In Silico Investigation of Spice Molecules as Potent Inhibitor of SARS-CoV-2

Janmejaya Rout, Bikash Chandra Swain, and Umakanta Tripathy*
Department of Physics, Indian Institute of Technology (Indian School of Mines), Dhanbad, 826004, Jharkhand, India.

*Corresponding author E-mail: utripathy@iitism.ac.in

Abstract

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a novel infectious disease that is in rapid growth. Several trials are going on worldwide to find a solution for this pandemic. The viral replication can be blocked by inhibiting the SARS-CoV-2 spike protein (SARS-CoV-2 Spro), and the SARS-CoV-2 main protease (SARS-CoV-2 Mpro). The binding of potential small molecules to these proteins can possibly inhibit the replication and transcription of the virus. The spice molecules that are used in our food have the properties of antiviral, antifungal, and antimicrobial nature. As spice molecules are consumed in the diet, hence its antiviral properties against SARS-CoV-2 will benefit in a significant manner. Therefore, in this work, the blind molecular docking of 30 selected spice molecules (through ADME property screening) was performed for the identification of potential inhibitors for the Spro and Mpro of SARS-CoV-2. We found that all the molecules bind actively with the SARS-CoV-2 Spro and Mpro. However, the molecule, Piperine, is found to have the highest binding affinity among the 30 screened molecules. We anticipate immediate wet-lab experiments and clinical trials in support of this computational study might be helpful in inhibiting the SARS-CoV-2 virus.
Keywords: SARS-CoV-2; COVID-19; spike proteins; main protease; spice molecules; inhibition.

Abbreviations: COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome Coronavirus 2; Spro: Spike protein; Mpro: Main protease; MEP: Molecular Electrostatic Potential; WHO: World Health Organization; ADME: Absorption, Distribution, Metabolism, Excretion.
1. Introduction

The novel coronavirus disease 2019 (COVID-19) has become a major threat worldwide due to its fast spreading. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The entry of this Coronavirus to the host cell is mediated through the transmembrane spike glycol proteins. This glycol protein consists of two subunits and is reported to have a similar affinity to the human angiotensin-converting enzyme as that of the severe acute respiratory syndrome coronavirus (SARS-CoV), which in turn results in efficient spreading of SARS-CoV-2 in humans (Walls et al. 2020). On the other hand, the SARS-CoV-2 Mpro, also known as chymotrypsin-like protease, or 3-C like protease (3CL\textsuperscript{pro}), plays a vital role in processing the polyproteins through the translation from viral RNA. This protease is reported to have a minimum of 11 cleavage sites resulting in viral replication and toxicity (Zhang et al. 2020). The inhibition of these two viral targets can actively block the fusion and replication of SARS-CoV-2.

Currently, researchers are working globally for finding treatment for this disease in identifying a specific drug or vaccine that can inhibit viral replication at the earliest possible. The devastation of this disease is clearly seen from the data on the WHO website, which shows the infected patient number more than 35 lakhs and casualties more than 2.5 lakhs, worldwide from 215 countries, and still, it is continuing (https://www.who.int/emergencies/diseases/novel-coronavirus-2019 07-05-2020). Meanwhile, one of the computational tools, molecular docking, has gained attention as an essential tool to investigate potential inhibitor molecules (Anurag, Nem Kumar, Neeraj & Giriraj T 2020; Gupta et al. 2020; Sourav, Sharat, Sona & Atanu 2020). Choy et al. reported \textit{in-vitro} studies showing remdesivir, lopinavir, emetine, and homoharringtonine inhibits SARS-CoV-2 replication (Choy et al. 2020). Similarly, Wang \textit{et al.} reported the inhibition property of remdesivir and chloroquine against novel coronavirus (Wang et al. 2020). In addition to
different drug compounds, researchers also searched for natural molecules having antiviral activity. Natural constituents from foods, spices, herbs are also being found to have anti-infective properties. In this context, small active molecules present in natural products and their derivatives have gained tremendous attention as a source of therapeutic agents, and structural diversity for many years.

