation

The peppermint leaf contains sixteen flavonoids [52, 55], classified into three subcategories: Flavones (Flavonols), Flavonols, and Flavanones [52, 55]. The flavonoids studied here are Acacetin, Apigenin, Apigenin 7-O-neohesperidoside (Apigenin*), Chryseoriol, Hesperidin, Hesperitin, Ladanein, Luteolin, Luteolin 7-O-glucoside (Luteolin*), Luteolin 7-O-glucuronide (Luteolin**), Luteolin 7-O-neohesperidoside (Luteolin***), Narigenin, Pebrellin, Sakuranetin, Thymusin, and Xanthomicrol. Their 3D structures were extracted from PubChem [69]. The chemical structures of these flavonoids can be seen in figure 2, while relevant information such as PubChem ID, molecular weight, molecular formula, and subcategory of the flavonoid is presented in table 1.

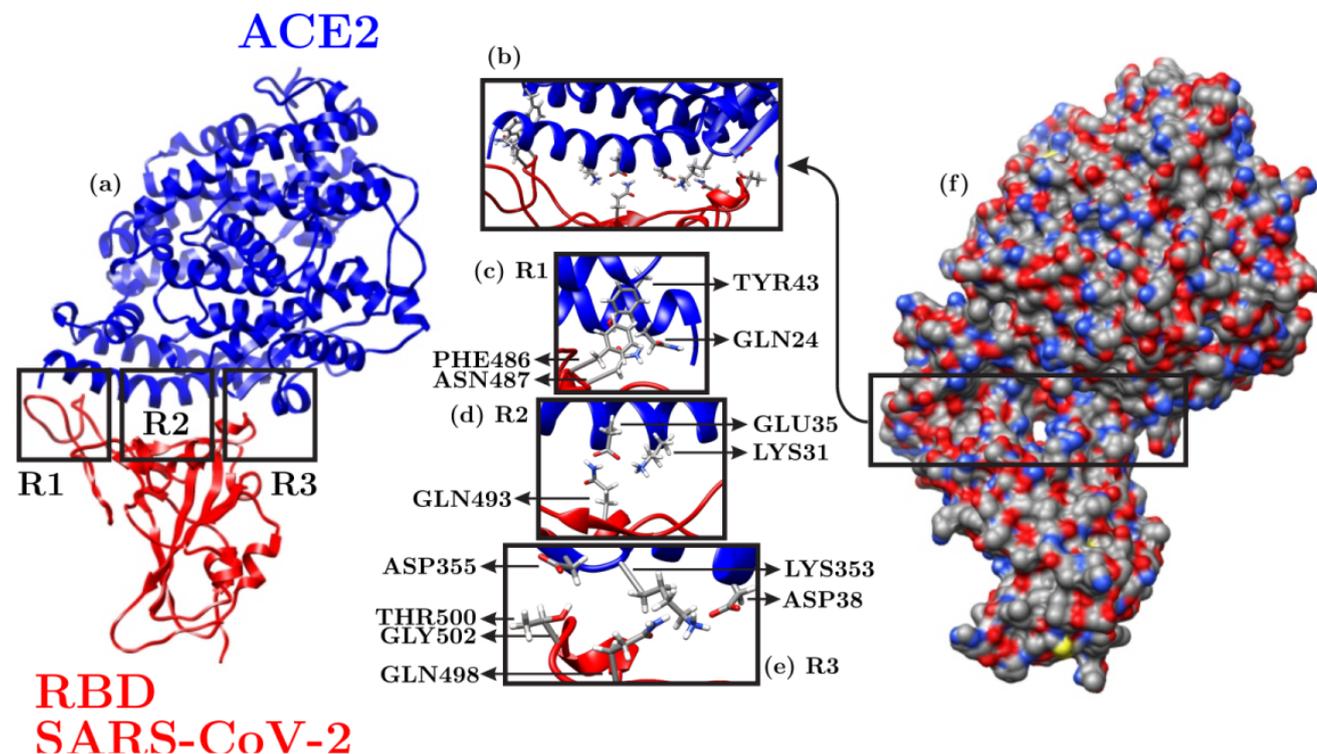


Fig. 1 Schematic representation of the (a) main proteins involved RBD/ACE2 interaction. These proteins were obtained from Protein Data Bank, ID 6M0J [67]. (b) The binding site surface has the following color scheme: gray, red, blue, and white for carbon, oxygen, nitrogen, and hydrogen atoms, respectively. Only the three regions (R1, R2, and R3) were considered in the docking processes since they define the whole RBD/ACE2 interface. The TYR4, GLN24, PHE486, and ASN487 are the residues present in the region R1; GLU35, LYS31, and GLN493 are the residues present in the region R2; ASP355, THR500, GLY502, GLN498, LYS353, and ASP38 are the residues present in the region R3.

