MOLECULAR DOCKING OF SECONDARY METABOLITES FROM *Psidium guajava* L. AND *Piper nigrum* L. TO COVID-19 ASSOCIATED RECEPTORS ACE2, SPIKE PROTEIN RBD, AND TMPRSS2

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ABSTRACT

The SARS-CoV-2 virus has spread worldwide, affecting millions, and showing no signs of slowing down or stopping. Secondary metabolites have been important sources of medicine for millennia. In this study, the secondary metabolites of *Psidium guajava* L. and *Piper nigrum* L. were screened for binding to three key coronavirus disease (COVID-19) associated proteins, namely, the viral spike protein, its target ACE2, and its primer TMPRSS2. Through molecular docking, the compounds isoquercetin, terpinyl acetate, morin-3-O-lyxoside, guineensine and brachyamide A were found to have considerable binding to these three receptors. With almost benign ADME-Tox profiles and energetically favorable binding, the secondary metabolite compounds caryophyllene, terpinyl acetate, morin and morin glycosides may be considered for assays, further development, and clinical investigations.

Keywords SARS-CoV-2 · *Psidium guajava* L. · *Piper nigrum* L. · ACE2 · spike protein · TMPRSS2

1 Introduction

The novel coronavirus SARS-CoV-2, etiologic agent of the pandemic COVID-19, has infected people across continents in just four months after its first detection. Now, eight months since its emergence in Wuhan, China, a total of 215 countries report a combined 817,000 deaths, 15.4 million recoveries, and more than 6 million active infections.^[1] COVID-19 is transmitted through droplets and targets the human respiratory system. While its symptoms have been

characterized, the signs manifest up to a week after exposure on average, and around 80% of individuals that test positive for COVID-19 will be asymptomatic.^[2] It progresses in severity by triggering host defenses to cause excessive inflammatory damage to the lungs.

The SARS-CoV-2 viral particle contains a (+)-single strand 30k nucleotide RNA genome, among other organelles. Structural proteins encoded in the genome include the viral replicase, spike, membrane, envelope and nucleocapsid proteins, and numerous nonstructural proteins.^[3] Similar to SARS-CoV, the entry of SARS-CoV-2 into the host cell involves the virus' spike protein to the host's angiotensin converting enzyme 2 (ACE2) receptor.^[4,5] However, the affinity of SARS-CoV-2 to the receptor protein is up to 20 times greater than SARS-CoV. Unlike SARS-CoV, the spike protein of SARS-CoV-2 makes use of furin and TMPRSS2, proteases commonly found in epithelial cells lining the respiratory tract.^[6] This makes the virus as invasive as influenza, HIV and Ebola viruses.^[7,8] SARS-CoV-2 also lessens the expression of type I and type III interferons and instead promotes the production of inflammatory cytokines such as of interleukin 6 (IL-6).^[9] This results to the rapid exhaustion of antigen-specific lymphocytes and the recruitment of nonspecific neutrophils, causing damage to both healthy and infected cells.^[10] This cytokine storm can ultimately lead to acute respiratory distress syndrome (ARDS).^[11,12]

The search for COVID-19 treatments commonly involve the viral spike protein, its associated human receptor ACE2, and the human primers of spike protein TMPRSS2, cathepsin B/L, and furin.^[13] A large number of virtual screening studies recognize the importance of inhibiting viral entry by binding ligands on the interface of the primed spike protein receptor binding domain (RBD) and ACE2 structures^[14–16]. Studies on the inhibition of TMPRSS2 protease also support the discovery of compounds that affect the priming process to limit the recognition of spike RBD to ACE2 receptors.^[6] With the availability of these protein structures in databases^[17–20], investigations on the potential of repurposed drugs^[21], essential oils^[22], and ligands available online^[23] as treatments for COVID-19 are being initiated.

Secondary metabolites have a long history of antiviral activity.^[24] Numerous medicines for viral diseases either occur naturally or are derivatives.^[25] Plants commonly found in tropical regions have been established as great sources of potential antiviral compounds. Examples of which include guava (*Psidium guajava* L.) and black pepper (*Piper nigrum* L.). Among the many documented antiviral effects of guava and black pepper are on the illnesses influenza A^[26–28] and hepatitis B^[29], and nonspecific protection from viral pathogenesis through immunomodulation^[30,31].