From 1940 to 2014, the US Food and Drug Administration (FDA) has approved about 49% of all small molecules that are natural products or derivates linked directly to the spice molecules (Newman & Cragg 2016). The compounds of essential garlic oil, a spice used in food, is reported as an inhibitor using the molecular docking method (Thuy et al. 2020). Recently, Das et al. using blind molecular docking, investigated for the potential inhibitors of SARS-CoV-2 Mpro (Sourav et al. 2020). Molecules studied by Das et al. are drug molecules, antivirals, antifungals, anti-nematodal, and anti/protozoal in addition to natural compounds. Besides, natural molecules such as alkaloids and terpenoids from African medicinal plants were studied by Gyebi et al. for the inhibition property against SARS-CoV-2 Mpro (Gyebi, Ogunro, Adegunloye, Ogunyemi & Afolabi 2020). Recently, Umesh et al. screened compounds from Indian spices as potent inhibitors of SARS-CoV-2 Mpro (Umesh, Kundu, Selvaraj, Singh & Dubey 2020). Every spice has a particular aroma, colour, and flavour due to the presence of specific molecules in them, and hence have antiviral properties (Astani, Reichling & Schnitzler 2010; Chang, Wang, Yeh, Shieh & Chiang 2013; Zhang et al. 2014; ABOUBAKR et al. 2016; Choi 2016; Mair et al. 2016; Brochot, Guilbot, Haddioui & Roques 2017). This compels us to conduct the present study, where we have investigated the inhibition property of molecules present in various spices against the SARS-CoV-2 Spro and SARS-Cov-2 Mpro. The compounds tested and their source of origin with PubChem ID are listed in Table S1.
2. Materials and Methods

Molecular modeling is implemented as an essential tool for the prediction of drug-macromolecule interaction. This technique helps to enhance the success rate of an experiment and cuts down the experimental cost. Hence, the molecular docking study can help to analyze the possible binding pose of a small molecule on the active site of a macromolecule. Here we used blind docking to screen some biologically active spice molecules with the SARS-CoV-2 Spro and SARS-Cov-2 Mpro.

2.1. Drug likeness properties of the small molecules

The property of the small molecules for drug-likeness was estimated using the Lipinski’s rule. This rule works on five parameters viz. no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, molecular mass < 500 Da, and the octanol-water partition coefficient, i.e., log P should not exceed 5. The Lipinski’s parameters were obtained by using the SwissADME server (www.swissadme.ch/index.php) (Daina, Michielin & Zoete 2017).

2.2. Structure preparation of the proteins and ligands

The crystal structures of the SARS-CoV-2 Spro (PDB ID: 6M0J) and SARS-CoV-2 Mpro (PDB ID: 6Y84) were obtained from the RCSB protein data bank. All the non-standard residues, including water, were removed from the PDB file using Chimera (Pettersen et al. 2004). The 3D conformer of the ligands was obtained from the PubChem and was optimized using the Steepest-Descent and conjugate gradient steps with General Amber Force Field (GAFF) (Wang, Wolf, Caldwell, Kollman & Case 2004) in Chimera (Pettersen et al. 2004).
2.3. Molecular docking study

The prepared structures of the protein and ligand were subjected to molecular docking analysis using AutoDock Vina (Trott & Olson 2010). AutoDock Vina is the newest member of the AutoDock family that has improved speed and accuracy. It uses a hybrid scoring function and a quasi-Newtonian optimization algorithm to find the lowest energy confirmations within the search space. A grid box of $40 \times 65 \times 70$ was built with the center of the box at $(11.98, 0.60, 4.79)$ for the SARS-CoV-2 Mpro. A grid box of size $61 \times 72 \times 115$ with center at $(-26.74, 18.36, -14.16)$ was prepared for the SARS-CoV-2 Spro. The exhaustiveness of search was increased to 20 and 40 for the SARS-CoV-2 Mpro and the SARS-CoV-2 Spro, respectively, to compensate for the larger box volume and reliable results. The docked poses were ranked as per their binding affinities at the end of the docking run. The ligand interactions of the best-docked poses at the active sites of the macromolecule were extracted using PyMol (Schrödinger). The ligand interactions were analyzed using the 2D interaction plot in the Discovery Studio visualizer (Visualizer 2005). The Coulombic electrostatic potential surface was determined with the help of the APBS plugin available in PyMol (Schrödinger).