Compound	PubChem CID	Mol. Weight (g/mol)	Mol. Formula	Type
Acacetin	5280442	284.26	C ₁₆ H ₁₂ O ₅	Flavones and Flavonols
Apigenin	5280443	270.24	C ₁₅ H ₁₀ O ₅	Flavones and Flavonols
Apigenin*	5282150	578.5	C ₂₇ H ₃₀ O ₁₄	Flavones and Flavonols
Chryseoriol	5280666	300.26	C ₁₆ H ₁₂ O ₆	Flavones and Flavonols
Hesperidin	10621	610.6	C ₂₈ H ₃₄ O ₁₅	Flavorings
Hesperitin	72281	302.28	C ₁₆ H ₁₄ O ₆	Flavanones
Ladanein	3084066	314.29	C ₁₇ H ₁₄ O ₆	Flavones and Flavonols
Luteolin	5280445	286.24	C ₁₅ H ₁₀ O ₆	Flavones and Flavonols
Luteolin*	5280637	448.4	C ₂₁ H ₂₀ O ₁₁	Flavones and Flavonols
Luteolin**	5280601	462.4	C ₂₁ H ₁₈ O ₁₂	Flavones and Flavonols
Luteolin***	5282152	594.5	C ₂₇ H ₃₀ O ₁₅	Flavones and Flavonols
Naringenin	932	272.25	C ₁₅ H ₁₂ O ₅	Flavorings
Pebrellin	632255	374.3	C ₁₉ H ₁₈ O ₈	Flavones and Flavonols
Sakuranetin	73571	286.28	C ₁₆ H ₁₄ O ₅	Flavanones
Thymusin	628895	330.29	C ₁₇ H ₁₄ O ₇	Flavones and Flavonols
Xanthomicrol	73207	344.3	C ₁₈ H ₁₆ O ₇	Flavones and Flavonols

Table 1 Potential inhibitors (peppermint leaf flavonoids) of RBD/ACE2 complex and their compound information.

2.3 Molecular Docking Simulation

Molecular docking consists of computationally analyze the non-covalent binding between macromolecules (receptor) and small molecules (ligand). Here, the macromolecule is the RBD/ACE2 protein complex (Figure 1), while the ligands are the sixteen flavonoids present

in the peppermint leaf (Figure 2). SWISSDOCK server was used for the docking simulations [70, 71]. In SWISSDOCK, the docking energies are obtained through the CHARMM (Chemistry at HARvard Macromolecular Mechanics) force field [70, 71] using a blind docking strategy that spans over 100 trial configurations for each target/ligand input [72]. The target/ligand con-