In this study, secondary metabolites from *P. guajava* L. and *P. nigrum* L. were screened for potential binding to proteins that facilitate recognition and priming of SARS-CoV-2. Their docking can provide information on the affinity and binding sites of these compounds to key proteins involved in COVID-19. However, the ultimate curative property of these secondary metabolites against the pandemic is beyond the scope of this study. This research provides to the pool of *in silico* data.

2 Methodology

A. Secondary metabolites from *P. guajava* L. and *P. nigrum* L.

The screened *P. guajava* L. secondary metabolites were derived from a study by Arima and Danno^[32], while those of *P. nigrum* L. were obtained from the work of Dawid, et. al^[33]. Docking was performed on the ligands (Figure 1). All of the compounds originating from *P. guajava* L. are terpenoids, except isoquercetin, morin, and the two morin glycosides, which are flavonoids. All compounds from *P. nigrum* L. are alkaloids with extensive conjugation. With the exception of piperlongumine and guineensine, the *P. nigrum* L. alkaloids are either pyrrolidine or piperidine derivatives.

B. Protein preparation

The structures of human ACE2–SARS-CoV spike protein RBD complex were accessed from the RCSB Protein Data Bank (PDB IDs 2AJF, 3SCI, 6ACK, 6M17). The homology model of TMPRSS2, on the other hand, was retrieved from the SwissModel repository using the code O15393. Single chain ACE2 and spike protein RBD receptors were derived from the RCSB structures.

C. Docking and ADME-Tox analysis

The secondary metabolites from *P. guajava* L. and *P. nigrum* L. were docked to the nine prepared receptors using AutoDock Vina^[34]. The docking search space encloses the entire receptor in a box with 5Å distance from each side of the structure. To determine all possible interactions between the ligands and receptors, all docking poses and binding energy values were considered in the PLIP^[35] analysis. Determination of drug-likeness was done using the SwissADME^[36] and ProTox-II webserver^[37].

3 Results

Based on Table 1, the average docking score for all secondary metabolites from *P. guajava* L. and *P. nigrum* L. was around -6.1 kcal/mol. Among the compounds, morin-3-O-lyxoside had the lowest binding energy average on all receptors. Next to morin and the 2 morin glycosides, the secondary metabolites isoquercetin, piperoleine B and piperonaline are among the top binding ligands on all receptors. These ligands show better binding affinities than the serine protease inhibitor, camostat. All ligands bind with greater affinity to the ACE2 structures than to the other receptors.

In a previous work^[22], the docking of camostat to its putative receptor TMPRSS2 was determined. The interacting residues of camostat were found to be distal from the charge transfer pocket of TMPRSS2. As shown in Figure 2 and listed in Table 2, no interactions were found with the TMPRSS2 charge transfer pocket.^[38] Instead, the docked poses

are all found on the same cleft occupied by camostat. The residues identified in the binding of camostat (Cys148, Ile221, Lys223, and Gly370) are also the common interacting residues for the screened molecules. The compound morin recorded the lowest binding energy value while isoquercetin had the most hydrophobic, hydrogen bonding, and π -stacking interactions to TMPRSS2 receptor.

There are two druggable sites in the human ACE2 receptor. The first site is a catalytic pocket containing Arg273, His345, His505, the principal catalytic residue Glu375, and the three residues (His374, His378, and Glu402) that hold a zinc cofactor in place^[39]. The second site consists of residues 19 to 85 (helices $\alpha 1$ and $\alpha 2$) and 351 to 357 (residues that connect sheets $\beta 3$ and $\beta 4$) which are found in the interface that accommodates the SARS-CoV-2 Spike protein RBD^[4]. The interactions of ACE2 and the docked compounds are listed in Table 3 and shown in Figures 3 and 4. At a glance, it can be seen that the majority of the binding interactions occur at regions away from the two sites. Most of the docking poses are located in the ridge within ACE2. Interestingly, this region, referred to as the central core of the protein, is the site wherein all other sections of the protein fold into as a newly expressed ACE2 polypeptide chain morphs into its active form. This happens in the late intermediate stage of ACE2 folding, and at this point, the preformed ACE2 contains transient druggable sites.^[40] Since the *P. guajava* L. and *P. nigrum* L. secondary metabolites are located near residues on both the central core and adjacent sections of ACE2, the binding of these compounds to the late intermediate stages of ACE2 folding may warrant investigation.