3. Results and Discussion

3.1. Molecular Electrostatic Potential (MEP) surface analysis

The electrostatic potential is an essential property for the analysis and prediction of the reactive behaviour of a molecule. The study of the molecular electrostatic potential (MEP) surface can provide information about the active site of the macromolecule with the indication of relative ligand orientation and nature of the active site at which an approaching electrophile is attracted (Politzer, Laurence & Jayasuriya 1985). In a biological macromolecule, the electrostatic potential surface is plotted by analyzing the electron-rich and deficient regions of
the molecule. The detailed insight at the molecular label helps to predict the potentiality of the ligands to take part in chemical reactions and their mechanism of interaction. The electronically poor regions (blue) are referred to as potential, whereas the dense electron regions (red) are at a negative potential, and the white zone is considered as neutral. The MEP surface representation of SARS-CoV-2 Spro and Mpro ligand-binding sites with the simultaneous presence of all docked molecules are provided in Figure S1. From the figure, it is observed that most of the selected molecules actively bound at the red regions that are referred to as highly negative electrostatic potential regions. This implies that the molecules are polar nature and can actively take part in the binding process with stable interactions, which in turn could help to block the viral replication.

3.2. Lipophilicity

Lipophilicity or fat friendliness of a molecule defines the dissolving capability in fat, oil, or any nonpolar solvent (Lindsley 2010). The water n-octanol partition coefficient (log Po/w) is used as the measure of lipophilicity (Constantinescu, Lungu & Lung 2019). Various computational methods were developed for the estimation of log Po/w for diverse performance upon different chemical sets. The swissADME provides five different predictive models such as XLOGP3 (Cheng et al. 2007), WLOGP (Wildman & Crippen 1999), MLOGP (Moriguchi, HIRONO, LIU, NAKAGOME & MATSUSHITA 1992), SILICOS-IT (http://silicos-it.be.s3website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html 2016), and iLOGP (Daina, Michielin & Zoete 2014) for better prediction accuracy.

Predicted lipophilicity (Log P) values of the spice molecules obtained from different calculation models are shown in Figure 1. All the molecules subjected to lipophilicity test lie in the range of +1.2 to +4.19 of consensus value that obeys the Lipinski’s limit of log P < 5,
Figure 1. Predicted lipophilicity (Log P) values of the spice molecules obtained from different calculation models.

which suggests they can be used for further clinical trials (Arnott & Planey 2012). The lowest lipophilicity is observed for Vanillin and highest for Nerolidol, among the screened molecules. From Figure 1, it is found that all the ligand molecules have positive lipophilicity value. Hence, these molecules satisfy the essential criteria to be drug molecules.

3.3. Water Solubility

Solubility is the measure of homogeneity of the system from the mixture of solute and solvent. It is considered one of the vital parameters in drug concentration determination for a desired pharmacological response (Savjani, Gajjar & Savjani 2012). Poor solubility of drugs
is a major issue in drug discovery and development. Solubility acts as a driving force to attain high drug concentration in blood for therapeutic effectiveness (Bergström & Larsson 2018).

![Image](https://example.com/image.png)

**Figure 2:** Predicted solubility (Log S) values of the spice molecules obtained from different calculation models.

The drug solubility property of the proposed small molecules is obtained from the swissADME. The server uses three models, such as Ali (Ali, Camilleri, Brown, Hutt & Kirton 2012), ESOL (Delaney 2004), and Silicos-IT (http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html 2016) solubility that is comprised of different topological methods to check the water solubility of these small molecules. The plot for solubility of the proposed small molecules based on these three different models is shown in **Figure 2**. The Log S values obtained for the ligand molecules based on these three models are in the range of -1.8 to -3.94 for ESOL method, -1.68 to -4.99 for Ali method, and -1.48 to -5.52 for Silicos-IT method. The values from different models suggest to the moderately
soluble to very soluble nature of the molecules. The reference value of Log S for moderately soluble and highly soluble molecules range from -4 to -6 and -2 to -4, respectively. The solubility values suggest for the oral administration of these molecules.