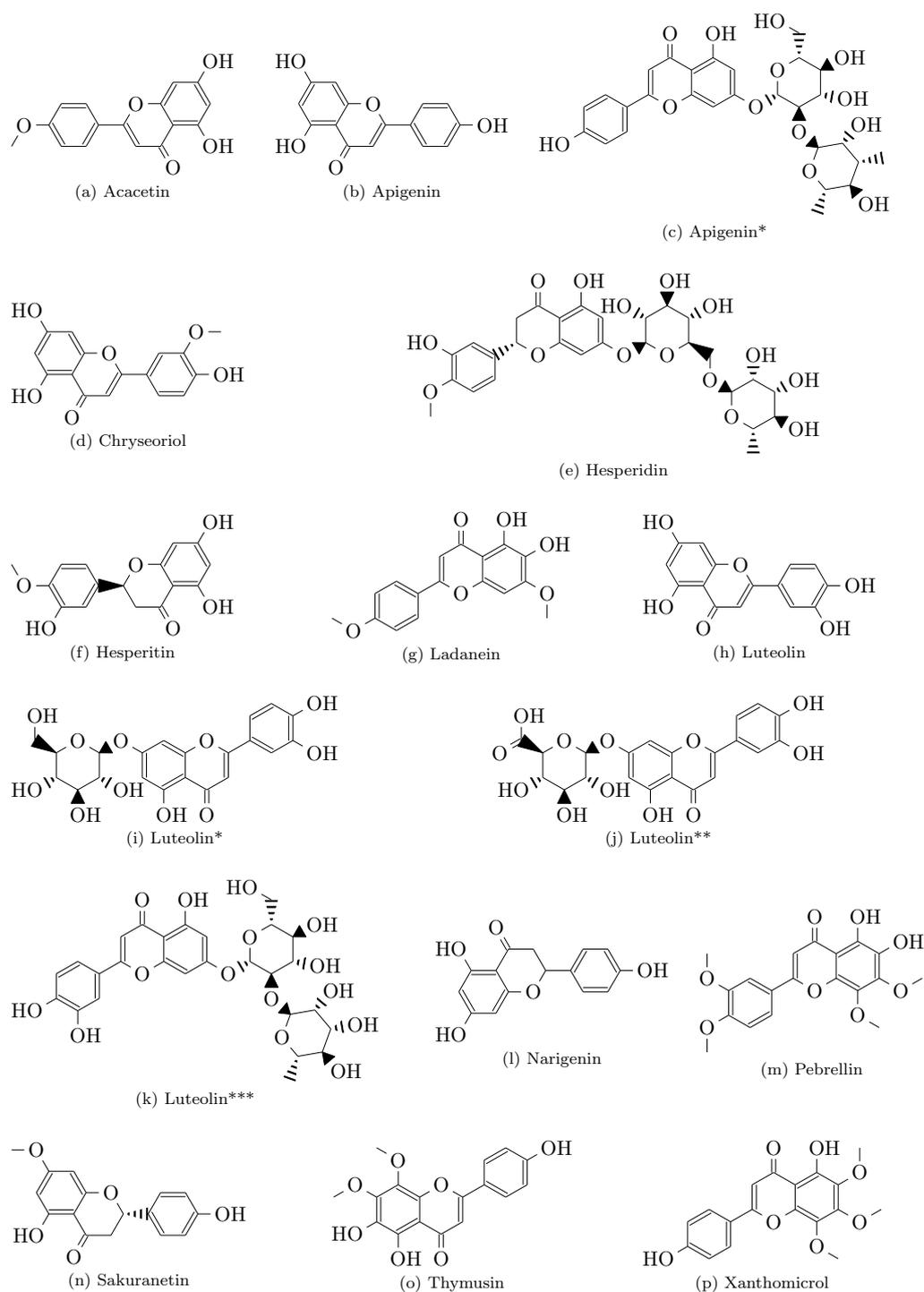


Fig. 2 Chemical structure of peppermint leaf flavonoids: (a) Acacetin, (b) Apigenin, (c) Apigenin 7-O-neohesperidoside (Apigenin*), (d) Chryseoriol, (e) Hesperidin, (f) Hesperitin, (g) Ladanein, (h) Luteolin, (i) Luteolin 7-O-glucoside (Luteolin*), (j) Luteolin 7-O-glucuronide (Luteolin**), (k) Luteolin 7-O-neohesperidoside (Luteolin***), (l) Narigenin, (m) Pebrellin, (n) Sakuranetin, (o) Thymusin, and (p) Xanthomicrol.

figuration with higher binding affinity is selected using the UCFS CHIMERA software [73], a visualization tool capable of directly import data from the SWISS-DOCK server. Finally, the Protein-Ligand Interaction

Profiler (PLIP) server [74] is used to characterize the target/ligand interaction for the configuration with a higher binding affinity for each flavonoid regarding the RBD/ACE2 complex. It is worth mentioning that the

screening for the ligand position was limited just to the ACE2/RDB interface (regions R1, R2, and R3 in the left panel of Figure 1). This interface is the crucial region to be considered for blocking the coronavirus entry and replication cycle. The simulation (docking) box used in the screening for the ligand position was limited just to the ACE2/RDB interface (regions R1, R2, and R3 in the left panel of Figure 1). The docking box has $27.5 \text{ \AA} \times 9.0 \text{ \AA} \times 8.5 \text{ \AA}$ of dimension and it was centered at $(31.5, -36.0, 1.5) \text{ \AA}$. These parameters cover the three regions depicted in Figure 1. The accuracy in estimating the ligand positions and related binding affinities are $\pm 2 \text{ \AA}$ and $\pm 0.01 \text{ Kcal/mol}$, respectively.

3 Results

Compound	ΔG [Kcal/mol]
Acacetin	-6.70
Apigenin	-6.87
Apigenin 7-O-neohesperidoside	-8.08
Chryseoriol	-6.78
Hesperidin	-8.67
Hesperetin	-6.80
Ladanein	-6.56
Luteolin	-7.24
Luteolin 7-O-glucoside	-8.01
Luteolin 7-O-glucuronide	-7.74
Luteolin 7-O-neohesperidoside	-9.18
Naringenin	-6.44
Pebrellin	-7.07
Sakuranetin	-6.38
Thymusin	-6.94
Xanthomicrol	-6.83

Table 2 Peppermint leaf-based flavonoid candidates undergoing docking experiment with their most favorable conformation (lowest binding affinity ΔG in Kcal/mol).