In general, the binding of secondary metabolites to spike protein receptors yielded less affinity compared to their binding on ACE2 receptors. The interactions with spike protein are recorded in Table 4 and displayed in Figures 5 and 6. Interestingly, the docking poses clustered around one site per receptor. The spike protein structures 2AJF.E and 3SCI.E have interactions with the *P. guajava* L. and *P. nigrum* L. secondary metabolites on or near their $\beta 1$ region. These receptors' spike proteins belong to the 2002 SARS-CoV virus.^[17,18] On the receptor 6ACK.A, another spike protein RBD from SARS-CoV^[19], most of the docking poses are in the vicinity of the loop between $\beta 1$ and $\beta 2$. On receptor 6M17.E, a SARS-CoV-2 RBD structure^[20], all of the secondary metabolite compounds docked in this site as well. Isoquercetin, guineensine and brachyamide A, however, were located on the region next to the $\beta 5$ and $\beta 6$ sheets of 6M17.E.^[41] Residues in this region are at the interface of the ACE2 complex and either SARS-CoV or SARS-CoV-2 spike protein RBD. These three compounds that bind to the interface portion of 6M17.E may be considered for further studies into their effects on complex disruption.

Since the secondary metabolites have generally lower binding energies on the ACE2 receptor versus the respective spike protein receptor (Table 1), most of the docking poses on the ACE2-spike complexes lie on the side of the human peptidase enzyme. Listed in Table 5 and shown in Figures 7 and 8 are the interactions of the *P. guajava* L. and *P. nigrum* L. secondary metabolites with the complex of spike protein RBD and ACE2. With the exemption of those of terpinyl acetate on 2AJF and caryophyllene on 6M17, all of the interacting residues listed belong to ACE2. Even though caryophyllene has higher affinity towards ACE2 than spike protein individually, on the complex, the ligand is entirely located on the spike protein RBD. The binding of terpinyl acetate involves residues from the interfaces of both proteins. The compound did not associate with these residues on both the ACE2 and the spike protein monomers

only. This preference of terpinyl acetate to bind between the receptors merits further assays and clinical investigation. Contrary to the previous results where isoquercetin, guineensine, and brachyamide A were bound to the spike protein interface region, these three compounds were located on a different area on the complex. These secondary metabolites have higher surface area than terpinyl acetate, which might explain the reason why these compounds are not found in the narrow gap between the two proteins. As a recommendation, the development of ACE2-spike protein disruptors must consider the size of the ligand besides its affinity to the interface region of each protein.

The last step in determining how viable secondary metabolites can be for therapy is through ADME-Tox analysis. Tables 6 and 7 outline their abridged prediction profiles. All of the compounds except for the flavonoids had favorable bioavailability scores and lipophilicities at high certainties of toxicity prediction. The compounds guineensine and brachyamide A are markedly less hydrophilic and soluble as compared to the rest of the compounds, and are flagged as highly flexible. Terpinyl acetate, morin, and all of the *P. nigrum* L. secondary metabolites had high tendencies of intestinal absorption, while only terpinyl acetate and longicyclene had potential to pass through the blood-brain barrier. All of the compounds' leadlikeness violations did not exceed 3 and their estimated LD₅₀ values did not fall below 300 mg/kg. Both terpinyl acetate and β -bisabolene have a high chance to bind to PGH1 (or cyclooxygenase 1), while all *P. nigrum* L. secondary metabolites bind to amine oxidase, as reported in literature.^[42] The compounds from *P. nigrum* L. and the flavonoid glycosides from *P. guajava* L. all had high probabilities of immunotoxicity.

4 Discussion

Secondary metabolites have always had great importance in the search for remedies of various diseases. In this research, a handful of *P. guajava* L. and *P. nigrum* L. isolates have been extensively studied for their antiviral properties against the novel SARS-CoV-2 coronavirus. The protein targets are the viral spike protein, its priming enzyme TM-PRSS2, and its receptor ACE2. Eight guava and seven black pepper secondary metabolites were docked *in silico* to these three receptors and the ACE2-spike protein complex. Flavonoids, particularly morin-3-O-lyxoside, had the highest affinities to all of the receptors. However, the screened flavonoid glycosides had the most structural alerts among the secondary metabolite ligands with regard to ADME-Tox predictions. In order to become viable candidates, the adverse effects of these compounds must be minimized, through iterative lead optimization.