3.4. Pharmacokinetic Properties

The pharmacokinetic property is the prime factor for the selection of a drug candidate that describes the drug disposition in the body. The significant parameters that quantify the pharmacokinetics of a drug are its ADME (absorption, distribution, metabolism, excretion) properties (Jang, Harris & Lau 2001). All the molecules subjected to ADME tests are qualified for drug approval with their high value of gastrointestinal (GI) absorption (Daina & Zoete 2016), which in turn implies for their use as an oral drug. Table 1 represents the pharmacokinetic properties of the proposed drug candidates. The passive gastrointestinal absorption and blood-brain barrier (BBB) permeation is a fundamental criterion for the distribution of the drug molecules. From Table 1, it is observed that all the ligand molecules are BBB permeant that implies their underlying distribution index. The high negative skin permeable coefficient (Kp) values indicate a less skin permeability that is useful for their transdermal delivery. The interaction of the drug molecules with cytochromes P450 (CYP) is an essential property as they play a crucial role in drug elimination through biotransformation metabolism. The noninhibition of CYP isoforms such as CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 revealed that these molecules are not the substrate for these enzymes that resembles for the lower degradation rate of these molecules which will make it effectively available for blocking the SARS-CoV-2 Spro, and SARS-CoV-2 Mpro. The synthetic accessibility values suggest the facile synthesis of these molecules. All these parameters infer these close to drug-like molecules, which may be used as successful drug candidates.
| Sl. No. | Molecule                  | Binding Energy (kcal/mol) | ESOL Log S | Ali Log S | Silicos-IT LogSw | GI absorption | BBB permeant | Pgp substrate | Log Kp (cm/s) | Bioavailability Score | Synthetic Accessibility |
|--------|---------------------------|---------------------------|------------|-----------|-----------------|---------------|--------------|--------------|--------------|-------------------------|--------------------------|
| 1.     | 2-decenoic acid           | -5.4                      | -5.4       | -2.8      | -4.23           | High          | Yes          | No           | -4.68        | 0.56                    | 2.44                     |
| 2.     | alpha-terpinyl acetate    | -5.5                      | -6.4       | -3.35     | -4.21           | High          | Yes          | No           | -4.69        | 0.55                    | 3.13                     |
| 3.     | capsaicin                 | -6.4                      | -6.9       | -3.53     | -4.5            | High          | Yes          | No           | -5.62        | 0.55                    | 2.32                     |
| 4.     | Carvone                   | -6.2                      | -7.0       | -2.41     | -2.72           | High          | Yes          | No           | -5.29        | 0.55                    | 3.33                     |
| 5.     | Cinnamaldehyde            | -5.7                      | -6.6       | -2.17     | -1.88           | High          | Yes          | No           | -5.76        | 0.55                    | 1.65                     |
| 6.     | Cuminaldehyde             | -5.9                      | -6.8       | -2.52     | -2.37           | High          | Yes          | No           | -5.52        | 0.55                    | 1                        |