After successful docking of the peppermint flavonoids to the RBD/ACE2 complex, several modes of ligand/target interactions were generated with a particular docking score (binding affinity). The binding mode with the lowest binding affinity is regarded as the best one, once it tends to be the most stable. The binding affinity results (ΔG) obtained here are summarized in Table 2. SWISSDOCK simulations for all the ligands in Figure 2 revealed significant binding affinities with the target RBD/ACE2 proteins. Luteolin 7-O-neohesperidoside is the peppermint flavonoid with a higher binding affinity regarding the RBD/ACE2 complex (about -9.18 Kcal/mol). On the other hand, Sakuranetin was the one with the lowest affinity (approximately -6.38 Kcal/mol). Binding affinities of the other peppermint flavonoids ranged from -6.44 Kcal/mol up to -9.05 Kcal/mol. As one can

note in Tables 1 and 2, the best docked flavonoids have greater molecular weight. All the binding affinities are close to the ones reported for the RBD/ACE2 interaction with other species of flavonoids [48, 49, 59–66]. Moreover, they can outperform the binding affinities reported by docking studies using other types of compounds targeting RBD/ACE2 [62, 75–81], such as Chloroquine and Hydroxychloroquine, which are lower than -8.0 Kcal/mol [62]. This fact can be attributed to the abundant phenolic hydroxyl group in flavonoids. The hydroxyl group in the sugar group of flavonoids tends to bind more easily with the heteroatoms of amino acids from RBD/ACE2, as will be shown later. In this sense, peppermint flavonoids can compose the list of potential phytochemical inhibitors for the RBD/ACE2 interaction.

Figures 3 and 4 illustrate the binding site surface (BSS) for the putative best docking target/ligand configurations. For the sake of clarity, these figures show the BSS only for the RBD/ACE2 region highlighted by the yellow rectangle in Figure 1(b). The following color scheme is adopted for the BSSs: gray, red, blue, and white for carbon, oxygen, nitrogen, and hydrogen atoms, respectively. In the ball-stick representation for the flavonoids, the carbon, oxygen, and hydrogen atoms are shown in the colors cyan, red, and white, respectively. As a general trend, one can note that the flavonoids fit inside the core pocket region (cavity) of the RBD/ACE2 complex. This cavity is displayed as region 2 in Figure 1(a). Acacetin, Luteolin*, Luteolin**, Thymusin, and Xanthomicrol were adsorbed on region 1 (see Figure 1(a)) of the RBD/ACE2 complex. The ligands tend to interact with the oxygen atoms (red spots in the BSS) in regions 1 and 2. These regions establish pocket-like media that yield interactions (mostly hydrogen bonds) between flavonoids and amino acid residues of proteins.

Figures 5 and 6 provide a clear picture of the interaction between the amino acid residues of the proteins and peppermint flavonoids. The docked poses (obtained using PLIP [74] show the residues names and the bond types. In the stick representation of flavonoids, the carbon and oxygen atoms are in the orange and red colors, respectively. The hydrogen, hydrophobic, and π -stacking bonds are denoted by the blue, dashed gray, and dashed yellow lines, respectively. The yellow sphere represents the charge center. In Figure 5 one can note that Acacetin, Apigenin, Apigenin*, Chryseoriol, Hesperidin, Hesperetin, Ladanein, and Luteolin interact with RBD/ACE2 mainly through 4, 5, 5, 6, 12, 5, 4, and 8 hydrogen bonds with distinct amino acid residues in both RBD and ACE2 proteins. Similarly, Figure 6 shows the interaction mechanism between Luteloin*, Luteloin**, and