In the context of SARS-CoV-2 infection, inhibition of TM-PRSS2 protease leads to viral pathogenesis suppression^[6,30,31]. The druggable sites of the enzyme, however, has yet to be explored. Here, it was observed that none of the screened molecules bind to the TM-PRSS2 charge transfer pocket. Instead, the ligands bind to the same region as the binding site of the known TM-PRSS2 inhibitor drug, camostat^[22]. In the absence of a molecular evidence of TM-PRSS2 inactivation by camostat, this homogeneity in terms of binding sites might provide insights on the effect of these secondary metabolites on the protease's function.

For the ACE2, spike protein, and ACE2-spike complex systems, the ligands were seen to have higher binding affinities toward the ACE2 monomer. In terms of binding sites, however, some ligands were seen to bind to the interface of the complex rather than their respective ACE2 binding sites. The interactions of isoquercetin, terpinyl acetate, guineensine, and brachyamide A with this region can be further analyzed to determine if their binding leads to a reduced virulence of SARS-CoV-2.

Besides their potential to associate with the ACE2-spike complex, the screened secondary metabolites may also provide remedy to COVID-19 in another manner. A study showed that the immunomodulatory activity of dexamethasone, an immunosuppressant and steroid drug, reduced mortalities in COVID-19 patients that required respiratory support^[43]. The secondary metabolites considered in this study also showed similar immunomodulatory activities^[31,44]. If not as antivirals, the secondary metabolites are recommended for development as immunosuppressants. This strategy on addressing infection by attenuating host defenses, however, remains highly controversial and is still under critical discussion.^[45]

5 Conclusion

Secondary metabolites from *P. guajava* L. and *P. nigrum* L. have shown considerable binding to key proteins involved in the virulence of SARS-CoV-2, while also having relatively benign ADME-Tox profiles. The screened molecules share a binding site on the priming protease TMPRSS2 with the known inhibitor camostat. Whether or not the secondary metabolites affect TMPRSS2 function and spike protein priming should be investigated in succeeding studies.

Terpinyl acetate locates itself between spike protein RBD and ACE2. Remarkably, this compound does not bind to the interface region of either spike protein or ACE2 monomer. Considering that this compound has the least molecular weight among the screened secondary metabolites, the design of small and light disruptors of spike protein RBD recognition might be important in determining a potential COVID-19 drug.

While the pace of COVID-19 drug discovery has gone up, and countries are recording weeks of zero incidence, the SARS-CoV-2 virus will likely keep recurring.^[46] The "new normal" impacts the economy negatively and creates obstacles in the development of antivirals and vaccines. Secondary metabolites, which are inexpensive and readily obtainable, can be a great source of antiviral compounds. In this study, *P. guajava* L. and *P. nigrum* L. compounds were reported to have considerable interactions with TMPRSS2, spike protein, and ACE2. More secondary metabolites from these flora and from other natural products may soon be docked in the following months, to enrich the pool of anti-COVID-19 therapeutics with candidate compounds.

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Table 1: Docking results of *P. guajava* L. and *P. nigrum* L. extract secondary metabolite compounds against the ACE2-Spike complex, ACE2, Spike protein, and TMPRSS2 models.

compound	Binding energy (kcal/mol) to											
	TMPRSS2	ACE2-spike			ACE2				spike protein			
	O15393	2AJF	3SCI	6M17	2AJF.A	3SCI.A	6ACK.D	6M17.B	2AJF.E	3SCI.E	6ACK.A	6M17.E
Isoquercetin	-6.2	-7.7	-8.0	-8.3	-7.8	-7.4	-7.6	-7.7	-5.4	-5.7	-4.8	-6.0
Terpinyl acetate	-4.0	-5.0	-5.2	-4.6	-5.6	-5.2	-5.1	-4.7	-4.4	-3.6	-4.2	-4.7
Longicyclene	-4.9	-6.2	-5.8	-6.1	-5.9	-6.3	-6.1	-5.8	-4.7	-4.5	-4.6	-5.3
β -bisabolene	-4.1	-6.3	-6.4	-4.6	-5.8	-5.8	-5.6	-5.7	-4.0	-4.4	-4.9	-5.1
Caryophyllene	-4.7	-5.9	-6.2	-6.1	-5.9	-6.5	-6.4	-6.4	-4.4	-4.5	-4.9	-6.0
Morin	-6.6	-7.5	-7.7	-7.4	-7.0	-7.6	-7.0	-7.4	-5.5	-5.8	-5.0	-6.5
Morin-3-O-lyxoside	-6.3	-8.1	-7.8	-7.4	-7.9	-7.8	-7.9	-7.3	-6.0	-6.0	-5.1	-6.6
Morin-3-O-arabinoside	-6.2	-8.2	-7.8	-7.3	-8.1	-7.7	-7.5	-7.3	-5.7	-6.0	-4.8	-6.5
Piperine	-5.8	-7.5	-7.4	-6.8	-6.9	-6.9	-7.4	-7.6	-5.5	-5.4	-5.3	-6.5
Piperlyline	-5.6	-7.5	-7.6	-7.2	-6.6	-7.0	-7.2	-7.1	-5.2	-5.4	-5.0	-6.4
Piperlongumine	-6.0	-6.7	-7.2	-6.6	-6.2	-6.6	-6.8	-6.5	-4.7	-5.2	-5.0	-6.2
Guineensine	-5.3	-7.0	-7.4	-6.5	-6.1	-5.9	-5.9	-5.8	-4.4	-4.6	-4.8	-4.8
Brachyamide A	-5.5	-7.8	-7.6	-6.2	-6.3	-6.1	-6.3	-6.2	-4.4	-4.8	-4.6	-5.1
Piperoleine B	-6.5	-6.5	-7.5	-6.3	-6.2	-7.0	-6.5	-6.3	-5.0	-5.1	-5.2	-6.1
Pipernonaline	-6.5	-7.6	-7.7	-6.8	-6.2	-7.1	-7.2	-6.0	-5.0	-5.6	-4.9	-5.1
Camostat ^[22]	-6.0	-7.2	-7.1	-6.5	-6.6	-7.3	-7.2	-6.4	-5.0	-5.4	-5.1	-5.9