| 7.     | Dipropyl disulfide        | -3.1                      | -3.8       | -2.14     | -3.42           | High          | Yes          | No           | -5.3         | 0.55                    | 2.79                     |
| 8.     | Eucalyptol                | -5.2                      | -5.7       | -2.52     | -2.59           | High          | Yes          | No           | -5.3         | 0.55                    | 3.65                     |
| 9.     | Linalool                  | -5.5                      | -5.5       | -2.4      | -3.06           | High          | Yes          | No           | -5.13        | 0.55                    | 2.74                     |
| 10.    | Vanillin                  | -5.7                      | -6.1       | -1.82     | -1.78           | High          | Yes          | No           | -6.37        | 0.55                    | 1.15                     |
| 11.    | Thymol                    | -5.8                      | -7.2       | -3.19     | -3.4            | High          | Yes          | No           | -4.87        | 0.55                    | 1                        |
| 12.    | Sabinene hydrate          | -5.2                      | -5.3       | -2.07     | -2.18           | High          | Yes          | No           | -5.74        | 0.55                    | 2.82                     |
| 13.    | Piperine                  | -7.3                      | -7.8       | -3.74     | -3.96           | High          | Yes          | No           | -5.58        | 0.55                    | 2.92                     |
| 14.    | Menthol                   | -5.6                      | -6.5       | -2.88     | -3.5            | High          | Yes          | No           | -4.84        | 0.55                    | 2.63                     |
| 15.    | Eugenol                   | -6.0                      | -6.8       | -2.46     | -2.79           | High          | Yes          | No           | -5.69        | 0.55                    | 1.58                     |
|   | Compound           | 1 | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 |   |
|---|-------------------|---|----|----|----|----|----|----|----|----|----|---|
| 16| Estragole         | -5.7| -6.4| -3.09| -3.24| -3.35| High| Yes| No| -4.81| 0.55| 1.28|
| 17| Gingerol          | -6.1| -6.5| -2.96| -3.82| -4.58| High| Yes| No| -6.14| 0.55| 2.81|
| 18| Shogaol           | -5.8| -6.2| -3.7| -4.67| -4.8| High| Yes| No| -5.15| 0.55| 2.51|
| 19| Paradol           | -6.0| -6.5| -3.72| -4.79| -5.52| High| Yes| No| -5.08| 0.55| 2.28|
| 20| Zingerone         | -6.0| -7.2| -1.8| -1.68| -3.1| High| Yes| No| -6.7| 0.55| 1.52|
| 21| Borneol           | -5.7| -5.7| -2.51| -2.8| -1.91| High| Yes| No| -5.31| 0.55| 3.43|
| 22| Bornyl acetate    | -5.3| -5.9| -3.63| -4.57| -2.58| High| Yes| No| -4.44| 0.55| 3.64|
| 23| Citral            | -5.5| -6.1| -2.43| -3.05| -1.96| High| Yes| No| -5.08| 0.55| 2.49|
| 24| Citronellal       | -4.8| -6.0| -2.88| -3.88| -2.33| High| Yes| No| -4.52| 0.55| 2.57|
| 25| 2-Undecanone      | -4.9| -5.2| -2.94| -4.15| -3.83| High| Yes| No| -4.43| 0.55| 1.72|
| 26| Geranyl acetate   | -5.4| -6.7| -3.21| -4.3| -2.52| High| Yes| No| -4.63| 0.55| 2.72|
| 27| Nerolidol         | -5.8| -6.6| -3.8| -4.99| -3.15| High| Yes| No| -4.23| 0.55| 3.53|
| 28| Terpinen-4-ol     | -5.2| -6.3| -2.78| -3.36| -1.91| High| Yes| No| -4.93| 0.55| 3.28|
| 29| Terpineol         | -5.7| -6.8| -2.87| -3.49| -1.69| High| Yes| No| -4.83| 0.55| 3.24|
| 30| Decanal           | -4.7| -5.6| -2.67| -3.85| -3.44| High| Yes| No| -4.56| 0.55| 1.62|
3.5. Molecular Docking Study