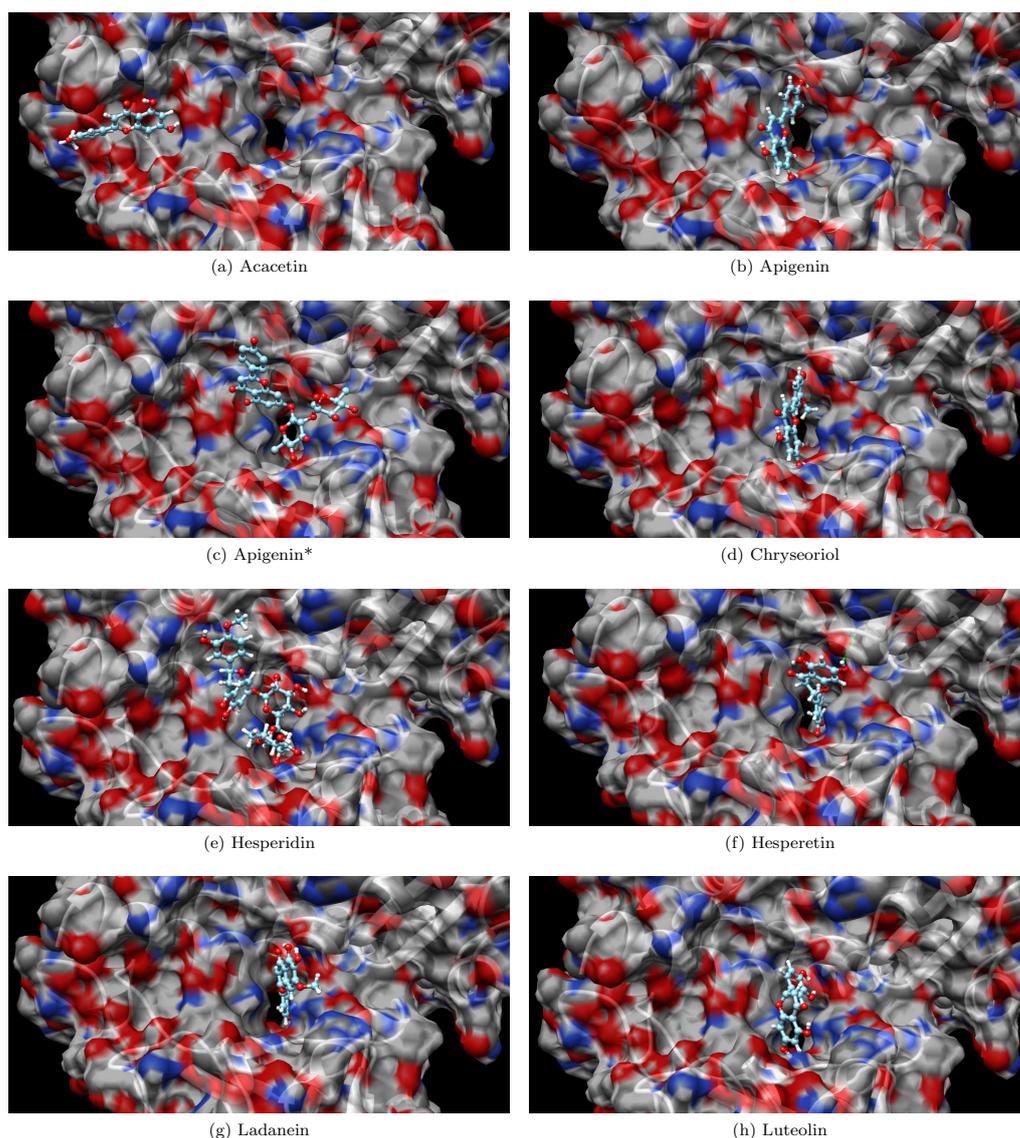


Fig. 3 binding site surface (BSS) for the putative best docking target/ligand configurations of (a) Acacetin, (b) Apigenin, (c) Apigenin*, (d) Chryseoriol, (e) Hesperidin, (f) Hesperetin, (d) Ladanein, and (d) Luteolin.

Luteolin^{***}, Naringenin, Pebrellin, Sakuranetin, Thymusin, and Xanthomicrol with RBD/ACE2 is mediated by 7, 5, 9, 8, 5, 5, 4, and 4 hydrogen bonds with distinct amino acid residues in both RBD and ACE2 proteins, respectively. In total, 12 hydrophobic bonds were found. The flavonoids and amino acid residues of the proteins involved in this kind of interaction are highlighted below. Some π -stacking bonds are also present in the RBD/ACE2 interactions with flavonoids expecting for the Hesperidin (Figure 5(e)), Luteolin* (Figure 6(a)), and Xanthomicrol (Figure 6(h)) cases.

Generally speaking, we identified 31 distinct amino acid residues of the RBD/ACE2 interacting with the peppermint flavonoids. The RBD amino acid residues

(and their occurrence) are TYR738 (4), LYS682 (5), GLU761 (6), GLN674 (6), TYR770 (6), ARG688 (8), ASP670 (2), GLY761 (4), GLY741 (2), GLN39 (1), ALA740 (1), LYS723 (3), ARG673 (1), and SER759 (1). The ACE2 amino acid residues (and their occurrence) are GLU5 (3), SER1 (5), ASP12 (7), PHE372 (4), ARG375 (9), ASN15 (8), GLU19 (9), PRO371 (1), ANS15 (1), THR71 (1), ALA369 (4), ARG37 (1), ALA368 (1), LYS335 (2), ASP20 (1), TYR760 (1), and LYS8 (1). This result suggests that the target RBD/ACE2 amino acid residues for this class of phytochemicals are ARG375, ASN15, and GLU19 from ACE2, and ARG668 from RBD, based on their higher occurrence. The flavonoids that present hydrophobic bonds with the RBD/ACE2