Table 2: List of interactions of *P. guajava* L. and *P. nigrum* L. secondary metabolite compounds with human TMPRSS2 receptor. Residue text are colored according to the nature of non-covalent bonding to the ligand: black if hydrophobic, red if H-bonding, green if salt bridge, blue if π -stacking, and brown if π -cation.

compound	O15393
Isoquercetin	V479,F480,W483,N343,M478,D482,W483,R486,W483
Terpinyl acetate	I221,P369,V479
Longicyclene	I221,P369
β -bisabolene	I221,P369
Caryophyllene	I221,T481,D482
Morin	I221,K223,C148,V149,K223,P369,K223
Morin-3-O-lyxoside	D482,N336,W483,R486,W483
Morin-3-O-arabinoside	D482,W483,N336,W483,R486,W483
Piperine	I221,P369,W483,N336,W483
Piperyline	V149,I221,K223,K224,P369,C148,V149
Piperlongumine	D220,I221,P369,T481,D482,W483,D482,R486,W483
Guineensine	P369,P422,A423,V479,F480,T481,D482,W483
Brachyamide A	P369,P422,A423,V479,F480,D482,W483
Piperoleine B	I221,K223,P369,T481,C148
Pipernonaline	I221,K223,P369,C148,G370

Table 3: List of interactions of *P. guajava* L. and *P. nigrum* L. secondary metabolite compounds with human ACE2 receptors. Residue text are colored according to the nature of non-covalent bonding to the ligand: black if hydrophobic, red if H-bonding, green if salt bridge, blue if π -stacking, and brown if π -cation.