3.5.1. Docking Study of SARS-CoV-2 Spro

In addition to the above, a molecular docking study was performed to estimate the binding affinity and their binding pose of the ligand molecules at the binding site of the SARS-CoV-2 Spro. From the study, it is observed that Piperine has the highest interaction affinity among the screened compounds. The docked poses of the three ligand molecules along with their 2D interaction diagram having the highest binding affinity are presented in descending order in Figure 3. From Table 1, it is observed that these three molecules follow the trend for their binding affinity with Piperine (-7.8 kcal/mol) at the highest then Thymol and Zingerone (both having -7.2 kcal/mol) among all the selected molecules. From Figure 3(a), it is observed that Piperine is associated with hydrogen bond interaction with THR416. PRO397 and PHE420 are involved with pi-alkyl and pi-pi stacking interaction, respectively, with the Penta-membered ring of Piperine. The residue ILE273 is forming a pi-sigma bond with Piperine. The binding process is also governed by van der Waals interactions with the residues of SARS-CoV-2 Spro. Hence, the interaction of Piperine with SARS-CoV-2 Spro is stabilized by covalent hydrogen bonding, sigma-pi, and pi-pi stacking interactions with a good affinity score. Thymol interacts with the residue THR416 through hydrogen bonds, ILE273 through pi-sigma interactions with the benzene ring, PHE420 through pi-stacking interaction, PRO397, and MET348 through alkyl and pi-alkyl interactions, respectively (Figure 3(b)). The residues ASN272, ALA395, PHE410, GLU412, GLU417, ASN 419, and HIS522 are involved with van der Waals interaction with Thymol.

On the other hand, Zingerone is stabilized by various kinds of interactions with the SARS-CoV-2 Spro (Figure 3(c)). The oxygen atom of the OH-group in the benzene ring of Zingerone is interacting with ILE273 by hydrogen bond interaction. Other than the hydrogen bond interaction ILE273 is also having a pi-sigma interaction with the benzene ring of
Zingerone. The residues PRO271 and THR416 are in carbon-hydrogen bond interaction with the OH-group attached to the benzene ring. The residue PHE420 is involved in pi stacked interaction while ASN272, PRO397, GLU417, ASN419, HIS522, and LYS523 residues are involved in van der Waals interactions. The lowest energy poses of the rest 27 molecules along with their 2D interaction diagrams are provided in **Figure S2**.
Figure 3: Lowest energy docked pose of (a) Piperine, (b) Thymol, and (c) Zingerone with SARS-CoV-2 Spro and their 2D interaction diagram. The colour codes represent the nature of interactions.

3.5.2. Docking Study of SARS-CoV-2 Mpro

The above-selected molecules were also docked with the SARS-CoV-2 Mpro to observe the inhibitory effect of these molecules. The docking study reveals that all the molecules are interacting with the SARS-CoV-2 Mpro with certain binding affinity. The docking data are again presented in Table 1. From Table 1, once more, it is seen that Piperine has the highest affinity at the binding site of SARS-CoV-2 Mpro among all the selected molecules, which is similar to the case of SARS-CoV-2 Spro. The ΔG value, known as binding free energy, for the three molecules having the highest affinity among all the selected
molecules, along with their 2D interaction diagram, are given in Figure 4. The three molecules followed the binding affinity trend as Piperine (-7.3 kcal/mol) > Capsaicin (-6.4 kcal/mol) > Carvone (-6.2 kcal/mol). From Figure 4(a), it is observed that the interaction of Piperine at the binding site of the SARS-CoV-2 Mpro is stabilized by hydrogen bonding, electrostatics, and van der Waals interactions. The residues GLN299, and VAL303 are associated with hydrogen bonding interaction, ASP295, and ARG298 with charged interactions while MET6, and PRO9 are associated with hydrophobic interactions with Piperine. The molecule is also stabilized through van der Waals interactions with residues PHE8, GLY127, ILE152, PHE291, and THR304 at the binding site of the SARS-CoV-2 Mpro. The molecule Capsaicin is stabilized in the binding pocket through van der Waals and hydrophobic interactions (Figure 4(b)). The residues MET6, PHE8, PRO9, and ILE152 are interacting through hydrophobic interactions such as alkyl and pi-alkyl with the Capsaicin. Capsaicin is interacting with residues ALA7, GLY11, LYS12, GLN127, TYR154, PHE291, ASP295, ARG298, GLN299, VAL303, and THR304 through van der Waals interaction. The interaction of Carvone with the SARS-CoV-2 Mpro is stabilized through hydrophobic and van der Walls interactions (Figure 4(c)). Carvone interacts with the residues MET6, PHE8, and ARG298 of SARS-CoV-2 Mpro through hydrophobic contacts. The residues ALA7, PRO9, GLN127, ASP295, GLN299, GLY302, and VAL303 are in van der Waals interactions with Carvone. The lowest energy binding poses of the rest 27 molecules along with the ligand interaction diagram at the binding sites of the SARS-CoV-2 Mpro are provided in Figure S3.
Figure 4. Lowest energy docked pose of (a) Piperine, (b) Capsaicin, and (c) Carvone with SARS-CoV-2 Mpro and their 2D interaction diagram. The colour codes represent the nature of interactions.