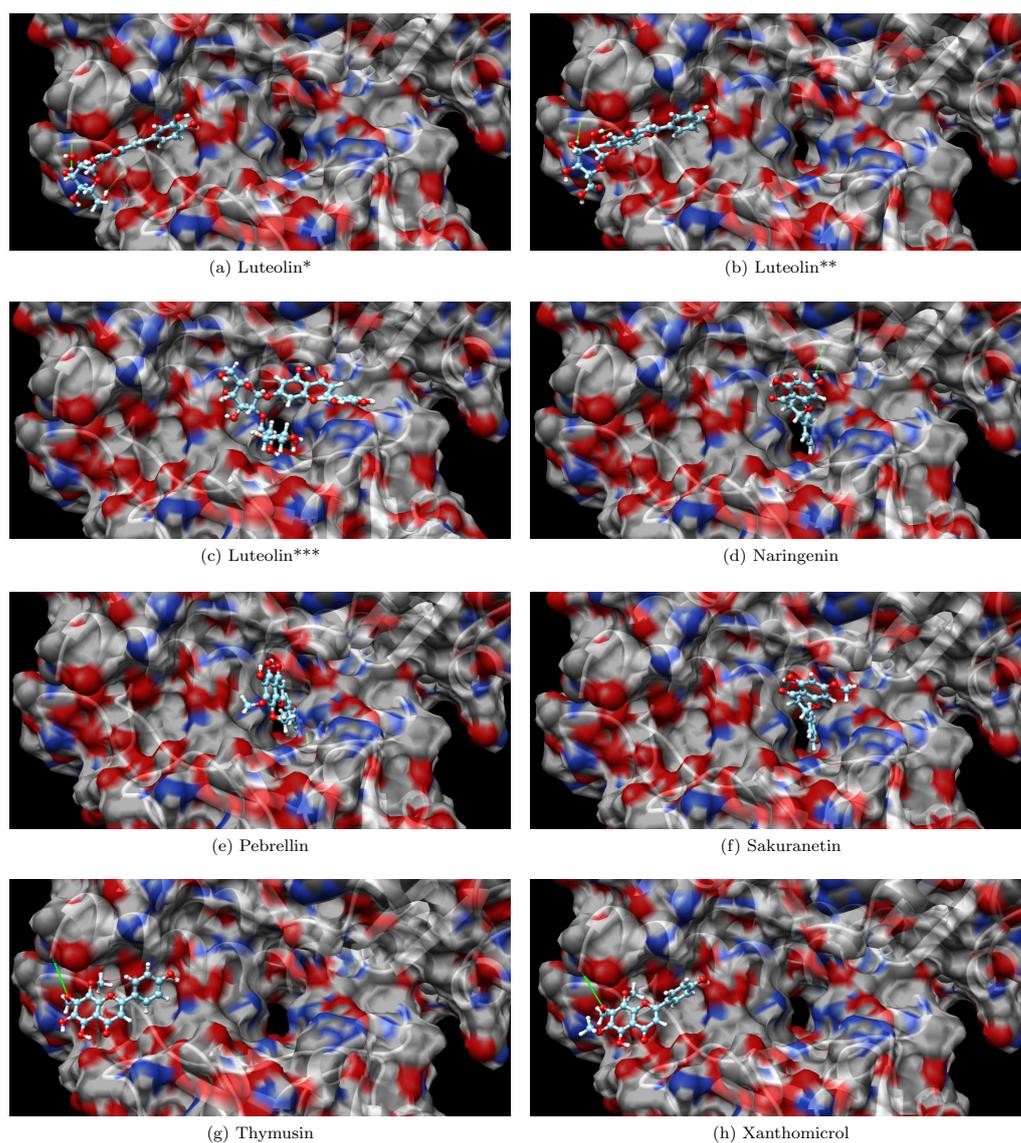


Fig. 4 binding site surface (BSS) for the putative best docking target/ligand configurations of (a) Luteloin*, (b) Luteloin**, (c) Luteloin***, (d) Naringenin, (e) Pebrellin, (f) Sakuranetin, (d) Thymusin, and (d) Xanthomicrol.

amino acids, highlighted in the following as (flavonoid/residue): SWISSDOCK [70, 71], subsequently the ranking of the are Ladanein/GLU19, Luteolin/LYS682, Hesperetin/ASN15, locked compounds with Quimera [73] and interaction Hesperetin/GLU19, Pebrellin/TYR760, Sakuranetin/GLU19, analysis with PLIP [74]. Results revealed that Luteolin Thymusin/LY58, Acacetin/GLU5, Apigenin/ASN15, Api- 7-O-neohesperidoside has a binding affinity of about genin/PRO371, Apigenin/TYR770, and Chryseoriol/LYS682.

4 Conclusions

In summary, a set of phytochemicals (peppermint flavonoids) values outperform the binding affinities reported by docking were screened against the SARS-CoV-2 Spike receptor-binding domain interacting with the human ACE2 receptor. The approach is based on computationally fitting small molecules for the target RBD/ACE2 complex proteins using the 3D structure of the active site with docking studies using other types of compounds in which the RBD/ACE2 complex was also the target [82, 83].