compound	2AJF.A	3SCI.A	6ACK.D	6M17.B
Isoquercetin	F274,L410,I446, L370,H374 , E406,S409,Q442,R518	S47,D350,D382,Y385, N394, W349	F274,K441, T371,E406	D350,N394,H401, D350 , G395,H401
Terpinyl acetate	Q98, K562	F40,W349, D350	L144,W271,F504, R273	L370,K441
Longicyclene	F32,L73,A99,L100,L391	L95,V209,K562,P565	Y127,L144,W271,F504	L144,W271,F274,L503
β -bisabolene	D269,W271,F504	D269,W271,F504	W271,F274,F504	F40,W349,D350
Caryophyllene	F40,L73,F390,L391	V209,K562,P565	L144,D269,W271,F504	L95,V209,K562,P565
Morin	A348,G395,E398,H401, H378	L95,K562, L95,Q98,Q102 , Y196,N210,E564	Y202,D206, Q102,Y199 , W203,G205,D206,S511	L95, Y196,W566,K564
Morin-3-O-lyxoside	F40,T347, S43,S47,N51 , D350,D382,W349	F40,T347, S43,S47,N51 , D350,D382,W349	A99,L391,L95, Y202 , D206,E208,K562,K562	D350, D350,F40
Morin-3-O-arabinoside	F40,T347, S43,S47,N51 , T347,D350,W349	F40,T347, S43,S47,N51 , T347,D350,W349	T276,T445, H374,Q522	W349, S47,D350,F40
Piperine	F40,W69,A99,L100,F390, D350,N394	Y202	Q98,Y202,K562, Q102 , W203,S511	F40,W69,L73,F390, L391,R393, K353,R393
Piperyline	F40,W69,F390, D350,N394	Y127,L144,E145,W271,F274, F504, E145,R273,Y127	Q98,A99,Y202,D206,K562, Q102,Y196,Y199	F40,W69,L73,F390, R393, N394,R393
Piperlongumine	Y127,L144,E145,W271, F274, Y127,N149	Y127,L143,L144,E145, W271,L503,F504, R273	Q98,Y202,D206,V209,K562, Q102,Y196,Y199,D206	I291,L370,P415,E430, T434,E435,F438
Guineensine	F40,W349,H378,H401, W349	W349,F390, D350,H401	F274,L370,T371,K441, S409,Q442	Y127,L144,E145,W271, F504, F504
Brachyamide A	F40,W349, D350,W349	F40,W349, D350,W349	F274,L370,T371,K441, S409,Q442	F40,W69,F390, D350 , N394
Piperoleine B	T347,W349,D350, S47,W349	Y127,L144,E145,D269, W271,L503,F504	F274,L370,H374,K441,T445	Y127,L144,E145,W271, F274,F504, F504,H505
Pipernonaline	F40,W349,D350, W349	L144,N149,A153,D269,W271, F274,F504, E145,D269,Y127	F40,W69,L73,F390,L391, F40	Y127,L144,E145,W271, F504

Table 4: List of interactions of *P. guajava* L. and *P. nigrum* L. secondary metabolite compounds with spike protein RBD receptor. Residue text are colored according to the nature of non-covalent bonding to the ligand: black if hydrophobic, red if H-bonding, green if salt bridge, blue if π -stacking, and brown if π -cation.

compound	2AJF.E	3SCI.E	6ACK.A	6M17.E
Isoquercetin	W340,R342, W340 , R342 ,F451	W340,F451, W340 , R342 ,R453	K390,I405, D392 , Q396 ,Y442, N479	Y491, R390 ,Y436,Y481, Q484 , N487 ,G488,Y491
Terpinyl acetate	P335,A339,N437,Y438, S336	W340,R342	V404,I405,Y440,Y442	F329,V354,L355,F361, W423
Longicyclene	P335,Y338,A339,Y438, K439	W340	V404,I405,Y440	F329,V354,L355,F361
β -bisabolene	P335,N437,Y438,K439	W340,R342,R453	K390,V404,I405,Y440,Y442	F329,V354,L355,F361, W423
Caryophyllene	Y338,A339,Y438	W340	V404,Y440,Y442,L443	F329,L355,F361,W423
Morin	W340,R342,E452,R453, W340 , R342 , R453 , R453	W340,F451, W340 , R342	I405, Q396 ,Y442,Y440,Y442	V354,L355, S358 , S360 , F325
Morin-3-O- lyxoside	W340,R342,R453, E341 , R342	R342, W340 , R342 , W340	I405, K390 , D393 ,V404,I405,Y440, Y442,N479,Y481, K390 ,Y442	F329,F361, N330 , S360 , N427 , W423
Morin-3-O- arabinoside	R342,R453, E341 , R342 , R453 , R453	R342, W340 , R342 , W340	V404,I405, K390 , Q396 ,V404, I405 ,Y440	F329,F361, S360 , N427 , W423
Piperine	W340,F451,R453	R342,R453, R342 , W340 , R453	V404,I405,Y408,Y442	T363,V394,V489, T363
Piperyline	W340,R342,E452, R342 , R453	R342,R449,R453, R342 , W340 ,R453	V404,I405,Y408,Y442	V354,W423, S360 , F325
Piperlongumine	W340,R342,F451,R453	R342,R449,E452,R453, R342 , W340 ,R453	V404,I405,Y408,Y440,Y442, Q396	F329,V354,L355,F361, W423, N330 , F325
Guineensine	W340,R342,K344,Y383, R453	R342,K344,R453, R342 , W340 ,R453	V404,I405,Y408,Y442, N479	L439,F477, Q479 , S480
Brachyamide A	W340,R342,K344,Y383, R453	W340,R453, R342 , W340 , R453	V404,I405,Y408,Y442, N479 , K390	L439,Y475,F476,L478, S480
Piperoleine B	W340,R342,K344,Y383, R453	W340,R342,K344,F451, R342	V404,I405,Y408,Y442, N479 , Y442	F329,V354,F361,W423, N424, S360
Pipernonaline	W340,F451,R453, R342 , R453	W340,R342,K344,Y383	V404,I405,Y408,Y442, N479	T363,K365,V394,R395, A398