4. Conclusion

This study used blind molecular docking as a potential tool to study the inhibitory efficiency of natural spice molecules against SARS-CoV-2, which emerged as a global threat to millions of people across the globe. It is observed that all the proposed spice molecules qualified the ADME test with their suitable pharmacokinetic properties to be useful as a drug candidate. The docking study revealed that all the molecules actively took part in binding to the SARS-CoV-2 Spro and Mpro with their low or high value of binding affinity. This binding of these molecules will be helpful in inhibiting the replication of the viral proteins with specific hindrances upon their mutarotation. For both the viral targets, Piperine performed well with its highest binding affinity of -7.8 and -7.3 kcal/mol for SARS-CoV-2 Spro and Mpro, respectively. Hence, the study proposes Piperine as an active molecule for the inhibition of SARS-CoV-2. Since this study is performed computationally, therefore, it requires wet-lab experiments in-vivo as well as in-vitro for further validation.
Acknowledgements

The authors are thankful to IIT(ISM) Dhanbad for providing infrastructure facilities. We are also extremely grateful to Dr. Anand Kant Das, New York University, Abu Dhabi, for a fruitful scientific discussion.

Declaration of interest statement

The authors declare no conflict of interest.
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Supplementary Information

In Silico Investigation of Spice Molecules as Potent Inhibitor of SARS-CoV-2

Janmejaya Rout, Bikash Chandra Swain, and Umakanta Tripathy*

Department of Physics, Indian Institute of Technology (Indian School of Mines), Dhanbad, 826004, Jharkhand, India.

*Corresponding author E-mail: utripathy@iitism.ac.in
Table S1: List of selected spice molecules with their PubChem ID and source supplement.