The binding site surface analysis showed pocket-like regions on the RBD/ACE2 complex that yield sev-

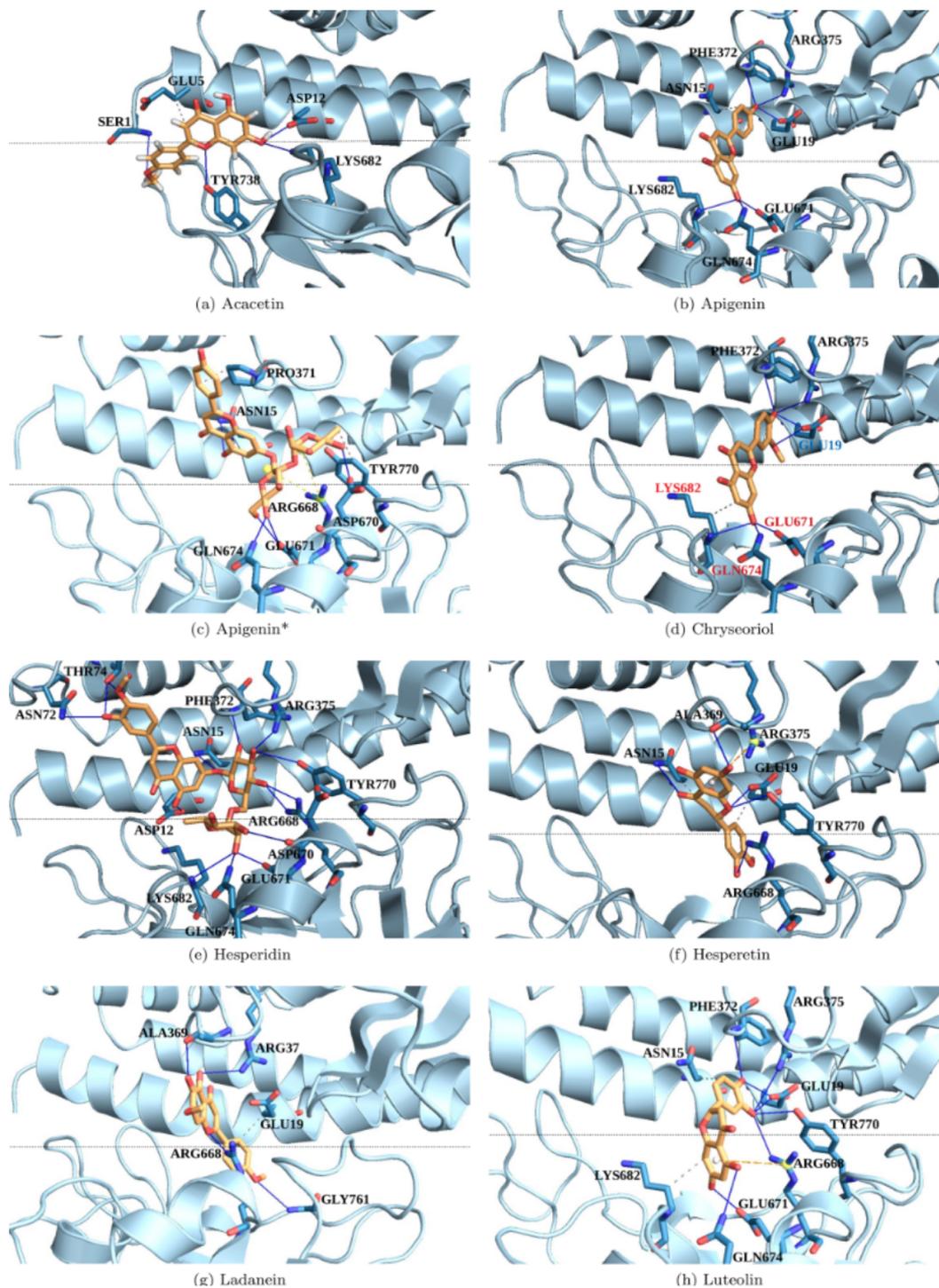


Fig. 5 PLIP docked poses for the RBD/ACE2 interaction with (a) Acacetin, (b) Apigenin, (c) Apigenin*, (d) Chryseoriol, (e) Hesperidin, (f) Hesperetin, (d) Ladanein, and (d) Luteolin. The hydrogen, hydrophobic, and π -stacking bonds are denoted by the blue, dashed gray, and dashed yellow lines, respectively. The yellow sphere represents the charge center.

eral interactions (mostly hydrogen bonds) between the flavonoid and the amino acid residues of the proteins. The interaction mechanism between the flavonoids and amino acid residues of the proteins is mediated by hydrogen bonds, essentially. The presence of some hy-

drophobic and π -stacking bonds was also observed. In total, we identified 31 distinct amino acid residues of the RBD/ACE2 interacting with the peppermint flavonoids. The target RBD/ACE2 amino acid residues for this class of phytochemicals are ARG375, ASN15, and GLU19