Table 5: List of interactions of *P. guajava* L. and *P. nigrum* L. secondary metabolite compounds with ACE2-spike protein complex receptors. Residue text are colored according to the nature of non-covalent bonding to the ligand: black if hydrophobic, red if H-bonding, green if salt bridge, blue if π -stacking, and brown if π -cation. All residues belong to the ACE2 receptor unless marked with an asterisk, meaning they are located on the spike protein.

compound	2AJF	3SCI	6M17
Isoquercetin	F274,L410,I446, L370,H374,E406,S409,Q442,R518	K562, Q98,Y196,E208,G395,A396,K562,K562,K562	L95,Q98,N210,K562, L95,Q98,G205,D206,N210,A396,K562,K562
Terpinyl acetate	E35,D38,L39,Y436*,D480*, D480*	F40,W349, D350	W271,F274,T276
Longicyclene	F40,W69,F390,R393	L95,Q98,A99	I291,L370,A413,F438,K441
β -bisabolene	F40,W69,L73,L100,F390,L391	F32,F40,L73,L100,F390,L391	E527,Q531,H535,L539
Caryophyllene	D269,W271,R273,F274,F504	F32,W69,L73,L391	F329*,L355*,F361*,W423*
Morin	F390, D350,R393,N394,F40	E208,K562, Q98	F40,F390, K353,R393
Morin-3-O-lyxoside	F40,T347, S43,S47,N51,D350,W349	Q98,E208, Q102,Y202,D206,E208,K562,K562	F40,Y385, L391,R393,N394,F40
Morin-3-O-arabinoside	F40,T347, S43,S47,N51,T347,D350,W349	Q98, Q98,Q102,Y202,D206,E208,K562,K562	W349,D350, S47,D350,R393,F40
Piperine	F32,F40,L100,D350,F390,L391	F32,F40,L73,D350,F390,L391	L95,Q102, N210
Piperyline	F32,F40,W69,L73,L100,F390,L391,R393	F32,F40,W69,L73,L100,F390,L391,R393	F40,L73,L391,R393, K353,N394,R393
Piperlongumine	F32,F40,W69,L73,L100,D350,F390,L391, R393	F32,F40,W69,L73,L100,F390,R393	F40,A99,F390,R393, N394,R393
Guineensine	F40,W69,D350,F390	F32,F40,L73,L100,W349,D350,F390,L391	F40,D350,F390,R393, S47
Brachyamide A	F40,W69,L73,L100,D350,H378,F390,L391,R393	F32,F40,W69,L73,L100,A348,F390,L391, N394	F40,T347,W349,F390,R393, S47
Piperoleine B	W349,D350, S47,W349	F32,F40,W69,L73,D350,F390,L391	W349,D350,F390,R393, F40,F390
Pipernonaline	F40,W69,W349,D350,F390,L391	F32,F40,L73,L100,D350,F390,L391, Y385	L85,L95,V209,N210,P565, N210,R219,W566

Table 6: ADME-Tox predictions for guava secondary metabolite compounds. Key: PGH1 = prostaglandin G/H synthase 1 or cyclooxygenase 1, ANDR = androgen receptor, GCR = glucocorticoid receptor. Organ toxicity predictions POS for positive and NEG for negative are reported with the corresponding prediction accuracy.