| Sl No | Molecules                        | Source of origin                                                                 |
|-------|----------------------------------|----------------------------------------------------------------------------------|
| 1.    | 2-decenoic acid (5282724)        | Coriander (Coriandrum sativum L.) essential oil (Laribi, Kouki, M'Hamdi & Bettaieb 2015; Mandal & Mandal 2015) |
| 2.    | alpha-terpinyl acetate (111037)  | Cardamom (E. cardamomum) seed (Chowdhury & Kumar 2020)                           |
| 3.    | Capsaicin (1548943)              | Hot peppers or red chillies (Hayman & Kam 2008)                                  |
| 4.    | Carvone (7439)                   | Caraway (Baysal & Starmans 1999)                                                |
| 5.    | Cinnamaldehyde (637511)          | Cinnamon (Masghati & Ghoreishi 2018)                                             |
| 6.    | Cuminaldehyde (326)              | Cumin essential oil (Chen et al. 2011)                                           |
| 7.    | Dipropyl disulfide (12377)       | Onion essential oil (Mnayer et al. 2014)                                         |
| 8.    | Eucalyptol (2758)                | Aromatic plants (De Vincenzi, Silano, De Vincenzi, Maialetti & Scazzocchio 2002; Juergens et al. 2003) |
| 9.    | Linalool (6549)                  | Coriander seed essential oil (Mandal & Mandal 2015)                               |
| 10.   | Vanillin (1183)                  | Vanilla bean pods (Jadhav, B.N, Gogate & Rathod 2009)                            |
| 11.   | Thymol (6898)                    | Essential oil from ajwain seed (Anwar, Ahmed, Habibatni & Abusamra 2016) and of thyme (Nagoor Meeran, Jagadeesh & Selvaraj 2016) |
| 12.   | Sabinene hydrate (62367)         | Origanum majorana (Novak et al. 2000)                                            |
| 13.   | Piperine (638024)                | Pepper (Raman & Gaikar 2002)                                                     |
| 14.   | Menthol (1254)                   | Mint (Nair 2001)                                                                 |
| 15.   | Eugenol (3314)                   | Clove oil, nutmeg oil, cinnamon (Khalil et al. 2017)                              |
| 16.   | Estragole (8815)                 | Basil oil (Pushpangadan & George 2012)                                           |
| 17.   | Gingerol (442793)                | Ginger (Mao et al. 2019)                                                         |
|   | Chemical | Source |
|---|----------|--------|
|18.| Shogaol (5281794) | Ginger (Mao et al. 2019) |
|19.| Paradol (94378) | Ginger (Mao et al. 2019) |
|20.| Zingerone (31211) | Ginger (Mao et al. 2019) |
|21.| Borneol (64685) | Branches and leaves of Cinnamomum camphora (L.) Presl (Sheng, Du, Qiang & Du 2018) |
|22.| Bornyl acetate (6448) | Pine oil (Fu, McCue & Boesenberg 2007; Bonikowski, Celinski, Wojnicka-Poltorak & Malinski 2015) |
|23.| Citral (638011) | citrus fruit's peel oil (Tamer, Suna & Özcan-Sinir 2019) |
|24.| Citronellal (7794) | Citronella essential oil (Silva, Moura, Mendes & Pessoa 2011; Pujiastuti, Cahyono & Sumarni 2017) |
|25.| 2-Undecanone (8163) | Leaf essential oils of Zanthoxylum armatum DC (Rutaceae) (Bisht & Chanotiya 2011), Essential oil obtained from H. cordata (Chen, Wang, Shi & Fang 2014) |
|26.| Geranyl acetate (1549026) | Palmarosa oil (Dubey & Luthra 2001) |
|27.| Nerolidol (5284507) | Baccharis dracunculifolia DC (Asteraceae) (Klopell et al. 2007) |
|28.| Terpinen-4-ol (11230) | Tea-tree oil (Shapira, Pleban, Kazanov, Tirosch & Arber 2016) |
|29.| Terpineol (17100) | Cardamom oil (Bernhard, Wijesekera & Chichester 1971) |
|30.| Decanal (8175) | Essential oil of Iris pallida rhizomes and leaves (Mykhailenko 2018) |
Figure S1: Molecular electrostatic surface potential of (a) SARS CoV2 Spro, (b) SARS CoV2 Mpro in presence of all docked ligands. Red and Blue coloured regions represent the most electronegative and most electropositive regions, respectively.

1. 2-Decenoic acid
2. Alpha-terpinyl acetate

3. Capsaicin
4. Carvone

5. Cinnamaldehyde
6. Cuminaldehyde

7. Dipropyl disulfide
8. Eucalyptol

9. Linalool
10. Vanillin

11. Sabinene hydrate
12. Menthol

13. Eugenol
14. Estragole

15. Gingerol
16. Shogaol

17. Paradol
18. Borneol

19. Bornyl acetate
20. Citral

21. Citronellal
22. 2-Undecanone

23. Geranyl acetate
24. Nerolidol

25. Terpinen-4-ol
26. Terpineol

Figure S2: Lowest energy docked pose of 27 spice molecules with SARS-CoV2 Spro (PDB ID: 6M0J) and their 2D interaction diagram.

27. Decanal
1. 2-Decenoic acid

2. Alpha-terpinyl acetate
3. Cinnamaldehyde

4. Cuminaldehyde
5. Dipropyl disulfide

6. Eucalyptol
7. Linalool

8. Vanillin
9. Thymol

10. Sabinene hydrate
11. Menthol

12. Eugenol
13. Estragole

14. Gingerol
15. Shogaol

16. Paradol
17. Zingerone

18. Borneol
19. Bornyl acetate

20. Citral
21. Citronellal

22. 2-Undecanone
23. Geranyl acetate

24. Nerolidol
25. Terpinen-4-ol

26. Terpineol
27. Decanal

Figure S3: Lowest energy docked pose of 27 molecules with SARS-CoV2 Mpro (PDB ID: 6Y84) and their 2D interaction diagram.
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