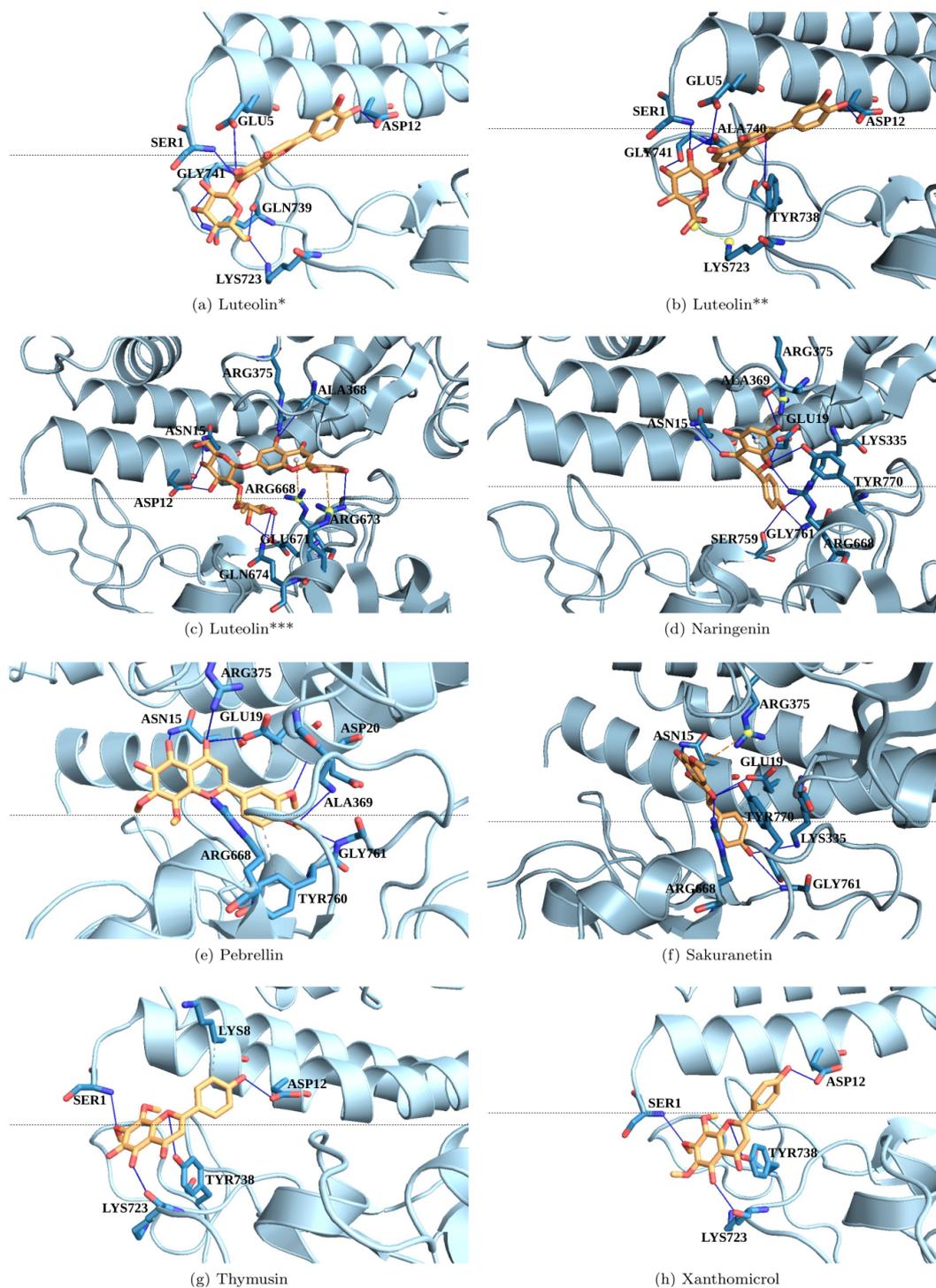


Fig. 6 PLIP docked poses for the RBD/ACE2 interaction with (a) Luteloin*, (b) Luteloin**, (c) Luteloin***, (d) Naringenin, (e) Pebrellin, (f) Sakuranetin, (d) Thymusin, and (d) Xanthomicrol. The hydrogen, hydrophobic, and π -stacking bonds are denoted by the blue, dashed gray, and dashed yellow lines, respectively. The yellow sphere represents the charge center. ACE2 and RBD moieties are shown above and below the horizontal line, respectively.

from ACE2, and ARG668 from RBD, based on their higher occurrence.

Some *in vitro* studies investigated the antiviral activity of flavonoids in combating SARS-CoV [66, 84]

and SARS-CoV2 [85–88] infection. Hesperetin, Luteolin, and Apigenin have been demonstrated as potent inhibitors of SARS-CoV-2 3CLpro *in vitro* and can be considered proper candidates for further optimization

and development of therapeutic interventions, particularly those related to inflammation processes and immunity [88]. A Luteolin derivative and Apigenin showed the best docking scores in our study.

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