	isoquercetin	terpinyl acetate	longicyclene	β -bisabolene	caryophyllene	morin	morin-3-O-lyxoside	morin-3-O-arabinoside
Consensus logP	-0.58	3.04	4.39	4.83	4.25	1.15	-0.25	-0.21
Consensus solubility	Soluble	Soluble	Moderately soluble	Moderately soluble	Soluble	Soluble	Soluble	Soluble
GI absorption	Low	High	Low	Low	Low	High	Low	Low
BBB permeant	No	Yes	Yes	No	No	No	No	No
Bioavailability score	0.11	0.55	0.55	0.55	0.55	0.56	0.11	0.11
Leadlikeness violations	1	2	2	2	2	0	1	1
Predicted LD50 (mg/kg)	500	4800	3660	4400	5000	500	500	500
High probability binding target	(no prediction)	PGH1		PGH1		(no prediction)	(no prediction)	(no prediction)
Moderate prob. binding target	(no prediction)			ANDR,GCR		(no prediction)	(no prediction)	(no prediction)
Hepatotoxicity	NEG, 80%	POS, 53%	NEG, 86%	NEG, 82%	NEG, 80%	NEG, 69%	NEG, 79%	NEG, 79%
Carcinogenicity	NEG, 84%	NEG, 66%	NEG, 70%	NEG, 74%	NEG, 70%	POS, 64%	NEG, 79%	NEG, 79%
Immunotoxicity	POS, 84%	NEG, 97%	NEG, 95%	POS, 60%	POS, 54%	NEG, 72%	POS, 99%	POS, 99%
Mutagenicity	NEG, 75%	NEG, 94%	NEG, 65%	NEG, 93%	NEG, 95%	NEG, 53%	NEG, 78%	NEG, 78%
Cytotoxicity	NEG, 69%	NEG, 80%	NEG, 68%	NEG, 81%	NEG, 75%	NEG, 98%	NEG, 68%	NEG, 68%

Table 7: ADME-Tox predictions for black pepper secondary metabolite compounds. Key: AOFA = amine oxidase A. Organ toxicity predictions POS for positive and NEG for negative are reported with the corresponding prediction accuracy.

	piperine	piperyline	piperlongumine	guineensine	brachyamide A	piperoleine B	pipernonaline
Consensus logP	3.04	2.75	3.17	5.58	5.31	4.47	4.34
Consensus solubility	Soluble	Soluble	Moderately soluble	Poorly soluble	Moderately soluble	Moderately soluble	Moderately soluble
GI absorption	High	High	High	High	High	High	High
BBB permeant	No	No	No	No	No	No	No
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Leadlikeness violations	0	0	1	3	3	2	2
Predicted LD50 (mg/kg)	330	760	890	760	760	1000	1000
High probability binding target	AOFA	AOFA	AOFA	AOFA	AOFA		AOFA
Moderate prob. binding target						AOFA	
Hepatotoxicity	NEG, 91%	NEG, 85%	NEG, 80%	NEG, 86%	NEG, 91%	NEG, 93%	NEG, 92%
Carcinogenicity	POS, 53%	POS, 58%	NEG, 53%	NEG, 50%	POS, 59%	POS, 54%	POS, 54%
Immunotoxicity	POS, 96%	POS, 96%	POS, 98%	POS, 99%	POS, 99%	POS, 96%	POS, 79%
Mutagenicity	NEG, 96%	NEG, 80%	NEG, 64%	NEG, 72%	NEG, 82%	NEG, 87%	NEG, 92%
Cytotoxicity	NEG, 53%	NEG, 52%	NEG, 70%	NEG, 71%	NEG, 54%	NEG, 52%	NEG, 51%

Figure 1: Screened secondary metabolites secondary metaboliteed from *P.guajava* (top) and *P. nigrum* L. (bottom). The molecular weight and torsional degrees of freedom for each molecule are shown below their respective structure.

Figure 2: Docking to TMPRSS2 (homology model O15393) of (a) *P. guajava* L. and (b) *P. nigrum* L. secondary metabolites.

Figure 3: Binding poses of *P. guajava* L. secondary metabolites against the ACE2 models (A: 2AJF.A, B: 3SCI.A, C: 6ACK.D, and D: 6M17.B).

Figure 4: Binding poses of *P. nigrum* L. secondary metabolites against the ACE2 models (A: 2AJF.A, B: 3SCI.A, C: 6ACK.D, and D: 6M17.B).

Figure 5: Binding poses of *P. guajava* L. secondary metabolites against the spike protein models (**A**: 2AJF.E, **B**: 3SCI.E, **C**: 6ACK.A, and **D**: 6M17.E).

Figure 6: Binding poses of *P. nigrum* L. secondary metabolites against the spike protein models (A: 2AJF.E, B: 3SC1.E, C: 6ACK.A, and D: 6M17.E).

Figure 7: Binding poses of *P. guajava* L. secondary metabolites against the ACE2-Spike protein RBD complex models (A: 2AJF.AE, B: 3SCI.AE, and C: 6M17.BE).

Figure 8: Binding poses of *P. nigrum* L. secondary metabolites against the ACE2-Spike protein RBD complex models (A: 2AJFAE, B: 3SCI.AE, and C: 6M17.BE).